New Substituted 2,3-Dimethoxy-1,4-benzoquinones as Inhibitors of Coenzyme Q Systems[1]

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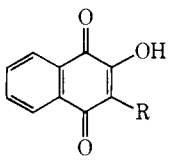
New coenzyme Q analogs have been synthesized in which the 5-Me function is replaced by OH, MeO, Cl, and Br. The alkyl groups in the 6 position of the 2,3-dimethoxy-5-hydroxy-1,4-benzoquinones are: geranyl, farnesyl, tetraprenyl, solanesyl, decaprenyl, phytyl, dihydrophytyl, pentadecyl, heptadecyl, nonadecyl, and 8′,11′,14′-(heptadecatrienyl)- and 8′-(cyclohexyl)octyl. The phytyl derivatives of 2,3,5-trimethoxy-, 2,3-dimethoxy-5-chloro- and -bromo-1,4-benzoquinones, and the dihydrophytyl and 8′,11′,14′-(heptadecatrienyl) derivatives of 2,3-dimethoxy-5-chloro-1,4-benzoquinones were also synthesized. Some of these new analogs of coenzyme Q have already shown inhibition of biochemical systems containing coenzyme Q and are of interest for further studies in both *in vitro* and *in vivo* systems.

2-Hydroxy-3-alkyl-1,4-naphthoquinones (I) were reported 20 years ago to have antimalarial activity against *Plasmodium lophurae* in ducks.[2] Certain of these compounds had also undergone clinical trials and were found to exhibit antimalarial activity in man. This research on naphthoquinones is being newly extended, and additional 2-hydroxy-3-alkyl-1,4-naphthoquinones have been prepared,[3] and other investigators are progressing toward the preparation of quinones containing other bicyclic ring systems.[4]



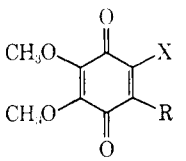
I

Some 2-hydroxy-3-alkyl-1,4-napthoquinones (I) are inhibitors of respiration and it was reported that this activity is due to inhibition of succinate oxidase in the region between cytochromes *b* and *c* in the electron transport chain. The suggestion was made by Ball, *et al.*,[5] that I inhibits an enzyme or enzymes between cytochromes *b* and *c*. Coenzyme Q may function in this region of the electron transport chain[6] or in two alternative sites as reported recently by Lenaz, *et al.*[7a] The inhibition of succinate oxidase by I can be reversed partially by CoQ_{10} according to Hendlin and Cook.[7b]

Heymann and Fieser,[8] after comparing the inhibition of succinate oxidase by various 2-hydroxy-3-alkyl-1,4-napthoquinones with their *in vivo* activity against *P. lophurae* concluded: "Activity in the inhibition of the succinate oxidase system does not appear to provide a reliable guide to antimalarial activity *in vivo*." This lack of correlation between inhibition of the succinate oxidase system and antimalarial activity *in vivo* may be due to differences in the transport of the compounds to the enzyme sites or due to an importance of DPNH-oxidase which is greater than that of succinate oxidase or due to the importance of the biosynthetic sites. It has been shown recently[9] that a naphthoquinone antimalarial does inhibit both the succinate oxidase and DPNH-oxidase systems which do involve coenzyme Q. While the mode of antimalarial activity of these particular naphthoquinones is not established, it is apparent today that they might act by inhibiting the function of coenzyme Q or its biosynthesis.

The occurrence of coenzymes Q_8 and Q_9 in *P. lophurae* was recently discovered by isolation of the compounds by Rietz, *et al.*[10] Coenzyme Q_8 was found to be the dominant CoQ in *P. knowlesi*, *P. cynomolgi*, and *P. berghei*.[11] These results were confirmed by the isolation and identification of ^{14}C-labeled coenzyme Q_8 and Q_9 from *in vitro* cultures of the blood of Rhesus monkeys infected with *P. knowlesi*[12] and *P. falciparum*.[13]

As an approach to new antimalarials which might be effective inhibitors of the functionality or the biosynthesis of coenzyme Q, we have synthesized some new analogs of coenzyme Q in which the 5-Me group is replaced by OH, MeO, Cl, and Br (IIa,b,c,d) groups.



