= haloalkyl; 0.01 mol) in DMF (50 ml) at 0° and the mixture was stirred until it became neutral (time/temperature given). Acidification (AcOH) and dilution with H_2O afforded the crude product, which was recrystallized from the appropriate solvent.

3-Substituted 1-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]-hydantoins and -hydrouracils (IV, Table V). NaH (50% in oil, 0.03 mol) was added in portions to a suspension of the hydantoin or hydrouracil III (0.03 mol) in DMF (60 ml) at 0°, followed by the appropriate alkylating agent. The mixture was then stirred until neutral (time/temperature listed), acidified (AcOH), and diluted with H_2O. The product was filtered off, washed with H_2O, dried, and recrystallized.

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Antimetabolites of Coenzyme Q. 20.† Synthesis of New Alkyl-5,8-quinoxalinequinones as Potential Inhibitors of Coenzyme Q and as Antimalarial Drugs

Thomas H. Porter, Alexander von Klaudy, and Karl Folkers*

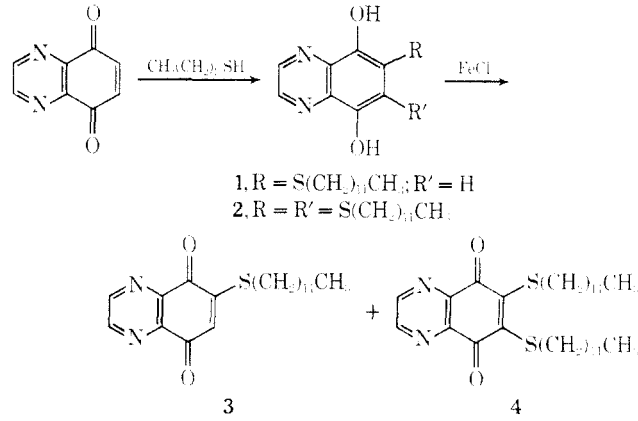
Institute for Biomedical Research, The University of Texas at Austin, Austin, Texas 78712. *Received March 19, 1973*

The synthesis is described of representative compounds of a new category of alkyl-5,8-quinoxalinequinones as potential antimetabolites of coenzyme Q for testing as antimalarials and other biological activities. In view of the effective antimalarial activity of some of our recently synthesized alkylmercapto-5,8-quinolinequinones,[1] it is of interest to synthesize and bioassay 5,8-quinoxalinequinones, especially those with sulfur-containing side chains. The side chains were designed to impart the necessary lipoidal character to the molecule and toward simulation of the highly lipoidal coenzyme Q.

The initial step in the two-step synthesis of 6-*n*-dodecylmercapto- and 6,7-di-*n*-dodecylmercapto-5,8-quinoxalinequinones (3 and 4, respectively) (Scheme I) consisted of the 1,4 addition of *n*-dodecyl mercaptan to 5,8-quinoxalinequinone in a manner similar to that described by Snell and Weissberger[2] for the syntheses of certain alkylmercaptobenzoquinones. Oxidation of the isolated mono- and dialkylated dihydroxyquinoxalines (1 and 2, respectively) with $FeCl_3$ gave the alkylated quinoxalinequinones 3 and 4, respectively, in high yield. Attempts to oxidize the dihydroxyquinoxalines with Ag_2O resulted in extensive decomposition. Acetylation of 6-*n*-dodecylmercapto-5,8-dihydroxyquinoxaline (1) with acetic anhydride and H_2SO_4 as catalyst was accomplished to give the corresponding diacetyl derivative 5.

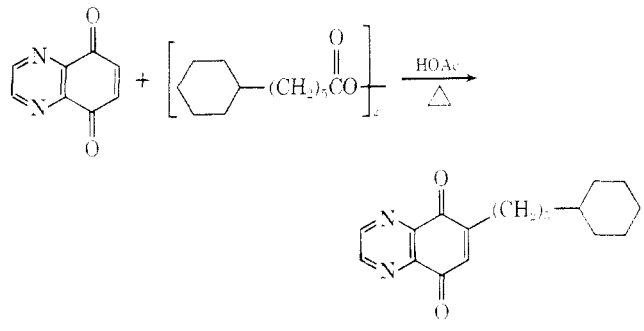
†Coenzyme Q. 163.

Scheme I



The synthesis of 6-ω-cyclohexylpentyl-5,8-quinoxalinequinone (6) was effected by treating 5,8-quinoxalinequinone with di-ω-cyclohexylhexanoyl peroxide in acetic acid (Scheme II). The yield of 6-ω-cyclohexylpentyl-5,8-quinoxalinequinone (6) was very low.

Scheme II



Compounds 2–4 were tested for antimalarial activity against blood-induced *Plasmodium berghei* in mice[3] and were inactive at 640 mg/kg each. Compounds 3 and 4 were tested against *Plasmodium gallinaceum* in the sporozoite-induced chick test[4] and were inactive at 80 mg/kg. Compound 2 was also inactive against *P. gallinaceum* (blood-induced) in the chick[3] at 100 mg/kg. Additional compounds, particularly analogs of 3, merit synthesis and testing.

Compounds 2 and 3 were tested *in vitro* for inhibitory activity in mitochondrial DPNH-oxidase and succinoxidase enzyme systems (Table I). Neither compound showed significant inhibition in DPNH-oxidase at levels of 120 nmol of inhibitor/mg of mitochondrial protein; however, compounds 2 and 3 showed 25 and 29% inhibition, respectively, in succinoxidase at this same concentration level. The mitochondria were prepared by a method similar to that described by Blair.[5]

Experimental Section

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 values. Nmr spectra were taken on all new compounds and were consistent with the proposed structures.

6-*n*-Dodecylmercapto- and 6,7-Di-*n*-dodecylmercapto-5,8-dihydroxyquinoxaline (1 and 2, respectively). 5,8-Quinoxalinequinone[6] (1.0 g, 6.24 mmol) in EtOH was treated with *n*-dodecyl mercaptan (1.5 g, 7.41 mmol). The reaction mixture was stirred

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

Daniel J. McCaustland, Ping-Lu Chien, C. C. Cheng,*

Midwest Research Institute, Kansas City, Missouri 64110

Jaroslav Novotny, Walter L. Schreiner, and Fred W. Starks

Starks Associates, Inc., Buffalo, New York 14313.
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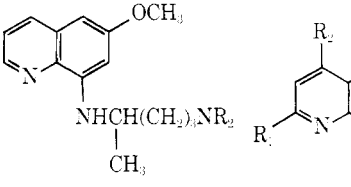
Among a number of 8-aminoquinolines synthesized during World War II, pamaquine[1,2] (**1**, R = C_2H_5) and primaquine[3] (**1**, R = H) were found to exhibit good prophylactic antimalarial activity in animals[4,5] and in man.[6] The major drawback to the use of these compounds is their toxicity—the 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]



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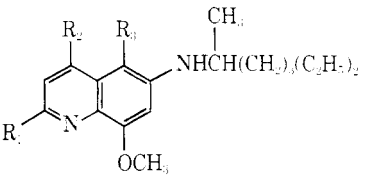

2

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).