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The synthesis and antimalarial activity of six new 2-arylquinoline-4-methanols is described. The compounds bearing a sulfur were prepared to determine if antimalarial activity can be retained while photoreactivity and phototoxicity is diminished by such substituents. The observed antimalarial activity of some of the new compounds show this to be possible.

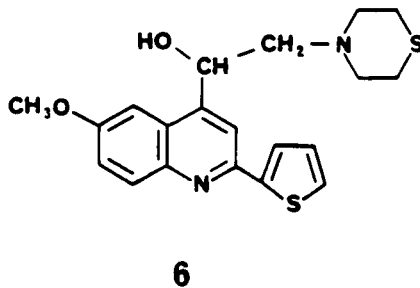
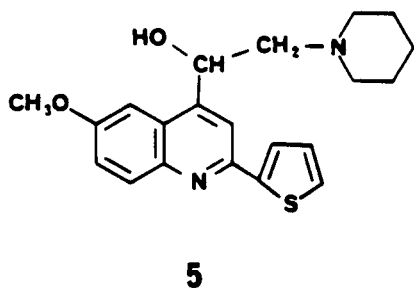
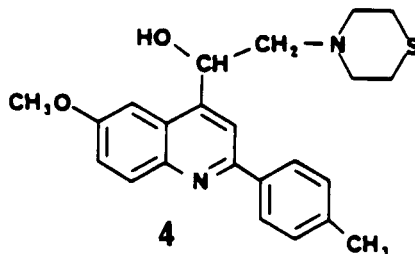
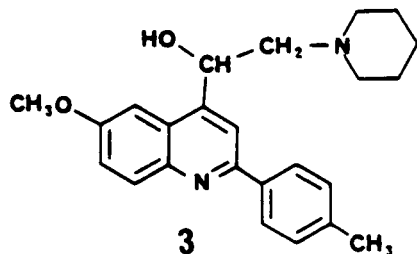
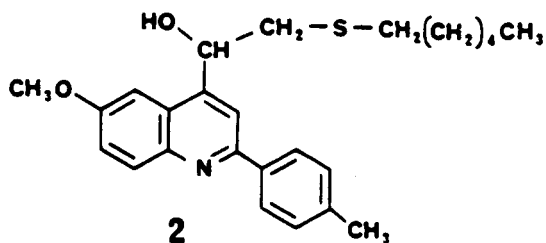
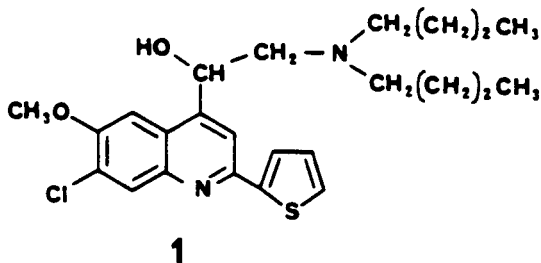
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## Introduction.

The growing problem of resistance to currently-used antimalarial compounds [1] has created new interest in the development of replacement drugs. The class of  $\alpha$ -alkyl-amino-2-arylquinolinemethanol compounds has shown excellent antimalarial activity [2] but an accompanying side effect of phototoxicity [3] has been problematical. We have reported [4] that rapid photofragmentation of such compounds is a likely cause of this phototoxicity, and have sought to incorporate photochemical "quenchers" into the structure of such compounds as a means of decreasing their photoreactivity while retaining their antimalarial ac-

tivity. We present evidence that this strategy holds promise for success.

Our observation that sulfur-containing compounds can quench the excited singlet state of 2-phenylquinoline compounds [5] led us to synthesize analogs containing sulfur, both aliphatic and aromatic. Compounds **1-6** were selected as target compounds. Compounds **1**, **5**, and **6** contain a sulfur in a thiophene ring. Compounds **2**, **4**, and **6** contain a sulfide group (as a *substitute* for nitrogen in compound **2**). Compound **3** contains no sulfur, and will serve as a convenient reference for the effect of sulfur on both antimalarial and photochemical reactivity.

