μL on scintillation counting. The enzyme was made up in 0.1 M KH_2PO_4 buffer, pH 6.2, containing 0.1% BSA and 1 mM NADPH, and this stock solution was divided into 0.5-mL aliquots, which were kept frozen at −20 °C until use. The charcoal mixture used to remove nonbound ligand consisted of 10 g of prewashed neutral activated charcoal, 2.5 g of BSA, and 0.1 g of dextran in 100 mL of 0.1 M KH_2PO_4 buffer, pH 7.4, containing 0.1% swine gelatin. The charcoal was washed initially with three portions of the pH 7.4 buffer to remove the "fines" and then twice more with buffer containing 0.1% gelatin. All reagents were made up fresh with deionized H_2O and kept cold during use.

In a typical experiment, freshly thawed enzyme was diluted 250-fold with pH 7.4 buffer containing 2 mM NADPH. At this dilution, the enzyme had the capacity to bind approximately 10% of the added counts of [^{3}H]MTX under the conditions described below. A suitable amount of diluted enzyme (usually 0.8–1.0 mL) was added to a 15-mL Falcon plastic tube containing an equal volume of either 200 nM test compound (1 or MTX) or control buffer. The assay mixture was incubated in the dark at 37 °C, and at each time point a 200-μL aliquot was transferred to one of the wells of a cold microtiter plate (ice bath). A 67-μL aliquot of ice-cold charcoal mixture was then pipetted into each well to remove excess nonbound ligand, and the contents of the well were mixed thoroughly with the aid of the pipet. To ensure reproducibility in this step and the subsequent charcoal treatment (see below), the contents of the well were always *drawn up and released exactly five times*. After centrifugation at 100*g* (10 min, 2 °C), the supernatant in each well was removed and immediately dispensed in triplicate 67-μL portions to a second microtiter plate, each well of which contained 100 μL of [^{3}H]MTX and 1 mM NADPH. After 24 h at room temperature to allow displacement of reversibly bound drug by [^{3}H]MTX, the plate was cooled on ice for 5 min, and 50 μL of cold charcoal mixture was added to remove excess nonbound [^{3}H]MTX. As in the first charcoal treatment, repeated pipetting (5 times) of the contents of each well was performed to ensure good mixing. After a second centrifugation at 1000*g* (10 min, 2 °C), 108 μL of the supernatant was added to a vial containing 5 mL of Biofluor, and the amount of enzyme-bound radioactivity was determined by scintillation counting. Appropriate background corrections were made with the aid of a blank, and results were expressed as % T/C values from the following equation (see Figure 1 for results):

$$\% \text{ T/C} = \frac{\text{DHFR-bound [}^3\text{H]MTX (cpm) after treatment with 1}}{\text{DHFR-bound [}^3\text{H]MTX (cpm) after treatment with MTX}}$$

The assay described above was also performed at several pH values ranging from 6.2 to 7.8 to generate a pH profile for the time-dependent inactivation of the enzyme by 1. The inhibitor concentration in this series of experiments was 1 μM. The results are presented in Figure 2.

In a control experiment using iodoacetamide as the inhibitor, no time-dependent incactivation of enzyme was observed.

Acknowledgment. This work was supported by Grant RO1-CA-25394 from the National Cancer Institute, NIH. We are indebted to Dr. John A. Montgomery, Southern Research Institute, Birmingham, AL, for his help in obtaining mass spectral data, and to Dr. James H. Freisheim, University of Cincinnati Medical Center, Cincinnati, OH, for helpful discussions.

Antimalarials. 13. 5-Alkoxy Analogues of 4-Methylprimaquine

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Ash Stevens, Inc., Detroit, Michigan 48202. *Received December 28, 1981*

A series of nuclear and side-chain analogues of 4-methylprimaquine incorporating an alkoxy group in the 5-position of the quinoline nucleus has been prepared. The compounds were tested for suppressive antimalarial activity against *Plasmodium berghei* in mice and for radical curative antimalarial activity against *Plasmodium cynomolgi* in the rhesus monkey. Although the toxicity problems characteristic of the 8-aminoquinolines were not overcome, several of the compounds, surprisingly, were highly effective as both blood and tissue schizonticidal agents.

