A sample (10 mg) of XVII upon boiling with H_2O (5 ml) and Raney nickel (50 mg) for 30 min gave a solution with uv spectrum identical with that of 6-formylpurine hydrazone[5] (I).

6-Formylpurine 1-Oxide (XVIII). A solution of XVII (300 mg, 1.7 mmol) in 2 *N* HCl (5 ml) and EtOH (5 ml) was kept at 5°. Ethyl nitrite (7 ml) was added slowly and the reaction kept at 5° for 15 min and at 25° for 2 hr. The resulting solution showed a uv spectrum and R_f values identical with those of 6-formylpurine.[5]

6-Monobromomethylpurine 3-Oxide (XII). A solution of X (0.75 g, 5 mmol) in trifluoroacetic acid (6 ml) and *N*-bromosuccinimide (0.9 g, 5 mmol) was gently refluxed for 30 min and worked up as for XI: yield, 0.48 g (43%) of yellow needles; mp 165° explodes. *Anal.* ($C_6H_4N_4OBr$) C, H, N, Br.

Elementary analysis as well as nmr data indicated in some instances the presence of a small proportion of the dibromomethyl derivative. Attempts to isolate it were unsuccessful. This product can be used for the subsequent reactions without further purification, as both mono- and dibromethyl derivatives will react identically toward the carbonyl group reagents.[18]

6-Formylpurine Oxime 3-Oxide (XIII). A solution of XII (0.90 g, 4 mmol) in 1 *M* ethanolic hydroxylamine solution (300 ml) was kept in the dark; after 1 hr a copious precipitate appeared and the mixture was kept 48 hr at 25°. The resulting white crystalline material was collected, washed with EtOH, dissolved in H_2O (5 ml), and acidified to pH 3 with AcOH. Solid NaOAc was then added; the resulting precipitate was collected, washed, and dried to yield 0.35 g (48%) of thin white needles, mp 155° dec. *Anal.* ($C_6H_5N_5O_2 \cdot {}^1/_3H_2O$) C, H, N.

Reactions of IX with Sulfuryl Chloride. Reaction of IX with 50% sulfuryl chloride in trifluoroacetic acid or AcOH at refluxing, 25 or 5°, caused profound decomposition and no new crystalline product could be obtained. When IX (300 mg, 2 mmol) was treated in AcOH (3 ml) with 3 equiv of sulfuryl chloride (0.3 ml) at 25° for 30 min and worked up as for XI, 80 mg of 6-carboxypurine,[5,24] mp 200° dec, was isolated.

Reaction of XII with H_2NNH_2. A solution of XII (23 mg, 0.1 mmol) in 10% aqueous H_2NNH_2 (3 ml) was heated at 70° for 15 min. A product (11 mg) was obtained which was identical with the known 6-formylpurine hydrazone (I).[5] The same results were obtained when the reaction was carried out at 25° for several days.

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Synthesis and Inhibitory Activity of New Ethylenedioxyquinones as Analogs of Coenzyme Q†

