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Ubiquinone and Related Compounds. XXVII.[1] Synthesis of Urinary Metabolites of Phylloquinone and α-Tocopherol[2]

Masazumi Watanabe, Mitsuru Kawada, Masao Nishikawa,
Isuke Imada, and Hiroshi Morimoto

Chemical Research Laboratories, Takeda Chemical Industries, Ltd.[3]

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The syntheses of the metabolites of phylloquinone, α-tocopherol and ubiquinones are described.

1. 2,3,5-Trimethyl-6-(3′-carboxybutyl)-1,4-benzoquinone (VIIa), 2-methyl-3-(3′-carboxybutyl)-1,4-naphthoquinone (VIIb) and 2,3-dimethoxy-5-methyl-6-(3′-carboxybutyl)-1,4-benzoquinone (VIIc) were synthesized by two routes. 2,3,5-Trimethylphenol (Ia) and 3-methyl-1-naphthol (Ib) were condensed with methylsuccinic anhydride (II), followed by reduction of the carbonyl groups and oxidation of the phenols to quinones (VIIa, VIIb). 2,3,5-Trimethyl-1,4-benzoquinone (XVIIIa), 2-methyl-1,4-naphthoquinone (XVIIIb) and 2,3-dimethoxy-5-methyl-1,4-benzoquinone (XVIIIc) were treated with γ,γ′-dimethoxycarbonylvaleryl peroxide (XVII) on one step to give the esters (VIIIa, VIIIb, VIIIc) of these quinones.

2. 2,3,5-Trimethyl-6-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XXVa), 2-methyl-3-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-naphthoquinone (XXVb) and 2,3-dimethoxy-5-methyl-6-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XXVc) were synthesized by boron trifluoride-catalyzed condensation of 2,3,5-trimethyl-1,4-benzohydroquinone (XXIIIa), 2-methyl-1,4-naphthohydroquinone derivatives (XXIIIb, XXVII, XXVIII) and 2,3-dimethoxy-5-methyl-1,4-benzohydroquinone (XXIIIc) with methyl ε-hydroxy-γ-methyl-γ-hexenoate (XX) or methyl γ-hydroxy-γ-vinylvalerate (XXII), followed by hydrolysis of the esters to carboxylic acids and subsequent oxidation of the hydroquinones to quinones.

We have isolated and characterized the metabolites of phylloquinone and α-tocopherol in rabbit urine dosed with these vitamins.[1] In this paper we report the syntheses of these metabolites and related compounds.

2,3,5-Trimethyl-6-(3′-carboxybutyl)-1,4-benzoquinone (VIIa), 2-Methyl-3-(3′-carboxybutyl)-1,4-naphthoquinone (VIIb) and 2,3-Dimethoxy-5-methyl-6-(3′-carboxybutyl)-1,4-benzoquinone (VIIc)

Proceeding *via* Friedel-Crafts Reaction (Chart 1)——2,3,5-Trimethylphenol (Ia) was condensed with methylsuccinic anhydride (II) in the presence of $AlCl_3$ to give α-methyl-β-(2-hydroxy-3,4,6-trimethylbenzoyl)propionic acid (IIIa, 27%) and its isomer, β-methyl-β-(2-hydroxy-3,4,6-trimethylbenzoyl)propionic acid (IV, 11%). IIIa was converted into α-methyl-γ-(2-hydroxy-3,4,6-trimethylphenyl)butyric acid (Va) by Clemmensen reduction. IV was similarly converted into β-methyl-γ-(2-hydroxy-3,4,6-trimethylphenyl)butyric acid (VI). Oxidation of Va with Fremy's salt by the method of Teuber and Jellinek[4] gave the desired VIIa as yellow plates, mp 79—81°.

Condensation of 3-methyl-1-naphthol (Ib) with II gave IIIb, mp 191—192°. Elevated temperature and longer reaction time gave not IIIb, but only a small amount of the product

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[1] Part XXVI: M. Watanabe, M. Toyoda, I. Imada, and H. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 176 (1974).

[2] H. Morimoto, M. Watanabe, I. Imada, and M. Nishikawa, *Ger. Offen*, 2104871 (1971) [*C.A.*, **75**, 140493m (1971)]; H. Morimoto, M. Watanabe, I. Imada, and M. Nishikawa, *ibid.*, 2112147 (1971) [*C.A.*, **76**, 14181r (1972)].

[3] Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*

[4] H.J. Teuber and G. Jellinek, *Chem. Ber.*, **85**, 95 (1952).

IX (mp 159—161°) having unknown structure. Carbonyl absorption at 1630 cm^{-1} of IIIb and that at 1620 cm^{-1} of IX in the infrared (IR) spectra suggested the presence of the intramolecular hydrogen bonding in their structure. The product (Vb) obtained from IIIb by Clemmensen reduction showed γ-methylene (τ 7.2) merged with methine, and β-methylene (τ 8.1) in nuclear magnetic resonance (NMR) spectra. Oxidation of Vb with Fremy's salt gave VIIb, structure of which was unequivocally identified by synthesis as described below. Thus, IIIb and Vb could be assigned to α-methyl-β-[2-(1-hydroxy-3-methylnaphthoyl)]propionic acid and α-methyl-γ-[2-(1-hydroxy-3-methylnaphthyl)]butyric acid, respectively. The reduced product (X) obtained from IX showed γ-methylene (τ 7.25) and β-methylene (τ 8.05) in NMR, suggesting an α-methylbutyric acid derivative. But X was recovered without being oxidized with Fremy's salt, unlike Vb, indicating that the acylation occurred on the ring other than 2 position. By reaction with II at lower temperature, Ia and Ib were not acylated on the ring and only their phenolic esters were obtained. Since Friedel–Crafts reaction of free phenols generally requires more drastic conditions than that of phenolic ethers, IIIa, IIIb, IV and IX may be produced *via* Fries rearrangement of the ester intermediates which could be detected by thin-layer chromatography (TLC) at an early stage of reaction. Pure crystals of Vb appeared to be stable to air but the crude product was easily oxidized to quinone on standing in atmosphere or during a chromatographic purification. 2-Alkyl-1-naphthols are known to be considerably susceptible to air oxidation and are assumed to produce easily phenoxy radical due to the electron-donating property of the ortho alkyl group.