In an earlier paper[1] in this series, we reported the preparations of several 4-substituted primaquine analogues. Such a study was undertaken based on the fact that 4-methylprimaquine[2a,b] was approximately twice as effective as primaquine itself against exoerythrocytic forms of *Plasmodium cynomolgi* in the rhesus monkey.[3] Additionally, the compound was slightly less toxic and slightly more effective than primaquine as a blood schizonticide in the *Plasmodium berghei* Rane mouse screen. However, none of the other 4-substituted primaquine analogues prepared by us possessed appreciable activity in either of these screens.

The present investigation was undertaken in view of findings that 5-methoxypentaquine and related 5,6-disubstituted 8-aminoquinolines possessed higher therapeutic indexes relative to the corresponding 5-unsubstituted analogues.[4]

A logical course to pursue, therefore, was to prepare 5-alkoxy analogues of 4-methylprimaquine. It was felt that the presence of a 4-methyl substituent would both enhance antimalarial activity and reduce toxicity as was the case in the primaquine series. Also, it was of interest to prepare related bridged 5,6-alkylenedioxy analogues in order to compare their efficacies with those of the acyclic analogues.

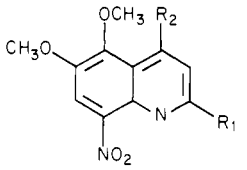
Chemistry. The synthetic sequence shown in Scheme I is representative of that used to prepare the 11 target compounds reported herein and is essentially identical with that described earlier[1] to prepare a series of 4-substituted primaquine analogues.

The three requisite substituted nitroanilines have been reported. 4-Amino-5-nitroveratrole was prepared by Drake et al.,[5] and 4-amino-5-nitro-1,4-benzodioxane and 4-

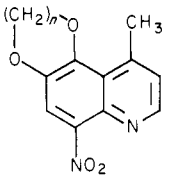
(1) LaMontagne, M. P.; Markovac, A.; Menke, J. R. *J. Med. Chem.* **1977**, *20*, 1122.
(2) (a) Elderfield, R. C.; Mertel, H. E.; Mitch, R. T.; Wempen, I. M.; Werble E. *J. Am. Chem. Soc.* **1955**, *77*, 4816. (b) Nodiff, E. A., Germantown Laboratories, Franklin Institute, Philadelphia, PA, unpublished results.
(3) Steck, E. A., Walter Reed Army Institute of Research, Washington, DC, personal communication.
(4) Thompson, P. E.; Werbel, L. M. "Antimalarial Agents, Chemistry and Pharmacology", Academic Press: New York, 1972; p 105.
(5) Drake, N. L.; Anspon, H. D.; Draper, J. D.; Haywood, S. T.; Van Hook, J.; Melamed, S.; Peck, R. M.; Sterling, Jr., J.; Walton, E. W.; Whiton, A. *J. Am. Chem. Soc.* **1946**, *68*, 1536.

0022-2623/82/1825-0964$01.25/0

Table I. Substituted 8-Nitroquinolines



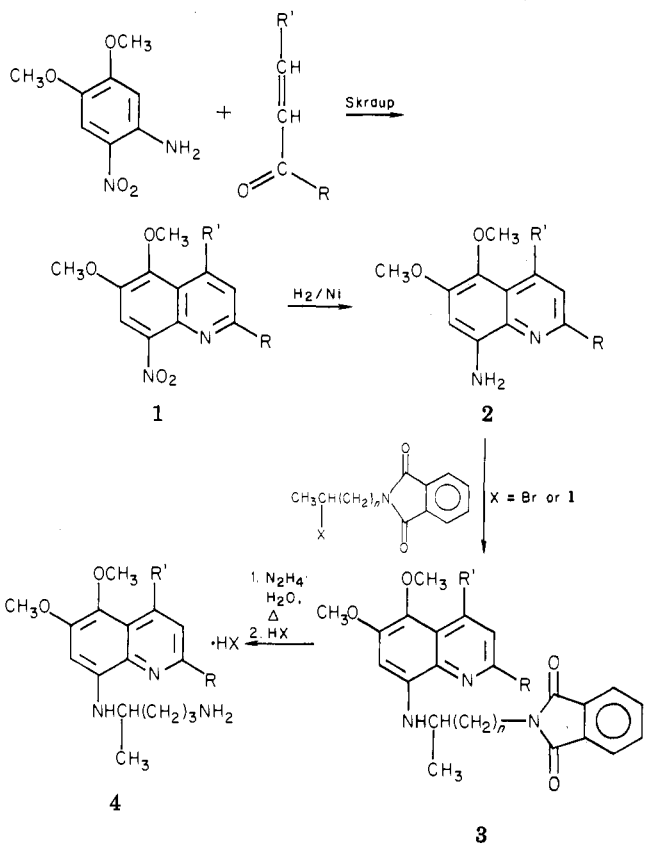
no.	R_1	R_2	mp, °C (solvent)	yield, %	formula	anal.
1a	H	CH_3	123-125 (CH_3OH)	30	$C_{12}H_{12}N_2O_4$	C, H, N
1b	CH_3	CH_3	80-82 (*i*-PrOH)	26	$C_{13}H_{14}N_2O_4$	C, H, N
1c	H	H	127-128 (EtOH)[a]	22		