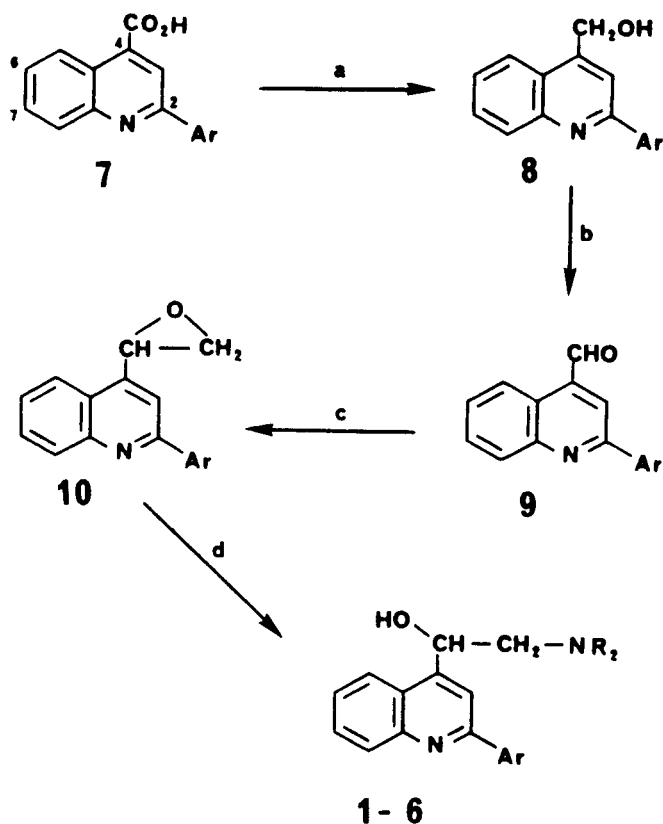


## Results and Discussion.

## Synthesis.

Scheme 1 outlines the general route to these compounds, modifying synthetic strategy used earlier [6]. The starting 2-arylquinoline-4-carboxylic acids **7** were prepared by a Doebner condensation. Generally, lithium aluminum hydride in tetrahydrofuran or ether was used to reduce these acids to the alcohol, **8**. Oxidation of the alcohol to aldehyde **9** was accomplished using manganese dioxide. The aldehyde was subsequently treated with one molar equivalent of dimethylsulfonium methylide for conversion to epoxide **10**. Condensation of the epoxide with an amine or mercaptan in acetonitrile or methanol gave reasonable yields of the desired compounds **1-6**.

Scheme 1



The target compounds were chosen upon several considerations. First, a photochemical "quencher" was selected based on the type of structures effective in this manner [5] which would possibly be bioisosteric with substituents on active compounds. Structure-activity correlations have been examined for a number of 2-phenylquinoline-4-carbinols [7], and conclusions emerging from this study, such as length and lipophilicity of the side chain, were kept in mind. The presence or absence of chlorine in **1** vs. **5** would probe whether these structure-activity relation-

ships were valid for quinoline bearing a 2-thieno substituent, since the side chains on these compounds have a comparable effect on antimalarial activity in the 2-phenyl series [8].

## Antimalarial Activity.

All compounds were screened for antimalarial activity in three ways. *In vitro* tests used two strains of drug-resistant *Plasmodium falciparum* (Table 1). Compounds **2** and **6** were not active, but the activity of **1** was extraordinary. By way of comparison, mefloquine (WR 142490) has an  $ID_{50}$  of 3.9 and 2.9 ng/ml while chloroquine has an  $ID_{50}$  of 7.4 and 60, respectively against the Camp and Smith Strains [8]. Compounds **3**, **4**, and **5** were also active in this screen.

Table 1

*In Vitro* Antimalarial Activity

Compound	$ID_{50}$ (ng/ml)	
	Smith	Camp
<b>1</b>	0.35	1.21
<b>2</b>	100	100
<b>3</b>	4.6	10
<b>4</b>	36	100
<b>5</b>	5.4	11
<b>6</b>	37	121
chloroquine [a]	60	7.4
quinine [a]	50	40
pyrimethamine [a]	1355	415
mefloquine [a]	2.9	3.9

[a] Values from reference [8].

