our results illustrated in Figure 5. The viscometric studies suggest that both mefloquine (4) and 6 simply interact with DNA through weak external counterion electrostatic attraction.

We have shown with naphthothiopheneethanolamines that addition of a trifluoromethyl substituent to a planar aromatic ring system can actually enhance DNA binding.[13,20] In this case, however, model building studies indicated that the side chain can lie in one groove of the DNA double helix and the trifluoromethyl substituent in the other. The enhancement of binding on introduction of a trifluoromethyl substituent in this system is presumably due to electronic factors, a point which we have under investigation. Positioning of bulky substituents on small molecules can, thus, lead either to significant increases or to decreases in DNA binding depending on their relative position with respect to other bulky substituents, the electronic characteristics of the substituent, and the structure of the DNA–drug complex.

Acknowledgment. The authors thank Dr. E. A. Steck of the Walter Reed Army Institute of Research for supplying samples of compounds 4–6 and for encouragement and helpful advice in this research. Dr. Harry B. Wood, Jr., of the National Cancer Institute generously supplied us with a daunorubicin sample. We thank Dr. Daniel Vapnek for supplying a culture of *E. coli* JC 411 *thyA* (Col E_1) and for helpful advice on its growth and isolation of plasmid DNA. This work was supported in part by grants from the Research Corporation and from the Georgia State University Arts and Sciences Research Fund.

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Antimalarials. 10. Synthesis of 4-Substituted Primaquine Analogues as Candidate Antimalarials

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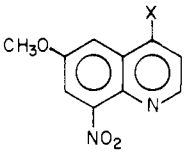
Primaquine (I) has been extensively used in combination with other drugs in the radical cure of relapsing malaria as well as for prophylaxis or the interruption of transmission. This, coupled with the activity data reported for 4-methylprimaquine (II), has led to the synthesis of a series of 14 4-substituted analogues of I. In addition, three side-chain analogues of II were prepared. The compounds were tested for suppressive antimalarial activity against *Plasmodium berghei* in the Rane mouse screen and for radical curative activity against *Plasmodium cynomolgi* in the rhesus monkey. Four of the 17 compounds prepared (1a, 9c, 15, and 17) exhibited activity in at least one of the test systems.

Several 8-quinolinediamines were synthesized during the 1940's and tested for antimalarial activity. The majority of these early compounds were 6-methoxyquinolines containing a wide variety of diamine side chains in the 8

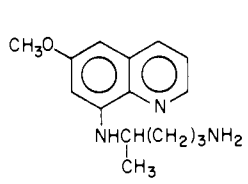
Table I. 4-Substituted 6-Methoxy-8-nitroquinolines



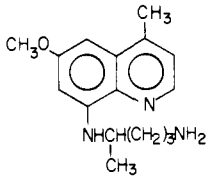
No.	X	Mp, °C (solvent)	Yield, %[a]	Formula	Analyses
1a	OC_6H_4-*p*-Cl	145-147 (EtOH)	75	$C_{16}H_{11}ClN_2O_4$	C, H, Cl
2a	OC_6H_4-*p*-OCH_3	156-158 (EtOH)	84	$C_{17}H_{14}N_2O_5$	C, H, N
3a	OC_6H_3-*m*,*p*-Cl_2	178-180 ($EtOCH_2CH_2OH$)	45	$C_{16}H_{10}Cl_2N_2O_4$	C, H, N
4a	OC_6H_4-*m*-CF_3	*b*			
5a	NHC_6H_4-*p*-Cl	221-223 (EtOH)[c]	62	$C_{16}H_{14}ClN_3O$	C, H, N
6a	SC_6H_4-*p*-Cl	151-153 ($CHCl_3$-EtOH)	75	$C_{16}H_{11}ClN_2O_3S$	C, H, N, S
7a	SC_6H_4-*p*-OCH_3	170-172 ($CHCl_3$-EtOH)	70	$C_{17}H_{14}N_2O_4S$	C, H, N, S
8a	OCH_3	152-154 (EtOH)	94	$C_{11}H_{10}N_2O_4$	C, H, N
9a	SCH_3	136-138 (EtOH)	75	$C_{11}H_{10}N_2O_3S$	C, H, N
10a	$NHC(O)CH_3$	254-256 (EtOH)	83[d]	$C_{12}H_{11}N_3O_4$	C, H, N
11a	NH_2	180-185[e] 185-189[f]	61	$C_{10}H_9N_3O_3$	C, H, N
12a	$NHCH_3$	215-217 (EtOAc)	76	$C_{11}H_{11}N_3O_3$	C, H, N
13a	$OCH_2C_6H_4$-*p*-Cl	186-188 (CH_3CN)	64	$C_{17}H_{13}ClN_2O_4$	C, H, N

