Table I. *In Vitro* Assay of Certain Quinoxaline Derivatives in Coenzyme Q Enzyme Systems, DPNH-Oxidase and Succinoxidase

	DPNH-oxidase		Succinoxidase	
Compd	Concn[a]	% inhibition	Concn[a]	% inhibition
2	120	7	120	25
3	120	0	120	29

[a] Nanomoles of inhibitor per mg of mitochondrial protein.

for 1 week at room temperature, and the resulting orange precipitate was collected by filtration. Fractional recrystallization from EtOH-Et_2O-$CHCl_3$ and $CHCl_3$-EtOH gave ~300 mg of **1**, mp 144–145°, as bright orange crystals (yield 13.2%); recrystallizations from EtOH of solids from filtrates gave ~600 mg of **2**, mp 81–83° (yield 17.2%). *Anal.* (**1**, $C_{20}H_{30}N_2O_2S$) C, H, N, S. *Anal.* (**2**, $C_{32}H_{54}N_2O_2S_2$) C, H, N, S.

6-*n*-Dodecylmercapto-5,8-quinoxalinequinone (3). 6-*n*-Dodecylmercapto-5,8-dihydroxyquinoxaline (**1**, 1.0 g, 2.76 mmol) dissolved in EtOH-$CHCl_3$ was treated with $FeCl_3$ (3 g, 18.5 mmol, in H_2O). The $CHCl_3$ layer separated and was collected. Further $CHCl_3$ extractions were made, and the combined $CHCl_3$ extracts were dried (anhydrous Na_2SO_4). Addition of hexane to the concentrated $CHCl_3$ extracts gave ≃860 mg of yellow crystals. Recrystallization from $CHCl_3$-EtOH-Et_2O yielded ≃760 mg of **3**, mp 152–153° (yield 76.5%). *Anal.* (sample of **3**, mp 152–153° from another preparation) ($C_{20}H_{28}N_2O_2S$) C, H, N, S.

6,7-Di-*n*-dodecylmercapto-5,8-quinoxalinequinone (4). 6,7-Di-*n*-dodecylmercapto-5,8-dihydroxyquinoxaline (2 g, 3.55 mmol) was prepared in a manner similar to that described for the synthesis of **3**, except the $CHCl_3$ extracts were allowed to evaporate at room temperature to a solid residue. The residue was recrystallized from EtOH-Et_2O-hexane (filtered) two times to yield ≃705 mg of orange crystals, mp 72–73° (yield 35.5%). *Anal.* (sample of **4**, mp 72–73° from another preparation) ($C_{32}H_{52}N_2O_2S_2$) C, H, N, S.

6-*n*-Dodecylmercapto-5,8-diacetoxyquinoxaline (5). 6-*n*-Dodecylmercapto-5,8-dihydroxyquinoxaline (**1**, ≃100 mg, 0.276 mmol) was treated with excess acetic anhydride and a catalytic amount of H_2SO_4. After 1 day, addition of ice to the reaction mixture caused the mixture to boil vigorously for a few seconds. A white solid precipitated upon addition of more ice. The reaction mixture was filtered to yield a white solid which was recrystallized from EtOH-H_2O and EtOH-Et_2O (charcoal, Celite, cornstarch) to give a white powder tinged with yellow, mp 107–108°. This material was recrystallized from EtOH-Et_2O and then EtOH-Et_2O (charcoal, Celite, cornstarch) to yield crystals, mp 110–112°. *Anal.* (**5**, $C_{24}H_{34}N_2O_4S$) C, N, S; H: calcd, 7.67; found, 7.27.

