References and Notes

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Synthesis of 4-Alkyl and 4-(β-Alkylvinyl) Derivatives of Primaquine as Potential Antimalarials

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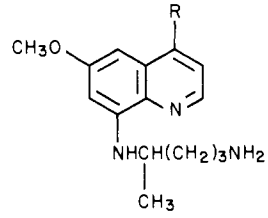
4-(β-Alkylvinyl)-6-methoxy-8-nitroquinolines (**6**) were prepared from 6-methoxy-8-nitroquinoline-4-carboxaldehyde (**5**) via a Wittig reaction. Stannous chloride reduction of **6** gave 4-(β-alkylvinyl)-8-amino-6-methoxyquinolines (**8**), whereas catalytic reduction of **6** using Raney nickel catalyst gave 4-alkyl-8-amino-6-methoxyquinolines (**7**). Alkylation of **7** and **8** with 4-iodo-1-phthalimidopentane, followed by removal of the phthaloyl-protecting group with hydrazine, gave 4-alkyl and 4-(β-alkylvinyl) derivatives of primiquine, respectively. These compounds were evaluated for antimalarial activity against *P. berghei* and *P. berghei yoelii* in mice and against *P. cynomolgi* in rhesus monkeys. Several of the compounds were active in the *P. bergheii yoelii* screen. None of the compounds showed significant activity in the other two screens.

In a recent study,[1] we reported that 8-[(4′-amino-1′-methylbutyl)amino]-4-ethyl-6-methoxyquinoline (**1a**, 4-

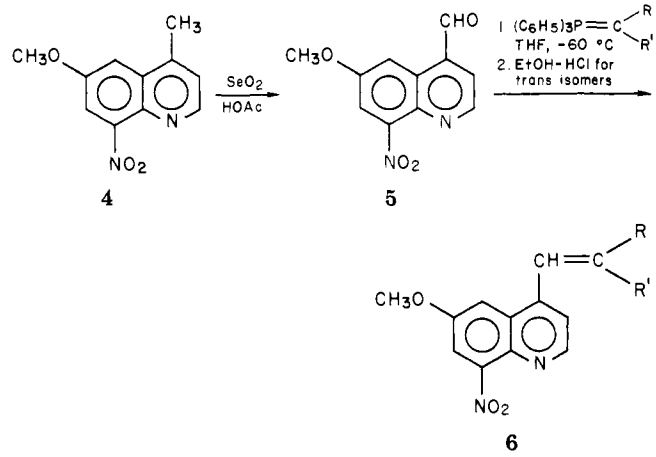


1a, R = C_2H_5
b, R = CH=CH_2
c, R = H

ethylprimaquine) and 8-[(4′-amino-1′-methylbutyl)-amino]-6-methoxy-4-vinylquinoline (**1b**, 4-vinylprimaquine) showed antimalarial activity against *Plasmodia cynomolgi* in rhesus monkeys comparable to that of primaquine (**1c**) but were less toxic. As a continuation of this study, we have synthesized several new 4-(alkylvinyl)- and 4-alkyl-8-[(4′-amino-1′-methylbutyl)amino]-6-methoxyquinolines (**2** and **3**, respectively) for antimalarial evaluation. In this paper, we describe the synthetic procedures used to prepare **2** and **3** and report antimalarial test data for these compounds.

Chemistry. We envisioned that the 4-(alkylvinyl)-6-methoxy-8-nitroquinoline (**6**) could serve as an intermediate for the syntheses of both **2** and **3**. Thus, we developed a synthetic scheme for the preparation of these intermediates (see Scheme I). By modification of the literature procedure,[2] we were able to effect the selenium dioxide oxidation of 6-methoxy-4-methyl-8-nitroquinoline (**4**) to the corresponding 4-carboxaldehyde **5** in 80% yield. Condensation of **5** with the appropriate alkylidenetriphenylphosphorane in tetrahydrofuran at −60 °C gave the

Scheme I



olefin **6**. The use of higher temperatures resulted in lower yields. In addition, the quinoline aldehyde **5** was extremely sensitive to strong bases. Thus, it was essential to use conditions that avoided even trace amounts of excess strong base.