[a] From 4-chloro-6-methoxy-8-nitroquinoline. [b] Oil, not purified. [c] Lit.[5] mp 221-223 °C. [d] From 11a. [e] Sublimed material. [f] Hydrate.

position of the quinoline nucleus. From this program primaquine (I) emerged as the most effective and least



I



II

toxic of the 8-aminoquinolines. Since primaquine, and the 8-aminoquinolines in general, is notably effective against more of the life-cycle stages of the plasmodia than any other class of drugs,[1] it is used in combination with drugs such as chloroquine, amodiaquine, and pyrimethamine for the radical cure of relapsing malaria and for prophylaxis or the interruption of transmission. However, primaquine still suffers from one major drawback, its relatively low chemotherapeutic index. As a result, general clinical experience with primaquine has led to the use of only small doses in man on a regular basis or larger doses on an intermittent basis. The toxic effects of primaquine are most pronounced in populations which suffer from a deficiency of glucose-6-phosphate dehydrogenase. This deficiency is most common among Negro people and primaquine is most likely to induce hemolytic reactions in these subjects.

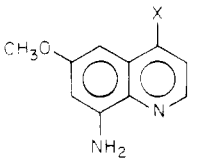
4-Methylprimaquine (II), which was prepared also during the World War II research effort,[2a] has recently been resynthesized by Nodiff and co-workers[2b] and retested for radical curative antimalarial activity against *Plasmodium cynomolgi* in the rhesus monkey. 4-Methylprimaquine was approximately twice as active as primaquine in this test with 8/12 cures at a dose of 0.25 mg/kg (×7). Primaquine, on the other hand, was not effective at 0.25 mg/kg (×7) and effected 10/12 cures at 0.5 mg/kg (×7). Also, 4-methylprimaquine was somewhat less toxic in the Rane *Plasmodium berghei* mouse screen.

Since relatively little has been reported on the effects of substitution in the 4 position upon the antimalarial activity of the 8-aminoquinolines, we have synthesized a series of 17 analogues of II. Fourteen of the 17 compounds contain substituents other than methyl in the 4 position, and all contain the noval diamine side chain in the 8 position. The remaining three examples are analogues of II bearing different diamine side chains in the 8 position (**15–17**).

Chemistry. The key intermediate in the preparation of most of the 4-substituted target compounds was 4-chloro-6-methoxy-8-nitroquinoline. 4-Hydroxy-6-methoxy-8-nitroquinoline was prepared via the procedure of Riegel et al.[3] and converted to 4-chloro-6-methoxy-8-nitroquinoline via the procedure of Price et al.[4] Most of the intermediate 4-substituted 6-methoxy-8-nitroquinolines (Table I) were prepared by treating 4-chloro-6-methoxy-8-nitroquinoline with the appropriate nucleophile as shown in Scheme I. Therefore, fusion of the 4-chloro intermediate with the appropriate phenol afforded intermediates **1a–4a**. The 4-(4-chloroanilino) intermediate **5a** was prepared via a modification of the procedure of Bennett et al.[5] The two thiophenoxy intermediates **6a** and **7a** were prepared by treating the 4-chloroquinoline with the appropriate thiophenol in 10% ethanolic potassium hydroxide. This procedure represents a modification of that reported by Brooker et al.[6] The 4-methoxy and 4-methylthio analogues, **8a** and **9a**, were prepared by treating the 4-chloro precursor with sodium methoxide[7] and with sodium thiomethylate, respectively. The 4-amino and 4-methylamino analogues, **11a** and **12a**, were best prepared by treating the 4-(4-chlorophenoxy) intermediate **1a** with ammonium acetate and methylammonium acetate, respectively. Attempts to effect displacement of the chlorine atom in the 4 position with either ammonia or methylamine were unsuccessful. Acylation of **11a** with acetic anhydride afforded the 4-acetamido derivative **10a**. The preparation of 4-(4-chlorobenzyloxy)-6-methoxy-8-nitroquinoline (**13a**) could be effected by treating 4-hydroxy-6-methoxy-8-nitroquinoline with 4-chlorobenzyl chloride either with sodium hydride in dimethylformamide or in aqueous sodium hydroxide. We found that the latter method, used by Talati et al.,[8] could not be increased in scale without suffering a significant decrease in yield. Formation of the aryloxide with a slight excess of sodium hydride followed by alkylation with 4-chlorobenzyl chloride in DMF gave reproducible yields of **13a** in runs of from 1 to 20 g.