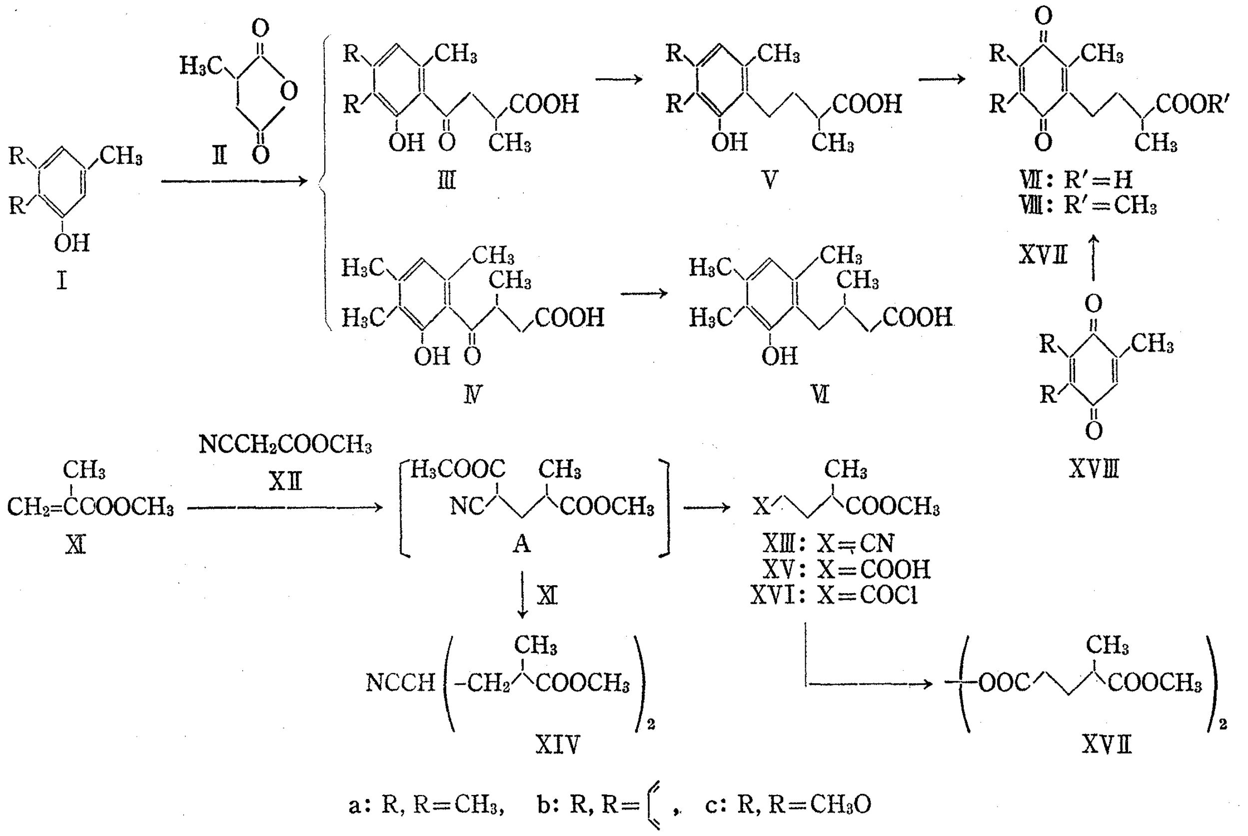

Chart 1

Introduction of the Side Chain with Diacyl Peroxide (Chart 1)——Fieser and Oxford[5] synthesized 2-methyl- and 2-hydroxy-3-alkyl-1,4-naphthoquinones in one step by condensation of quinone with the alkyl radical which is generated from the diacyl peroxide by thermal

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5) L.F. Fieser and A.E. Oxford, *J. Am. Chem. Soc.*, **64**, 2060 (1942).

Table I. Physical Properties of Quinone Compounds

Compound	mp (°C)	UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$)		IR ν_{max} cm^{-1} Quinone[a]	Formula	Analysis (%)			
						Calcd.		Found	
		Oxidized	Reduced			C	H	C	H
VIIa	79—81	261(723), 268(741)	290(122)	1650, 1620	$C_{14}H_{18}O_4$	67.18	7.25	66.90	7.31
VIIIa	oil	261(622), 268(633)	289(84)	1650, 1620	$C_{15}H_{20}O_4$	68.16	7.63	67.87	7.73
VIIb	112—113	244(597), 248(607), 264(542), 272(563), 330(90)	245(1515), 323(220), 333(220)	1660, 1620	$C_{16}H_{16}O_4$	70.57	5.92	70.32	5.98
VIIIb	44—45	244(595), 248(604), 264(562), 272(587), 330(93)	245(1525), 323(168), 333(168)	1660, 1620	$C_{17}H_{18}O_4$	71.31	6.34	71.17	6.61
trans-XXIVa	39—40	260(632), 267(647)	288(103)	1640, 1630	$C_{17}H_{22}O_4$	70.32	7.64	70.17	8.01
cis-XXIVa	Oil	260(612), 267(624)	288(97)	1640, 1630	$C_{17}H_{22}O_4$	70.32	7.64	70.36	7.59
trans-XXVa	103—104	260(675), 267(691)	288(107)	1640, 1630	$C_{16}H_{20}O_4$	69.54	7.30	69.65	7.18
cis-XXVa	102—104	260(678), 267(692)	288(105)	1640, 1630	$C_{16}H_{20}O_4$	69.54	7.30	69.73	7.62
trans-XXIVb	oil	244(580), 248(593), 263(514), 270(532), 330(104)	245(1395), 323(144), 333(144)	1660, 1620	$C_{19}H_{20}O_4$	73.06	6.45	72.93	6.37
cis-XXIVb	48—49	244(573), 248(589), 263(516), 270(535), 330(97)	245(1503), 323(154), 333(154)	1660, 1620	$C_{19}H_{20}O_4$	73.06	6.45	73.12	6.46
trans-XXVb	130—131.5	244(605), 248(620), 263(529), 270(547), 330(100)	245(1438), 323(162), 333(162)	1660, 1630	$C_{18}H_{18}O_4$	72.46	6.08	72.54	6.00
cis-XXVb	118—119	244(612), 248(630), 263(539), 270(554), 330(109)	245(1500), 323(160), 333(160)	1660, 1630	$C_{18}H_{18}O_4$	72.46	6.08	72.21	6.00
trans-XXVc	60—65	275(468)	290(132)	1660, 1650, 1610	$C_{16}H_{20}O_4$	62.32	6.54	62.21	6.61

[a] IR spectra of crystals were recorded in KBr and those of oily materials were recorded in film.

