into a large amount of ice and water and neutralized with ammonium hydroxide. The solid thus separated was collected by filtration. It was dried and recrystallized from hexane to give *N*,17β-diacetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime: mp 142–144°; λ_{max}^{EtOH} 244 nm; λ_{max}^{KBr} 3.09, 4.17, 5.68, and 5.72 μ. *Anal.* ($C_{24}H_{31}NO_4$) C, H, N.

3-(*O*-Carboxymethyl)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one Oxime (9). 17α-Ethynyl-17β-acetoxy-19-norandrost-4-en-3-one oxime (2.0 g) was dissolved in 10 ml of pyridine and treated with 1.0 g of carboxymethoxylamine hemihydrochloride. The mixture was heated on a steam bath for 0.5 hr and poured into a large amount of ice and water. The solid material was collected by filtration and recrystallized from methanol–water to give 3-(*O*-carboxymethyl)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime: mp 236–237°; λ_{max}^{EtOH} 248 mμ; λ_{max}^{KBr} 3.08, 4.71, 5.65, and 5.89 μ. *Anal.* ($C_{24}H_{31}NO_5$) C, H, N.

N-(2'-Tetrahydropyranyloxy)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one Oxime. 17β-Acetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime (0.5 g) was treated with 20.0 ml of dry benzene, 0.2 g of *p*-toluenesulfonic acid, and 10 ml of dihydropyran and was stirred at room temperature for 0.5 hr. The mixture was treated with a large amount of ice and water followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. Repeated crystallization from methylene chloride–hexane gave *N*-(2'-tetrahydropyranyloxy)-17β-acetoxy-17α-ethynyl-19-norandrost-4-en-3-one oxime: mp 172–174°; λ_{max}^{EtOH} 244 nm; λ_{max}^{KBr} 3.10, 4.75, and 5.75 μ. *Anal.* ($C_{27}H_{37}NO_4$) C, H, N.

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Antimetabolites of Coenzyme Q. 16. New Alkylmercaptoquinones Having Antimalarial Curative Activity†

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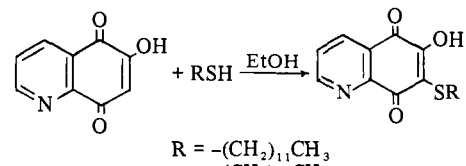
Coenzyme Q_8 is apparently indispensable in the metabolism of *Plasmodium*. Based on this knowledge, a new class of lipoidal 5,8-quinolinequinones and a new 1,4-naphthoquinone have been synthesized as potential inhibitors of the biosynthesis and/or function of coenzyme Q_8 in the metabolism of *Plasmodium* and as potential antimalarials. Four new 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones and the new 3-alkylmercapto-2-hydroxy-1,4-naphthoquinone have been synthesized and tested for antimalarial activity against *Plasmodium berghei* in the mouse. Each of the new 5,8-quinolinequinones showed marked *in vivo* antimalarial activity without acute toxicity; two of these compounds were curative, and one of these two was completely curative. The 1,4-naphthoquinone derivative exhibited only marginal antimalarial activity in the murine assay. Three alkylmercapto-5,8-quinolinequinones and the alkylmercapto-1,4-naphthoquinone were also tested for antimalarial activity against *Plasmodium gallinaceum* in the chick. One quinolinequinone was somewhat curative, but the 1,4-maphthoquinone exhibited no activity in this avian test. The alkylmercapto-5,8-quinolinequinones, represented by three of the four compounds, and the alkylmercapto-1,4-naphthoquinone showed marked inhibition of both NADH- and succinoxidase mitochondrial CoQ-enzyme systems.

The background research for this work has recently been described.[1] In previous papers[1-3,‡] new 5,8-quinolinequinones and 1,4-naphthoquinones have been synthesized and tested for antimalarial activity against *Plasmodium berghei* in the mouse and for inhibition of mitochondrial NADH- and succinoxidase systems. This paper describes the syntheses and biological activities of four new 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones and one new 3-alkylmercapto-2-hydroxy-1,4-naphthoquinone. In view of the promising antimalarial activity of some of our recently synthesized 5,8-quinolinequinone derivatives,[1,2] it was of interest to synthesize 5,8-quinolinequinones and a 1,4-naphthoquinone with sulfur-containing side chains. The side chains were made long enough to impart lipoidal character to the molecule and in an attempt to design molecules which could function as antimetabolites of the highly lipoidal coenzyme Q. 7-*n*-Octadecylmercapto-6-hydroxy-5,8-quinolinequinone, the most active *in vivo* derivative, was totally curative in the mouse assay (5/5 cures at both 320 and 640 mg/kg) without toxicity.