In the course of this study it was also discovered that the stereochemistry of the disubstituted olefins could be influenced to a certain degree by the workup conditions. If the Wittig reaction mixture was treated with ethanolic hydrogen chloride, followed by basification and isolation of product, essentially pure *trans*-olefins were obtained. However, if no acid was used in the isolation procedure, the product was predominantly *cis*-olefins. This finding afforded an additional variable to our syntheses of the 4-(alkylvinyl) compounds **2**. Since reports in the literature[3] indicated that the use of Me_2SO as solvent in the Wittig

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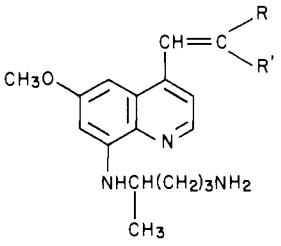
Table I. Prophylactic Antimalarial Test Data



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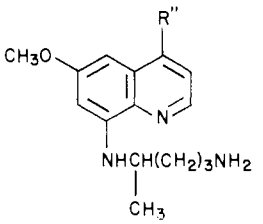


3

			P. berghei yoelii[a,b]				*P. cynomolgi*[b,c]		
no.	R, R'	R''	dose, mg/kg	cures, sc	cures, po	toxic	dose, mg/kg	cures	relapses[d]
2a	CH_3, H		160	7/10	4/5	3 (sc), 1 (po)	1.0	0/1	18
			40	1/10	8/10	1 (po)	0.5	0/1	8
			10	0/10	7/15				
			2.5		1/10				
2b	C_2H_5, H		160	7/10	3/5	2 (sc), 2 (po)	1.0	0/1	10
			40	10/15	7/10	1 (sc)	0.5	0/1	6
			10	3/15	3/10				
			2.5	0/5	0/5				
2d	C_6H_{11}, H		160	0/10	5/15	1 (po)			
			40	1/10	2/15				
			10	0/10	0/15				
2h	CH_3(cis), H		40		3/5		1.0	0/1	6
			10		5/5		0.5	0/1	6
			2.5		0/5		0.25	0/1	7
3a		$-C_3H_7$					1.0	0/1	23
							0.5	0/1	7
3b		$-(CH_2)_3CH_3$	160	6/10	5/5	4 (sc)	1.0	0/1	22
			40	4/10	7/10		0.5	0/1	5
			10	0/10	6/15				
			2.5		0/10				
			0.63		1/5				
3d		$(CH_2)_3C_6H_{11}$	160	1/10			1.0	0/1	8
			40	1/10			0.5	0/1	6
			10	1/10					
3e		$CH_2CH(CH_3)C_2H_5$					1.0	0/2	14, 9
							0.5	0/2	8, 7
3f		$CH_2C_6H_{11}$	160	5/5			1.0	0/1	7
			40	3/5			0.5	0/1	6
			10	5/15	2/10				
			2.5	2/15	3/15				
			0.63	4/15	3/15				
			0.16	2/5	1/5				

[a] These tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using sporozoite-induced *P. berghei yoelii* infected mice (ref 4). The test compound was dissolved or suspended in 0.5% hydroxyethylcellulone-0.1% Tween 80 and administered either orally (po) or subcutaneously (sc) at several dose levels to groups of five mice on the day of challenge. Prophylactic activity is evidenced by survival of drug-treated mice to 30 days. Survival of 40% or more of the mice in the treated group may be considered as an indication of activity. [b] Test data were supplied by Drs. E. A. Steck and R. E. Strube of Walter Reed Army Institute of Research. [c] Tests were carried out by Dr. L. H. Schmidt, Southern Research Institute, Birmingham, Ala. (ref 5). Dose administered via stomach tube once daily for 7 days with 2.5 mg of base/kg of chloroquine. Monkeys that did not relapse in 90 days are considered cured. [d] The number given is the days between end of treatment and relapse.

reaction gave high yields of pure olefins (cis isomers), we also investigated the use of this solvent for the conversion of **5** to **6**. We found that the condensation of **5** with ethylidenetriphenylphosphorane did not proceed at room temperature. At 90 °C the yield of olefin was 48%, but the product was a mixture of cis and trans isomers, with the *trans*-olefin being the major product.