*In vivo* tests using mice (Rane test) showed modest levels of activity for some of the compounds (Table 2), though total cures were not evident with **1** until 640 mg/kg were reached. Nevertheless, as shown in Table 2, the *in vivo* activity of some compounds exceeded or was comparable to that of presently-available drugs [9], with a better therapeutic index (all but compound **2** were tolerated without toxic deaths, even at high dose levels). Note that the Rane test does not use a "chloroquine-resistant" strain of *Plasmodia*.

Table 2

*In Vivo* Antimalarial Activity

Compound	$\Delta$ MST (days)		
	160 mg/kg	320 mg/kg	640 mg/kg
<b>1</b>	5.4	8.7	13.7 + 2C
<b>2</b>		0.5 + 1T	
<b>3</b>	2.8	2.9	6.2
<b>4</b>	0.4		0.6
<b>5</b>	1.0	1.3	4.6
<b>6</b>	0.0		0.2
chloroquine [a]	10.0	17 + 2T	... 5T
quinine [a]	2.0	3.2	5.4
primaquine [a]	7.0	... 5T	... 5T

[a] Values of reference [9]. C = Cure, T = Toxic Death.

Table 3  
Quinoline-4-Carboxylic Acids

Compound	Substituents	Reflux (hours)	Yield (%)	mp	Formula	Analysis	
						Calcd.	Found
<b>7a</b>	6-OCH <sub>3</sub> , 2- <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	60	26	243-244	C <sub>18</sub> H <sub>15</sub> NO <sub>3</sub>	C, 74.71; H, 5.15	C, 74.73; H, 5.26
<b>7b</b>	6-OCH <sub>3</sub> , 2-(2-thienyl)	18	16	223-225	C <sub>15</sub> H <sub>11</sub> NO <sub>3</sub> S	C, 63.14; H, 3.88	C, 63.32; H, 3.67
<b>7c</b>	6-OCH <sub>3</sub> , 7-Cl, 2-(2-thienyl)	24	42	270-275	C <sub>15</sub> H <sub>10</sub> ClNO <sub>3</sub> S	C, 56.34; H, 3.15	C, 56.58; H, 3.23

Table 4  
Quinoline-4-methanols

Compound	Reaction Solvent	Yield (%)	mp	Formula	Analysis	
					Calcd.	Found
<b>8a</b>	tetrahydrofuran	49	121-122	C <sub>18</sub> H <sub>17</sub> NO <sub>2</sub>	C, 77.40; H, 6.13	C, 77.28; H, 6.30
<b>8b</b>	diethyl ether	90	110-114	C <sub>15</sub> H <sub>13</sub> NO <sub>2</sub> S	C, 66.40; H, 4.82	C, 66.22; H, 4.72
<b>8c</b>	tetrahydrofuran	84	181-182	C <sub>15</sub> H <sub>12</sub> ClNO <sub>2</sub> S	C, 58.92; H, 3.96	C, 58.81; H, 3.88

Table 5  
Quinoline-4-carboxaldehydes

Compound	Reflux (hours)	Yield (%)	mp	Formula	Analysis	
					Calcd.	Found
<b>9a</b>	2	92	139-140	C <sub>18</sub> H <sub>15</sub> NO <sub>2</sub>	C, 77.96; H, 5.45	C, 78.04; H, 5.58
<b>9b</b>	5	68	105-106	C <sub>15</sub> H <sub>11</sub> NO <sub>2</sub> S	C, 66.90; H, 4.12	C, 66.78; H, 4.29
<b>9c</b>	1	81	172-174	C <sub>15</sub> H <sub>10</sub> ClNO <sub>2</sub> S	C, 59.31; H, 3.32	C, 59.54; H, 3.49