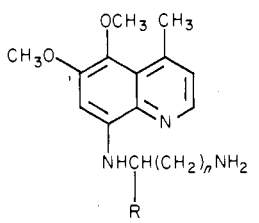
	n					
1d	1	183-185 (Me_2CO)	63	$C_{11}H_8N_2O_4$	C, H, N
1e	2	187-188 (Me_2CO)	32	$C_{12}H_{10}N_2O_4$	C, H, N

[a] Literature[5] mp 127.5-129 °C.

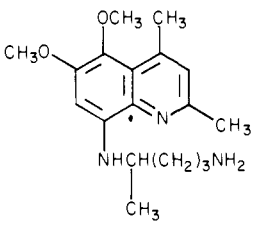
Scheme I



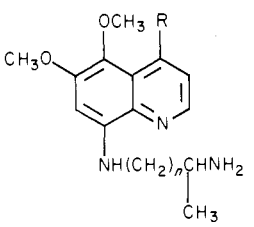
amino-5-nitro-1,2-(methylenedioxy)benzene were prepared by Lott et al.[6] Treatment of the appropriately substituted *o*-nitroaniline with the appropriate α,β-unsaturated aldehyde or ketone afforded the requisite 5,6-disubstituted 8-nitroquinolines 1. Reduction with commercially available wet Raney nickel yielded the substituted 8-aminoquinolines 2. Condensation with the appropriate haloalkylphthalimides afforded the protected 8-quinolinediamines, which upon treatment with hydrazine hydrate, followed by conversion to a suitable salt, afforded target compounds 4.



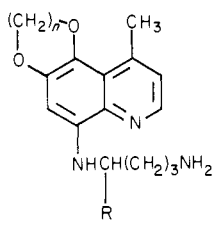
4a, R = CH_3; *n* = 3
c, R = C_2H_5; *n* = 3
e, R = CH_3; *n* = 4



4f



4b, R = CH_3; *n* = 3
d, R = CH_3; *n* = 4
g, R = H; *n* = 3



4h, R = CH_3; *n* = 1
j, R = C_2H_5; *n* = 1
i, R = CH_3; *n* = 2
k, R = C_2H_5; *n* = 2

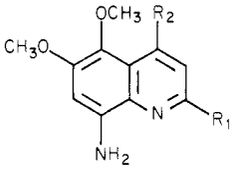
Biological Activity. The 11 target compounds were tested for both suppressive antimalarial activity against *P. berghei* in mice[7a,b] and for radical curative antimalarial activity against *P. cynomologi* in the Rhesus monkey.[8] The data are shown in Tables V and VI. The data for

(6) Lott, W. A.; Yale, H. L; Sheehan, J. T.; Bernstein, J. *J. Am. Chem. Soc.* **1948**, *70*, 3621.

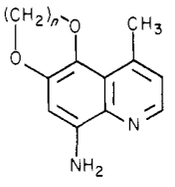
(7) (a) Osdene, T. S.; Russel, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431. (b) The testing was done at the Dr. Leo Rane Laboratory, University of Miami, Miami, FL. The test results were supplied through the courtesy of Drs. T. R. Sweeney and R. E. Strube of the Walter Reed Army Institute of Research, Washington, DC. 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 subcutaneously administered 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.

(8) Schmidt, L. H.; Rossan, R. N.; Fisher, K. F. *Am. J. Trop. Med. Hyg.* **1963**, *12*, 494.