Table II. Nuclear Magnetic Resonance Spectral Data for Quinone Compounds in CCl_4

Compound	Carboxyl	Ring proton	Ester methyl	Methine, Ring methylene	Ring methyl	Methylene	Methyl
VIIa	−1.48(b)	—	—	7.4—7.7(m)	8.02, 8.05(s)	8.2—8.6(m)	8.76(d)
VIIIa	—	—	6.35(s)	7.5—7.6(m)	8.03(s)	8.2—8.7(m)	8.82(d)
VIIb	−1.30(b)	2.00, 2.40(m)	—	7.0—7.6(m)	7.83(s)	8.0—8.5(m)	8.68(d)
VIIIb	—	2.00, 2.40(m)	6.36(s)	7.0—7.6(m)	7.87(s)	8.0—8.6(m)	8.78(d)

decomposition. This reaction was applied to the synthesis of the metabolites. Condensation of methyl α-methylacrylate (XI) with methyl cyanoacetate (XII) gave methyl γ-cyano-α-methylbutyrate (XIII), and methyl α,α'-dimethyl-γ-cyanopimelate (XIV). XIV showed nitrile (2250 cm^{-1}) and ester carbonyl (1740 cm^{-1}) in IR, two secondary methyls (τ 8.82, doublet), two methylenes (τ 8.6—7.6, multiplet) and two methines adjacent to the carboxyl merged with methine adjacent to nitrile (τ 7.6—7.0, multiplet) in NMR, and a molecular ion (m/e 241) in mass spectrum. XIV may have resulted from the reaction of XI with an intermediary product A. XIII was hydrolyzed to γ-methoxycarbonylvaleric acid (XV) and subsequently converted to the acid chloride (XVI). Treatment of XVI with aqueous sodium peroxide in petroleum ether produced only α-methylglutaric acid, but that with sodium peroxide in ether at $-10°$ under anhydrous conditions gave the desired γ,γ'-dimethoxycarbonylvaleryl peroxide (XVII). Without further purification, XVII was allowed to react with 2-methyl-1,4-naphthoquinone (XVIIIb) in acetic acid to obtain 2-methyl-3-(3'-methoxycarbonylbutyl)-1,4-naphthoquinone (VIIIb) in 56% yield. The hydrolysis of VIIIb with methanolic potassium hydroxide in the presence of pyrogallol in a stream of nitrogen resulted in very poor yield of VIIb. Fieser and Turner⁶⁾ hydrolyzed successfully the ester of 2-methyl-1,4-naphthoquinone having an acidic side chain in the 3 position through its hydroquinone form. VIIIb was then converted into the hydroquinone with sodium hydrosulfite and hydrolyzed with potassium hydroxide to the corresponding carboxylic acid, followed by oxidation with silver oxide (Ag_2O) to quinone giving VIIb in 88% yield. When the reaction product of XVII with XVIIIb was immediately hydrolyzed in a similar manner without being isolated, VIIb was obtained in 54% yield from XVII. Similarly, condensation of 2,3,5-trimethyl-1,4-benzoquinone (XVIIIa) and 2,3-dimethoxy-5-methyl-1,4-benzoquinone (XVIIIc) with XVII gave 2,3,5-trimethyl-6-(3'-methoxycarbonylbutyl)-1,4-benzoquinone (VIIIa) in 27% yield, and 2,3-dimethoxy-5-methyl-6-(3'-methoxycarbonylbutyl)-1,4-benzoquinone (VIIIc)⁷⁾ which is the ester derivative of a ubiquinone metabolite (VIIc)⁸⁾ in 29% yield, respectively. VIIc was obtained by hydrolysis of VIIIc in a manner similar to that for VIIb. The physical properties of VIIa, VIIb and their esters (VIIIa, VIIIb) are summarized in Tables I and II.

2,3,5-Trimethyl-6-(5'-carboxy-3'-methyl-2'-pentenyl)-1,4-benzoquinone (XXVa), 2-Methyl-3-(5'-carboxy-3'-methyl-2'-pentenyl)-1,4-naphthoquinone (XXVb) and 2,3-Dimethoxy-5-methyl-6-(5'-carboxy-3'-methyl-2'-pentenyl)-1,4-benzoquinone (XXVc) (Chart 2)

In order to synthesize a ubiquinone metabolite (XXVc),⁸⁾ we obtained *trans*-methyl ε-hydroxy-γ-methyl-γ-hexenoate (XX) by oxidation of *trans*-ε-acetoxy-γ-methyl-γ-hexenal (XIX), which was prepared by ozonolysis of geranyl acetate, with argentic oxide (AgO) in neutral medium, followed by hydrolysis of acetate to alcohol and esterification with diazomethane.⁹⁾ In the present work, XX was prepared in good yield by oxidation of aldehyde (XIX) with silver oxide (Ag_2O) in alkaline medium, followed by esterification. 2,3,5-Trimethyl-1,4-benzohydroquinone (XXIIIa) was condensed with XX in the presence of boron trifluoride, and the product was oxidized with ferric chloride to 2,3,5-trimethyl-6-(5'-methoxycarbonyl-3'-methyl-2'-pentenyl)-1,4-benzoquinone (XXIVa) which consisted of *trans,cis*-mixture (3:1) by NMR assignment,¹⁰⁾ in 74% yield. It was hydrolyzed and the resulting *trans,cis*-XXVa were separated into each isomer by recrystallization from ether–hexane. They could not be distinguished by melting point (Table I), although they showed depression of the mixed melting point. Unequivocal structural assignments of these isomers were made

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6) L.F. Fieser and R.B. Turner, *J. Am. Chem. Soc.*, **69**, 2338 (1947).

7) The synthesis of this compound was presented independently by Y. Watanabe, K. Nakashima, T. Suzuki, and T. Seki, at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.

8) I. Imada, M. Watanabe, N. Matsumoto, and H. Morimoto, *Biochemistry*, **9**, 2870 (1970).

9) M. Watanabe, I. Imada, and H. Morimoto, *Biochemistry*, **9**, 2879 (1970).

10) *cf.* R.B. Bates and D.M. Gale, *J. Am. Chem. Soc.*, **82**, 5749 (1960); R.B. Bates, R.H. Carnighan, R.O. Rakutis, and J.H. Schauble, *Chem. Ind.*, 1962, 1020.

by examination of NMR spectra (Table III). Condensation of 2-methyl-1,4-naphthohydroquinone (XXIIIb) with XX resulted in only a low yield of the desired *trans,cis*-2-methyl-3-(5′-methoxycarbonyl-3′-methyl-2′-pentenyl)-1,4-naphthoquinone (*trans,cis*-XXIVb) and large amounts of 2-methyl-2-(5′-methoxycarbonyl-3′-methyl-2′-pentenyl)-2,3-dihydro-1,4-naphthoquinone (XXVI). Such undesired condensation has been reported in the synthesis of phylloquinone.[11] To overcome this drawback, bulky group was introduced to the phenolic hydroxyl adjacent to methyl and the 2 position has been blocked to condensation.[12] Reaction of bis(tetrahydropyranyl)ether (XXVII) with XX decreased not only the formation of XXVI but also that of the desired XXIVb. While, 1-acetoxy-4-hydroxy-2-methylnaphthalene (XXVIII) was condensed with XX to give XXIVb which was a mixture of *trans,cis*-isomers (3: 1). *trans,cis*-XXVb obtained from *trans,cis*-XXIVb by hydrolysis through the hydroquinone form, followed by oxidation was separated into each isomer by recrystallization. In order to synthesize *trans*-XXVa and *trans*-XXVb stereoselectively, we utilized *trans*-allylic alcohol (XX) prepared from geranyl acetate, but the *cis-trans* isomerization occurred during the condensation.