6-ω-Cyclohexylpentyl-5,8-quinoxalinequinone (6). 5,8-Quinoxalinequinone[6] (1.0 g, 6.24 mmol) in HOAc was treated with crude di-ω-cyclohexylhexanoyl peroxide in a manner similar to the syntheses of certain alkylated 5,8-quinolinequinones described by Pratt and Drake.[7,8] The acid peroxide was prepared from ω-cyclohexylhexanoic acid (5.0 g, 25.2 mmol) by a procedure similar to that described for other alkanoyl peroxides by Silber and Swern,[9] except 30% H_2O_2 was used. The reaction mixture was stirred at ≃80–90° for 8 hr and then was stirred at room temperature over the weekend. Acetic acid was removed *in vacuo*, and the oily residue after the addition of H_2O was extracted repeatedly with Et_2O and/or $CHCl_3$. Addition of hexane to the ether extracts yielded an orange powder. Repeated recrystallizations from Et_2O-$CHCl_3$, and Et_2O-EtOH-hexane gave bright orange crystals, mp 139–141° *Anal.* (**6**, $C_{19}H_{24}N_2O_2$) C, H, N.

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Deaza Analogs of Some 4-, 6-, and 8-Aminoquinolines

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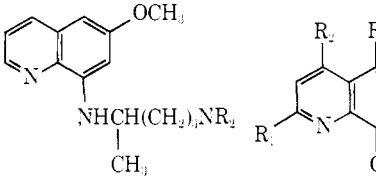
Among a number of 8-aminoquinolines synthesized during World War II, pamaquine[1,2] (**1**, R = C_2H_5) and primaquine[3] (**1**, R = H) were found to exhibit good prophylactic antimalarial activity in animals[4,5] and in man.[6] The major drawback to the use of these compounds is their toxicity—the most severe being acute hemolytic anemia, particularly in persons whose red blood cells are susceptible to drug-induced hemolysis due to glucose-6-phosphate dehydrogenase deficiency.[7] Neurotoxicity produced by certain 8-aminoquinolines has also been noted.[8]



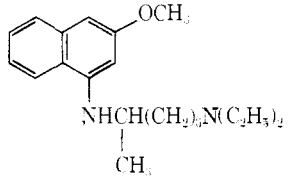
1 **2**

Prophylactic antimalarial activity has also been observed in certain 6-aminoquinolines of type **2**,[1,9-11] Again the high toxicity of these compounds in experimental animals hampered realization of their clinical usefulness. Previous structural modification study on compounds of type **1** disclosed that reduction of the pyridine ring of these 8-aminoquinolines resulted in compounds with inferior antimalarial activity.[12,13] Since reduction of the pyridine ring system not only destroys the planarity of the parent ring structure, but also increases the basicity of the ring nitrogen, it suggests that an increase in basicity of the ring system may have an adverse effect on antimalarial activity. This information, together with the fact that compounds with more than one basic center in the quinoline ring (as exemplified by the synthesis of a number of 1,2-, 1,3-, 1,4-, 1,5-, and 1,7-diaza analogs) do not show the expected high antimalarial activity,[4,14-16] implies that the nitrogen atom in the quinoline ring may not be entirely necessary for the activity. This postulation has been supported by reports that: (1) it is the aliphatic side chain (sometimes together with the methoxyl function) rather than the ring which contributes to the binding of these compounds to some enzyme system and nucleic acids;[17-19] (2) in another series of antimalarial compounds whose mode of action may be different, activity is not only retained but increased by replacing the quinoline unit of quinoline amino alcohols with a naphthalene ring.†

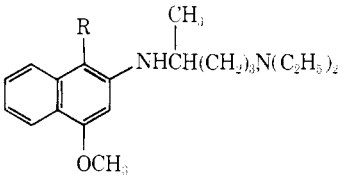
†J. S. Gillespie, personal communication (WRAIR Antimalarial Conference, July 14, 1973).

The latter results in elimination of the troublesome phototoxicity normally associated with 2-arylquinoline amino alcohols.[20]

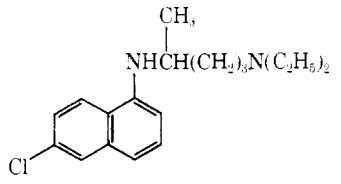
Synthesis of some analogs of **1** and **2** was therefore investigated with the hope that these naphthalene derivatives may lead to compounds with causal prophylactic activity and more favorable therapeutic indices. Initially, compounds **3**, **4a**, and **4b** were studied. For comparison, synthesis of the deaza analog **5** of chloroquine, a 4-aminoquinoline, was also carried out.