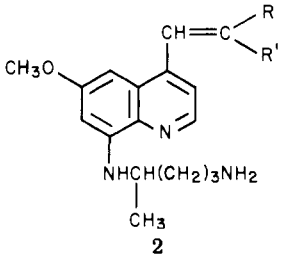
The 4-(alkylvinyl)- and 4-alkylprimaquine analogues **2** and **3** were prepared from **6** as outlined in Scheme II. Catalytic reduction of **6** in methanol at 50 °C using Raney nickel catalyst gave the 4-alkyl-8-aminoquinoline (**7**). Reduction of **6** with stannous chloride and tin give 4-(β-alkylvinyl)-8-aminoquinoline (**8**). Attachment of the 8-amino side chain to **7** and **8** by procedures reported for other 8-aminoquinolines[1] gave the desired 4-(alkylvinyl)- and 4-alkylprimaquine analogues **2** and **3**. The 4-alkyl analogue **3e** could also be prepared by catalytic reduction of compound **2f** under conditions analogous to that used to convert **6** and **7**.

Biological Testing. Compounds **2a,b,d,h** and **3b,d,f** were tested for prophylactic activity against sporozoite-induced *P. berghei yoelii* in rodents at the Rane Laboratory,[4] University of Miami, Miami, Fla. (see Table I). Survival of 40% or more of the mice in the treated group may be considered as an indication of activity in this test. Inspection of Table I shows that all the compounds except **2d** and **3d** were active at one or more dose levels.

Compounds **2a,b,h** and **3a,b,d–f** were tested for radical curative activity against *P. cynomolgi* in rhesus monkeys by Dr. L. H. Schmidt[5] (see Table I). These compounds were found to be inactive in this screen.

Two 4-(alkylvinyl)primaquine analogues (**2b** and **2e**) and two 4-alkylprimaquine analogues (**3c** and **3d**) were tested for blood schizonticidal activity against *P. berghei* in mice[6,7]

Table II. Antimalarial Activity against *P. berghei* in Rodents[a]



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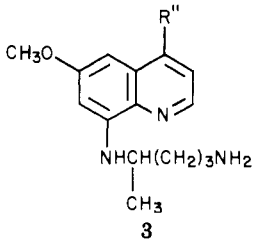