Table 6  
Quinoline-4-ethylene Epoxides

Compound	Reaction Time (hours)	Yield (%)	mp	Formula	Analysis	
					Calcd.	Found
<b>10a</b>	3	44	112-114	C <sub>19</sub> H <sub>17</sub> NO <sub>2</sub>	C, 78.33; H, 5.88	C, 78.45; H, 6.02
<b>10b</b>	4	37	141-142	C <sub>16</sub> H <sub>13</sub> NO <sub>2</sub> S	C, 67.82; H, 4.62	C, 67.67; H, 4.58
<b>10c</b>	1	77	195-198	C <sub>16</sub> H <sub>12</sub> ClNO <sub>2</sub> S	C, 60.47; H, 3.81	C, 60.29; H, 3.87

Table 7  
2-Aryl- $\alpha$ -dialkylaminomethyl- or alkylthiomethylquinoline-4-methanols **1-6**

Product	Reactant Epoxide	Nucleophile	Reflux (hours)	Solvent	Yield (%)	mp	Formula	Analysis	
								Calcd.	Found
<b>1</b>	<b>10c</b>	<i>n</i> -Bu <sub>2</sub> NH	10	AcCN	63	68-69	C <sub>24</sub> H <sub>31</sub> ClN <sub>2</sub> O <sub>2</sub>	C, 64.66; H, 6.99	C, 64.66; H, 6.84
<b>2</b>	<b>10a</b>	<i>n</i> -Hex-SH	1	MeOH	25	100-102	C <sub>25</sub> H <sub>31</sub> NO <sub>2</sub> S	C, 73.31; H, 7.63	C, 72.98; H, 7.60
<b>3</b>	<b>10a</b>	piperidine	48	AcCN	54	119-121	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub>	C, 76.56; H, 7.50	C, 76.52; H, 7.57
<b>4</b>	<b>10a</b>	thiomorpholine	3	MeOH	54	144-145	C <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub> S	C, 70.02; H, 6.64	C, 69.85; H, 6.62
<b>5</b>	<b>10b</b>	piperidine	2	MeOH	72	112-114	C <sub>21</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	C, 68.45; H, 6.56	C, 68.24; H, 6.78
<b>6</b>	<b>10c</b>	thiomorpholine	3	MeOH	68	135-137	C <sub>20</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	C, 62.15; H, 5.74	C, 61.83; H, 6.00

Compound **1** was also tested for casual propylactic activity. Though at 160 mg/kg the mean survival time of the test group increased by 6.6 days and there was one (out of five total) cure, this increase in survival time is not sufficiently indicative of significant propylactic activity.

Consideration of the results outlined in Tables 1 and 2 allows several important observations. The most impressive activity (by compound **1**) in the *in vitro* tests was unfortunately not quite as great in the *in vivo* test. This is possibly due to *in vivo* metabolism of the compound,

which would lead to lowered activity in the Rane test (which uses a single dose administered after the disease is well established). Future synthetic efforts will focus on modifications to test this hypothesis by reduction of susceptibility to metabolism. The substitution of sulfur for nitrogen (compound **2**) leads to total loss of antimalarial activity, as well as increasing the toxicity. Side chain substitution by sulfur leads to a diminution of activity. Of importance was the comparison of the activity of compounds **1** and **5**, differing primarily in the 7-chloro substituent on **1**. The resulting greater antimalarial activity is consistent with the substituent effects previously observed [7] in the 2-phenyl compounds, suggesting that structure-activity relationships of analogs may be of value in the design of compounds of even greater activity.

#### Photoreactivity.

The rate of photoreaction of compounds **1-6** was examined, and all but compound **3** (which lacked the built-in "quencher" showed diminished photoreactivity [10] in comparison with known phototoxic compounds. For example, the rate of photoreaction of compound **1** was 0.0091, much lower than the value of the least phototoxic compound previously examined [11]. Similarly, the phototoxicity measured by photo-erythrohemolysis [12] was diminished. The amount of irradiation time needed to destroy red blood cells in the presence of known phototoxic materials was much greater than the compounds of interest. Specifically, the time required for 50% lysis [13] using compound **1** was 23.5 minutes under oxygen (45.5 minutes under argon), in comparison with SN10275 (a phototoxic compound in clinical trials [3a]) which required only 3.5 minutes under oxygen and 11 minutes under argon.