The 4-substituted 6-methoxy-8-aminoquinolines (Table II), with the exception of the sulfur-containing analogues **6b**, **7b**, and **9b**, were prepared via catalytic hydrogenation of the corresponding 8-nitro precursor with commercially

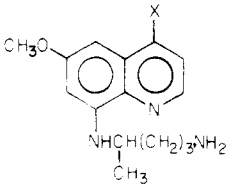
Table II. 4-Substituted 6-Methoxy-8-aminoquinolines



No.	X	Mp, °C (solvent)	Yield, %[a]	Formula	Analyses
1b	OC_6H_4-*p*-Cl	106-112[b] (C_6H_6-ligroine)	83	$C_{16}H_{13}ClN_2O_2$	C, H, N
2b	OC_6H_4-*p*-OCH_3	128-131 (C_6H_6-ligroine)	84	$C_{17}H_{16}N_2O_3$	C, H, N
3b	OC_6H_3-*m*,*p*-Cl_2	115-117 (EtOH)	71	$C_{16}H_{12}Cl_2N_2O_2$	C, H, N
4b	OC_6H_4-*m*-CF_3	158-160 (EtOH)	61	$C_{17}H_{10}F_3N_2O_4$	C, H, F, N
5b	NHC_6H_4-*p*-Cl	178-180 (EtOH)[c]	86	$C_{16}H_{12}ClN_3O_3$	C, H, N
6b	SC_6H_4-*p*-Cl	125-127 (MeOH)	77	$C_{16}H_{13}ClN_2OS$	C, H, N, S
7b	SC_6H_4-*p*-OCH_3	138-140 (MeOH)	77	$C_{17}H_{16}N_2O_2S$	C, H, N
8b	OCH_3	247-249 (EtOH-Et_2O)[d]	83	$C_{11}H_{13}ClN_2O_2$	C, H, N
9b	SCH_3	136-138 (EtOH)	53	$C_{11}H_{12}N_2OS$	C, H, N
10b	$NHC(O)CH_3$	221-223 (EtOAc)	98	$C_{12}H_{13}N_3O_2$	C, H, N
11b	NH_2	135-137 (C_6H_6)	90[e]	$C_{10}H_{10}N_3O$	C, H, N
12b	$NHCH_3$	310 dec (EtOH)[d]	85	$C_{11}H_{14}ClN_3O$	C, H, N
13b	$OCH_2C_6H_4$-*p*-Cl	165-167 (CH_3CN)	83	$C_{17}H_{15}ClN_2O_2$	C, H, N

[a] From 8-nitro precursor. [b] Mixture of two crystalline forms melting at 105 and 115 °C. [c] Lit.[5] mp 174-176 °C. [d] Hydrochloride salt. [e] From **10b**.

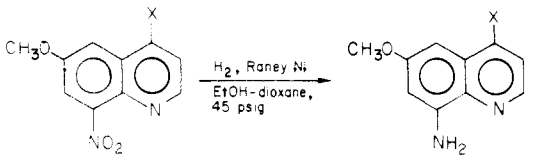
Table III. 4-Substituted Primaquine Analogues



No.	X	Mp, °C (solvent)	Yield, %[a]	Formula	Analyses
1c	OC_6H_4-*p*-Cl	155-156.5 (EtOH-H_2O)	23	$C_{21}H_{24}ClN_3O_2 \cdot 2H_3PO_4$	C, H, N[b]
2c	OC_6H_4-*p*-OCH_3	140-142 (EtOH-CH_3CN)	36	$C_{22}H_{27}N_3O_3 \cdot C_4H_6O_4$	C, H, N
3c	OC_6H_3-*m*,*p*-Cl_2	187-189 (EtOH-H_2O)	31	$C_{21}H_{23}Cl_2N_3O_2 \cdot 2H_3PO_4$	C, H, N, P
4c	OC_6H_4-*m*-CF_3	155-157 (EtOH-H_2O)	23	$C_{22}H_{24}F_3N_3O_2 \cdot 2H_3PO_4$	C, H, N[c]
5c	NHC_6H_4-*p*-Cl	174-176 (EtOH-CH_3CN)	27	$C_{21}H_{25}ClN_4O \cdot C_4H_6O_4$	C, H, N
6c	SC_6H_4-*p*-Cl	172-175 (EtOH-H_2O)	37	$C_{21}H_{24}ClN_3OS \cdot H_3PO_4$	C, H, N, P
7c	SC_6H_4-*p*-OCH_3	176-179 (EtOH-H_2O)	21	$C_{22}H_{27}N_3O_2S \cdot 2H_3PO_4$	C, H, N, S
8c	OCH_3	180-183 (EtOH-H_2O)	38	$C_{16}H_{23}N_3O_2 \cdot H_3PO_4$	C, H, N, P
9c	SCH_3	188-190 (EtOH-H_2O)	34	$C_{16}H_{23}N_3OS \cdot 1.5H_3PO_4$	C, H, N, P[d]
10c	$NHC(O)CH_3$	220 (EtOH-H_2O)	41	$C_{17}H_{24}N_4O_2 \cdot 2H_3PO_4$	C, H, N, P
11c	NH_2	100+[e]	60	$C_{15}H_{22}N_4O \cdot H_3PO_4$	C, H, N[d]
12c	$NHCH_3$	250-252 (EtOH-H_2O)	57	$C_{16}H_{24}N_4O \cdot H_3PO_4$	C, H, N, P[d]
13c	$OCH_2C_6H_4$-*p*-Cl	244-246 (EtOH-H_2O)	47	$C_{22}H_{26}ClN_3O_2 \cdot H_3PO_4$	C, H, N, P
14c	OH	265 (EtOH-CH_3CN)	76[f]	$C_{15}H_{21}N_3O_2 \cdot HCl$	C, H, Cl, N[b]