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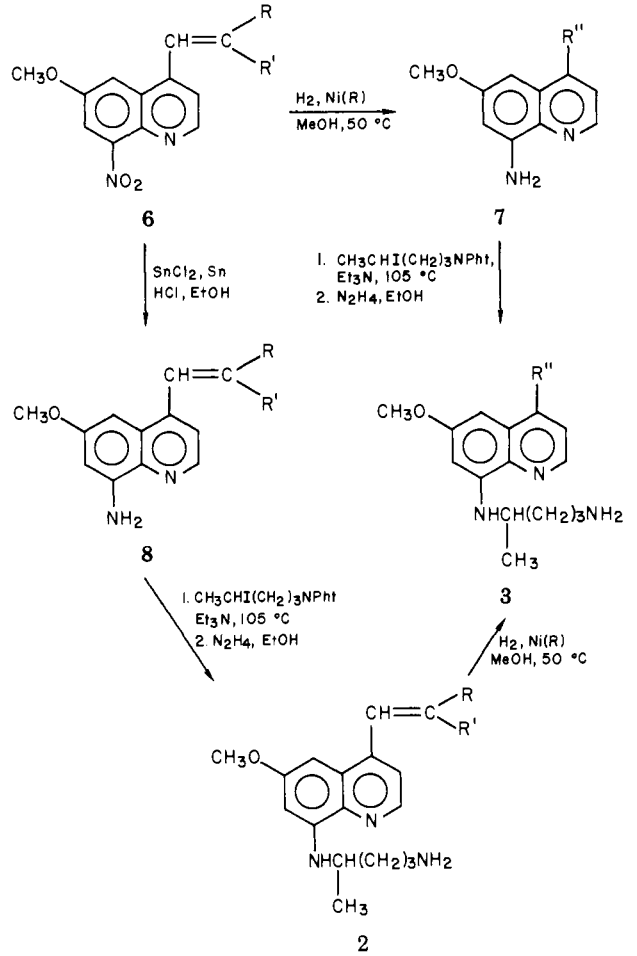
compd	R, R′	R″	ΔMST, C or T:[b] dose, mg/kg 20	40	80	160	320	640
2b	C_2H_5, H		3.1	5.1	6.5	7.5	9.5	10.3
2e	$C_6H_{11}CH_2$, H		0.4		0.9		−0.4	
3c		$(CH_2)_2C_6H_{11}$		0.3		0.3		0.5
3d		$(CH_2)_3C_6H_{11}$	0.3		0.4		0.9	
primaquine			4.0	5.0	9.4	2T	5T	5T

[a] Tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using blood-induced *P. berghei* infected mice (five animals per group) by the method described by Osdene et al.[6] Test data were supplied by Drs. E. A. Steck and R. E. Strube of Walter Reed Army Institute of Research. [b] ΔMST, mean survival time over controls (6.2 ± 0.5 days). A compound is considered active if MST of the treated group is more than twice that of the control group: C, number of cures (mice surviving 60 days); T, number of toxic deaths occurring on days 2–5 after infection.

Scheme II



6, 8, and 2a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = R′ = CH_3
d, R = C_6H_{11}; R′ = H
e, R = $CH_2C_6H_{11}$; R′ = H
f, R = CH_3; R′ = C_2H_5
g, R = R′ = $(CH_2)_5$
h, R = CH_3(cis), R′ = H

7 and 3a, R″ = C_3H_7
b, R″ = C_4H_9
c, R″ = $(CH_2)_2$-C_6H_{11}
d, R″ = $(CH_2)_3$-C_6H_{11}
e, R″ = $CH_2CH(CH_3)C_2H_5$
f, R″ = $CH_2C_6H_{11}$

(Table II). Testing was carried out at the Rane Laboratory, University of Miami, Miami, Fla. Examination of the data shows that **2b**, which contains a 4-(β-ethylvinyl) substituent, was active at 80–640 mg/kg. The other three compounds were inactive.[8]

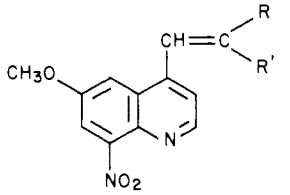
In an earlier paper, we reported that 4-ethylprimaquine (**1a**) and 4-vinylprimaquine (**1b**) showed activity similar to that of primaquine in both the *P. cynomolgi* and *P. berghei* screens but were less toxic. While several of the compounds described in this paper were active in the presumptive causal prophylactic *P. berghei yoelii* screen, none of the compounds tested showed tissue schizonticidal cures in the radical curative *P. cynomolgi* screen. In addition, in contrast to **1a** and **1b**, none of the four compounds tested showed cures in the *P. berghei* blood schizonticidal screen. The above data indicated that lengthening the 4-substituent of 4-ethylprimaquine with either additional methylene groups or methylene groups terminated with a cyclohexane ring resulted in loss of activity. In addition, the incorporation of 4-β-alkyl substituents to 4-vinylprimaquine also resulted in loss of activity.