Table II. Substituted 8-Aminoquinolines



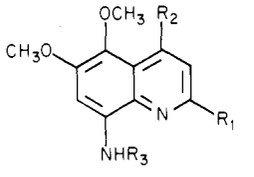
no.	R_1	R_2	mp, °C (solvent)	yield, %	formula	anal.
2a	H	CH_3	100-102 (C_6H_{12})	80	$C_{12}H_{14}N_2O_2$	C, H, N
2b	CH_3	CH_3	107-109 (C_6H_{12})	86	$C_{13}H_{16}N_2O_2$	C, H, N
2c	H	H	147-149 (EtOH)[a]	86		



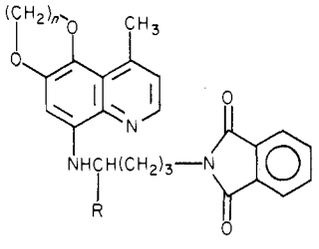
	n				
2d	1	118-120 (C_6H_{12})	89	$C_{11}H_{10}N_2O_2$	C, H, N
2e	2	101-103 (C_6H_{12})	87	$C_{12}H_{12}N_2O_2$	C, H, N

[a] Literature[5] mp 149.5-150.5 °C.

Table III. Phthalimido-Protected 8-Quinolinediamines



no.	R_1	R_2	R_3	mp, °C (solvent)	yield, %	formula	anal.
3a	H	CH_3	$CH(CH_2CH_3)(CH_2)_3$Pht	163-166 (EtOH)	63	$C_{26}H_{29}N_3O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N
3b	H	CH_3	$(CH_2)_4CH(CH_3)$Pht	101-103 (EtOH)	44	$C_{26}H_{29}N_3O_4$	C, H, N
3c	H	CH_3	$CH(CH_3)(CH_2)_4$Pht	182-184 (EtOH)	53	$C_{26}H_{29}N_3O_4 \cdot HCl$	C, H, N
3d	CH_3	CH_3	$CH(CH_3)(CH_2)_3$Pht	200-202 (EtOH)	75	$C_{26}H_{29}N_3O_4 \cdot HCl$	C, H, N
3e	H	H	$(CH_2)_3CH(CH_3)$Pht	138-140 (EtOH)	69	$C_{24}H_{25}N_3O_4$	C, H, N



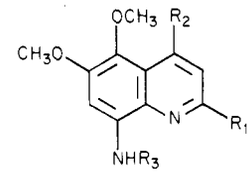
	R	n				
3f	CH_3	1	110-112 (EtOH)	71	$C_{24}H_{23}N_3O_4 \cdot HCl$	C, H, N, Cl
3g	CH_3	2	205-208 (EtOH)	66	$C_{25}H_{25}N_3O_4 \cdot HCl$	C, H, N
3h	C_2H_5	1	196-199 (EtOH)	52	$C_{25}H_{25}N_3O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N
3i	C_2H_5	2	174-176 (EtOH)	71	$C_{26}H_{26}N_3O_4 \cdot HCl \cdot 1.5H_2O$	C, H, N

primaquine and 4-methylprimaquine have been included for comparison. In terms of radical curative antimalarial activity, only limited data are available at the lower dosage levels. However, examples **4a** and **4c** are curative at 0.125 (mg/kg)/day (×7, free base). More valid comparisons, however, can be made at the 0.25 (mg/kg)/day (×7, free base) dosage level. Primaquine, the current drug of choice, is not curative at this level. 4-Methylprimaquine is 57% curative. Compounds **4c** and **4d** are 100% curative, and examples **4a** and **4b** are 75 and 83% curative, respectively. The remaining examples are either inactive at this level or show no enhanced activity relative to 4-methylprimaquine. Examination of the *P. berghei* suppressive antimalarial activity data indicate that examples **4a**,**b**,**d**–**f**,**i**,**k** possess greater activity at lower dosage levels than primaquine and 4-methylprimaquine. One example (**4e**) is active at 1.25 mg/kg, while two additional examples (**4a** and **4b**) are active at 40 and 20 mg/kg, respectively. Example **4e** is curative at 20 mg/kg. Compounds **4i** and **4k** are active at 5 mg/kg. The data also clearly indicate, however, that toxicity problems associated with primaquine and its analogues have not been overcome. However, the surprisingly high level of activity, both suppressive and radical curative, possessed by certain of these 5-substituted 4-methylprimaquine analogues prompts one to pursue the preparation of less toxic and more effective analogues, and work directed to this end is in progress in these laboratories.