Organic Syntheses. The synthesis of the 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones was accomplished by treating 6-hydroxy-5,8-quinolinequinone[4,5] in ethanol with the appropriate alkyl mercaptan as depicted in Scheme I.

Scheme I



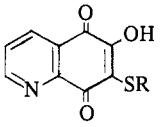
R = $-(CH_2)_{11}CH_3$
$-(CH_2)_{13}CH_3$
$-(CH_2)_{15}CH_3$
$-(CH_2)_{17}CH_3$

Dodecyl, tetradecyl, hexadecyl, and octadecyl mercaptans were chosen because of their ready availability and because they provided side-chain lengths near the optimal length

†Coenzyme Q. 153.

‡C. M. Bowman, F. S. Skelton, T. H. Porter, and K. Folkers, unpublished results.

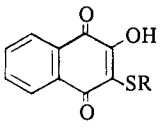
Table I. Chemical Data and Antimalarial Activity of Certain 7-Alkylmercapto-6-hydroxy-5,8-quinolinequinones



Compd no.	R	Mp, °C	% yield[c]	*In vivo* antimalarial activity mouse test (*P. berghei*)[a]	
				$T - C$,[b] mg/kg	Cures and/or toxicity, mg/kg
1[d]	$-(CH_2)_{11}CH_3$	dec 127 136–138	15	13.9 at 320	0/5 cures at 320, 0/5 deaths at 320
2	$-(CH_2)_{13}CH_3$	137–139	14	3.7 at 160	0/5 cures at 160, 0/5 deaths at 160
3	$-(CH_2)_{15}CH_3$	137–139	14	5.9 at 20 17.9 at 160	2/5 cures at 80 3/5 cures at 160, 0/5 deaths at 160
4	$-(CH_2)_{17}CH_3$	137–138	19	9.5 at 160	5/5 cures at 320, 0/5 deaths at 320 5/5 cures at 640, 0/5 deaths at 640

[a]All compounds were administered subcutaneously, in graded doses, to groups of five mice. [b]$T - C$ = change in survival time, in days, of treated and nontreated (control) mice. [c]Yields were based on starting quinone. [d]Mass spectrum of this compound indicated trace impurities.

Table II. Chemical Data and Antimalarial Activity of 3-*n*-Dodecylmercapto-2-hydroxy-1,4-naphthoquinone and 1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene



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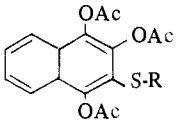


6

Compd no.	R	Mp, °C	% yield[c]	*In vivo* antimalarial activity mouse test (*P. berghei*)[a]	
				$T - C$,[b] mg/kg	Cures and/or toxicity, mg/kg
5	$-(CH_2)_{11}CH_3$	71–73	6	3.3 at 640	0/5 cures at 640, 0/5 deaths at 640
6	$-(CH_2)_{11}CH_3$	67–69	77	0.9 at 640	0/5 cures at 640, 0/5 deaths at 640

[a]All compounds were administered subcutaneously, in graded doses, to groups of five mice. [b]$T - C$ = change in surival time, in days, of treated and nontreated (control) mice. [c]Yields were based on starting quinone.

for maximal *in vivo* activity found in the 7-*n*-alkyl-6-hydroxy-5,8-quinolinequinone series.[1]

The reaction of Scheme I took place slowly over a period of several days to a week. Apparently, the hydroquinone, formed by 1,4 addition of the alkyl mercaptan to 6-hydroxy-5,8-quinolinequinone, was air oxidized or, more likely, oxidized by starting quinone to the desired product. Each of the 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones was a dark purple crystalline compound with a relatively sharp melting point (Table I).

The new sulfur-containing 1,4-naphthoquinone derivative, 3-*n*-dodecylmercapto-2-hydroxy-1,4-naphthoquinone, was synthesized in a similar fashion from 2-hydroxy-1,4-naphthoquinone and *n*-dodecyl mercaptan. Reductive acetylation of 3-*n*-dodecylmercapto-2-hydroxy-1,4-naphthoquinone with acetic anhydride, zinc dust, and pyridine gave 1,2,4-triacetoxy-3-*n*-dodecylmercaptonaphthalene. Syntheses of additional 3-*n*-alkylmercapto-2-hydroxy-1,4-naphthoquinones were terminated because of the low antimalarial activity of the *n*-dodecylmercapto derivative against *P. berghei* in the mouse.