Experimental Section

Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. IR spectra were measured with a Perkin-Elmer Model 267 or 467 grating infrared spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. MS were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill., or Integral Microanalytical Laboratories, Inc., Raleigh, N.C. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

6-Methoxy-8-nitroquinoline-4-carboxaldehyde (5). 6-Methoxy-8-nitrolepidine (4, 20 g) was dissolved in 230 mL of acetic acid and placed in a 500-mL flask equipped with a magnetic stirrer and reflux condenser. Selenium dioxide (14.7 g) which was purified by sublimation immediately prior to the oxidation was added with stirring, and the resulting mixture was heated under reflux for 2 h. The red-brown suspension was immediately filtered. Upon cooling the filtrate to room temperature, crude **5** separated as a light-brown material. The solid was collected on a filter, washed with water and methanol, and recrystallized from THF and methanol. The final product (17 g, 80%) obtained as yellow-brown crystals had mp 190–195 °C (lit.[2] mp 192 °C); IR (KBr) 1690 (CHO), 1528 and 1363 (NO_2) cm^{-1}.

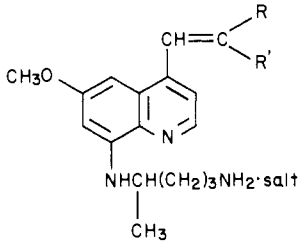
Table III. 4-(β-Alkylvinyl)-6-methoxy-8-nitroquinolines



no.	R, R′	yield,[a] %	mp, °C	recrystn solvent	formula	IR[b] ν (NO_2), cm^{-1}	H¹ NMR, δ ($CDCl_3$)[c] CH_3O	ArCH= C*H*-	ArC*H*= CH
6a	CH_3, H	33	170-172	EtOH	$C_{13}H_{12}N_2O_3$	1525	3.96	6.50	6.95
6b	C_2H_5, H	39	124-127	MeOH	$C_{14}H_{14}N_2O_3$	1550	3.97	6.50	6.95
6c	CH_3, CH_3	66	130-131	MeOH	$C_{14}H_{14}N_2O$	1534	3.96		6.54
6d	C_6H_{11}, H	71	134-137	MeOH	$C_{18}H_{20}N_2O_3$	1537	3.96	6.43	6.90
6e	$CH_2C_6H_{11}$, H	71	113-115	MeOH	$C_{19}H_{22}N_2O_3$	1531	3.92	6.46	6.90
6f	CH_3, C_2H_5[d]	44	60-70	EtOH	$C_{15}H_{16}N_2O_3$	1540	3.93		6.47 6.50
6g	$(CH_2)_5$	32	130-131	MeOH	$C_{17}H_{18}N_2O_3$	1524	3.96		6.45
6h	CH_3(cis), H[e]	50	110-119	EtOH	$C_{13}H_{12}N_2O_3$	1543	3.93	6.18	6.75

[a] Total yield of olefins obtained. [b] As compressed potassium bromide disks. [c] Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. [d] This compound is a mixture of olefins. [e] NMR analysis indicated that the compound contained 5% of the trans isomer.

Table IV. 4-Alkyl- and 4-(β-Alkylvinyl)primaquine Analogues



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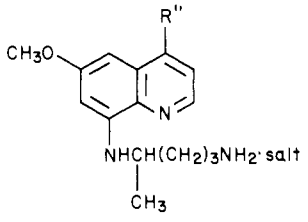