IIa, X = OH
b, X = OCH_3
c, X = Cl
d, X = Br

Even if inhibition of the function or biosynthesis of coenzyme Q and antimalarial activity are not correlated, compounds of structural type II may still have anti-

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(1) Coenzyme Q. 124.

(2) See L. F. Fieser, *et al.*, *J. Amer. Chem. Soc.*, **70**, 3151 (1948).

(3) L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Loreny, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967).

(4) G. R. Pettit, W. C. Fleming, and K. D. Paull, *J. Org. Chem.*, **33**, 1089 (1968).

(5) E. G. Ball, C. B. Anfinsen, and O. Cooper, *J. Biol. Chem.*, **168**, 257 (1947).

(6) M. E. Pullman and G. Schatz, *Annu. Rev. Biochem.*, 54 (1967).

(7) (a) G. Lenaz, G. Doyle Daves, Jr., and K. Folkers, *Arch. Biochim. Biophys.*, **123**, 539 (1968); (b) D. Hendlin and T. M. Cook, *Biochem. Biophys. Res. Commun.*, **2**, 71 (1960).

(8) H. Heymann and L. F. Fieser, *J. Biol. Chem.*, **176**, 1359 (1968).

(9) F. S. Skelton, R. S. Pardini, J. C. Heidker, and K. Folkers, *J. Amer. Chem. Soc.*, **90**, 5334 (1968).

(10) P. J. Rietz, F. S. Skelton, and K. Folkers, *Int. Z. Vitaminforsch.*, **37**, 405 (1967).

(11) F. S. Skelton, P. J. Rietz, and K. Folkers, *J. Med. Chem.*, **13**, 602 (1970).

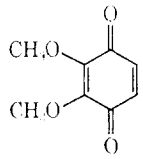
(12) F. S. Skelton, K. D. Lunan, K. Folkers, J. V. Schnell, W. A. Siddiqui, and Q. M. Geiman, *Biochemistry*, **8**, 1284 (1969).

(13) J. V. Schnell, W. A. Siddiqui, Q. M. Geiman, F. S. Skelton, K. D. Lunan, and K. Folkers, *J. Parasitol.*, in press (1970).

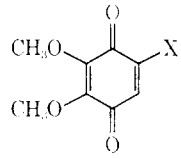
malarial activity due to other biological mechanisms. Compounds of type II are also of interest for other studies on the fundamental biochemistry of coenzyme Q.

Recently, a 2-methoxy-5-hydroxy-6-alkyl-1,4-benzoquinone has been isolated from Myrsinaceae plants.[14]

Our synthesis of these new 5-hydroxy analogs of coenzyme Q, IIa, and preliminary data on the inhibitory activity of some of these analogs in systems of coenzyme Q have been communicated.[15] A synthesis of 2,3-dimethoxy-1,4-benzoquinone (III) has been improved, and procedures are described for the conversion of III into 2,3-dimethoxy-5-substituted-1,4-benzoquinones (IVa,b,c,d). Alkylation of the 2,3-dimethoxy-5-substituted-1,4-benzoquinones or benzohydroquinones gave the desired 2,3-dimethoxy-5-hydroxy-, methoxy-, chloro-, or bromo-6-alkyl-1,4-benzoquinones (IIa,b,c,d).



III

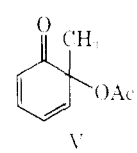


IV

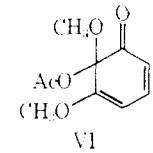
a. X = OH
b. X = OCH_3
c. X = Cl
d. X = Br

2,3-Dimethoxy-1,4-benzoquinone (III) has been prepared previously by a variety of procedures including a long sequence from pyrogallol[16] and the oxidation of 2,3-dimethoxyphenol by a persulfate method[17] or with potassium nitrodisulfonate (Fremy's salt).[18,19] These procedures gave poor yields and the Fremy's salt oxidation seemed particularly sensitive to the reaction conditions.