Results of Antimalarial Tests. These compounds were tested for antimalarial activity against *P. berghei* in mice.[6] A single dose at the desired level was given subcutaneously 72 hr after the mice were infected with *P. berghei*. A minimum mean survival time of 13.0 days was required for the compound to be declared "active"; control mice exhibited a mean survival time of ~6.2 days. Mice living 60 days or more after treatment were considered as cured.

As seen in Table I, each of the 6-alkylmercapto-6-hydroxy-5,8-quinolinequinones showed marked activity in the *in vivo* antimalarial test against *P. berghei* in the mouse by procedures described by Rane.[6] Compound 3, 7-*n*-hexadecylmercapto-6-hydroxy-5,8-quinolinequinone ($T - C$ = 17.9 and 3/5 cures at 160 mg/kg), and compound 4, the 7-*n*-octadecyl homolog (5/5 cures at 320 mg/kg), exhibited striking curative antimalarial activity. None of these new alkylmercapto-5,8-quinolinequinones showed any acute toxicity at the highest dose levels tested.

As seen in Table II, 3-*n*-dodecylmercapto-2-hydroxy-1,4-naphthoquinone showed only marginal antimalarial activity. This compound exhibited a $T - C$ value of 3.3 at 640 mg/kg in contrast to its more active 5,8-quinolinequinone analog, 7-*n*-dodecylmercapto-6-hydroxy-5,8-quinolinequinone, which had $T - C$ = 13.9 at 320 mg/kg.

1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene, the triacetate of the dihydronaphthoquinone, was inactive as an antimalarial against *P. berghei* in mice (Table II).

Representative 5,8-quinolinequinones were also tested for antimalarial activity against *Plasmodium gallinaceum* in chicks. A single dose at the desired level was given subcutaneously immediately after the chicks were infected with *P. gallinaceum*. An increase of 100% in survival time was required for the compound to be considered "active" as an antimalarial. Control chicks exhibited a mean survival time of ~4.0 days. Chicks living 30 days or more after treatment were considered as cured.

As seen in Table III, 7-*n*-tetradecylmercapto-6-hydroxy-5,8-quinolinequinone, compound 2, exhibited a higher antimalarial activity in the chick test than 7-*n*-octadecylmercapto-6-hydroxy-5,8-quinolinequinone. Compound 2 was even curative (1/5 cures) in the chick at dose levels of 160 and 320 mg/kg. Notably, compound 2 showed distinctly greater activity than compound 4 in the chick

assay, but the reverse was true in the mouse test.

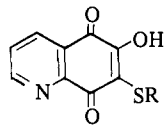
3-*n*-Dodecylmercapto-2-hydroxy-1,4-naphthoquinone and 1,2,4-triacetoxy-3-*n*-dodecylmercaptonaphthalene both showed no increase in survival time at dose levels of 100 and 120 mg/kg, respectively, in the avian assay (not shown in tables).

Inhibition of CoQ_{10}-Enzyme Systems. Data are summarized in Table IV for three representative alkylmercapto-5,8-quinolinequinones and the one alkylmercapto-1,4-naphthoquinone. The assays were conducted in a Warburg respirometer using mitochondria from beef heart. As seen in Table IV, each of the newly synthesized derivatives tested showed significant inhibition of both NADH- and succinoxidase systems. The succinoxidase system appeared to be slightly more sensitive to these inhibitors than the DPNH-oxidase system. Of the quinolinequinones, 7-*n*-octadecylmercapto-6-hydroxy-5,8-quinolinequinone was found to have the greatest inhibitory activity in the DPNH-oxidase system (Table IV). Notably, this derivative also exhibited the greatest *in vivo* activity against *P. berghei* in the mouse (Table I).

3-*n*-Dodecylmercapto-2-hydroxy-1,4-naphthoquinone was also a potent inhibitor in the mitochondrial DPNH- and succinoxidase enzyme system but exhibited only marginal antimalarial activity *in vivo* against *P. berghei* in the mouse ($T - C = 3.3$ at 640 mg/kg) and no activity in the avian assay ($T - C = 0.0$ at 100 mg/kg).

An analog of CoQ could function as an antimetabolite at either one or both of the two enzyme sites in the respiratory chain requiring CoQ. If antimalarial activity of the analog were due to such functional enzyme site inhibitions, then correlation of antimetabilite and antimalarial activity might be observed. If the analog functioned only as an inhibitor of the biosynthesis of CoQ as the basis for antimalarial activity, then correlation of functional inhibition of the analog and antimalarial activity would not be observed. However, a measurement of inhibition of biosynthesis of CoQ could be found to correlate with antimalarial activity.