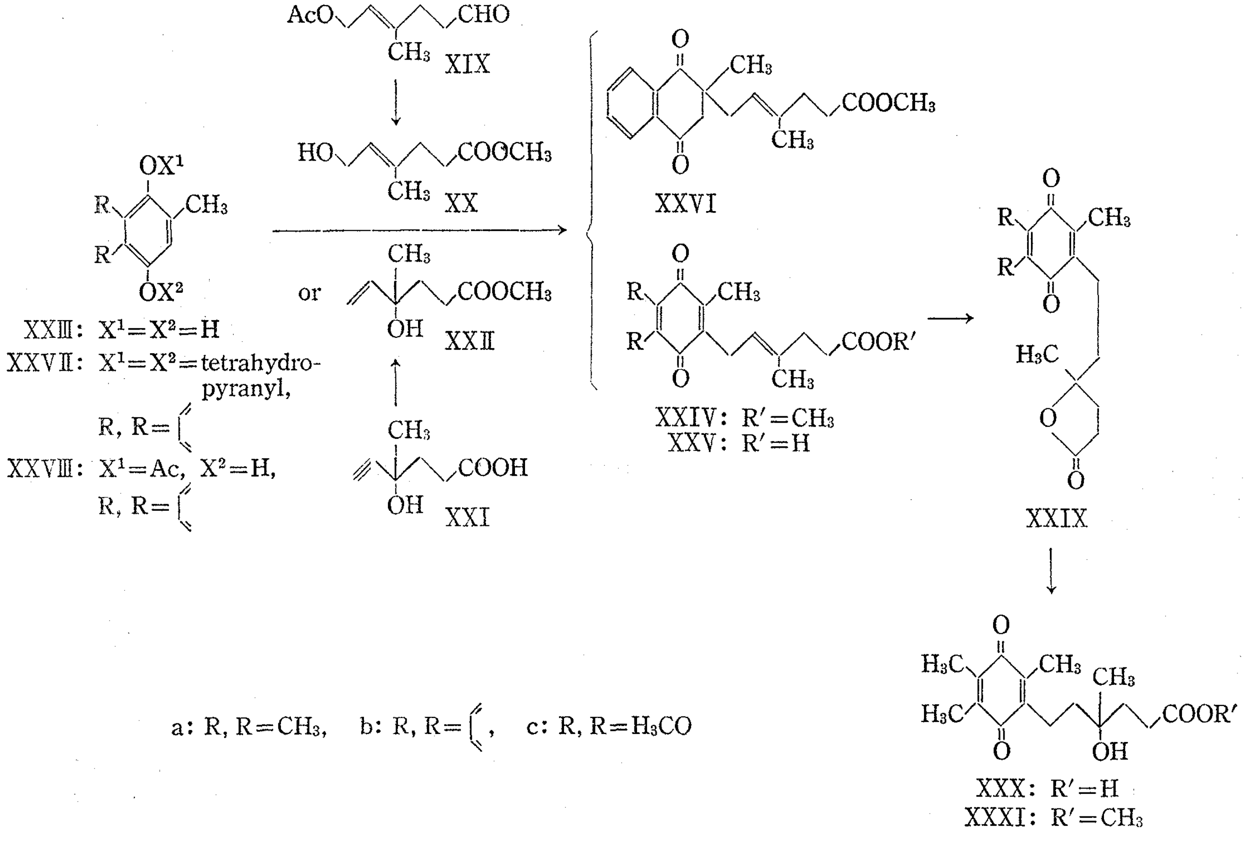

Chart 2

Next, the alternative approach was carried out by utilizing methyl γ-hydroxy-γ-vinylvalerate (XXII) which could be prepared more easily than XX. γ-Ethynyl-γ-hydroxyvaleric acid (XXI)[13] which was prepared from levulinic acid and sodium acetylid was subjected to catalytic reduction with palladium on barium sulfate in the presence of quinoline, followed by hydrolysis of contaminated γ-vinyl-γ-valerolactone and esterification with diazomethane to obtain XXII. XXII was easily lactonized even by distillation below 100°, but could be

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[11] M. Tishler, L.F. Fieser, and N.L. Wendler, *J. Am. Chem. Soc.*, **62**, 1982 (1940).

[12] R. Hirschmann, R. Miller, and N.L. Wendler, *J. Am. Chem. Soc.*, **76**, 4592 (1954); M. Matsui and S. Kitamura, Japan Patent 44—28297 (1969).

[13] O.R. Kreimeier and N.J. Woodstown, U.S. Patent 2122719 (1938) [C.A., 32, 6669^6 (1938)].

purified effectively by chromatography on silicic acid in 90% yield from XXI. The condensed products of hydroquinones (XXIIIa, XXIIIc and XXVIII) with XXII were hydrolyzed and oxidized with ferric chloride to XXVa, XXVc and XXVb, respectively. These products were *trans,cis*-mixtures (3: 1) as in the case where *trans*-allylic alcohol (XX) was used. In this work, we succeeded in isolating the pure *trans*-XXVc as crystals by recrystallization from ether-hexane. The free acids (XXVa, XXVb and XXVc) were lactonized to 2,3,5-trimethyl-6-(5'-carboxy-3'-hydroxy-3'-methylpentyl)-1,4-benzoquinone lactone (XXIXa), 2-methyl-3-(5'-carboxy-3'-hydroxy-3'-methylpentyl)-1,4-naphthoquinone lactone (XXIXb) and 2,3-dimethoxy-5-methyl-6-(5'-carboxy-3'-hydroxy-3'-methylpentyl)-1,4-benzoquinone lactone (XXIXc),[9] respectively, by heating with mineral acid. But this conversion resulted in very low yield, and it was accomplished in a good yield through the hydroquinone form. This fact strongly supported our observation[1,8] that intaken phylloquinone and ubiquinone homologs are excreted in urine as a conjugate of hydroquinone form of the corresponding metabolite XXVb and XXVc, respectively. Simon, *et al.*[14] reported the isolation of 2,3,5-trimethyl-6-(5'-carboxy-3'-hydroxy-3'-methylpentyl)-1,4-benzoquinone (XXX) as the metabolite of α-tocopherol. Since XXX is considerably unstable to mineral acid and easily lactonized to XXIXa, its methyl ester (XXXI) was prepared from XXIXa as the authentic sample for study of α-tocopherol metabolites in urine. The physical properties of XXVa, XXVb, XXVc and their esters (XXIVa, XXIVb) are summarized in Table I and III.