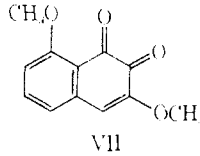
The oxidations[20] of guaiacol and 2,6-dimethoxyphenol with $Pb(OAc)_4$ gave the corresponding quinones in yields of 57 and 78%. The oxidation of *o*-cresol[21] gave only a 2% yield of toluquinone and a 22% yield of cyclohexadienone V. We found that oxidation of 2,3-dimethoxyphenol with $Pb(OAc)_4$ with either AcOH or $CHCl_3$ as solvent gave a cyclohexadienone (VI) as the major product, and none of the desired quinone, III, could be detected. By a combination of column chromatography and tlc, it was possible to isolate a quinone from the reaction mixture. This quinone, VII, has been previously prepared by Adler, *et al.*, by the periodate oxidation of 3-methoxycatechol[22] (see Table II for the spectra of VI and VII). As predicted, VI rearranged to 2,3-dimethoxy-4,5-diacetoxybenzene upon treatment with acidic Ac_2O.[23]



V



VI



VII

We found that 2,3-dimethoxy-1,4-benzoquinone (III) can be regularly prepared in at least a 40% yield and in acceptable purity by the method of Smith, *et al.*[24] In this procedure, diazotized sulfanilic acid is coupled with the appropriate phenol; the coupling product is reduced to an aminophenol and oxidized to the quinone. We isolated the coupling product, reduced it catalytically (Pd–C), and oxidized the aminophenol with CrO_3.

Thiele–Winter acetylation of 2,3-dimethoxy-1,4-benzoquinone (III) gives 2,3-dimethoxy-1,4,5-triacetoxybenzene which can be hydrolyzed in acidic MeOH to 2,3-dimethoxy-5-hydroxy-1,4-benzohydroquinone ($IVa \cdot H_2$). When BF_3·etherate was used in place of H_2SO_4[25] for catalysis, the acetylation reaction occurred in higher yield and there was less side reaction. Using HCl in place of H_2SO_4 in the hydrolysis of the triacetate increased the recovery of the product since less washing was required. The hydroquinone ($IVa \cdot H_2$) was converted into 2,3-dimethoxy-5-hydroxy-1,4-benzoquinone (IVa) by treatment with Ag_2O.

2,3,5-Trimethoxy-1,4-benzoquinone (IVb) was prepared in good yield by reaction of IVa with CH_2N_2. The procedure of Huisman[26] to obtain IVb is equally satisfactory. Pyrogallol is converted to 2,6-dimethoxy-1,4-benzoquinone which is then chlorinated; the 2-chloro-3,5-dimethoxy-1,4-benzoquinone is converted into IVb with NaOMe.[26]

2,3-Dimethoxy-5-chloro-1,4-benzoquinone (IVc) and 2,3-dimethoxy-5-bromo-1,4-benzoquinone (IVd) were prepared by addition of HCl and HBr to 2,3-dimethoxy-1,4-benzoquinone (III) followed by oxidation of the resulting hydroquinones ($IVc \cdot H_2$, $IVd \cdot H_2$). This procedure gave a good yield of IVc after recrystallization; IVd was obtained in poor yield. It is likely that IVd could be more satisfactorily prepared by addition of Br_2 to $III \cdot H_2$.[27] The halohydroquinones, $IVc \cdot H_2$ and $IVd \cdot H_2$, were prepared when needed from the corresponding quinones by catalytic reduction.