3

no.	R, R′	R″	salt	mp, °C (recrystn solv)	yield,[a] %	formula[b]
2a	CH_3, H		$C_4H_4O_4$	147-149 (EtOH-EtOAc)	59	$C_{22}H_{29}N_3O_5 \cdot 0.5H_2O$
2b	C_2H_5, H		$C_4H_4O_4$	150-153 (EtOH-EtOAc)	83	$C_{23}H_{31}N_3O_5 \cdot 0.5H_2O$
2c	CH_3, CH_3		2HBr	228-230 (EtOH-THF-H_2O)	60	$C_{19}H_{29}Br_2N_3O$
2d	C_6H_{11}, H		2HBr	150-151 (EtOH-THF)	76	$C_{23}H_{35}Br_2N_3O \cdot 0.5H_2O$[c]
2e	$CH_2C_6H_{11}$, H		2HBr	131-132 (EtOH-THF)	85	$C_{24}H_{37}Br_2N_3O \cdot 0.25H_2O$[c]
2f	CH_3, C_2H_5		$C_4H_4O_4$	158-160 (EtOH)	67	$C_{24}H_{33}N_3O_5 \cdot 0.5H_2O$
2h	CH_3(cis), H[d]		$C_4H_4O_4$	142-145 (EtOH)	37	$C_{22}H_{29}N_3O_5 \cdot 0.5H_2O$
3a		$-C_3H_7$	$C_4H_4O_4$	155-158 (EtOH-EtOAc)	51	$C_{22}H_{31}N_3O_5 \cdot {}^1/_3H_2O$
3b		$-(CH_2)_3CH_3$	$C_4H_4O_4$	160-165 (EtOH-EtOAc)	71	$C_{23}H_{33}N_3O_5 \cdot 0.5H_2O$
3c		$-(CH_2)_2C_6H_{11}$	$0.5C_4H_4O_4$	168-170 (EtOH-H_2O)	85	$C_{25}H_{37}N_3O_3 \cdot 0.5H_2O$[c]
3d		$-(CH_2)_3C_6H_{11}$	$C_4H_4O_4$	172-174 (EtOH-EtOAc)	62	$C_{28}H_{41}N_3O_5$
3e[e]		$CH_2CH(CH_3)C_2H_5$	$C_4H_4O_4$	159-162 (EtOH-H_2O)	57	$C_{24}H_{35}N_3O_5$
3f		$CH_2C_6H_{11}$	$0.5C_4H_4O_4$	180-183 (EtOH)	83	$C_{24}H_{35}N_3O_3 \cdot 0.75H_2O$

[a] Overall yield starting from 7 and 8. [b] Analysis for C, H, and N are within ±0.4% of the theoretical value. [c] The compound also contained $0.25C_2H_5OH$. [d] An NMR analysis indicated the product was a 60:40 mixture of the cis and trans isomers. A study showed that the isomerization took place during the alkylation of 8h with 4-iodo-1-phthalimidopentane. [e] Compound 3e was prepared by catalytic reduction of 2f under conditions similar to that used for the reduction of 6 to 7.

General Procedure for 4-(β-Alkylvinyl)-6-methoxy-8-nitroquinolines 6. The reaction was performed in equipment which had been oven dried at 120 °C. The phosphonium salt (prepared by standard methods[9]) was suspended in 200 mL of freshly dried and distilled THF (CaH_2). After saturating the mixture with argon, the amount of butyllithium in hexane required

to form a clear orange solution was injected. In small (~100 mg) portions an additional amount of phosphonium salt was added to the solution until a trace remained undissolved within 20 min. The mixture was then cooled to −60 °C. An equivalent solution of 6-methoxy-8-nitroquinoline-4-carboxaldehyde (5) in dry THF (1 g/100 mL) was saturated with argon at −60 °C and added to the ylide solution. Stirring was continued for about 2 h. For the preparation of the trans isomers, the light gray-brown mixture was decomposed with an excess of ethanolic HCl. After basifying the yellow-brown solution with excess ammonia, the solvents were removed in vacuo. The residue was extracted with methylene chloride, 10 volumes of ether were added, and the decanted or filtered solution was evaporated to dryness. The residue crystallized upon addition of methanol. The product 6 was removed by filtration and the mother liquor chromatographed on Florisil with chloroform as the eluent to give additional amounts of 6. In a modified workup, the solution which resulted after 2 h of stirring at room temperature was not acidified with HCl but immediately evaporated to a syrup. Methylene chloride–ether fractionation as above gave an olefin which crystallized upon addition of methanol but contained about 60% of the cis isomer instead. The cis and trans isomers could be separated by chromatography on Florisil. Individual examples are described in Table III.