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A new series of analogs of coenzyme Q, 2,3-ethylenedioxy-5-hydroxy-6-alkyl-1,4-benzoquinones, has been synthesized on the basis of the minor differences in the electronic and rotational nature between the 2,3-ethylenedioxy group and 2,3-dimethoxy groups. These differences could affect the redox potential of the 1,4-benzoquinone and, in turn, affect inhibitory activity. The 6-alkyl groups were farnesyl, phytyl, nonyl, decyl, pentadecyl, heptadecyl, and 5′-(cyclohexyl)pentyl. The succinoxidase and DPNH-oxidase systems of intact mitochondria from beef heart were used in tests for inhibition. The nonyl, decyl, pentadecyl, and farnesyl analogs showed inhibitions of less than 40%; and the phytyl, heptadecyl, and 5′-(cyclohexyl)pentyl analogs showed inhibitions of about 50% in succinoxidase. All the analogs were less inhibitory in DPNH-oxidase. 2,3-Dimethoxy-5-hydroxy-6-*n*-pentadecyl-1,4-benzoquinone showed 91% inhibition at a concentration of 97 nmol of inhibitor/mg of mitochondrial protein, while 2,3-ethylenedioxy-5-hydroxy-6-*n*-pentadecyl-1,4-benzoquinone exhibited only 37% inhibition at the higher concentration of 140 nmol of inhibitor/mg of mitochondrial protein in the succinoxidase system. Similarly, this 2,3-dimethoxyquinone was a more potent inhibitor in DPNH-oxidase than the corresponding 2,3-ethylenedioxyquinone. Apparently, 2,3-dimethoxy groups are more favorable than the 2,3-ethylenedioxy group on the 5-hydroxy-6-alkyl-1,4-benzoquinone nucleus for inhibition of these two CoQ oxidases.

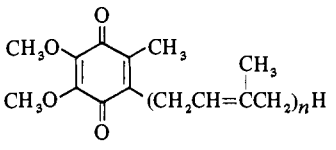
Coenzyme Q (I) is intrinsically involved in oxidative metabolism as a component of the electron-transfer process and coupled oxidative phosphorylation. Active enzyme sites for coenzyme Q are in succinoxidase,[1] DPNH-oxidase,[1] and α-glycerol phosphate dehydrogenase[2] of mitochondria. Coenzyme Q was reported to have a regulatory role and to be necessary for the interaction of succinate dehydrogenase and DPNH-dehydrogenase, respectively, with the cyto-

†Coenzyme Q. 165. Antimetabolites of Coenzyme Q. 18.

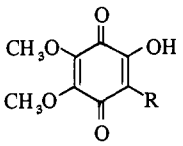
chrome system.[3] The vitamin activity of coenzyme Q has been observed for several mammalian species on deficient diets including the rabbit,[4] monkey,[5] rat,[6] chicken and turkey,[7] and hamster.[8]

The indispensable biochemical role of coenzyme Q in electron-transfer mechanisms and the vitamin activity in several mammalian species including man[9] constitute a basis for our continuing synthesis of analogs of coenzyme Q as potential antimetabolites of coenzyme Q. Some analogs[10,11] have already exhibited antimetabolite activity in CoQ enzyme systems. Some of these analogs have shown a therapeutic activity *in vivo*[12] which is a curative antimalarial activity in mice and without toxicity at effective dose levels.[13-15] This progress on the therapeutic activity of antimetabolites of coenzyme Q in a disease system justifies continuing syntheses of new analogs and biological tests on them for additional leads, *in vivo*, of therapeutic promise.

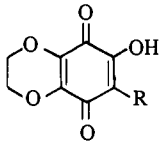
It was decided to investigate the effect of a minor structural modification on the antimetabolite activity of a series of known inhibitors of coenzyme Q, the 2,3-dimethoxy-5-hydroxy-6-alkyl-1,4-benzoquinones[16] (II). This modification constitutes a series of 2,3-ethylenedioxy-5-hydroxy-6-alkyl-1,4-benzoquinones (III), in which the conformationally flexible 2,3-dimethoxy groups of type II are incorporated into a relatively rigid 1,4-diox-2-ene ring structure. The new quinones would probably exhibit oxidation-reduction potentials different from corresponding 2,3-dimethoxy-1,4-benzoquinones and, consequently, could show different biological activity.