3

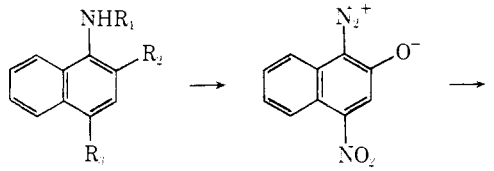


4a, R = H
b, R = OCH_3



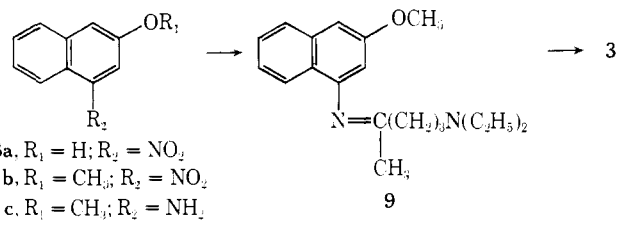
5

Chemistry. For the synthesis of the deazapamaquine **3**, the key intermediate, 3-methoxy-1-nitronaphthalene (**8b**), was prepared from α-naphthylamine (**6a**) by the method of Morgan and Evans,[21] with some modification. The β-naphthol **8a** was obtained by hydrolysis of the dinitronaphthylaminesulfonate followed by diazotization (to yield **7**) and reduction. Methylation of the naphthol **8a** was conveniently carried out in DMF with CH_3I, and the crude ether **8b** was purified by chromatography. Hydrogenation of the purified nitro compound **8b** proceeded smoothly to furnish fairly pure 1-amino-3-methoxynaphthalene (**8c**) in good yield. The latter was converted into the target compound **3** through the Schiff base **9** by heating with the dimethyl ketal of 5-diethylamino-2-pentanone in the presence of acid,[22] followed by $NaBH_4$ reduction.



6a, R_1, R_2, R_3 = H
b, R_3 = tosyl; R_2, R_1 = H
c, R_1 = tosyl; R_2, R_3 = NO_2

7

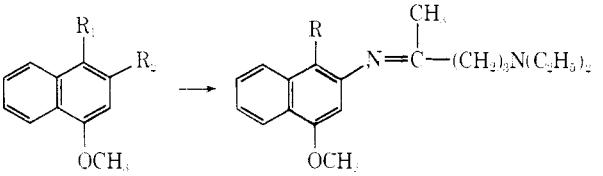


8a, R_1 = H; R_2 = NO_2
b, R_1 = CH_3; R_2 = NO_2
c, R_1 = CH_3; R_2 = NH_2

9

4-Methoxy-2-naphthylamine[23,24] (**10b**) was condensed with the dimethyl ketal of 5-diethylamino-2-pentanone[22] to give the Schiff base **11a**, which yielded 3-(4-diethylamino-1-methylbutylamino)-1-methoxynaphthalene (**4a**) on reduction.

Using the procedure of Inoue, *et al.*,[25] 1,4-dimethoxy-2-nitronaphthalene (**10d**) was prepared from 1,4-naphthoquinone *via* **10c**. Reduction of the nitro compound **10d** was best carried out by catalytic hydrogenation with Pd/C rather than Raney nickel as described in the original literature.[25] The resulting amine **10e** was condensed with the aforementioned acetal[22] to yield **11b**, which was reduced to give 2-(4-diethylamino-1-methylbutylamino)-1,4-dimethoxynaphthalene (**4b**).



