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Ubiquinone and Related Compounds. XXXI.[1] Synthesis of Urinary Metabolites of Ubiquinone, Phylloquinone, α-Tocopherol and Their Related Compounds

Masazumi Watanabe, Kayoko Okamoto, Isuke Imada, and Hiroshi Morimoto

Central Research Division, Takeda Chemical Industries, Ltd.[2]

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Metabolites (XVIIa, b, c) of ubiquinone, phylloquinone and α-tocopherol, and their 2′,3′-dihydro (XXa, b, c), dicarboxy (XVIa, b, XXIIIa, b, c, XXIVa, b and XXVa, b) and 3′-demethyl (XXIa, b) derivatives were synthesized. During the synthetic studies of these compounds, we found that *cis*-4-acetoxy-1-bromo-2-methyl-2-butene (*cis*-III) was more reactive to nucleophiles than the corresponding *trans* isomer. γ-Vinyl-γ-butyrolactone (XII), which was a useful starting material for the synthesis of XXIa, b, was synthesized in one step from 1,3-butadiene. The 3′-methyl group of XVIIa, b was not essential for the membrane-stabilizing activity in the rat-liver lysosome. Introduction of a carboxyl but not a carboxyl ester group into XVIIa, b resulted in a loss of the stabilizing activity.

Keywords——ubiquinone metabolite; phylloquinone metabolite; α-tocopherol metabolite; isoprene; butadiene; metabolite related compounds; structure-activity relationship

Ubiquinone, phylloquinone and α-tocopherol are metabolized into hexenoic acids (XVIIa, b, c) and butyric acids by ω-oxidation of the multiprenyl side chain followed by β-oxidation, and these metabolites are excreted in urine as the conjugates of their hydroquinone forms.[3] The effects of these metabolites on the lysosomal membrane of rat liver[1a] and on phagocytosis[4] and immune response[1b,c,4] in mice have been also reported. These earlier findings,[3,4] suggest that phylloquinone and α-tocopherol, as well as ubiquinone (at least exogenous one) might affect the membrane after being converted into the metabolite. In this report, the structure-activity relationships of these metabolites are discussed together with a convenient synthesis of XVIIa, b, c and their dihydro (XXa, b, c) as well as dicarboxy (XVIa, b, XXIIIa, b, c, XXIVa, b and XXVa, b) derivatives from isoprene (I), and the synthesis of 3′-demethyl derivatives (XXIa, b) of XVIIa, b from 1,3-butadiene (VII).

In previous studies,[5] we synthesized XVIIa, b, c using methyl 6-hydroxy-4-methyl-4-hexenoate (**A**) which was derived from geranyl acetate by selective degradation with ozone followed by oxidation and esterification, and also using methyl 4-hydroxy-4-methyl-5-hexenoate (**B**) which was obtained through three steps from levulinic acid. In the meanwhile, Sato *et al.*[6] have reported the synthesis of *trans*-4-acetoxy-1-bromo-2-methyl-2-butene (*trans*-III)

1) *a*) Part XXVIII: M. Watanabe, R. Negishi, I. Imada, M. Nishikawa, and H. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 183 (1974); *b*) Part XXIX: K. Sugimura, I. Azuma, Y. Yamamura, I. Imada, and H. Morimoto, *Internat. J. Vit. Nutr. Res.*, **46**, 192 (1976); *c*) Part XXX: K. Sugimura, I. Azuma, Y. Yamamura, I. Imada, and H. Morimoto, *ibid.*, **46**, 464 (1976).
2) Location: *Juso-honmachi, Yodogawa-ku, Osaka 532, Japan.*
3) I. Imada, M. Watanabe, N. Matsumoto, and H. Morimoto, *Biochemistry*, **9**, 2870 (1970); M. Watanabe, M. Toyoda, I. Imada, and H. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 176 (1974).
4) I. Imada, I. Azuma, S. Kishimoto, Y. Yamamura, and H. Morimoto, *Int. Arch. Allergy Appl. Immunol.*, **43**, 898 (1972).
5) *a*) M. Watanabe, I. Imada, and H. Morimoto, *Biochemistry*, **9**, 2879 (1970); *b*) M. Watanabe, M. Kawada, M. Nishikawa, I. Imada, and H. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 566 (1974).
6) K. Sato, S. Inoue, S. Ota, and Y. Fujita, *J. Org. Chem.*, **37**, 462 (1972).

by the partial acetylation of *trans*-1,4-dibromo-2-methyl-2-butene (*trans*-II) which was obtained by bromination of I. Thereupon we attempted to use *trans*-III for the synthesis of XVIIa, b, c (Chart 1).