[a] From 8-amino precursor. [b] Block-dried at 145 °C. [c] Hemihydrate. [d] Sesquihydrate. [e] Monohydrate. [f] From 13c.

available, wet Raney nickel at 45 psig in ethanol–dioxane solvent as shown below. The three sulfur-containing



examples (**6b**, **7b**, and **9b**) were prepared by reducing the precursor nitroquinolines with iron and acetic acid.

Side-chain introduction involved condensation of the 8-aminoquinolines with 4-bromo-1-phthalimidopentane[2a] (Scheme II). It was found that the alkylation could be expedited, relative to reported[2a] procedures, by heating the reaction mixture to 150 °C in a sealed tube. The presence of an acid acceptor (triethylamine) also aided in achieving more complete alkylation.[9] Under these conditions alkylation could be effected in 2 h whereas 70–80 h were required when the reaction was carried out in refluxing ethanol. Alkylation of **13b** with 4-bromo-1-phthalimidopentane was carried out at 80 °C for 6 days in order to avoid debenzylation which was observed at higher temperatures. Toward the end of our work it was brought to our attention that the alkylation of the 8-aminoquinolines was facilitated also by the use of 4-iodo-1-phthalimidopentane.[9] With this reagent alkylations could be carried out at 110 °C using 2-ethoxyethanol as solvent. This procedure was used in the preparations of target compounds **10c** and **12c**. Removal of the phthalimide protection with hydrazine hydrate in refluxing ethanol involved standard procedures and afforded the desired 8-quinolinediamines shown in Table III with the exception of **14c** which was prepared via catalytic debenzylation of **13c** with palladium.

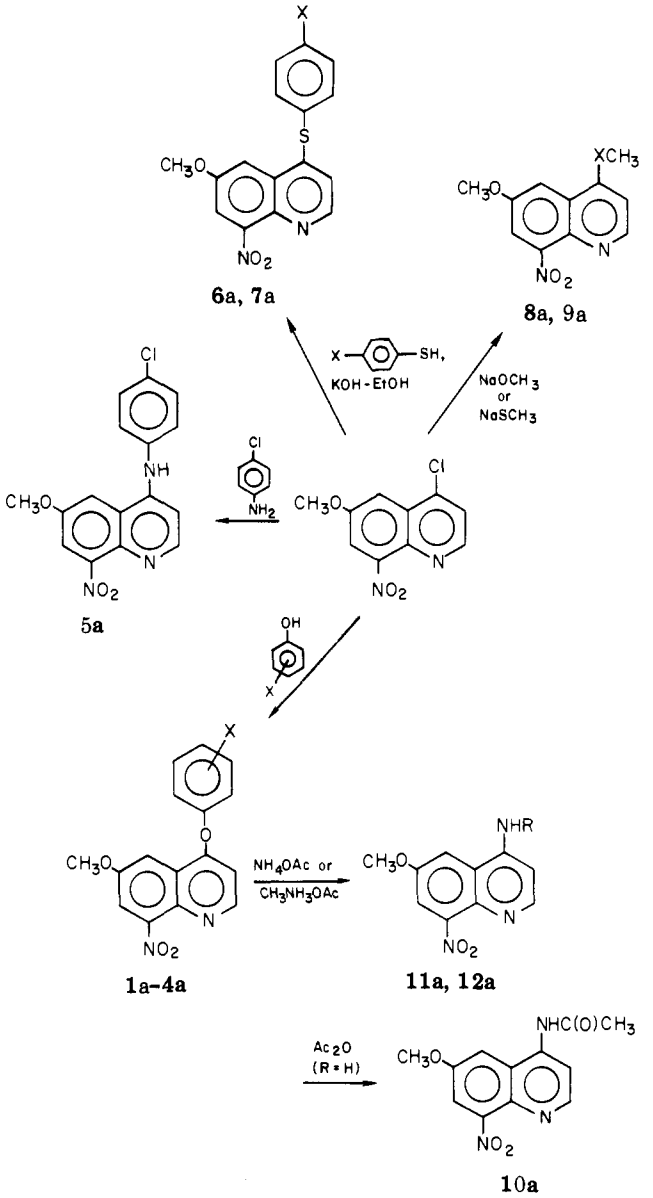
The side-chain analogue **15** was prepared by condensing 8-amino-6-methoxy-4-methylquinoline[10] with commercially available 1-bromo-3-phthalimidopropane via the procedure of Mosher[11] with the exception that triethylamine was added to the reaction mixture as an acid acceptor. Removal of the phthalimido protecting group with hydrazine gave **15**. Condensation of 8-amino-6-methoxylepidine with 3-isopropylamino-1-chloropropane hydrochloride[12] according to the procedure of Rohrmann and Shonle[13] af-