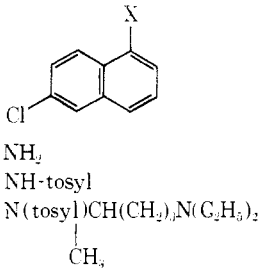
10a, R_1 = H; R_2 = NO_2
b, R_1 = H; R_2 = NH_2
c, R_1 = OCH_3; R_2 = H
d, R_1 = OCH_3; R_2 = NO_2
e, R_1 = OCH_3; R_2 = NH_2

11a, R = H
b, R = OCH_3

↓

4a, b

Refluxing a mixture of 6-chloro-1-naphthylamine[26,27] (**12a**) and *p*-toluenesulfonyl chloride in pyridine yielded 6-chloro-1-(*p*-toluenesulfonamido)naphthalene (**12b**). The latter was converted to 6-chloro-1-[[*N*-(1-methyl-4-diethylaminobutyl)]-*p*-toluenesulfonamido]naphthalene (**12c**) by successive treatment with sodium ethoxide and the hydrobromide salt of 4-bromo-1-diethylaminopentane. Without isolation, compound **12c** underwent acid hydrolysis to give the deazachloroquine analog **5**.



12a, X = NH_2
b, X = NH-tosyl
c, X = N(tosyl)$CH(CH_3)(CH_2)_3N(C_2H_5)_2$

Biological Activity. The deazapamaquine **3** was found to be without prophylactic activity in the sporozoite-induced mouse (IIT) test.[28] In the sporozoite-induced chick (Rane) test,[29] no activity was noted but toxicity was observed at 60 mg/kg. Compound **4a** was shown to be without activity but was toxic at 120 mg/kg in chick tests. On the other hand, compound **4b** had a quinine equivalent of 14 for SD_{90} (daily dose required for 90% suppression of the parasitemia) and Q = 20 for SD_{70} (Thompson).[30] The compound showed some activity in the sporozoite-induced mouse test at 10 mg/kg but was toxic at 160 mg/kg. The deazachloroquine **5** was found to be devoid of antimalarial activity. In view of possible implications of carcinogenicity of β-naphthylamines, work in this area will not be continued in our laboratories.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3-Methoxy-1-nitronaphthalene (8b). A mixture of 5.64 g (0.03 mol) of **8a**,[21] 4.14 g (0.03 mol) of K_2CO_3, and 10 ml of MeI was heated in 70 ml of DMF at 60° for 10 hr. Upon dilution of the reaction mixture with 300 ml of H_2O, a solid precipitated. This was collected by filtration to give, after chromatography through silica gel with $CHCl_3$, 4.6 g (76% yield) of **8b**, mp 95–98°. An analytical sample was prepared by recrystallization from MeOH as yellow needles, mp 101–102° (lit. mp 100–103°,[21] 101–102°[24]).

1-(4-Diethylamino-1-methylbutylamino)-3-methoxynaphthalene (3). A solution of 6.09 g (0.03 mol) of **8b** in 150 ml of EtOH was hydrogenated with 1 g of 10% Pd/C for 2 hr. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. The crude amine **8c** was mixed with 10 g (0.05 mol) of 4-diethyl-

amino-2,2-dimethoxypentane and 0.2 g of *p*-toluenesulfonic acid. The mixture was heated at 150–160° for 5 hr and then poured into 200 ml of H_2O. After being neutralized with dilute NaOH, the mixture was extracted with Et_2O (3 × 150 ml). The Et_2O extract was washed (H_2O), dried ($MgSO_4$), and evaporated *in vacuo* to a red colored oily residue. This Schiff base 8 was taken up on 100 ml of MeOH and treated portionwise with 4 g of $NaBH_4$. The resulting mixture was heated under reflux for 1 hr, diluted with 700 ml of H_2O, and extracted with Et_2O (3 × 200 ml). The Et_2O extract was washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was distilled rapidly *in vacuo* to give 5.5 g (58% yield) of a yellow oil, bp 207° (1 mm). An analytical sample was prepared by an additional distillation under the same conditions. *Anal.* ($C_{20}H_{30}N_2O$) C, H, N.