I, n = 1-10



II, R = isoprenyl or n-alkyl

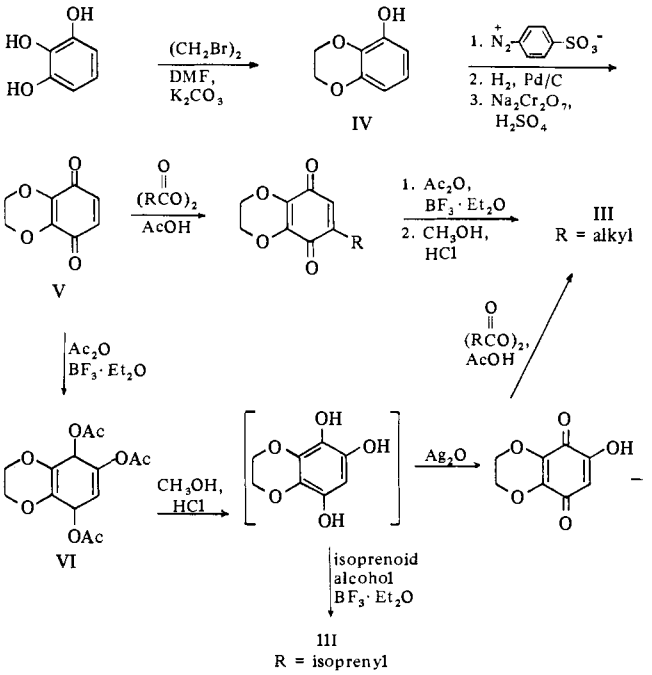


III, R = isoprenyl or n-alkyl

The pathway for synthesis of III is shown in Scheme I. 2,3-Ethylenedioxyphenol (IV) was obtained in an improved synthesis from 1,2-dibromoethane and pyrogallol in the presence of anhydrous K_2CO_3 and DMF. Pure IV was readily obtained by vacuum distillation. The parent quinone, 2,3-ethylenedioxy-1,4-benzoquinone (V), a new compound, was prepared from IV by the method of Smith, *et al.*[17] Coupling with diazotized sulfanilic acid gave the azo dye which was catalytically reduced. Subsequent oxidation of the aminophenol with $Na_2Cr_2O_7$ in H_2SO_4 gave the quinone V. Treatment of V with Ac_2O and BF_3·etherate gave the crystalline 1,4,5-triacetoxybenzene (VI) in good yield. VI was easily hydrolyzed to the substituted trihydroxybenzene by warming a methanol solution under N_2 with a catalytic amount of HCl.

At this stage in the sequence, two methods of alkylation were employed. Acid-catalyzed alkylation by BF_3·etherate with the appropriate isoprenoid alcohol was carried out in a dioxane solution on the immediately produced trihydroxybenzene and afforded the 6-farnesyl and 6-phytyl compounds III after oxidation. When analogs were synthesized where the 6-alkyl group was nonisoprenoid, the trihydroxybenzene was oxidized to the quinone with Ag_2O prior to

Scheme I. Synthesis of Ethylenedioxyquinones



alkylation. Radical alkylation was carried out by the thermal decomposition of the appropriate diacyl peroxide in AcOH at 90°. It was found that the yield could be maximized by careful monitoring *via* tlc of the appearance of the product. In the case of the n-decyl analog, the yield was improved by the use of MeCN as the reaction solvent.

In both methods, complex reaction mixtures were formed, and the desired products were obtained only after extensive chromatography. Preparative tlc on silica gel G revealed purple bands which were eluted from the silica gel with ether. Concentration of the ethereal solutions afforded the quinones as bright red residues. These 6-n-alkyl-substituted quinones were separated from the alkylating acids in the residues by fractional recrystallization from MeOH and from $CHCl_3$–hexane. The major contaminant of the 6-isoprenyl-quinones was the alkylating alcohol which was best removed by chromatography on a column of Florisil. The hydroxyquinones formed a purple complex with the Florisil and were finally eluted from the column with 5% AcOH in ether. The dark red oils obtained on removal of solvent were rechromatographed on deactivated silica gel using the dry column technique.[18] The purple bands were isolated, and the material yielded the pure quinones (Table I).