TABLE III. Nuclear Magnetic Resonance Spectral Data for Quinone Compounds

Compound	Solvent	Carboxyl	Ring proton	Olefinic	Methoxyl	Ester methyl	Ring methylene	Methylene	Ring methyl	Vinyl methyl
trans-XXIVa	CCl_4	—	—	5.06 (t)	—	6.47 (s)	6.89 (d)	7.74 (b)	8.04 (s)	8.26 (s)
cis-XXIVa	CCl_4	—	—	5.06 (t)	—	6.37 (s)	6.84 (d)	7.60 (b)	8.06 (s)	8.36 (s)
trans-XXVa	$CDCl_3$	0.75 (b)	—	4.96 (t)	—	—	6.78 (d)	7.62 (b)	8.00 (s)	8.20 (s)
cis-XXVa	$CDCl_3$	−0.60 (b)	—	4.96 (t)	—	—	6.76 (d)	7.46 (s)	8.00 (s)	8.30 (s)
trans-XXIVb	CCl_4	—	2.02, 2.40 (m)	4.98 (t)	—	6.48 (s)	6.70 (d)	7.72 (s)	7.86 (s)	8.20 (s)
cis-XXIVb	CCl_4	—	1.99, 2.39 (m)	4.98 (t)	—	6.33 (s)	6.64 (d)	7.52 (m)	7.82 (s)	8.31 (s)
trans-XXVb	$CDCl_3$	−0.20 (b)	2.01, 2.40 (m)	4.96 (t)	—	—	6.70 (d)	7.70 (b)	7.89 (s)	8.23 (s)
cis-XXVb	$CDCl_3$	0.60 (b)	1.95, 2.35 (m)	4.92 (t)	—	—	6.61 (d)	7.45 (s)	7.80 (s)	8.30 (s)
trans-XXVc	$CDCl_3$	0.24 (b)	—	5.00 (t)	6.03 (s)	—	6.80 (d)	7.64 (b)	8.00 (s)	8.24 (s)

Experimental[15]

α-Methyl-β-(2-hydroxy-3,4,6-trimethylbenzoyl)propionic Acid (IIIa) and β-Methyl-β-(2-hydroxy-3,4,6-trimethylbenzoyl)propionic Acid (IV)——To a stirred solution of anhydrous $AlCl_3$ (4 g) in tetrachloroethane

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14) E.J. Simon, A. Eisengart, L. Sundheim, and A.T. Milhorat, *J. Biol. Chem.*, 221, 807 (1956).

15) All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were recorded in EtOH with a Hitachi EPS-3T spectrophotometer. The spectra of the reduced forms of quinone compounds were taken in the same solvent, except naphthoquinone compounds which were run in EtOH containing 0.01 volume of 1 M ammonium acetate buffer (pH 5.0) after addition of sodium borohydride. IR spectra were recorded with a Hitachi EPI-S2 spectrophotometer. NMR spectra were run on a Varian HA-100 and T-60 spectrometers with TMS as an internal standard. Chemical shifts were given in τ values and signal multiplicities were represented by s (singlet), d (doublet), t (triplet), q (quartet), b (broad) and m (multiplet). Mass spectra were recorded on a Hitachi RMS-4 mass spectrometer at an ionization potential of 70 eV. The sample was vaporized at the ion source with a heated direct inlet system operating at 200°.

(10 ml), a solution of 2,3,5-trimethylphenol (Ia) (2 g) and methylsuccinic anhydride (II) (1.7 g) in tetrachloroethane (10 ml) was added dropwise over a period of 3 hr with cooling. The mixture was stirred for 6 hr at 135—140° then poured into 3 N HCl and subjected to steam distillation to remove tetrachloroethane. After cooling, the solidified mixture was separated into two fractions by column chromatography on silicic acid containing 6% H_2O eluting with $CHCl_3$. The first fraction was recrystallized from AcOEt to give IIIa as pale yellow needles, mp 182—184° (1.04 g, 27%). IR ν_{max}^{KBr} cm^{-1}: 2650, 1700 (COOH), 1605 (CO). NMR (d_6-DMSO): 8.87 (3H, d, side chain CH_3), 7.96 (3H, s, ring CH_3), 7.89 (3H, s, ring CH_3), 7.84 (3H, s, ring CH_3), 7.20 (1H, b, CH), 7.03 (2H, d, $COCH_2$), 3.45 (1H, s, ring H), 0.77 (1H, b, OH), −2.04 (1H, b, COOH). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.18; H, 7.35. The second fraction was recrystallized from AcOEt to give IV as pale yellow silky needles, mp 138—139° (0.43 g, 11%). IR ν_{max}^{KBr} cm^{-1}: 2650, 1700 (COOH), 1610 (CO). NMR (d_6-DMSO): 8.92 (3H, d, side chain CH_3), 7.92 (6H, s, ring CH_3), 7.82 (3H, s, ring CH_3), 7.64—7.18 (2H, m, CH_2), 6.49 (1H, m, CH), 3.42 (1H, s, ring H), 1.06 (1H, b, OH). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.36; H, 7.44.

α-Methyl-γ-(2-hydroxy-3,4,6-trimethylphenyl)butyric Acid (Va)——A mixture of IIIa (0.5 g), toluene (2 ml), AcOH (0.5 ml), conc. HCl (2 ml), H_2O (2 ml) and amalgamated zinc prepared from mossy zinc (1 g) was refluxed for 20 hr. After separation of the toluene layer, the aqueous layer was extracted with ether. The combined toluene layer and extracts were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from ether–petroleum ether to give colorless needles, mp 92—94° (0.32 g, 66%). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1685 (COOH). NMR (CCl_4): 8.79 (3H, d, side chain CH_3), 8.6—8.1 (2H, m, CH_2), 7.99 (3H, s, ring CH_3), 7.90 (3H, s, ring CH_3), 7.87 (3H, s, ring CH_3), 7.48 (2H, t, ring CH_2), 7.6—7.4 (1H, m, CH), 3.64 (1H, s, ring H), 1.48 (1H, b, OH). *Anal.* Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.88; H, 8.62.

β-Methyl-γ-(2-hydroxy-3,4,6-trimethylphenyl)butyric Acid (VI)——IV (65 mg) was treated in a manner similar to that for Va and recrystallized from ether–hexane to give colorless needles, mp 107—109° (22 mg). NMR ($CDCl_3$): 9.00 (3H, d, side chain CH_3), 7.7—7.2 (5H, m, CH_2, CH), 3.40 (1H, s, ring H).

2,3,5-Trimethyl-6-(3′-carboxybutyl)-1,4-benzoquinone (VIIa)——To a solution of Va (100 mg) in 1% NaOH (2 ml), potassium nitrosodisulfonate (300 mg) in H_2O (2ml) was added. The mixture was stirred at room temperature for 1 hr, then acidified with 3 N HCl and extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give yellow crystals, which were recrystallized from ether–petroleum ether to give yellow plates (90 mg, 85%).