3-(4-Diethylamino-1-methylbutylamino)-1-methoxynaphthalene (4a). A mixture of 3.5 g (0.02 mol) of 4-methoxy-2-naphthylamine[23,24] (**10b**), 4 g (0.022 mol) of 5-diethylamino-2,2-dimethoxypentane, and 10 mg of *p*-toluenesulfonic acid was heated at 140–150° for 40 min. The reaction mixture was cooled and to it was added 150 ml of Et_2O. The Et_2O solution was washed with 10% aqueous K_2CO_3 and dried (K_2CO_3). It was then filtered and solvent was removed *in vacuo*. The crude Schiff base **11a** thus obtained (possessing the expected 6.0-μ absorption in the ir) was dissolved in 50 ml of EtOH and treated with an EtOH solution (50 ml) of $NaBH_4$ (1 g). The resulting solution was allowed to stand overnight at room temperature. It was diluted with 200 ml of H_2O and the mixture extracted with Et_2O (2 × 100 ml). The Et_2O extract was dried (K_2CO_3) and the solvent removed *in vacuo*. The residual oil was then taken up in C_6H_{14} and placed on a column of neutral Al_2O_3 (Woelm, activity 1). Elution with 500 ml of C_6H_{14} containing 1% Et_3N gave, on evaporation of solvent, an amber oil. This was evaporatively distilled at 110–120° (0.05 mm) to give 2.7 g (43% yield) of **4a** as a pale yellow oil, $n^{25}D$ 1.5890. Infrared absorption of this product was as expected. *Anal.* ($C_{20}H_{30}N_2O$) C, H, N.

1,4-Dimethoxy-2-naphthylamine (10e). To a suspension of 11.6 g (0.05 mol) of **10d**[25] in 200 ml of MeOH was added 1 g of 10% Pd/C. The mixture was hydrogenated for 1 hr at 3.5 kg/cm^2. Catalyst was removed by filtration and the filtrate concentrated to 50 ml *in vacuo*. To this was added 500 ml of H_2O. Stirring and chilling of the resulting mixture induced precipitation of the crude product, which was collected by filtration and dried. The product was recrystallized from C_6H_{14} to give 9.2 g (84% yield) of **10c** as light red plates, mp 97–99°. An analytical sample was prepared by recrystallization from MeOH, mp 99–100°. *Anal.* ($C_{12}H_{13}NO_2$) C, H, N.

2-(4-Diethylamino-1-methylbutylamino)-1,4-dimethoxynaphthalene (4b). A mixture of 2.0 g (0.01 mol) of **10c**, 2.0 g (0.01 g) of 5-diethylamino-2,2-dimethoxypentane, and 10 mg of *p*-toluenesulfonic acid was heated to 140°. Evolution of CH_3OH from the reaction mixture ceased after 30 min. Heating at this temperature was continued for another 20 min. After cooling, the crude reaction mixture was dissolved in Et_2O (150 ml). The solution was washed with saturated aqueous Na_2CO_3 and dried (K_2CO_3), and the solvent was removed *in vacuo*. The ir spectrum of the residue **11b** showed a strong band at 6.0 μ (C=N). The NH_2 doublet (2.85–2.95 μ) had largely disappeared. The crude Schiff base **11b** was dissolved in 50 ml of EtOH and treated with a solution of 1 g of $NaBH_4$ in 25 ml of EtOH. After stirring overnight at room temperature, the reaction mixture was diluted with 400 ml of H_2O and extracted with Et_2O (3 × 50 ml). The Et_2O extract was dried (K_2CO_3) and the solvent removed *in vacuo*. The residue showed no absorption at 6.0 μ in the ir, indicating reduction was complete. Purification of the crude product was effected by elution through a 2.5 × 10 cm column containing neutral Al_2O_3 (Woelm, activity 1) with (a) 500 ml of C_6H_{14} containing 1% Et_3N and (b) 500 ml of C_6H_{14}–C_6H_6 (1:1) containing 1% Et_3N. The combined elutes were evaporated *in vacuo* and the residual oil was distilled at 110–120° (0.05 mm) to give a 4.0 g (59% overall yield) of **4b** as an amber oil, $n^{27}D$ 1.5683. The ir spectrum of this product was in accord with the structure. *Anal.* ($C_{21}H_{32}N_2O_2$) C, H, N.