The 2,3-ethylenedioxy-5-hydroxy-6-alkyl-1,4-benzoquinones were characterized by C and H analyses and nmr and mass spectra. These compounds are readily recognizable as a class by their distinct nmr spectra. The ethylenedioxy bridge protons give a single resonance peak at τ 5.7. The protons attached to the first carbon of the 6-alkyl chain, allylic to the quinoid double bond, give a characteristic triplet at τ 7.7 for the n-alkyl analogs and a doublet, shifted downfield, at τ 7.0 for the isoprenoid analogs.

In an alternate synthetic route, which provided additional structure proof, the parent quinone V was alkylated with dipalmityl peroxide to give the bright orange 2,3-ethylenedioxy-5-n-pentadecyl-1,4-benzoquinone. Reaction with acetic anhydride and boron trifluoride etherate and subsequent hydrolysis and air oxidation yielded 2,3 ethylenedioxy-5-hydroxy-6-n-pentadecyl-1,4-benzoquinone; this product and the one obtained from the other reaction sequence were identical. Although the yield of the acetylation

reaction was low, probably due to steric hindrance, this alternate synthesis may be preferable in cases where the separation of the final product from the alkylating acid is difficult. This separation can be accomplished more readily from the neutral, more stable 2,3-ethylenedioxy-5-alkyl-1,4-benzoquinone prior to acetylation.

Studies, *in vitro*, of the antimetabolite activity of the quinones III as inhibitors of the respiratory enzyme systems, DPNH-oxidase and succinoxidase, in mitochondria from beef heart have been made. Inhibition of respiration was determined manometrically,[19] and specific activities were calculated in microatoms of uptake of oxygen per minute per milligram of mitochondrial protein.[19] The data in Table II express the antimetabolite activity as per cent inhibition at the concentration of the analog which was tested.

Inhibitions of less than 40% were found for the nonyl, decyl, pentadecyl, and farnesyl analogs in succinoxidase. In this system, the greatest inhibition was about 50% and was observed for the phytyl, *n*-heptadecyl, and 5'-(cyclohexyl)pentyl analogs. The analogs were less inhibitory in the DPNH-oxidase system than in succinoxidase. A comparison (Table II) can be made between the inhibitions of the dimethoxypentadecyl analog II[16] and III; in principle, this comparison is between 2,3-dimethoxy and 2,3-ethylenedioxy groups. A concentration of 32 nmol/mg of protein of 2,3-dimethoxy-5-hydroxy-6-*n*-pentadecyl-1,4-benzoquinone gave 72% inhibition of oxygen uptake, and 65 nmol/mg increased the inhibition to about 90% which appeared to be a constant level of maximum inhibition. Increasing the concentration of the 2,3-ethylenedioxy-5-hydroxy-6-*n*-pentadecyl-1,4-benzoquinone III from 100 to 205 nmol/mg gave a little increase of inhibition, but the inhibition was only 30–37%. Comparing the inhibition of the two compounds at 100 nmol/mg in succinoxidase, the 2,3-ethylenedioxyquinone showed about one-third of the inhibition of the 2,3-dimethoxyquinone. Replacement of the dimethoxy groups of inhibitors of coenzyme Q of type II by a 1,4-dioxane ring (III) resulted in a reduction of inhibitory activity in these systems.

Table I. Characterization of 2,3-Ethylenedioxy-5-hydroxy-6-alkyl-1,4-benzoquinones

Formulas[a]	6-Alkyl	Mp, °C	Mass spectra,[b] M^+
$C_{17}H_{24}O_5$	*n*-Nonyl	139	308
$C_{18}H_{26}O_5$	*n*-Decyl	138	322
$C_{19}H_{26}O_5$	5'-(Cyclohexyl)pentyl	136–137	334
$C_{23}H_{26}O_5$	*n*-Pentadecyl	135–136	392
$C_{25}H_{40}O_5$	*n*-Heptadecyl	132–133	420
$C_{23}H_{30}O_5$[c,e]	Farnesyl		365
$C_{28}H_{44}O_5$[d,e]	Phytyl		460

[a] Analytical results for C and H were within ±0.4% of the theoretical values except when otherwise specified. [b] Molecular ions obtained from low-resolution mass spectra are in accord with the proposed formulas. [c] C: calcd, 71.38; found, 70.87. H: calcd, 9.60; found, 9.89. [d] C: calcd, 72.99; found, 74.92. H: calcd, 9.65; found, 10.89 (no impurities were spectroscopically detectable). [e] Analytical sample was obtained by extraction from silica gel with Et_2O.