The alkylquinones (IIa,b,c,d) were prepared from the appropriate hydroquinones ($IVa,b,c,d \cdot H_2$) or quinones (IVa,b,c,d) by two alkylation procedures. The isoprenoid quinones (R = geranyl, farnesyl, tetraprenyl, solanesyl, decaprenyl, and phytyl) were prepared by the acid-catalyzed ($BF_3 \cdot OEt_2$) alkylation[28] of the appropriate hydroquinone with an allylic alcohol to yield the quinone. Alkyl quinones without allylic unsaturation [R = pentadecyl, heptadecyl, nonadecyl, 8′,11′,14′-heptadecatrienyl and 8′-(cyclohexyl)octyl] were synthesized by the thermal decomposition of the appropriate diacylperoxide[29] in the presence of the desired quinone.[3] When the radical alkylation procedure

(14) H. Ogawa, S. Sakaki, K. Yoshihira, and S. Natori, *Tetrahedron Lett.*, 1387 (1968).
(15) J. C. Catlin, R. S. Pardini, G. D. Daves, Jr., J. C. Heidker, and K. Folkers, *J. Amer. Chem. Soc.*, **90**, 3574 (1968).
(16) W. Baker and H. A. Smith, *J. Chem. Soc.*, 2542 (1931).
(17) W. Baker and R. I. Savage, *ibid.*, 1602 (1938).
(18) F. Weygand, H. Weber, and E. Maekawa, *Chem. Ber.*, **90**, 1879 (1957).
(19) L. M. Weinstock, R. Tull, B. Handelsman, and E. F. Schoenewaldt, *J. Chem. Eng. Data*, **12**, 154 (1967).
(20) F. Wessely and J. Kotlan, *Monatsh. Chem.*, **84**, 291 (1953).
(21) F. Wessely and F. Sinwel, *ibid.*, **81**, 1055 (1950).
(22) (a) E. Adler, R. Magnusson, B. Berggren, and H. Thomelius, *Acta Chem. Scand.*, **14**, 515 (1960); (b) B. Sklary, *Quart. Rev.*, **21**, 3 (1967).
(23) H. Budzikiewicz, W. Metlesics, and F. Wessely, *Monatsh. Chem.*, **91**, 117 (1960).
(24) (a) L. I. Smith, J. W. Opie, S. Wawzonek, and W. W. Prichard, *J. Org. Chem.*, **4**, 318 (1939); (b) L. I. Smith and W. B. Irwin, *J. Amer. Chem. Soc.*, **63**, 1036 (1941).
(25) W. K. Anslow and H. Raistrick, *J. Chem. Soc.*, 1446 (1939).
(26) H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **69**, 1133 (1950).
(27) D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz, *J. Chem. Soc.*, 1600 (1958).
(28) G. D. Daves, Jr. H. W. Moore, D. E. Schwab, R. K. Olsen, J. J. Wilczynski, and K. Folkers, *J. Org. Chem.*, **32**, 1414 (1967).
(29) L. S. Silbert and D. Swern, *J. Amer. Chem. Soc.*, **81**, 2364 (1959).