General Procedure for 4-(β-Alkylvinyl)-8-amino-6-methoxyquinolines 8. To a mixture of 10 g of $SnCl_2 \cdot 2H_2O$ in 20 mL of ethanol, 40 mL of concentrated hydrochloric acid, and 330 mg of granular tin, 10 mmol of the 8-nitroquinoline derivative 6 was added in small portions with stirring while the temperature was kept at 0 °C. After 45 min, the external cooling was removed so the suspension could warm to room temperature. After warming the mixture at 30 °C for about 2 h, it was diluted with 40 mL of water, basified with 5 N sodium hydroxide, and extracted repeatedly with methylene chloride. The extract after drying with sodium sulfate was evaporated to give the 8-aminoquinoline derivative 8 in 80–90% yield. These products were used in the next step without further purification.

General Procedure for 4-Alkyl-8-amino-6-methoxyquinolines 7. A methanol solution (150 mL) of 2 g of 4-(β-alkylvinyl)-6-methoxy-8-nitroquinoline (6) was shaken with 3 g of wet Raney nickel under 45 lb/in.^{2} of hydrogen pressure while a temperature of 50 °C was maintained. The hydrogen pressure remained constant after 7 h. The cooled mixture was filtered, the solvent was evaporated, and the residue was vacuum dried. The amino compound (obtained in ~95% yield) was used for subsequent alkylation without further purification.

4-(Alkylvinyl)- and 4-Alkyl-8-[(4′-amino-1′-methylbutyl)amino]-6-methoxyquinolines (2 and 3). The amino compound 7 or 8 (~2 g) was heated with stirring at 105–110 °C under argon while a solution of 2 equiv of 4-iodo-1-phthalimidopentane in 2 g of triethylamine was added very slowly over a period of about 24 h. The pasty mixture was extracted with 30 mL of benzene, cooled, filtered, and concentrated under vacuum. The remaining yellow-brown syrup was purified by passing through a column of 200 g of silica gel 60 (Merck) using chloroform as the eluent. The pure alkylated amine recovered as a yellow syrup was refluxed with 4 equiv of hydrazine in 50 mL of ethanol. After 2–3 h, the cooled mixture was filtered and the filtrate concentrated under vacuum. The residue was treated with methylene chloride and filtered, and the filtrate was concentrated under vacuum. If needed, the methylene chloride treatment was repeated. Individual examples are described in Table IV.

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2-Acetylpyridine Thiosemicarbazones. 2. N^4,N^4-Disubstituted Derivatives as Potential Antimalarial Agents[1,2]

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The most effective antimalarial agents among the N^4-monosubstituted 2-acetylpyridine thiosemicarbazones recently described by us have a cyclohexyl or a phenyl substituent and produce cures in *Plasmodium berghei* infected mice at a dose of 160 and 320 mg/kg, respectively. We report here on a related series of N^4,N^4-disubstituted 2-acetylpyridine thiosemicarbazones. Several members of this group bearing alkyl or cycloalkyl substituents at N^4 show activity superior to the most active monosubstituted 2-acetylpyridine thiosemicarbazones. However, the greatest improvement in potency was seen when the N^4-nitrogen atom was incorporated into a six- or seven-membered ring, such as the piperidine, piperazine, or azabicyclo[3.2.2]nonane systems, to give compounds with curative properties at a dose level as low as 20 mg/kg.

Recently, we reported[1] on a series of thiosemicarbazones obtained from 2-acetylpyridine which we found to be among the first such derivatives to possess antimalarial activity. It was shown that the molecular features essential for activity are a 2-pyridylethylidene moiety, the presence of the thiocarbonyl group (in contrast to a carbonyl group),