Experimental Section

Melting points are uncorrected and were determined in a Thomas-Hoover melting point apparatus. Nmr spectra were obtained in $CDCl_3$ with a Varian No. 60A and are in accord with the assigned structure. Where analyses are indicated only by symbols of elements, analytical results obtained for these elements are within 0.4% of the theoretical values. Mass spectra (70 eV) were obtained on a CEC 21-491 mass spectrometer.

2,3-Ethylenedioxyphenol (IV). A mixture of pyrogallol (126 g, 1.0 mol) and anhydrous K_2CO_3 (138 g, 1.0 mol) in 500 ml of anhydrous DMF at 60° was stirred under N_2 for 2 hr. 1,2-Dibromoethane (188 g, 1.0 mol) was added dropwise over a 4-hr period. The reaction mixture was stirred for 2 hr, cooled, and filtered. The filtrate was concentrated *in vacuo*, diluted with 200 ml of H_2O, acidified (HCl), and extracted with benzene. The extracts were washed, dried (Na_2SO_4), and concentrated. Vacuum distillation of the residue gave 52 g (34%) of colorless oil,[20] bp 110–115° (3.0 mm).

2,3-Ethylenedioxy-1,4-benzoquinone (V). Coupling of 2,3-ethylenedioxyphenol (24.4 g, 0.16 mol) with diazotized sulfanilic acid (0.2 mol) according to the procedure of Fieser[21] afforded a

Table II. Inhibitions by 2,3-Ethylenedioxyquinones in the DPNH-oxidase and Succinoxidase Systems

	Intact mitochondrial systems[c]			
	Succinoxidase		DPNH-oxidase	
Compd, R =	Concn[a] level	% inhibition[b]	Concn[a] level	% inhibition[b]
III, nonyl	67	10	120	22
	130	24	180	24
	200	24		
III, decyl	125	21	100	26
	170	30	150	35
	250	34		
III, 5'-(cyclohexyl)pentyl	50	22	100	26
	115	40	150	45
	150	60		
III, pentadecyl	100	30	100	34
	140	37	205	35
	205	37		
III, heptadecyl	60	29	60	25
	120	45	100	37
	180	50	130	33
III, phytyl	64	34	64	22
	190	45	130	43
			190	59
III, farnesyl	130	23	130	0
	190	24	190	10
II, pentadecyl	32	72	32	61
	65	86	65	72
	97	91	130	74
	205	90	190	79

[a] Concentration of inhibitor is expressed in nmol/mg of mitochondrial protein. [b] Activity of the enzyme system was determined in microatoms of oxygen uptake per minute per milligram of protein. The per cent inhibition is equivalent to (specific activity of test system/specific activity of control system) × 100%. The general methodology has been described.[19] [c] Reference 15.

dark reddish brown suspension of the azo compound. With continued mechanical stirring, NaOH amounting to 2% of the reaction volume was added and at least 3 equiv of $Na_2S_2O_4$ was added portionwise until the solution became light yellow in color. Extraction with CH_2Cl_2, drying the organic layer (Na_2SO_4), and removal of solvent gave a tan residue which darkened upon standing. Oxidation according to the method used in the preparation of 2,3-dimethoxy-1,4-benzoquinone reported by Catlin, *et al.*,[16] yielded 8.1 g (30%) 2,3-ethylenedioxy-1,4-benzoquinone. The brick red material was recrystallized from EtOH and had mp 153–154°. *Anal.* ($C_8H_6O_4$) C, H.