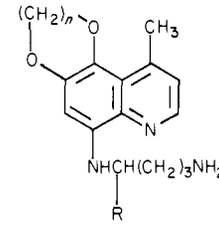
Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer.

Table IV. 5,6-Bis(alkoxy)-8-quinolinediamines



no.	R_1	R_2	R_3	mp, °C (solvent)	yield, %	formula	anal.
4a	H	CH_3	$CH(CH_3)(CH_2)_3NH_2$	100-104 (EtOH)	67[a]	$C_{17}H_{32}N_3O_{10.5}P_2$[b]	C, H, N, P
4b	H	CH_3	$(CH_2)_3CH(CH_3)NH_2$	88-92 (EtOH-H_2O)	42[a]	$C_{17}H_{37}N_3O_{13}P_2$[c]	C, H, N, P
4c	H	CH_3	$CH(CH_2CH_3)(CH_2)_3NH_2$	136-137 (CH_3CN-EtOH)	64[d]	$C_{20}H_{30}N_3O_4$[e]	C, H, N
4d	H	CH_3	$(CH_2)_4CH(CH_3)NH_2$	155-157 (EtOH-H_2O)	73[d]	$C_{18}H_{30}N_3O_6P$[f]	C, H, N, P
4e	H	CH_3	$CH(CH_3)(CH_2)_4NH_2$	130-133 (CH_3CN-EtOH)	82[d]	$C_{22}H_{33}N_3O_6$[g]	C, H, N
4f	CH_3	CH_3	$CH(CH_3)(CH_2)_3NH_2$	134-136 (EtOH-H_2O)	54[d]	$C_{18}H_{33}N_3O_{10}P_2$[h]	C, H, N, P
4g	H	H	$(CH_2)_3CH(CH_3)NH_2$	171-173 (EtOH-CH_3CN)	85[d]	$C_{20}H_{33}N_3O_6$[g]	C, H, N



	R	n				
4h	CH_3	1	185-187 (EtOH-H_2O)	50[d]	$C_{16}H_{24}N_3O_6P$[f]	C, H, N, P
4i	CH_3	2	215-217 (EtOH)	70[d]	$C_{17}H_{26}N_3O_6P$[f]	C, H, N, P
4j	C_2H_5	1	199-201 (EtOH-H_2O)	45	$C_{17}H_{26}N_3O_6P$[f]	C, H, N, P
4k	C_2H_5	2	193-195 (EtOH-H_2O)	69[d]	$C_{18}H_{28}N_3O_6P$[f]	C, H, N, P

[a] From 8-aminoquinoline. [b] Diphosphate hemihydrate. [c] Diphosphate trihydrate. [d] From phthalimido precursor. [e] Hemisuccinate. [f] Monophosphate. [g] Monosuccinate. [h] Diphosphate.

Table V. Suppressive Antimalarial Activity Data

compd[a]	*P. berghei* (Rane mouse):[b] ΔMST, days at mg/kg sc							
	5	10	20	40	80	160	320	640
4a			5.7	7.1 (A)	8.9 (A)	9.9 (A)/1T	11.9 (A)/4T	5T
4b			11.4 (A)/3T	5T		5T		5T
4c				0.1		5T		5T
4d			7.5 (A)/1T	8.7 (A)/1T		5T		5T
4e			3C[c]	1C/1T		5T		5T
4f			4.9	6.3 (A)/3T		5T		5T
4g			1.3	3.1	5.1	7.3 (A)	9.9 (A)/3T	5T
4h				0.1		0.1		0.3
4i	6.7 (A)	8.3 (A)	11.1 (A)	5T		5T		5T
4j				0.5		0.5		0.9
4k	7.8 (A)	7.6 (A)	7.2 (A)	7.6 (A)		5T		5T
primaquine diphosphate				5.0	9.4 (A)	2T	5T	5T
4-methylprimaquine diphosphate			3.1	4.9	5.5	9.1 (A)	10.1 (A)	3C/1T

[a] For structures see Table IV. [b] See ref 7. Abbreviations used: A, active; C, cure; T, toxic. [c] Active at 1.25 mg/kg.

Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. 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, v/v). Commercial Raney nickel was supplied by W. R. Grace (no. 30).