2,3,5-Trimethyl-6-(3′-methoxycarbonylbutyl)-1,4-benzoquinone (VIIIa)——1) VIIa (50 mg) was treated with an ether solution of CH_2N_2 to give a yellow oil.

2) A reaction of 2,3,5-trimethyl-1,4-benzoquinone (XVIIIa) (100 mg) with XVII (200 mg) was carried out in a manner similar to that described below (VIIb-2) to give VIIIa (46 mg, 27%).

α-Methyl-β-[2-(1-hydroxy-3-methylnaphthoyl)]propionic Acid (IIIb)——To a stirred solution of anhydrous $AlCl_3$ (2.6 g) in tetrachloroethane (10 ml), a solution of 3-methyl-1-naphthol (Ib) (2 g) and II (2 g) in tetrachloroethane (10 ml) was added dropwise with cooling. The mixture was stirred for 20 min at 140—150°, then poured into cold 3 N HCl and extracted with AcOEt. The AcOEt layer was extracted with 5% Na_2CO_3. The Na_2CO_3 layer was acidified with 3 N HCl and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give an oil, which was subjected to column chromatography on silicic acid, eluting with $CHCl_3$. The resulting crystal was recrystallized from AcOEt to give pale yellow needles, mp 191—192° (0.32 g, 9.3%). IR ν_{max}^{KBr} cm^{-1}: 2600, 1700 (COOH), 1630 (CO). NMR (d_6-DMSO): 8.78 (3H, d, side chain CH_3), 7.64 (3H, s, ring CH_3), 6.84 (3H, m, CH_2, CH), 2.75 (1H, s, ring H), 2.4 (3H, m, ring H), 1.8 (1H, m, ring H). *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.61; H, 6.07.

IX: A similar reaction mixture was stirred for 20 hr at 140—150°, then the extract was similarly treated to give pale yellow needles, mp 159—161°. IR ν_{max}^{KBr} cm^{-1}: 2600, 1700 (COOH), 1620 (CO). NMR (d_6-DMSO): 8.75 (3H, d, side chain CH_3), 7.43 (3H, s, ring CH_3), 7.0—6.5 (3H, m, CH_2, CH), 2.5—1.6 (5H, m, ring H).

α-Methyl-γ-[2-(1-hydroxy-3-methylnaphthyl)]butyric Acid (Vb)——IIIb (20 mg) was reduced in a manner similar to that for Va and subsequent recrystallization of the product from ether–hexane gave a colorless powder, mp 119—121° (16 mg). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 2600, 1700 (COOH). NMR ($CDCl_3$): 8.70 (3H, d, side chain CH_3), 8.1 (2H, m, CH_2), 7.55 (3H, s, ring CH_3), 7.2 (3H, m, ring CH_2, CH), 2.8—2.2 (4H, m, ring H), 1.86 (1H, m, ring H).

X: IX was reduced in a manner similar to that for Va. NMR ($CDCl_3$): 8.75 (3H, d, side chain CH_3), 8.6—7.6 (2H, m, CH_2), 7.42 (3H, s, ring CH_3), 7.4—7.0 (3H, m, ring CH_2, CH), 3.00 (1H, s, ring H), 2.58 (2H, m, ring H), 2.15 (1H, m, ring H), 1.80 (1H, m, ring H).

2-Methyl-3-(3′-carboxybutyl)-1,4-naphthoquinone (VIIb)——1) Vb (10 mg) was oxidized in a manner similar to that for VIIa and recrystallized from ether–hexane to give yellow columns.

2) To a stirred solution of 2-methyl-1,4-naphthoquinone (XVIIIb) (1 g) in AcOH (10 ml), XVII (2 g) was added dropwise at 90—95° and the mixture stirred for 5 hr. After cooling, it was diluted with H_2O and extracted with ether. The ether extract was successively washed with H_2O, aqueous solution of Na_2CO_3 containing $Na_2S_2O_4$, H_2O, dried over Na_2SO_4, and evaporated. The residue was dissolved in ether and shaken with Ag_2O and $MgSO_4$ to oxidize the hydroquinone to quinone. The solids were filtered off, the filtrate

was evaporated *in vacuo* and the residue subjected to column chromatography on silicic acid. The starting material (XVIIIb) (330 mg) was recovered from the fraction eluted with benzene. The fraction eluted with benzene–AcOEt (19: 1) gave 2-methyl-3-(3′-methoxycarbonylbutyl)-1,4-naphthoquinone (VIIIb) (932 mg, 56%). A solution of VIIIb (0.5 g) in ether (2 ml) was shaken with 20% $Na_2S_2O_4$ (2 ml). After the disappearance of yellow color, 30% KOH (7 ml) was added to the cooled reaction mixture with stirring in a stream of N_2. The mixture was stirred for 5 hr then acidified with 3 N HCl, extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was oxidized with Ag_2O as usual and recrystallized from ether–hexane to give VIIb (481 mg, 88%).

Methyl Ester (VIIIb): VIIb was treated with an ether solution of CH_2N_2 and recrystallized from ether–hexane to give yellow columns.

γ,γ′-Dimethoxycarbonylvaleryl Peroxide (XVII)——To a stirred solution of methyl cyanoacetate (XII) (133 g) in methanolic sodium methoxide (400 ml, prepared from 27 g of Na), methyl α-methylacrylate (XI) (135 g) was added in one portion with cooling. After 2.5 hr, 50 ml of H_2O was added and 300 ml of solvent removed. Then 150 ml of H_2O was added and 100 ml of solvent removed, finally 150 ml of H_2O added and 250 ml of solvent removed. The residue was acidified with 30% H_2SO_4, then extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting oil was separated into two fractions by fractional distillation. The first fraction, bp 117° (20 mmHg) was redistilled to give methyl γ-cyano-α-methylbutyrate (XIII) as a colorless oil, bp 91—93° (10 mmHg) (33 g, 18%). The second fraction, bp 140—170° (10 mmHg) (53 g) was identified as methyl α,α′-dimethyl-γ-cyanopimelate (XIV) by IR, NMR and mass spectral data. Conc. H_2SO_4 (36 ml) was added dropwise to XIII (17.5 g) at −10° with stirring. After 10 min, the temperature was allowed to rise to room temperature. The mixture was stirred for 20 min then cooled to −10°. Crushed ice (48 g) was added, followed by dropwise addition of 30% $NaNO_2$ (78 ml) and stirring at 0° for 1.5 hr. The reaction mixture was saturated with Na_2SO_4, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, the solvent removed and distilled *in vacuo* to give γ-methoxycarbonylvaleric acid (XV) as a colorless oil, bp 105—110° (0.07 mmHg) (12.6 g, 63%). A mixture of XV (4.3 g) and oxalyl chloride (2.5 ml) was stirred at room temperature for 30 min. Evaporation of excess oxalyl chloride gave the acid chloride (XVI). To a stirred solution of XVI (7 g) in ether (35 ml), Na_2O_2 (3.5 g) was added portionwise at −10°, and the mixture stirred for 3 hr. Ice-H_2O was added, and the reaction mixture extracted with ether. The extract was washed with H_2O and dried over $CaCl_2$. The solvent was removed *in vacuo* to give XVII as a colorless oil (3.9 g). This product was used for the next step without further purification.