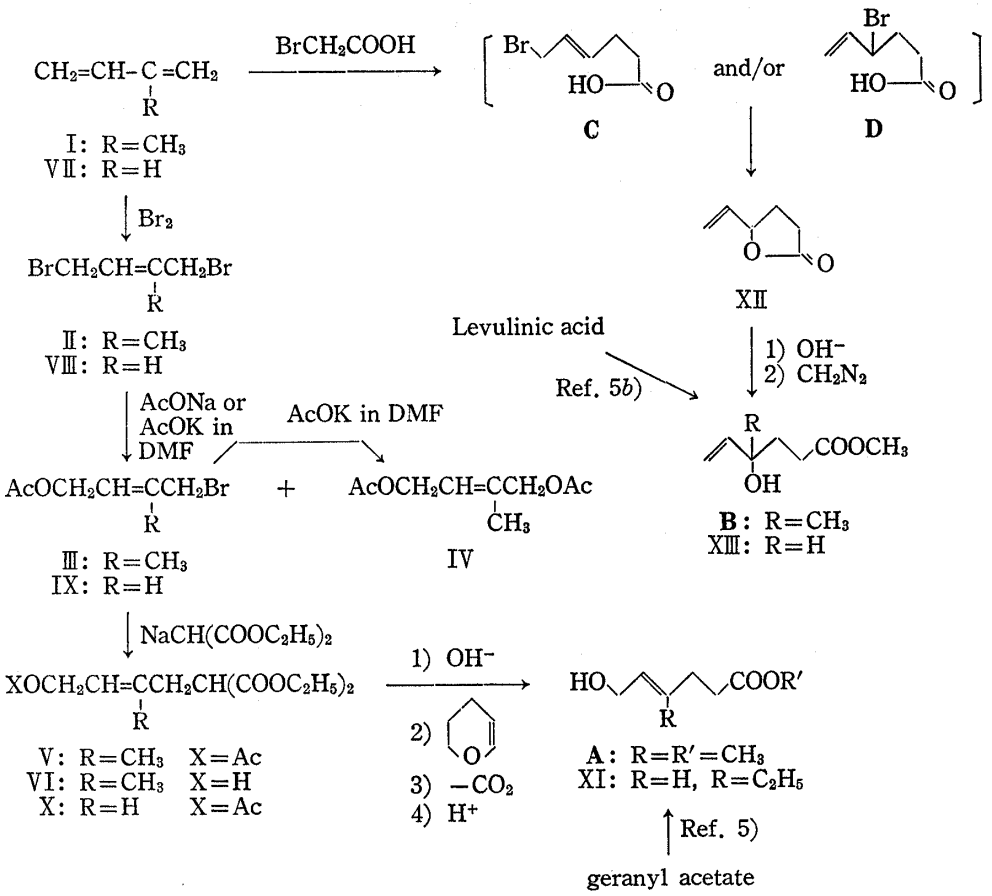


Chart 1

Although several researchers had reported that bromination of I gave exclusively *trans*-II,[7] Heasley *et al.* showed that *cis*-II was also formed on the bromination.[8] In our reexamination of this reaction, a mixture (*trans*, *cis*[9]-II) was obtained. The reaction of *trans*,

Table I. Products by Partial Acetylation of *trans,cis*-1,4-Dibromo-2-methyl-2-butene (*trans,cis*-II)[a]

Product	Yield (%)	*cis*/*trans* Ratio[b]
trans,cis-II (Recovered)	23.4	1/14.0
trans,cis-III	57.8	1/14.5
trans,cis-IV	14.9	1/ 2.7

a) Fraction 3 (*cis*/*trans*=1/7.3) described in the Experimental section was used.
b) Analyzed by GLC, procedure given in the Experimental section.

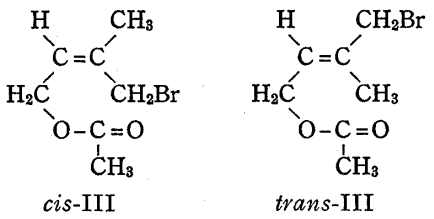


Chart 2

7) See the references cited in Ref. 8).
8) V.L. Heasley, C.L. Frye, R.T. Gore, Jr., and P.S. Wilday, *J. Org. Chem.*, 33, 2342 (1968).
9) Hereafter, a mixture of *trans* and *cis* isomers are referred to as *trans*, *cis*.

cis-II with one molar equivalent of potassium acetate in N,N-dimethylformamide (DMF) at 0° afforded *trans,cis*-III and *trans,cis*-1,4-diacetoxy-2-methyl-2-butene (*trans,cis*-IV). The *cis*/*trans* ratio (1/2.7) of the resulting IV increased to about three times that (1/7.3) of the starting material II, while that (1/14.5) of III decreased to one half the ratio (1/7.3) of II (Table I). Acetylation of *trans*-III gave exclusively *trans*-IV without isomerization to *cis*-IV. These results suggest that *cis*-III is more easily acetylated than *trans*-III. It seems that the acetyl carbonyl group of *cis*-III is located nearer the bromine atom than that of *trans*-III, and