Table IV. Antimalarial Activity Data

No.	*P. cynomolgi* (rhesus monkey)[a] Daily dose, mg/kg (×7)	Activity	*P. berghei* (mice),[b] ΔMST, days at mg/kg[c] 20	40	80	160	320	640
1a	1.00	Inactive	3.5	6.1	10.1	3C	5C	5C
9c	1.00	Inactive	0.1	0.1	1.3	3.5	6.7	8.1
15	0.25	Inactive				3.9	5.5	5T
	0.50	1/4C						
	1.00	2/4C						
17	0.50	Inactive	5.8	7.0	10.4	3C	5C	5C
	1.00	1/1C						
Primaquine	0.25	Inactive		5.0	9.4	2T	5T	5T
	0.50	10/12C						
	1.00	4/4C						
4-Methylprimaquine	0.25	8/12C						
	0.50	13/13C			5.5	9.0	10.1	3C, 1T
	1.00	1/1C						

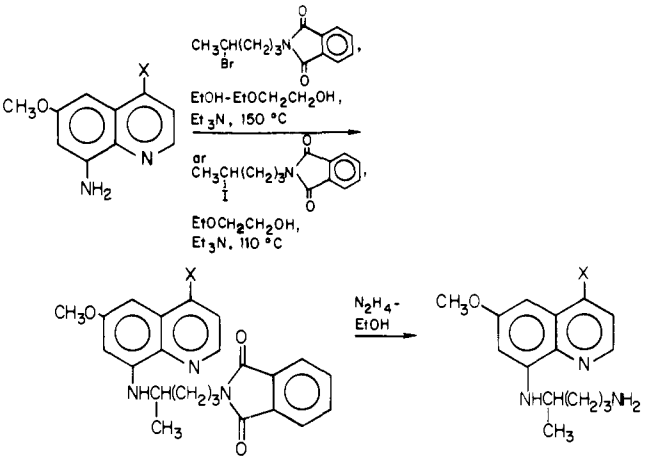
[a] See ref 17. [b] See ref 15 and 16. [c] C = cure; T = toxic death.

Scheme I

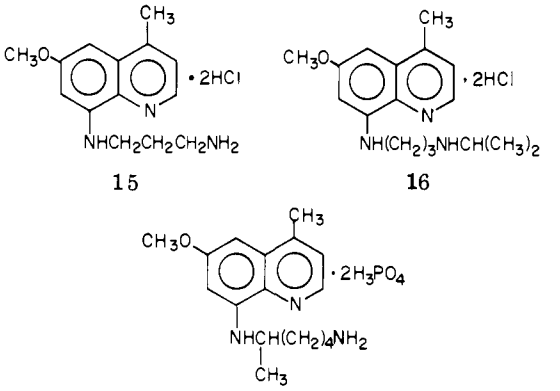


forded analogue **16**. In the preparation of compound **17**, 1,5-dibromohexane[14] was treated with potassium phthalimide in acetone to yield the required 5-bromo-1-phthalimidohexane. Condensation of this reagent with the 8-aminolepidine followed by hydrazine removal of the

Scheme II



phthalimide protection afforded **17**.



Biological Activity. The compounds were screened for suppressive antimalarial activity against *P. berghei* in mice[15,16] and for radical curative antimalarial activity against *P. cynomolgi* in the rhesus monkey.[17] The data for the active compounds are shown in Table IV. Also, the data for primaquine and 4-methylprimaquine have been included for purposes of comparison.

Four of the compounds tested displayed suppressive activity against *P. berghei* in mice. Examples **1a** and **17** were clearly superior to primaquine in this screen with curative activity at 160 mg/kg (3/5 cures) and no evidence of toxicity at 640 mg/kg. Both compounds were active also at 40 mg/kg. Against *P. cynomolgi* in the rhesus monkey, **1a** was inactive; **17** was curative at 1.0 mg/kg (×7) and inactive at 0.5 mg/kg (×7). Compound **9c** was active but

not curative against *P. berghei* at doses of 320 and 640 mg/kg but was inactive against *P. cynomolgi* in the rhesus. Compound **15** was almost inactive and toxic against *P. berghei* in the mouse and was probably inferior to primaquine against *P. cynomolgi* in the rhesus monkey based on the limited data available.