5,6-Dimethoxy-4-methyl-8-nitroquinoline (1a). The following procedure for the preparation of the title compound is representative of that used to prepare compounds **1a–e** (Table I).

A mixture of 4-amino-5-nitroveratrole (3.96 g, 0.02 mol), arsenic acid (5.68 g, 0.04 mol), and 85% phosphoric acid (20 mL) was placed in a three-neck flask fitted with a thermometer and a dropping funnel. The reaction mixture was warmed to 100 °C (internal) with stirring, and methyl vinyl ketone (2.1 g, 0.03 mol) was added at such a rate that the temperature was maintained at 100 ± 2 °C. After all the ketone was added, the mixture was stirred at 100 °C for an additional 30 min. The dark solution was poured into ice–water (100 mL), treated with charcoal (Norit), and filtered. The filtrate was made alkaline (NH_4OH) and extracted with $CHCl_3$. The extract was washed with H_2O and dried (K_2CO_3), the solvent was evaporated, and the dark residue was refluxed with C_6H_6 (100 mL). Insoluble tar was removed by filtration. The orange filtrate was concentrated to ca. 10 mL, placed on a silica gel column, and eluted with C_6H_6 (ca. 2 L). The solvent was evaporated, and the residue was recrystallized (×2) from MeOH to give 1.3 g (30%) of the title compound, mp 123–125 °C. Anal. ($C_{12}H_{12}N_2O_4$) C, H, N.

8-Amino-5,6-dimethoxy-4-methylquinoline (2a). The following procedure was also used to prepare analogues **2a–e** (Table II).

The above nitro compound (2.4 g, 0.01 mol) in EtOH (100 mL) was hydrogenated in a Parr apparatus (initial pressure 45 psig) for 1 h using active Raney nickel as catalyst (ca. 1 g wet weight). The solution was filtered, and the filtrate was evaporated to dryness. The solid residue was recrystallized from cyclohexane

Table VI. Radical Curative Antimalarial Data[a]

no.	*P. cynomolgi* (rhesus): mg/kg (base)/day (×7), po				
	0.75	0.5	0.25	0.125	0.0625
4a		1/1C	3/4C	11/13C	0/5C
4b		1/1C	5/6C		
4c	4/5C		4/4C	6/10C	0/2C
4d	3/3C		2/2C		
4e	3/3C		1/4C		
4f	3/5C		2/4C		
4g	0/2C		0/2C		
4h			NT		
4i	0/3C		0/3C		
4j	0/2C		0/3C		
4k	0/5C		0/3C		
primaquine diphosphate	4/4C	10/12C	0/2C		
4-methyl-primaquine diphosphate	1/1C	13/14C	8/14C		

[a] NT = not tested.

to give 1.8 g (80%) of product, mp 100–102 °C. Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

4-Acetyl-1-butanol. A mixture of 2-methyl-3-carbethoxy-Δ^2-dihydropyran[9] (100.0 g, 0.59 mol), dilute HCl (180 mL, concentrated HCl–water, 1:20), and EtOH (100 mL) was refluxed for 4 h. Ethanol was removed by distillation and the cold solution was saturated with K_2CO_3 and extracted with Et_2O. Evaporation of Et_2O gave a light yellow liquid (66.0 g, 97%), which was shown by NMR to be approximately a 1:1 mixture of acetobutanol and the hemiketal.

5-Amino-1-hexanol. The above mixture (66.0 g, 0.57 mol), concentrated NH_4OH (264.0 g), and Raney nickel (15 g) were shaken in a Parr hydrogenator at room temperature for 23 h under an initial hydrogen pressure of 55 psi (H_2 uptake 34 lbs). The mixture was saturated with N_2, filtered (Celite), and freed of H_2O by azeotropic distillation with xylene. The resulting turbid liquid was dissolved in C_6H_6, and the solution was clarified by filtration. The solvent was removed, and the residue was distilled to give the title compound as a colorless liquid (47.0 g, 71%), 65–67 °C (0.15 mm). Anal. ($C_6H_{15}NO$) C, H, N.