TABLE I

SPECTRAL DATA OF 2,3-DIMETHOXY-5-SUBSTITUTED-6-ALKYL-1,4-BENZOQUINONES

Empirical formulas	6-Alkyl	5-Group	Uv λ_{max}^{EtOH} (mμ)	Nmr[a] spectra				
				Vinyl	Methoxyls		Benzylic	Alkyl
$C_{18}H_{24}O_5$	Geranyl	OH	298	5.0 (m)	6.00 (s)	6.17 (s)	7.02 (d)	8.0–9.0 (m)
$C_{23}H_{32}O_5$	Farnesyl	OH	297	5.0 (m)	6.00 (s)	6.16 (s)	7.00 (d)	7.7–9.0 (m)
$C_{28}H_{40}O_5$	Tetraprenyl	OH	297	5.0 (m)	6.00 (s)	6.16 (s)	7.00 (d)	7.7–9.0 (m)
$C_{53}H_{80}O_5$	Solanesyl	OH	297	4.98 (m)	6.00 (s)	6.16 (s)	7.00 (d)	7.7–9.0 (m)
$C_{58}H_{88}O_5$	Decaprenyl	OH	297	4.98 (m)	6.00 (s)	6.16 (s)	7.00 (d)	7.8–9.0 (m)
$C_{28}H_{46}O_5$	Phytyl	OH	297	4.98 (t)	5.98 (s)	6.14 (s)	6.99 (d)	7.6–9.3 (m)
$C_{29}H_{48}O_5$	Phytyl	OCH_3	288	5.08 (m)	6.08 (s)	6.10 (s)	7.10 (d)	8.0–9.3 (m)
					6.15 (s)			
$C_{28}H_{45}O_4Cl$	Phytyl	Cl	283	5.08 (m)	6.09 (s)	6.08 (s)	6.78 (d)	8.0–9.4 (m)
$C_{28}H_{45}O_4Br$	Phytyl	Br	292	5.07 (m)	6.10 (s)		6.73 (d)	8.0–9.3 (m)
$C_{28}H_{48}O_5$	Dihydrophytyl	OH	297		5.98 (s)	6.16 (s)	7.00 (d)	7.4–9.4 (m)
$C_{28}H_{47}O_4Cl$	Dihydrophytyl	Cl	*b*		6.06 (s)		7.46 (m)	8.2–9.3 (m)
$C_{23}H_{38}O_5$	Pentadecyl	OH	299		6.00 (s)	6.15 (s)	7.68 (m)	8.5–9.3 (m)
$C_{25}H_{42}O_5$	Heptadecyl	OH	297		6.00 (s)	6.15 (s)	7.72 (m)	8.4–9.5 (m)
$C_{27}H_{46}O_5$	Nonadecyl	OH	299		6.01 (s)	6.18 (s)	7.70 (m)	8.4–9.5 (m)
$C_{25}H_{36}O_5$	8′,11′,14′-Heptadecatrienyl	OH	299	4.75 (m)	5.99 (s)	6.14 (s)	*c*	7.2–9.2 (m)
$C_{25}H_{35}O_4Cl$	8′,11′,14′-Heptadecatrienyl	Cl	285	4.75 (m)	6.08 (s)		*c*	7.10–9.2 (m)
$C_{22}H_{34}O_5$	8′-(Cyclohexyl)-octyl	OH	297		6.01 (s)	6.17 (s)	7.70 (m)	8.2–9.5 (m)

[a] Spectra were obtained in CCl_4 with a HR 100 spectrometer of Varian Associates. Values are in τ units. The letters in parentheses refer to peak shape: s = singlet, d = doublet, t = triplet, m = multiplet. [b] Value not available. [c] The absorption of the benzylic protons falls within the range of absorption of the alkyl protons.

was used with 2,3-dimethoxy-5-bromo-1,4-benzoquinone, the only alkylated quinone identified from the reaction had lost Br.

2,3-Dimethoxy-5-hydroxy-6-dihydrophytyl-1,4-benzoquinone (IIa) and 2,3-dimethoxy-5-chloro-6-dihydrophytyl-1,4-benzoquinone (IIc) have also been prepared. Catalytic reduction of IIa (R = phytyl) gave the dihydrophytyl derivative. IIc (R = dihydrophytyl) was prepared by addition of HCl to 1,2-dimethoxy-5-dihydrophytyl-1,4-benzoquinone.

The alkylquinones (IIa,b,c,d) were isolated by preparative tlc (silica gel G), column chromatography (silica gel), or by a combination of the 2 procedures. It was our experience that the R_f values varied from plate to plate, and were of minor help in the initial isolation of the desired quinones. The alkylation reactions gave quite complex mixtures of products, but by consideration of certain color tests and relative R_f values it was possible to locate easily the desired product and separate it from the side products. A final choice of which band was the desired product was made by comparison of no more than 2 or 3 nmr spectra.