2,3-Dimethoxy-5-methyl-6-(3′-carboxybutyl)-1,4-benzoquinone (VIIc)——A solution of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (XVIIIc) (50 mg) and XVII (150 mg) in AcOH (2 ml) was heated at 90—95° for 5 hr. The reaction mixture was worked up in a manner similar to that explained above (VIIb-2) to give 2,3-dimethoxy-5-methyl-6-(3′-methoxycarbonylbutyl)-1,4-benzoquinone (VIIIc) as an orange oil (24 mg, 29%).[9] VIIc was obtained by hydrolysis of VIIIc in a manner similar to that for VIIb as an orange oil.[9]

***trans*-Methyl ε-Hydroxy-γ-methyl-γ-hexenoate (XX)**——To a solution of *trans*-ε-acetoxy-γ-methyl-γ-hexenal (XIX) (5 g) in MeOH (25 ml), Ag_2O (3.4 g) and 10% NaOH (10 ml) were added and the mixture stirred at room temperature for 1 hr. The solids were filtered off and washed with hot water. The cooled, combined filtrate and washings were acidified with 3 N HCl, and extracted with AcOEt. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was treated with CH_2N_2, followed by purification by column chromatography on silicic acid, eluting with $CHCl_3$, to give a colorless oil (2.3 g, 49%).[9]

Methyl γ-Hydroxy-γ-vinylvalerate (XXII)——A solution of γ-ethynyl-γ-hydroxyvaleri cacid (XXI) (30 g) in MeOH (150 ml) was hydrogenated with 5% Pd-$BaSO_4$ (1.0 g) in the presence of quinoline (1.0 g). After one equivalent of hydrogen had been absorbed, the catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue was treated with 30% KOH to hydrolyze the contaminated γ-lactone. The aqueous solution was acidified carefully with 3 N HCl in the presence of crushed ice, then extracted with AcOEt. After being washed with H_2O and dried over Na_2SO_4, the AcOEt extract was treated with CH_2N_2 and evaporated *in vacuo*. Chromatographic purification on silicic acid gave a colorless oil (30 g, 90%). NMR (CCl_4): 8.75 (3H, s, CH_3), 8.20 (2H, m, CH_2), 7.67 (2H, m, CH_2COO), 7.36 (1H, b, OH), 6.40 (3H, s, $COOCH_3$), 5.00 (2H, m, $=CH_2$), 4.17 (1H, q, $=CH$). *Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.50; H, 9.10.

***trans,cis*-2,3,5-Trimethyl-6-(3′-methyl-5′-methoxycarbonyl-2′-pentenyl)-1,4-benzoquinone (*trans,cis*-XXIVa), *trans*-XXIVa and *cis*-XXIVa**——1) To a stirred solution of 2,3,5-trimethyl-1,4-benzohydroquinone (XXIIIa) (2.8 g) and XX (1.46 g) in dry dioxane (50 ml), BF_3-ether (3.65 ml) was added in a stream of N_2. The mixture was stirred for 4 hr at room temperature then diluted with H_2O, and extracted with ether. The ether extract was washed with H_2O then shaken with $FeCl_3$ (15 g) in H_2O–MeOH (2: 1). The organic layer was separated and washed with H_2O, then dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silicic acid. From the fraction eluted with hexane–ether, the oxidized starting material (XVIIIa) (1.3 g) was first recovered, then *trans,cis*-XXIVa was obtained as a yellow oil (1.98 g, 74%).

2) In a manner similar to that described above, the condensation of XXIIIa (6.08 g) with XXII (3.16 g), followed by chromatographic separation gave *trans,cis*-XXIVa (4.3 g, 78%) and the oxidized starting material (XVIIIa) (2.9 g).

3) *trans*-XXVa was methylated with CH_2N_2 and recrystallized from hexane to give *trans*-XXIVa as yellow needles.

4) *cis*-XXVa was methylated with CH_2N_2 and purified by column chromatography to give *cis*-XXIVa as a yellow oil.

***trans*-2,3,5-Trimethyl-6-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (*trans*-XXVa) and *cis*-XXVa**——*trans,cis*-XXIVa (1.98 g) was hydrolyzed in a manner similar to that for VIIb. The resulting solid was recrystallized from ether–hexane to give *trans*-XXVa as yellow needles (1.2 g). Recrystallization of the mother liquor from ether–hexane gave *cis*-XXVa as yellow plates (0.16 g).

1,4-Bis(α-tetrahydropyranyloxy)-2-methylnaphthalene (XXVII)——To a solution of 2-methyl-1,4-naphthohydroquinone (XXIIIb) (1 g) in AcOEt (10 ml), AcOEt (10 ml) saturated with dry HCl and dihydropyrane (2 ml) were added, and the mixture allowed to stand for 24 hr at room temperature. Then the reaction mixture was made alkaline with 2% NaOH, and the AcOEt layer was separated and successively washed with 2% NaOH then H_2O and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give a colorless syrup (980 mg, 50%).

***trans,cis*-2-Methyl-3-(5′-methoxycarbonyl-3′-methyl-2′-pentenyl)-1,4-naphthoquinone (*trans,cis*-XXIVb) and 2-Methyl-2-(5′-methoxycarbonyl-3′-methyl-2′-pentenyl)-2,3-dihydro-1,4-naphthoquinone (XXVI)**——1) XXIIIb (1.05 g) was condensed with XX (0.475 g) in a manner similar to that for XXIVa. The oil obtained was subjected to column chromatography on silicic acid. The oxidized starting material (XVIIIb) (0.487 g) was recovered from the fraction eluted with benzene. The second fraction eluted with benzene–AcOEt (19: 1) was subjected to preparative TLC using hexane–ether (3: 2) as the developing solvent. The upper *Rf* value gave *trans,cis*-XXIVb as a yellow oil (291 mg, 31%). The lower *Rf* value gave XXVI as a colorless oil (530 mg, 56%). IR ν_{max}^{film} cm^{-1}: 1740, 1290, 1250 ($COOCH_3$), 1690 (CO). NMR (CCl_4): 8.78 (3H, s, $COCCH_3$), 8.50, 8.47 (3H, s, *trans* and *cis*$=CCH_3$), 7.8—7.5 (6H, m, $=CCH_2$, CH_2COO, $COCH_2$), 7.20 (2H, d, $=CCH_2$), 6.46, 6.44 (3H, s, $COOCH_3$ of *trans* and *cis* forms), 4.96 (1H, t, $=CH$), 2.36, 2.08 (4H, m, ring H).