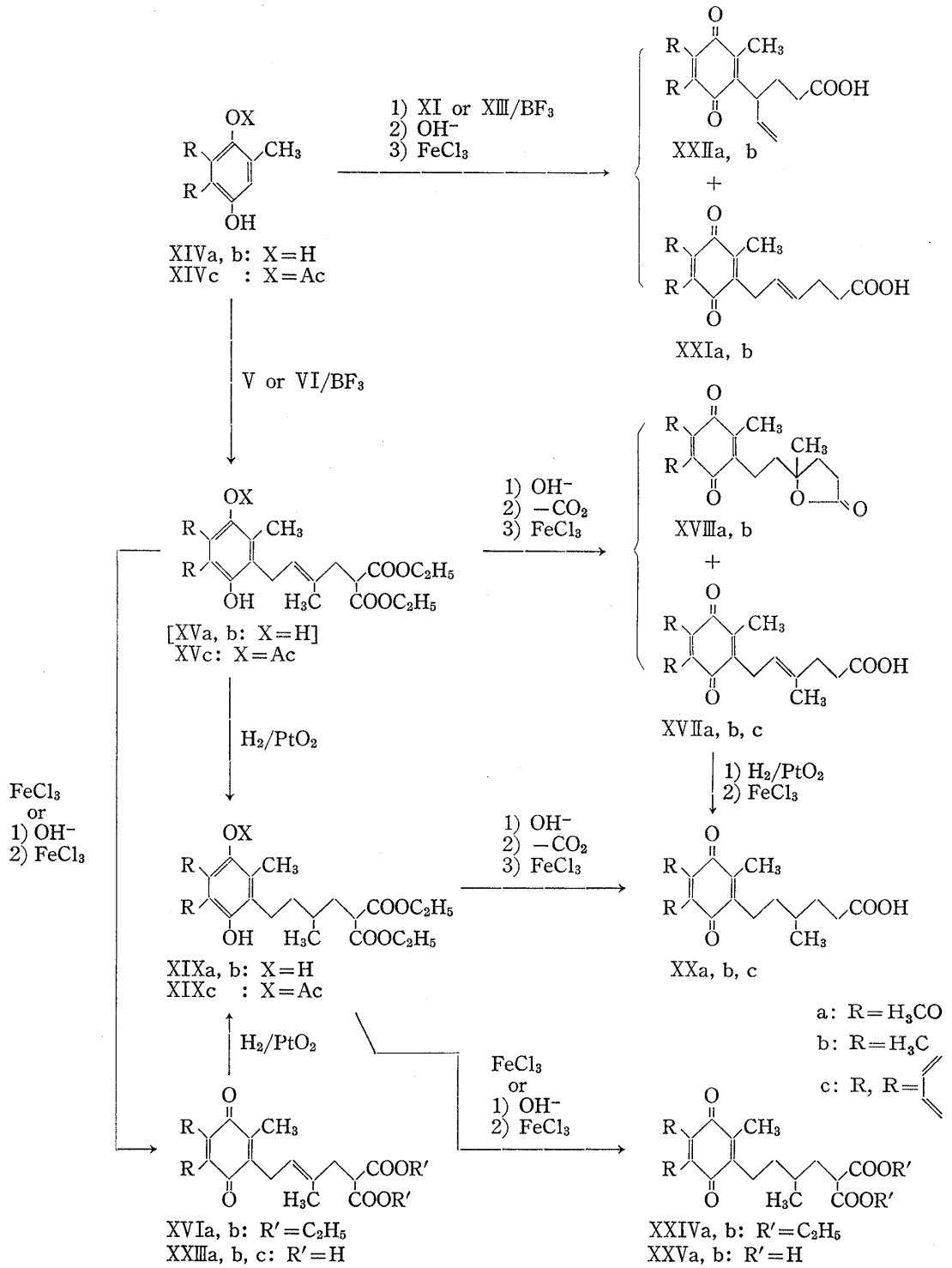


Chart 3

this may facilitate the formation of allylic cation upon the nucleophilic reaction (Chart 2). The reaction of *trans,cis*-III with sodiomalonic ester in ethanol afforded *trans,cis*-VI in which the ratio of *cis*-VI to *trans*-VI was higher than that of the starting III. A similar reaction of *trans*-III gave only *trans* isomers (*trans*-V and *trans*-VI). These results are consistent with that of the partial acetylation of II, and support our assumption that there may be a difference of reactivity to nucleophiles between *trans*-III and *cis*-III.