The data indicated that replacement of the hydrogen atom in the 4 position of primaquine with a variety of substituents other than alkyl results in a loss of radical curative antimalarial activity. It therefore appears that the possibilities of increasing the effectiveness of the 8-aminoquinolines via substitution in the 4 position are extremely limited.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. NMR spectra were determined on a Varian Model T60A spectrometer. Ethanol used in this work was specially denatured Grade 3A alcohol (90% ethanol, 5% 2-propanol, and 5% methanol by volume). Commercial Raney nickel was supplied by W. R. Grace Co. (No. 30).

4-(4-Chlorophenoxy)-6-methoxy-8-nitroquinoline (1a). A mixture of 4-chloro-6-methoxy-8-nitroquinoline[4] (6.0 g, 0.025 mol) and *p*-chlorophenol (12.0 g, 0.094 mol) was heated in an oil bath at 180 °C for 1 h. While still warm, the resulting melt was poured into aqueous KOH (10%, 100 mL) and the mixture was thoroughly stirred for 15 min. Filtration and washing with water afforded 7.0 g of crude product. Recrystallization from EtOH (300 mL) with decolorizing charcoal afforded yellow needles in two crops: 6.2 g (75%); mp 145–147 °C. Anal. ($C_{16}H_{11}ClN_2O_4$) C, H, Cl.

Similarly prepared were compounds **2a**, **3a**, and 4a.

4-(4-Chloroanilino)-6-methoxy-8-nitroquinoline (5a). A solution of 4-chloro-6-methoxy-8-nitroquinoline (8 g, 33 mmol) in 2-ethoxyethanol (150 mL) containing 4-chloroaniline (5.35 g, 39 mmol) was heated at reflux for 2 h. The solution was cooled and filtered and the solid was slurried in concentrated NH_4OH (600 mL). Filtration and recrystallization from EtOH (650 mL) afforded the title compound: 9.5 g (86%); mp 223–224 °C. Anal. ($C_{16}H_{12}ClN_3O_3$) C, H, N.

4-(4-Methoxyphenylthio)-6-methoxy-8-nitroquinoline (7a). 4-Methoxythiophenol (7.0 g, 0.05 mol) was dissolved in ethanolic KOH (2.8 g of KOH in 100 mL of ethanol) and carefully added to a suspension of 4-chloro-6-methoxy-8-nitroquinoline (7.2 g, 0.03 mol) in ethanol (200 mL). The reaction mixture was heated at reflux with stirring for 2 h. The solvent was partly evaporated under reduced pressure and the reaction mixture was poured into cold water (100 mL). The yellow precipitate was collected and recrystallized from a mixture of chloroform–ethanol (1:1) to yield the title compound: 6.9 g (70%); mp 170–172 °C. Anal. ($C_{17}H_{14}N_2O_4S$) C, H, N, S.

Similarly prepared was the 4-chloro analogue **6a**.

4,6-Dimethoxy-8-nitroquinoline (8a). The title compound was prepared according the procedure of Baker et al.[7]

4-Methylthio-6-methoxy-8-nitroquinoline (9a). To a slurry of 4-chloro-6-methoxy-8-nitroquinoline (3.0 g, 12 mmol) in DMF (75 mL) and methanol (25 mL) was added $NaSCH_3$ (1.0 g, 12 mmol). The mixture was allowed to stir at room temperature for 15 min, after which time an additional quantity of $NaSCH_3$ (0.6 g) was added. After stirring for 15 min, water (120 mL) was added. The crude solid product (3 g) was collected and recrystallized from EtOH to give the title compound (2.25 g, 75%), mp 136–138 °C, as yellow needles. Anal. ($C_{11}H_{10}N_2O_3S$) C, H, N.

4-Amino-6-methoxy-8-nitroquinoline (11a). A mixture of 4-(4-chlorophenoxy)-6-methoxy-8-nitroquinoline (24.2 g, 0.073 mol) and ammonium acetate (242 g) was stirred for 2 h in an oil bath at 180 °C under an ammonia atmosphere. The resulting mixture was dissolved in sufficient 20% KOH to give pH 13, cooled to 5 °C with stirring, and filtered. The crude product was washed with 50 mL of cold water and then dissolved in hot 10% acetic acid (800 mL). The acidic solution was treated with charcoal, filtered (Celite), and then basified with 40% KOH to pH 13. After cooling to 5 °C with stirring, the product was collected and washed with 50 mL of cold water. This material was air-dried (without heating) and then passed through silica gel (100 g) eluting with chloroform–methanol (4:1, 1.5 L). Concentration of the solution afforded 11.2 g (61%), mp 184.5–189 °C, of the title compound as orange crystals. Analysis indicated that this material was hydrated. A sublimed sample [150 °C (0.2 mm)] had mp 180–185 °C and analyzed as anhydrous material. Anal. ($C_{10}H_9N_3O_3$) C, H, N.