2) A mixture of XXVII (487 mg), XX (100 mg), BF_3–ether (0.5 ml) and dry dioxane (5 ml) was stirred at room temperature for 20 hr. The reaction mixture was diluted with H_2O then extracted with ether. The ether extract was shaken with 3 N HCl to remove the protecting group and washed successively with H_2O, 2% NaOH, and H_2O. The ether layer was dried over Na_2SO_4, then evaporated *in vacuo*. The resulting hydroquinones were oxidized with $FeCl_3$ in the usual manner, followed by separation by TLC using benzene–AcOEt (19: 1) as the developing solvent, to give *trans,cis*-XXIVb (60 mg, 30%) and XXVI (73 mg, 37%).

***trans*-2-Methyl-3-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-naphthoquinone (*trans*-XXVb) and *cis*-XXVb**——1) To a stirred solution of 1-acetoxy-4-hydroxy-2-methylnaphthalene (XXVIII) (1.36 g), BF_3–ether (0.5 ml) and $ZnCl_2$ (0.25 g) in dry dioxane (2 ml), a solution of XX (0.5 g) in dry dioxane (2 ml) was added dropwise at 50° in a stream of N_2. The mixture was heated at the same temperature for 5 hr, then diluted with H_2O and extracted with ether. The residue upon removal of the solvent was hydrolyzed in a manner similar to that described for VIIb to give yellow solid, which was subjected to column chromatography on silicic acid eluting with $CHCl_3$. The first fraction gave the oxidized starting material (XVIIIb) (590 mg). The second fraction gave *trans,cis*-XXVb (400 mg, 42%) which was recrystallized from ether to give *trans*-XXVb as yellow needles (184 mg). Recrystallization of the mother liquor from ether gave *cis*-XXVb as yellow plates.

2) The condensation of XXVIII (6.5 g) with XXII (3.16 g), followed by the hydrolysis of the product carried out in a manner similar to that described above gave the oxidized starting material (XVIIIb) (3 g) and *trans,cis*-XXVb (2.8 g, 47%) which was recrystallized from ether to give *trans*-XXVb (2.1 g) and *cis*-XXVb (0.33 g).

Methyl Ester (*trans*-XXIVb): Treatment of *trans*-XXVb with CH_2N_2, followed by chromatographic purification gave a yellow oil.

Methyl Ester (*cis*-XXIVb): Treatment of *cis*-XXVb with CH_2N_2, followed by recrystallization from ether–hexane gave yellow needles.

***trans*-2,3-Dimethoxy-5-methyl-6-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (*trans*-XXVc)**——The condensation of 2,3-dimethoxy-5-methyl-1,4-benzohydroquinone (XXIIIc) (1.8 g) with XXII (1.6 g) and the hydrolysis of the condensed product carried out in a manner similar to that for VIIb gave the oxidized starting material (XVIIIc) (0.5 g), and *trans,cis*-XXVc (1.4 g, 45%) which was crystallized from ether–hexane. The resulting crystals were recrystallized from the same solvent to give *trans*-XXVc as orange crystals.

2,3,5-Trimethyl-6-(5′-carboxy-3′-hydroxy-3′-methylpentyl)-1,4-benzoquinone Lactone (XXIXa)——A mixture of *trans,cis*-XXVa (50 mg), conc. H_2SO_4 (1.0 ml) and tetrahydrofuran (1 ml) was stirred at room temperature for 1 hr. The reaction mixture was diluted with H_2O and extracted with AcOEt. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to preparative TLC using benzene–AcOEt (4: 1) as the developing solvent to give yellow cubic crystals, mp 64—66° (lit.,[16] mp 64°) (31 mg, 62%).

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2-Methyl-3-(5′-carboxy-3′-hydroxy-3′-methylpentyl)-1,4-naphthoquinone Lactone (XXIXb)——1) *trans, cis*-XXVb (100 mg) was treated in a manner similar to that for XXIXa and purified by TLC using $CHCl_3$–EtOH (19:1) as the developing solvent. Recrystallization from ether–hexane gave yellow crystals, mp 93—96° (lit.,[17] mp 93—95°) (32 mg, 32%).

2) A solution of *trans,cis*-XXVb (1 mg) in ether was shaken with an aqueous solution of $Na_2S_2O_4$. The ether layer was separated and evaporated *in vacuo*. The resulting residue was heated with 1.5 N HCl at 75° for 2 hr in a stream of N_2. The mixture was stirred with 5% $FeCl_3$ and extracted with ether. The extract was washed with H_2O and dried over Na_2SO_4. The residue upon removal of the solvent was purified by TLC using $CHCl_3$–ether–EtOH (14:5:1) as the developing solvent to give XXIXb (0.77 mg, 77%).

2,3-Dimethoxy-5-methyl-6-(5′-carboxy-3′-hydroxy-3′-methylpentyl)-1,4-benzoquinone Lactone (XXIXc)——*trans,cis*-XXVc (5 mg) was treated in a manner similar to that described above (XXIXb-2) and purified by TLC using $CHCl_3$–ether–EtOH (2:3:1) as the developing solvent to give an orange oil (4.8 mg, 96%). This compound was identified with the authentic XXIXc.[9]

2,3,5-Trimethyl-6-(3′-hydroxy-3′-methyl-5′-methoxycarbonylpentyl)-1,4-benzoquinone (XXXI)——To a well-stirred mixture of XXIXa (500 mg), 20% $Na_2S_2O_4$ (5 ml) and ether (5 ml), 30% KOH (5 ml) was added in a stream of N_2. The mixture was stirred for 2 hr, then acidified with 3 N HCl in the presence of crushed ice, extracted with ether and the extracts were dried over Na_2SO_4. The ether extract was shaken with Ag_2O and $MgSO_4$ to oxidize the hydroquinone to the quinone (XXX). The solids were filtered off, and the filtrate treated with CH_2N_2 and evaporated *in vacuo*. The residue was chromatographed on silicic acid. The starting material (XXIXa) (119 mg) was recovered from the first fraction. The second fraction gave a yellow oil (178 mg, 32%). UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$): oxidized form 269 (584), 262 (564); reduced form 289 (92). IR ν_{max}^{film} cm^{-1}: 3500 (OH), 1740, 1310 ($COOCH_3$), 1640, 1620 (quinone). NMR ($CDCl_3$): 8.77 (3H, s, side chain CH_3), 8.65—8.15 (4H, m, CH_2), 8.02 (3H, s, ring CH_3), 7.99 (6H, s, ring CH_3): 7.79 (1H, s, OH), 7.67—7.15 (4H, m, ring CH_2, CH_2COO), 6.34 (3H, s, $COOCH_3$). *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.17; H, 7.79.

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