6-Chloro-1-(*p*-toluenesulfonamido)naphthalene (12b). A mixture of 15 g (0.084 mol) of 6-chloro-1-naphthylamine (**12a**) and 16 g (0.084 mol) of *p*-toluenesulfonyl chloride in 250 ml of pyridine was refluxed for 1 hr. The reaction mixture was cooled and poured into 2500 ml of stirred ice and water. At first a gummy material separated; this changed to a granular solid. This was collected on a filter and washed with H_2O to yield 26 g (93%) of crude product. Analytically pure material (6.1 g, 85% recovery) was obtained by recrystallizing 7.2 g of the crude material from absolute EtOH, mp 173–175°. The product was chromatographically homogeneous on an Eastman chromagram sheet (6060; petroleum ether (bp 30–60°)–EtOAc (8:2)). *Anal.* ($C_{17}H_{14}ClNSO_2$) C, H, Cl, N.

6-Chloro-1-[[*N*-(1-methyl-4-diethylaminobutyl)]-*p*-toluenesulfonamido]naphthalene (12c). A mixture of 600 ml of dry xylene, 3.7 g (0.16 mol) of Na, and 28 ml (0.47 mol) of absolute EtOH was stirred and refluxed until the Na was dissolved. After cooling the solution below 50°, 53.7 g (0.160 mol) of *p*-toluenesulfonamido-6-chloronaphthalene was added with stirring. The EtOH which formed was distilled off. The residual xylene solution was cooled to about 40°; 24.5 g (0.0810 mol) of 4-bromo-1-diethylaminopentane hydrobromide and 100 ml of dry xylene were added. The stirred reaction mixture was refluxed at about 140° overnight (18 hr) and then cooled to room temperature. The solids which formed were collected on a filter and washed with xylene. The xylene was removed *in vacuo* from the combined filtrates. The residue was slurried with about 800 ml of Et_2O and filtered to remove the undissolved solids 12b. The combined Et_2O filtrates were reduced in volume to about 1000 ml and extracted with 6 *N* HCl (5 × 200 ml). The Et_2O layer was dried then evaporated *in vacuo* to a residue to recover additional **12b**. The aqueous acid solution was basified to pH 12 by adding dropwise a 33% aqueous solution of NaOH. The basic aqueous solution was extracted with Et_2O to remove the desired base **12c**. After drying, the solvent was removed *in vacuo* from the ether solution, yielding 14.2 g (38%) of the crude product which was used in the following synthesis.

6-Chloro-1-[(1-methyl-4-diethylaminobutyl)amino]naphthalene (5). To 165 ml of 30% HBr to AcOH, decolorized with 6.7 g of C_6H_5OH, was added 14.2 g (0.030 mol) of **12c**. This mixture was stirred at room temperature for 20 hr and then added dropwise to 7000 ml of stirred Et_2O. A gummy layer separated on the walls of the flask. The ether was removed by decantation and the gummy solids were dissolved in water. The aqueous solution was basified to pH 12 by adding 8% aqueous NaOH solution. The liberated organic base was extracted into Et_2O. Removal of the solvent *in vacuo* yielded 8.5 g (89% yield) of crude product. Pure base **5** (6.0 g, 71% recovery) was obtained by two distillations *in vacuo*: bp 180–190° (0.125 mm); λ_{max} (EtOH) 260 nm (ϵ 17,600), 344 (6300). Infrared absorption of this product was as expected. *Anal.* ($C_{19}H_{27}ClN_2 \cdot 0.1H_2O$) C, H, Cl, N, O.

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Synthesis of Alkyl-4,7-dioxobenzothiazoles with Prophylactic Antimalarial Activity†

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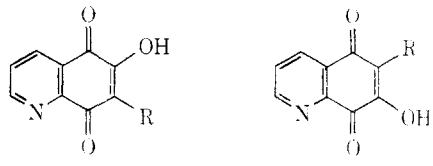
5-*n*-Undecyl- and 5-*n*-pentadecyl-6-hydroxy-4,7-dioxobenzothiazoles have been synthesized as examples of new lipoidal benzothiazoloquinones for study as potential antimetabolites of coenzyme Q. The 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole showed exemplary and effective prophylactic activity against *Plasmodium gallinaceum* in the chick without toxicity.