1,4,5-Triacetoxy-2,3-ethylenedioxy-1,4-benzoquinone (VI). A solution of 10 g (60.2 mmol) of 2,3-ethylenedioxy-1,4-benzoquinone in 30 ml of Ac_2O and 0.5 ml of BF_3·etherate was stirred for 24 hr at 25°. The reaction mixture was poured onto 50 ml of ice H_2O, and the triacetate was collected by filtration. After recrystallization from MeOH, the yield was 15 g (80%), mp 134°. *Anal.* ($C_{14}H_{14}O_8$) C, H.

2,3-Ethylenedioxy-5-hydroxy-6-alkyl-1,4-benzoquinones (III). The triacetate (5 g, 16.1 mmol) was hydrolyzed to the trihydroxy compound in 80 ml of anhydrous MeOH and 8 ml of HCl at 50° by stirring for 20 min under N_2. This solution was concentrated *in vacuo* prior to alkylation.

A. Acid-catalyzed alkylation was carried out by stirring a solution of the trihydroxy compound in dry dioxane and 1.0 ml of $BF_3 \cdot Et_2O$ with 1 equiv of the isoprenoid alcohol for 12 hr at 25° under N_2. The mixture was poured into H_2O and extracted with Et_2O. The Et_2O extracts were shaken with a solution of $FeCl_3$ (2 equiv) in H_2O–MeOH (1:1). The Et_2O layer was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*, leaving a dark brown oil. Chromatography on Florisil with successive elution with Et_2O and Et_2O–EtOH (1:1) removed yellow by-products. The hydroxyquinones formed a purple complex on the Florisil, which could be removed with 5% AcOH in Et_2O. The solvent was concentrated *in vacuo*. The dark red oil was chromatographed on deactivated silica gel using the dry column technique.[18] Elution with a mixture of Et_2O–petroleum ether separated a purple band which was cut out and washed with CH_2Cl_2. Removal of the solvent, *in vacuo*, gave the purified products as dark red waxy solids. A second chromatography on the silica gel column provided the analytical samples.

B. Prior to radical alkylation, the trihydroxy compound (0.01 mol) was oxidized to the benzoquinone by stirring for 30 min with 4 g (17.3 mmol) of Ag_2O and 4 g (28.2 mmol) of anhydrous Na_2SO_4 in 100 ml of Et_2O. This mixture was filtered and concentrated. To a solution of the residue in 100 ml of AcOH at 90°, 0.02 mol of the appropriate diacyl peroxide (prepared by treatment of a C_6H_6 solution of the acid chloride with H_2O_2 and pyridine)[22] was added portionwise over a 3-hr period. The solution was maintained at 95° for 6 hr and cooled, and the AcOH was evaporated. The concentrated hexane extracts of the residue were purified by tlc. The product was separated from the alkylating acid by fractional crystallization from MeOH and from hexane–$CHCl_3$.

2,3-Ethylenedioxy-5-hydroxy-6-*n*-pentadecyl-1,4-benzoquinone. 2,3-Ethylenedioxy-1,4-benzoquinone was alkylated with dipalmityl peroxide by the radical alkylation procedure. The orange product was isolated by column chromatography on silica acid eluted with $CHCl_3$. Recrystallization from MeOH afforded 2,3-ethylenedioxy-5-*n*-pentadecyl-1,4-benzoquinone, mp 88–89°. *Anal.* ($C_{23}H_{36}O_4$) C, H. Treatment with Ac_2O and BF_3·etherate gave the triacetate. Hydrolysis in MeOH–HCl afforded 2,3-ethylenedioxy-5-hydroxy-6-*n*-pentadecyl-1,4-benzoquinone which was identical with that obtained by the alternate synthetic pathway.

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