Similarly prepared was the 4-methylamino analogue **12a**.

4-Acetamido-6-methoxy-8-nitroquinoline (10a). Compound 11a was refluxed with acetic anhydride (75 mL) for 3 h. Excess acetic anhydride was removed in vacuo with warming to yield the imide (mp 174–179 °C from alcohol). The imide was hydrolyzed to the amide by dissolving in alcohol (150 mL), adding concentrated NH_4OH (100 mL), and stirring under reflux for 30 min. After cooling to 5 °C, the product was collected and washed with water and then alcohol to yield 11.1 g (83%) of the desired product: mp 254–256 °C. Anal. ($C_{12}H_{11}N_3O_4$) C, H, N.

4-(4-Chlorobenzyloxy)-6-methoxy-8-nitroquinoline (13a). To a slurry of 4-hydroxy-6-methoxy-8-nitroquinoline (5.0 g, 22 mmol) in dry DMF (55 mL) was added portionwise a 50% sodium hydride–oil dispersion (1.2 g, 25 mmol). The resulting solution was stirred at room temperature for 15 min. 4-Chlorobenzyl chloride (4.02 g, 25 mmol) was added and the resulting solution was stirred at room temperature for 2 h and then warmed to 75 °C for 2 h. The reaction mixture was diluted with H_2O (200 mL), adjusted to pH 7 with acetic acid, and extracted with $CHCl_3$ (2 × 150 mL). The combined extract was washed with water (twice), dried (K_2CO_3), and concentrated to dryness. The solid residue was crystallized from acetonitrile (50 mL) to yield the title compound (5.0 g, 64%): mp 186–188 °C. Anal. ($C_{17}H_{13}ClN_2O_4$) C, H, N.

The following procedure is typical of that used to prepare the 8-aminoquinolines **1b**, **2b**, **4b**, **5b**, **8b**, **10b**, **12b**, and **13b** (Table II).

8-Amino-4-(4-chloroanilino)-6-methoxyquinoline (5b). A solution of nitroquinoline **1a** (5 g, 15 mmol) in 1:1 dioxane–ethanol (500 mL) containing Raney nickel (7.5 g) was hydrogenated at 45 psig for 1 h. The catalyst was filtered and the solution was concentrated to dryness. Recrystallization from EtOH (75 mL) gave the title amine (2.8 g, 62%): mp 180–182 °C. Anal. ($C_{16}H_{14}ClN_3O$) C, H, N.

8-Amino-4-(4-methoxyphenylthio)-6-methoxyquinoline (7b). 8-Nitroquinoline **7a** (6.8 g, 0.02 mol) was dissolved in warm glacial acetic acid (100 mL) and iron filings (7 g) were added. The mixture was refluxed for 2 h. The unreacted iron was filtered and the dark filtrate was made strongly basic with 10% NaOH and extracted with $CHCl_3$. The dark chloroform solution was washed with water, dried (K_2CO_3), treated with charcoal, and evaporated to dryness. The residue was crystallized from methanol to give the amine (4.6 g, 77%): mp 138–140 °C. Anal. ($C_{17}H_{16}N_2O_2S$) C, H, N.

Similarly prepared were the 8-aminoquinolines **6b** and **9b** (Table II).

4,8-Diamino-6-methoxyquinoline (11b). Amide **10b** was readily saponified to the diamine in 2.5 h in hot 1 M alcoholic KOH. After standard work-up, recrystallization from benzene gave white crystals with mp 135–137 °C. Anal. ($C_{10}H_{11}N_3O$) C, H, N.

6-Methoxy-4-(4-methoxyphenoxy)-8-(1-methyl-4-phthalimidobutylamino)quinoline. A mixture of 8-amino-6-methoxy-4-(4-methoxyphenoxy)quinoline (9.7 g, 0.033 mol), 4-bromo-1-phthalimidopentane (14.6 g, 0.05 mol), diisopropylamine (5 g, 0.05 mol), and alcohol (5 mL) was sealed in a glass tube and heated in an oil bath at 150 °C for 3 h. The resulting mixture was treated with ether (1 L) and filtered and the filtrate was evaporated to dryness. Recrystallization of the ether-soluble material from alcohol afforded 2 g of product. The ether-insoluble material was dissolved in chloroform and washed with 10% KOH. The chloroform solution was dried (Na_2SO_4), filtered, and concentrated to dryness. Recrystallization of this material from alcohol afforded an additional 8 g of product, mp 150–152 °C, as yellow leaflets. Anal. ($C_{30}H_{29}N_3O_5$) C, H, N.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-(4-methoxyphenoxy)quinoline Succinate (2c). A mixture of the above phthalimide (9.2 g, 19 mmol) and hydrazine hydrate (75%, 2.4 mL, 2 equiv) in alcohol (150 mL) was stirred at reflux for 4.25