Table III. Antimalarial Activity of Certain 7-Alkylmercapto-6-hydroxy-5,8-quinolinequinones



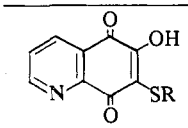
Compd no.	R	*In vivo* antimalarial activity[a] chick test (*P. gallinaceum*, blood induced) $T - C$,[b] mg/kg	Cures and/or toxicity, mg/kg
1[d]	$-(CH_2)_{11}CH_3$	7.6 at 120[c]	
2	$-(CH_2)_{13}CH_3$	3.2 at 10	
		5.6 at 20[c]	
		5.8 at 40[c]	
		6.8 at 80[c]	
		12.5 at 160	1/5 cures at 160, 0/5 deaths at 160
		13.5 at 320	1/5 cures at 320, 0/5 deaths at 320
3	$-(CH_2)_{17}CH_3$	5.2 at 100[c]	

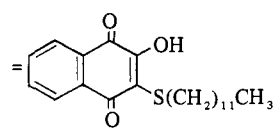
[a]All compounds were administered subcutaneously to groups of five chicks. [b]$T - C$ = change in survival time, in days, of treated and nontreated (control) chicks. [c]These compounds were declared "active" by the standard of 100% increase in survival time. [d]Mass spectrum of this compound indicated trace impurities.

Experimental Section

General Procedures. All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical

Table IV. *In Vitro* Assay of Certain Alkylmercapto-5,8-quinolinequinones and a 1,4-Naphthoquinone in the CoQ-Enzyme Systems DPNH-Oxidase and Succinoxidase[e]



	DPNH-oxidase[c]			Succinoxidase[c]		
	Specific activity[a]	Inhibitor concn[b]	% inhibition	Specific activity[a]	Inhibitor concn[b]	% inhibition
R = $-(CH_2)_{11}CH_3$[d]	0.31	0	0	0.30	0	0
	0.26	26	16	0.20	17	35
	0.12	51	63	0.14	26	88
	0.074	64	76	0.13	34	57
R = $-(CH_2)_{15}CH_3$	0.31	0	0	0.30	0	0
	0.27	13	15	0.19	13	36
	0.21	19	33	0.15	17	52
	0.079	26	75	0.17	19	45
	0	32	100	0.12	20	59
				0.10	20	66
R = $-(CH_2)_{17}CH_3$	0.31	0	0	0.30	0	0
	0.22	13	30	0.23	8.5	24
	0.18	16	41	0.21	13	30
	0.12	19	61	0.13	17	56
				0.15	17	52
R = 	0.31	0	0	0.32	0	0
	0.21	13	33	0.24	8.5	20
	0.16	13	48	0.14	13	53
	0.054	20	83	0.19	13	37

[a]Microatoms of oxygen per minute per milligram of protein. [b]Nanomoles of inhibitor per milligram of protein. [c]Reaction mixture contained no exogenous coenzyme Q. [d]Mass spectrum of this compound indicated trace impurities. [e]Each flask contained 0.2 ml of KOH (20%) in the center well and 0.2 ml of enzyme in the side arm. The order of addition of reagents and quantities used were as follows: Tris chloride (0.1 *M*; pH 7.5), 1 ml; sucrose (1 *M*), 0.5 ml; mitochondrial phospholipids (12.8 mg/ml), 0.05 ml; inhibitor, 0.05 ml (in absolute ethanol); EDTA (0.8 μM/ml), 0.1 ml; cytochrome c (3 μg/ml of H_2O), 0.05 ml; absolute ethanol (total volume not to exceed 0.1 ml). L. Szarkowska, *Arch. Biochem. Biophys.*, 113, 519 (1966).

values. Nmr spectra were taken on all new compounds except compound 2 and were consistent with proposed structures.

7-Alkylmercapto-6-hydroxy-5,8-quinolinequinones. Four new 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones were prepared by treating 6-hydroxy-5,8-quinolinequinone in ethanol with the appropriate alkyl mercaptan in a manner similar to that previously described for the syntheses of some sulfur-containing benzoquinones by Snell and Weissberger.[7] Generally, the reaction mixtures were stirred at both room temperature and at 50–60° for several days. The crude product was generally purified by repeated fractional recrystallizations from ether–ethanol–chloroform. The synthesis of 7-*n*-dodecylmercapto-6-hydroxy-5,8-quinolinequinone, which is described below, is representative.