Often, the undesired products were eliminated by the use of color tests. Hydroxyquinones, whether alkylated or not, are from yellow to red in color in organic solvents and violet in base (due to ionization of OH). When IIa or IVa is spotted on a silica gel G plate, a violet color is observed. Elution of the quinone restores the original color. This color behavior allowed an easy identification of 2,3-dimethoxy-5-hydroxy-6-alkyl-1,4-benzoquinone (IIa) from a chromatographic column. When tlc plates were used for the purification of IIa, two dark violet bands were observed; the lower one corresponded to the starting material (IVa) and the upper one contained the product, IIa. The upper band was scraped and eluted with Et_2O to yield a dark solution. When this solution was rechromatographed, the violet band, or bands, yielded solutions that were from yellow to red in color. In some cases, where 2 violet bands, excluding the starting material, were observed, the desired product was indicated by its spectrum. During chromatography, a portion of the 2,3-dimethoxy-5-hydroxy-6-alkyl-1,4-benzoquinone (IIa) decomposed to form a second violet material which has the same R_f as the desired quinone in the chromatography system used (silica gel G plates, 4:1 benzene–methanol). However, the desired quinone IIa was eluted preferentially with Et_2O, and the decomposition product was eluted with MeOH.

The alkylquinones with 5-MeO, Cl, and Br (IIb,c,d) were also purified on silica gel G plates. On these plates, the two largest yellow bands, both of which gave a positive leucomethylene blue test,[30] were the starting material and the alkylquinones (IIb,c,d).

As predicted, the hydroxyquinone (IIa) inhibits DPNH-oxidase and succinoxidase.[15] Knowledge of this enzyme inhibition could ultimately lead to new therapy of malaria, because it has been demonstrated that coenzyme Q_8 is biosynthesized by *Plasmodium knowlesi*, *P. cynomolgi*, and *P. berghei*.[11]

Experimental Section

General Comments.—The alkylated quinones, in which the lipoidal side chains contribute so significantly to their chemical nature, are characterized best by their nmr and uv spectra. The combination of nmr and uv spectra allow the unambiguous assignment of the structure to the alkylated quinones. Such unambiguous assignment is not true in the case of C and H analytical data. C and H analytical data were obtained on certain intermediates. When compounds described in the literature were prepared by new procedures, a comparison of the melting points with the appropriate literature values are recorded. The spectral data in Tables I and II are considered to be of significant value for the characterization of these unique lipoidal quinones.

Reaction of 2,3-Dimethoxyphenol with Lead Tetraacetate.—2,3-Dimethoxyphenol (5.0 g) was dissolved in 200 ml of glacial

(30) F. L. Crane and R. A. Dilley, *Methods Biochem. Anal.*, **11**, 279 (1963).

TABLE II

SPECTRA OF 2,3-DIMETHOXY-2-ACETOXY-3,4-CYCLOHEXADIENONE (VI) AND 3,8-DIMETHOXY-1,2-NAPHTHOQUINONE (VII)

	Uv λ_{max}^{ether} (mμ)	Nmr[a] MeO	Nmr[a] AcO	Nmr[a] Ring H
VI	300, 345	6.28 (s)	7.88 (s)	3.01 (J = 3.5)
$C_{10}H_{12}O_5$		6.58 (s)		4.18 (J = 5.0)
				3.01 (J = 3.5, 5.0)
VII	262, 364, 485	6.12 (s)		2.45 (J = 3.5, 0.5)
$C_{12}H_{10}O_4$		6.20 (s)		2.79 (J = 4, 3.5)
				2.96 (J = 4, 0.5)
				3.13 (s)

[a] See Table I for footnote *a*.

AcOH and 40 g of $Pb(OAc)_4$ was added with stirring. After standing overnight, the reaction mixture was diluted with 400 ml of H_2O, filtered and extd (Et_2O). The extract was washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on silica gel with C_6H_6–MeOH, 4:1–3:2 yielding 3 g of the cyclohexadienone (VI), and about 0.2 g of the naphthoquinone VII. The naphthoquinone VII was further purified by tlc on silica gel G plates using Et_2O as the solvent. When the reaction was carried out in 100 ml of $CHCl_3$ at the reflux temp for 1 hr, the cyclohexadienone was again obtained (see Table II for the spectra of VI and VII).