h. Most of the solvent was evaporated and the residue was dissolved in chloroform (300 mL) and washed with 10% KOH (2 × 75 mL). The resulting chloroform solution was dried (Na_2SO_4), filtered, and evaporated to yield the diamine base as an oil (7.6 g). The base was dissolved in alcohol containing succinic acid (2.4 g). Dilution with acetonitrile afforded the title compound (6.8 g yield), mp 140–142 °C, as pale pink crystals. Anal. ($C_{26}H_{33}N_3O_7$) C, H, N.

Similarly prepared were 8-quinolinediamines **1c** and **3c–13c** (Table III).

8-(4-Amino-1-methylbutylamino)-4-hydroxy-6-methoxyquinoline Dihydrochloride (14c). A solution of **13c** (3.2 g of base) in EtOH–H_2O (1:1, 40 mL) containing palladium black (0.4 g) and glacial acetic acid (2.2 mL) was hydrogenated at atmospheric pressure for 8 h. The catalyst was filtered and the yellow solution concentrated to dryness. The residue was slurried in 4:1 CH_3CN–EtOH (25 mL) and HCl–*i*-PrOH (2.7 N, 3.0 mL) was added. The crystals were filtered to yield the target compound (2.1 g, 76%): mp 265 °C dec. Anal. ($C_{15}H_{21}N_3O_2 \cdot 0.5H_2O$) C, H, Cl, N.

8-(3-Amino-1-propylamino)-6-methoxylepidine Dihydrochloride (15). The title compound was prepared from 8-amino-6-methoxylepidine[10] and 1-bromo-3-phthalimidopentane followed by hydrazinolysis as reported by Mosher[11] with the exception that triethylamine was added to the reaction mixture as an acid acceptor. The diamine free base (mp 97–100 °C, 6.8 g) was dissolved in *i*-PrOH (200 mL) and titrated with 2 equiv of *i*-PrOH–HCl. The mixture was further diluted with *i*-PrOH and filtered to give the crude dihydrochloride. Recrystallization from MeOH–Et_2O gave pure title compound (7.0 g, 32% based on the 8-amino precursor): mp 227 °C dec. Anal. (block-dried at 250 °C) ($C_{14}H_{19}N_3O \cdot 2HCl$) C, H, N.

8-(3-Isopropylamino-1-propylamino)-6-methoxylepidine Dihydrochloride (16). The title compound was prepared from 8-amino-6-methoxylepidine[10] and 1-chloro-3-isopropylaminopropane hydrochloride[12] via the procedure described by Rohrmann and Shonle.[13] The diamine base (mp 70–72 °C) was converted to the dihydrochloride salt as described for **15**. The yield was 10%; mp 220–222 °C dec (EtOH–Et_2O). Anal. ($C_{17}H_{25}N_3O \cdot HCl$) C, H, N.

5-Bromo-1-phthalimidohexane. A mixture of 1,5-dibromohexane[4] (21.6 g, 0.09 mol) in acetone (75 mL) containing potassium phthalimide (12.3 g, 0.066 mol) was heated at reflux for 24 h. The mixture was cooled, filtered, and concentrated. The excess dibromide (6.3 g) was recovered via distillation at 1.5 mm, 130 °C internal temperature, and recycled. The total yield of crude product was 20.6 g (74%): mp 48–51 °C. This material was used as such in the next step.

8-(5-Amino-1-methylpentylamino)-6-methoxylepidine Diphosphate (17). The title compound was prepared from 8-amino-6-methoxylepidine and the above phthalimide intermediate as described for **2c**. The yield was 36%; mp 154–156 °C (EtOH–H_2O). Anal. ($C_{17}H_{25}N_3O \cdot 2H_3PO_4 \cdot 2H_2O$) C, H, N, P.

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(16) The testing was done at the Dr. Leo Rane Laboratory, University of Miami, Miami, Fla. The test results were supplied through the courtesy of Drs. T. R. Sweeney and R. E. Strube of the Walter Reed Army Institute of Research, Washington, D.C. In the primary test against *P. berghei* five mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical. Routinely, the chemical was administered subcutaneously in sesame or peanut oil. The mean survival time (MST) of infected control mice is 6.2 ± 0.5 days. Extension in survival time (ΔMST) of the chemically treated mice is interpreted as evidence of antimalarial activity.
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