#### Conclusions.

The strategy of incorporating photochemical quenchers into a molecule to diminish photochemical reactivity appears practical. Further, the antimalarial activity of some compounds which result from such modification is retained.

### EXPERIMENTAL

Melting points were determined using a Mel-Temp apparatus and are uncorrected. The nmr spectra were recorded with a Bruker WH-90 or Varian EM-360. Elemental analyses were performed by Galbraith Laboratories (Knoxville, Tenn) or Baron Consulting Co. (Orange, Conn). Infrared spectra were recorded on a Perkin-Elmer 283 Spectrometer.

#### 2-Arylquinoline-4-carboxylic Acids **7**.

Doebner condensations proceeded by refluxing one molar equivalent of the aryl carboxaldehyde with one of the appropriately substituted anilines for one hour in ethanol. One equivalent of pyruvic acid was then added slowly, and reflux was continued. After an appropriate period the reaction mixture was cooled, the product isolated by filtration, and purified by digestion with acetone.

#### 2-Arylquinoline-4-methanols (**8**).

To a freshly distilled tetrahydrofuran or absolute ether solution of acid **7** was added excess lithium aluminum hydride in portions with stirring. After two hours the reaction was quenched by dropwise addition of saturated ammonium chloride solution. After filtration the grey precipitate was digested with ethyl acetate several times, and the solution added to the filtrate. Removal of solvent from the dried filtrate afforded alcohol **8**, which was purified by silica gel chromatography. The methanols characteristically showed a 2H singlet in the nmr spectra at  $\delta$  4.9-5.1 for the benzylic hydrogens.

#### 2-Arylquinoline-4-carboxaldehydes (**9**).

A chloroform solution of alcohol **8** was treated with a five-fold excess of manganese dioxide and heated on a steam bath. After the reaction was complete the manganese dioxide was removed by filtration through celite. The celite was thoroughly washed with chloroform, and the combined chloroform phases evaporated to give aldehyde **9**. A characteristic 1H singlet at  $\delta$  9.5-10.3 was observed for the aldehyde proton of **9**.

#### 2-Arylquinoline-4-ethylene Epoxide (**10**).

The required ylid [14] was prepared from one equivalent of freshly-washed sodium hydride and trimethylsulfonium iodide in tetrahydrofuran. The reaction was cooled in an ice-salt bath and a solution of one equivalent of the aldehyde in THF was added to the stirred solution. After reaction was complete water was added and epoxide **10** removed by benzene extraction. The benzene solution was washed with water, dried, and evaporated to give the epoxide, which was purified by silica gel chromatography. The nmr spectrum of epoxide hydrogens in **10** characteristically appeared as multiplets at  $\delta$  4.3, 3.2, and 2.7.

#### Dialkylaminomethyl-2-arylquinoline-4-methanols (**1-6**).

An excess of a dialkylamine (or sulfide) was refluxed in acetonitrile or methanol with epoxide **10** for an appropriate period. The reaction mixture was concentrated and excess amine removed under high vacuum. The products were purified by silica gel chromatography. A 1H multiplet appeared characteristically at  $\delta$  5.1-5.2 due to the benzylic hydrogen of compounds **1-6**.

#### Antimalarial Activity.

All biological tests were performed by the Walter Reed Army Institute of Research. *In vitro* activity measures drug effect on the uptake of radiolabeled hypoxanthine by the chloroquine-sensitive Camp strain of *P. falciparum* and the multidrug resistant Smith strain. *In vitro* tests (Rane test) [15] measured increase in mean survival time of mice infected with *P. berghei* as compared to an untreated control. Presumptive casual prophylactic activity in mice was tested by a single subcutaneous injection of the test compound four hours prior to parasitization by *P. berghei* [16].

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