2,3-Dimethoxy-1,4-benzoquinone (III).—$NaNO_2$ (4.0 g) in H_2O (10 ml) was slowly added to a slurry of 10 g of sulfanilic acid in 50 ml of H_2O and 10 ml of HCl and chilled in an ice bath. The chilled mixture was stirred for 1 hr, and then added over 1 hr to a mixture of 6.0 g of 2,3-dimethoxyphenol and 8.0 g of NaOH in 50 ml of H_2O, which was chilled in ice. After standing overnight at room temperature, the soln was chilled in ice and acidified with HCl. The azo compound was collected by filtration and dried *in vacuo*. A slurry of the azo compound and 1.0 g of 10% Pd–C in 200 ml of EtOH and 5 ml of HCl was reduced in the Parr shaker for 30 min. The EtOH soln was evapd *in vacuo* and the oil obtained was added to a cold mixture of 27 ml of 12 *N* H_2SO_4 and 400 ml of ice–H_2O. To this mixture, was added a cold soln of 157 ml of 10% sodium dichromate and 42 ml of 12 *N* H_2SO_4. The aq soln was then extd repeatedly with $CHCl_3$. Evaporation of the $CHCl_3$ soln gave, after recrystn from hexane, 4.0 g (60%) of III ($C_8H_8O_4$).

When the reaction was repeated on 120 g of the phenol, 56 g (~40%) of III was obtained; after recrystn, it melted at 65–67° (lit.[16,17] mp 66–67°).

1,4,5-Trihydroxy-2,3-dimethoxybenzene.—A soln of 32 g of 2,3-dimethoxy-1,4-benzoquinone in 60 ml of Ac_2O and 1.0 ml of BF_3·etherate was allowed to stand at room temp for 24 hr. The reaction mixture was poured into twice its vol of ice–water; the triacetate was collected by filtration and washed (Et_2O). The yield was 46 g after drying *in vacuo*.

The triacetate ($C_{14}H_{16}O_8$), (10 g), mp 94–96° [after being washed with Et_2O (lit.[24] 95–97°)], was dissolved in a soln of 100 ml of MeOH and 10 ml of HCl. The soln was refluxed for 1 hr under N_2 and then evaporated and the residue was dried under vacuum to give 5.0 g of product ($C_8H_{10}O_5$).

2,3,5-Trimethoxy-1,4-benzoquinone (IVb).—An Et_2O soln of 12 g of 2,3-dimethoxy-5-hydroxy-1,4-benzohydroquinone was treated for 0.5 hr with 15 g of Ag_2O for oxidn and 15 g of Na_2SO_4 for drying. The mixture was filtered and treated with CH_2N_2 (from 20 g of *N*-nitrosomethylurea).[31] IVb ($C_9H_{10}O_5$) was purified by chromatography on silica gel and eluting with $CHCl_3$. The yield was 8.5 g, mp 158–159° (lit.[26] 160–161°).

2,3-Dimethoxy-5-chloro-1,4-benzoquinone.—To 40 ml of chilled concd HCl was added 20 g of 2,3-dimethoxy-1,4-benzoquinone. The reaction mixture was stirred for 1 hr, and then poured into 200 ml of H_2O and extd ($CHCl_3$). The $CHCl_3$ soln, 1500 ml of ice–water, and 150 ml of 12 *N* H_2SO_4 were placed in a separatory funnel. A soln of 48 g of $Na_2Cr_2O_7$ in 500 ml of H_2O and 100 ml of 12 *N* H_2SO_4 was added. The oxidn mixture was extd with $CHCl_3$. The $CHCl_3$ soln was evapd *in vacuo*. After recrystn from hexane, 13 g of the quinone was obtained, mp 69–70°. *Anal.* ($C_8H_7ClO_4$) C, H.