7-*n*-Dodecylmercapto-6-hydroxy-5,8-quinolinequinone. A mixture of 6-hydroxy-5,8-quinolinequinone (2 g) and *n*-dodecyl mercaptan (3.5 g) in ethanol (~50 ml) was stirred at about 50–60° for 3 days and then at room temperature for 3 days. After cooling in the refrigerator, the solid material was collected by filtration and repeatedly recrystallized from ether–ethanol (charcoal) to yield 650 mg of the purple crystalline product, mp 136–138° (with decomposition from 127°).

3-*n*-Dodecylmercapto-2-hydroxy-1,4-naphthoquinone. A mixture of 2-hydroxy-1,4-naphthoquinone (6 g) and *n*-dodecyl mercaptan (10.5 g) in ethanol was allowed to stir at room temperature 3 days and then was heated at about 50° for 1 week. The reaction mixture was cooled in the refrigerator, and the solid material was collected by filtration and repeatedly recrystallized from ethanol–ether–chloroform and ether–hexane to yield 800 mg of the purple product, mp 72–74°.

1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene. 1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene was synthesized by a procedure similar to that described for the preparation of a certain hydroquinone diacetate by Fieser and Gates.[8] A mixture of 3-*n*-dodecylmercapto-2-hydroxy-1,4-naphthoquinone (1.0 g), acetic anhydride (6.0 ml), zinc dust (1.3 g), and pyridine (0.5 ml) was allowed to stand at room temperature overnight (hand stirring initially). Water was added, and the mixture was extracted with ether. The ether extract, after being washed with water and dilute potassium carbonate solution and being dried over anhydrous potassium carbonate, was evaporated. Solvent (ethanol–ether) was added and the turbid mixture heated until clear. The crystalline triacetate was obtained from the cooled, seeded solution. 1,2,4-Triacetoxy-3-*n*-dodecylmercaptonaphthalene (1.03 g), mp 67–69°, was obtained after recrystallization from ethanol–water (charcoal).

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3-Phenyl-5-quinolinemethanol Antimalarials†

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Special Skraup procedures have been developed for the synthesis of a series of new 3-phenyl-5-quinolinecarboxylic esters. These esters have been employed as starting materials for the elaboration of a series of α-dialkylaminomethyl-3-phenyl-5-quinolinemethanols *via* the corresponding acid chlorides, diazo ketones, bromo ketones, and epoxides. Alternate routes to the desired 3-phenyl-5-quinolinemethanols were also investigated. In the case of the reaction between the epoxide derived from 5-bromoacetyl-8-methyl-3-phenylquinoline with di-*n*-butylamine, both of the possible isomeric amino alcohols were isolated and characterized. Eight compounds (including intermediates) were tested for antimalarial activity against *Plasmodium berghei* in mice. α-Di-*n*-butylaminomethyl-3-(4-chlorophenyl)-8-methyl-5-quinolinemethanol dihydrobromide showed modest activity at doses of 160 mg/kg and higher.

The impressive activity of a number of 2-phenyl-4-quinolinemethanols against the malaria parasite in human and avian infections was discovered more than 20 years ago.[1-3] Pronounced photosensitization associated with the active compounds of this group has precluded extensive study or use in man. Recent research efforts in this area have led to the discovery of additional active compounds[4] and to the development of a practical and useful animal test for phototoxicity.[5] However, a clear-cut separation of the phototoxic liability and antimalarial activity has not been achieved with the 2-phenyl-4-quinolinemethanols, related heterocyclic analogs, or the positional isomers of the 2-phenylquinolinemethanols.

A small number of 5-quinolinemethanols have shown antimalarial activity in several species,[6-8] but the 2-aryl-5-quinolinemethanols have also produced phototoxic reactions at the effective dose levels.[8] Because of the antimalarial activity of the 5-quinolinemethanols and the concomitant phototoxicity of the 2-aryl analogs, we speculated that 3-aryl-5-quinolinemethanols, with no "blocking" group at the 2 position of the quinoline nucleus, might show antimalarial activity without phototoxicity. This paper describes the synthesis of a limited number of compounds to test this hypothesis.

Chemistry. In general, we chose to elaborate the 3-aryl-5-quinolinemethanols from the corresponding carboxylic acids, using procedures similar to those developed by Lutz and his coworkers[9] (see Scheme I). The absence of reports of 3-aryl-5-quinolinecarboxylic acids or esters in the literature necessitated the development of preparative methods for these starting materials.

3-Phenylquinoline has been prepared by Warren[10] using special Skraup conditions. Modification of this procedure, when applied to appropriately substituted anilines, proved to be an adequate preparative method for the 3-aryl-5-quinolinecarboxylic esters (**1-5**, *cf.* Table I). Synthesis of

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