5-Phthalimido-1-hexanol. A mixture of 5-amino-1-hexanol (36.0 g, 0.30 mol), phthalic anhydride (44.4 g, 0.30 mol), and xylene (300 mL) was heated under reflux for 12 h in a flask equipped with a Dean–Stark trap (6 mL of H_2O collected). The xylene was removed, and the residue was distilled to afford the title compound as a colorless viscous oil (68.5 g, 90%), bp 155–158 °C (0.05 mm). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

1-Chloro-5-phthalimidohexane. To a stirred solution of 5-phthalimido-1-hexanol (62.0 g, 0.25 mol) in dry C_6H_6 (180 mL) was added dropwise during 1 h at room temperature $SOCl_2$ (39 g, 0.33 mol). Stirring was continued at room temperature for 1.5 h and at 60–65 °C for 2.5 h. The C_6H_6 and excess $SOCl_2$ were removed in vacuo, and the residue was distilled to give the title compound as a light yellow oil (60.0 g, 90%), bp 145–147 °C (0.25 mm). Anal. ($C_{14}H_{16}ClNO_2$) C, H, N, Cl.

1-Iodo-5-phthalimidohexane. The above compound (26.5 g, 0.10 mol) and NaI (19.6 g, 0.13 mol) in Me_2CO (115 mL) were heated at reflux for 20 h. The solution was cooled, and the precipitated NaCl was filtered. The filtrate was concentrated to dryness, and the residual oil was dissolved in CH_2Cl_2. The solution was washed with H_2O (×2), dried (K_2CO_3), and concentrated to yield the title compound (34.4 g, 97%). This material was used in alkylation reactions without further purification. An analytical sample was obtained via crystallization from petroleum ether (bp 30–60 °C), mp 48–50 °C. Anal. ($C_{14}H_{16}NIO_2$) C, H.

1-Phthalimido-5-bromohexane. A mixture of 1,5-dibromohexane[10] (21.6 g, 0.09 mol) in Me_2CO (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 alkylation reaction.

N^1-Phthalimido-N^4-(5,6-dimethoxy-4-methyl-8-quinolinyl)-1,4-hexanediamine Hydrochloride (3a). The following procedure is typical of that used to prepare phthalimido intermediates **3a–i** (Table III).

A solution of 4-methyl-5,6-dimethoxy-8-aminoquinoline (0.042 mol) in 2-ethoxyethanol (21 mL) containing triethylamine (TEA; 5.8 mL) and 4-iodo-1-phthalimidohexane[11] (IPH; 14.9 g, 0.042 mol) was heated at 110 °C for 2.5 h. An additional equivalent of TEA and IPH was added, and the heating was continued for 4 h. A third equivalent of IPH and TEA was added, and the mixture was heated at 110 °C overnight. The reaction mixture was diluted with $CHCl_3$ and washed with H_2O (×2). The organic layer was dried (K_2CO_3), and the solvents were removed in vacuo. The residue was dissolved in Et_2O, filtered, and acidified with excess ethereal HCl. The red gum which separated was crystallized from EtOH (150 mL) to yield the title compound (13 g, 63%), mp 163–166 °C. Anal. ($C_{26}H_{30}ClN_3O_4 \cdot 0.5H_2O$) C, H, N, Cl.

N^4-(5,6-Dimethoxy-4-methyl-8-quinolinyl)-1,4-hexanediamine Hemisuccinate (4c). The following procedure is typical of that used to prepare target compounds **4a–k** (Table IV).

The above phthalimide (12.2 g, 0.025 mol) was converted to the base by shaking with dilute NH_4OH and CH_2Cl_2. The organic layer was concentrated in vacuo. The oily residue was heated at reflux for 3 h in EtOH (300 mL) containing 75% hydrazine hydrate (4.9 mL). After the solution was cooled, the solid (phthalyl hydrazide) was filtered, and the filtrate was concentrated. The residue was shaken with 10% aqueous KOH and CH_2Cl_2. The organic layer was dried (K_2CO_3) and concentrated. The oil was dissolved in petroleum ether (bp 30–60 °C), treated with charcoal, filtered (Celite), and concentrated. The base (7 g) was dissolved in MeOH (100 mL), and succinic acid (1.4 g, 0.54 molar equiv) was added with stirring. The MeOH was removed under reduced pressure, and the yellow foam was boiled in CH_3CN (100 mL). The solid was filtered and recrystallized from CH_3CN–EtOH (9:1, 150 mL) to yield the title compound (6 g, 64%), mp 136–137 °C. Anal. ($C_{20}H_{30}N_3O_4$) C, H, N.

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