Recent studies[1] have shown that a variety of substituted quinones (*e.g.*, structures 1 and 2) function as effective *in vivo* antimalarial agents, presumably as antimetabolites of coenzyme Q_8[2] (CoQ_8) 3, which is intrinsic to the growth of the malaria-causing protozoan genus, *Plasmodium*. *In vitro* inhibition has been demonstrated by such analogs of coenzyme Q for both the succinoxidase and DPNH-oxidase enzyme systems which need coenzyme Q.[3] On the basis of the effective inhibition observed for such



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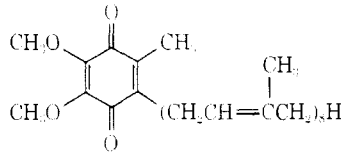

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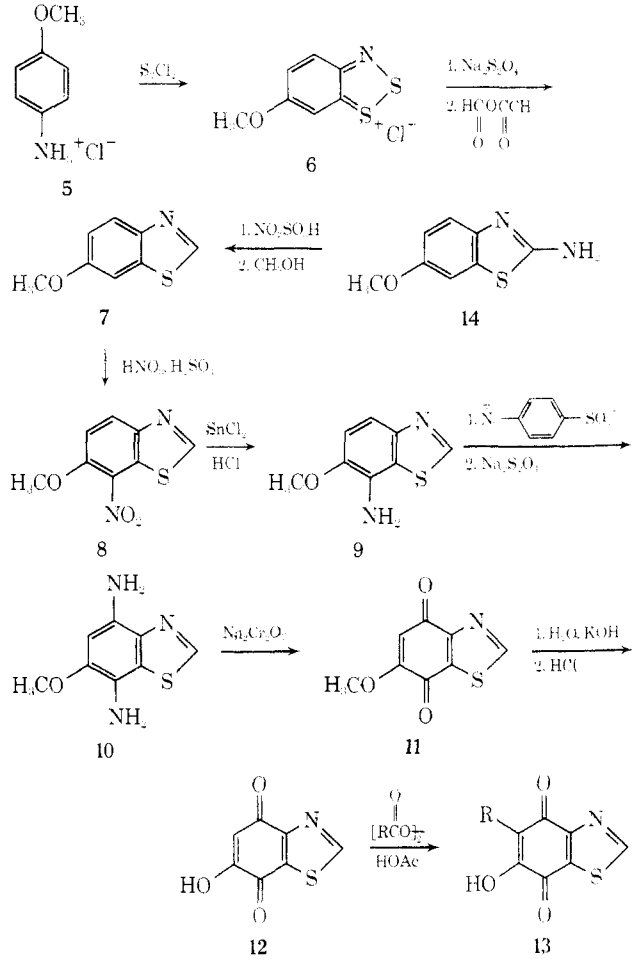
coenzyme Q analogs and the obvious possibility of their use as antimalarial agents, we have been investigating other fused bicycloheterocyclic quinones with the hope of designing even better new antimalarial agents, as well as elucidating the nature of an inhibition mechanism and/or the enzymatic site of CoQ.

The synthesis of two alkyl derivatives of the previously unknown 6-hydroxy-4,7-dioxobenzothiazole (12) is described herein (Scheme I), and exemplary assay data for the undecyl derivative are included (Table I).

6-Methoxybenzothiazole (7) was prepared by two methods. In 62% yield, by a modification of a known procedure,[4] *p*-anisidine hydrochloride (5) was converted to 7 by sequential exposure to sulfur monochloride, aqueous base, sodium dithionite, and formic-acetic anhydride[5] (Scheme I). After distillation and one recrystallization, the 6-methoxybenzothiazole melted at 66–68°. 6-Methoxybenzo-

Scheme I



† Coenzyme Q. 166. Antimetabolites of Coenzyme Q. 21.