(31) F. Arndt, *Org. Syn.*, **2**, 165, footnote 3 (1943).

2,3-Dimethoxy-5-bromo-1,4-benzoquinone.—To 20 ml of concd HBr was added 10 g of 2,3-dimethoxy-1,4-benzoquinone. After standing at room temp for 1 hr, the reaction mixture was poured into H_2O and extd ($CHCl_3$). The $CHCl_3$ soln was dried (Na_2SO_4), then 30 g of Na_2SO_4 and 15 g of Ag_2O were added. After standing with occasional shaking for 1 hr, the soln was filtered and evapd *in vacuo*. Crystallization of the residue from hexane yielded 1.7 g of material. An analytical sample, mp 69–72°, was prepd by chromatography on silica gel G plates with development by 1:1 hexane–Et_2O. *Anal.* ($C_8H_7BrO_4$) C, H.

Alkylation of 2,3-Dimethoxy-5-substituted-1,4-benzohydroquinone (IVa,b,c,d). Acid-Catalyzed Alkylation.—To a soln of 0.01 mole of 2,3-dimethoxy-5-substituted-1,4-benzohydroquinone in 25 ml of dry dioxane was added 1 equiv of the appropriate isoprenoid alcohol (in certain cases where the alcohol was difficult to obtain, less than an equiv amt was used). To the well-stirred dioxane soln, protected by a drying tube, was added dropwise 1.5 ml of redistd BF_3·etherate. The reaction mixture was stirred for 2 hr and then poured into 100 ml of H_2O. The alkylation product was extd into Et_2O and the Et_2O soln was dried (Na_2SO_4) and concd *in vacuo*. The alkylation product was purified by tlc on silica gel plates using 4:1 C_6H_6–MeOH as solvent. The violet band was collected and eluted with Et_2O. The product could also be purified by column chromatography using hexane–Et_2O as solvent. The hydroxyhydroquinones were air-oxidized to the quinone during purification. The other quinones were oxidized (Ag_2O) before purification.

Radical Alkylation.—To 5 g of 2,3-dimethoxy-5-substituted-1,4-benzoquinone was added 0.05 mole of the appropriate diacyl peroxide (prepared by treatment of an Et_2O soln of the appropriate acid chloride with H_2O_2 and pyridine)[29] in 100 ml of AcOH, and the mixture was heated on the steam bath overnight. The AcOH was evaporated *in vacuo*, and the hexane extract was purified *via* column chromatography on silica gel, eluting with increasing fractions of Et_2O in hexane, or *via* tlc on silica gel G using 4:1 C_6H_6–MeOH as solvent.

2,3-Dimethoxy-5-hydroxy-6-dihydrophytyl-1,4-benzoquinone.—To a soln of 250 mg of 2,3-dimethoxy-5-hydroxy-6-phytyl-1,4-benzoquinone in 25 ml of EtOH, was added 100 mg of 10% Pd/C. The resulting mixture was shaken on the Parr apparatus under 2.46 kg of H_2/cm^2 for 3 hr. The reaction mixture was then filtered, and the soln was evapd to dryness *in vacuo*. The 2,3-dimethoxy-5-hydroxy-6-dihydrophytyl-1,4-benzohydroquinone was air-oxidized and purified by chromatography on silica gel G plates which were developed with 4:1 C_6H_6–MeOH. The quinone was eluted with Et_2O.

2,3-Dimethoxy-5-chloro-6-dihydrophytyl-1,4-benzoquinone.—HCl was bubbled through a $CHCl_3$ soln (2 ml) of 16 mg of 2,3-dimethoxy-5-dihydrophytyl-1,4-benzoquinone for 1 hr. The $CHCl_3$ was evaporated under N_2, and the chloroquinone was purified by chromatography on a silica gel G plate which was developed in 1:1 C_6H_6–$CHCl_3$.

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