In an attempt to synthesize 3′-demethyl derivatives (XXIa, b) we tried to synthesize *trans*-ethyl 6-hydroxy-4-hexenoate (*trans*-XI), as the side chain of XXIa, b (Chart 1). It has been reported that bromination of VII gave predominantly *trans* isomer (*trans*-VIII) in contrast to bromination of I.[10] According to the method used for the synthesis of V, *trans*-4-acetoxy-1-bromo-2-butene (*trans*-IX) which was derived from *trans*-VIII was condensed with sodiomalonic ester. The resulting malonic ester derivative (X) was decarboxylated to *trans*-XI in a manner similar to the synthesis of *cis*-XI.[11]

As an alternative route (Chart 1) for XI, VII was condensed with bromoacetic acid to obtain 6-bromo-4-hexenoic acid (**C**) according to the method stated in a United States patent.[12] However, the product was not **C** but γ-vinyl-γ-butyrolactone (XII) according to analysis by infrared (IR) and nuclear magnetic resonance (NMR) spectra. It is well known that some electrophiles react with VII to give both 1,4- and 1,2-adducts,[13] and that γ-halocarboxylic acid[14] and γ,δ-unsaturated carboxylic acid[15] are easily converted into γ-lactone derivatives on heating. Therefore, XII may be formed from **C** and/or 4-bromo-5-hexenoic acid (**D**) which resulted from the 1,2-addition of bromoacetic acid to VII. Here we found one step synthesis of XII from VII. XII was converted into methyl 4-hydroxy-5-hexenoate (XIII) by the method used for **B**.[5b] This route seems to be convenient for the synthesis of the side chain of XXI compared with the method described above.

These side chain moieties (*trans*-V, *trans*-VI, *trans*-XI and XIII) were condensed with hydroquinones (XIVa, b, c) to obtain metabolites (XVIIa, b, c) and related compounds (Chart 3). The condensation of *trans*-V or *trans*-VI with the hydroquinones (XIVa, b, c) gave XVa, b, c which were oxidized to XVIa, b, hydrolyzed and oxidized to XXIIIa, b, c, and hydrolyzed, decarboxylated and subsequently oxidized to XVIIa, b, c. In this decarboxylation, small amounts of γ-lactone derivatives (XVIIIa, b) were obtained as by-products, which might have been formed from XVIIa, b by attack of a proton on the 2′-carbon atom followed by lactonization.[15] The catalytic hydrogenation of XVIIa, b, c followed by oxidation of the resulting hydroquinone derivatives yielded 2′,3′-dihydro derivatives (XXa, b, c). XXa, b, c could also be obtained by decarboxylation of XIXa, b, c derived from XVIa, b and XVc without producing the undesired XVIIIa, b, c. XIXa, b were oxidized to XXIVa, b, and hydrolyzed and oxidized to XXVa, b. Next, XIII was condensed with XIVa, b to obtain 3′-demethyl derivatives (XXIa, b) of XVIIa, b. The products were the 6: 7 mixture of (5′-carboxy-2′-hexenyl)-1,4-benzoquinone derivatives (XXIa, b) and (3′-carboxy-1′-vinylpropyl)-1,4-benzoquinone derivatives (XXIIa, b). Each of them was isolated by recrystallization and preparative thin-layer chromatography (TLC). To avoid the production of XXII, the primary allylic alcohol derivative (*trans*-XI) was condensed with XIVb, however, a 6: 7 mixture of XXIb and XXIIb was obtained. Therefore, the allylic cations produced from *trans*-XI and XIII might reach the same equilibrium between primary and secondary cations, and both cations could condense with XIV. On the other hand, the condensation of XIV with V, VI, **A**[5] or **B**[5b] afforded exclusively the products condensed with primary

10) V.L. Heasley and S.K. Taylor, *J. Org. Chem.*, **34**, 2779 (1969).
11) E.J. Corey and H.A. Kirst, *J. Am. Chem. Soc.*, **94**, 667 (1972).
12) I.L. Mador, U.S. Patent 3338960 [*C.A.*, **68**, 21543*y* (1968)].
13) V.L. Heasley, G.E. Heasley, R.A. Loghry, and M.R. McConnell, *J. Org. Chem.*, **37**, 2228 (1972).
14) H. Plieninger, *Chem. Ber.*, **83**, 265 (1950).
15) R.P. Linstead and H.N. Rydon, *J. Chem. Soc.*, **1933**, 580.

cations. This difference of products may be due to the steric hindrance of methyl group of tertiary cation produced from V, VI, **A** or **B**.

Previously,[1a] we reported that the 2′,3′-double bond of XVIIb was not essential for stabilizing the lysosomal membrane of rat liver, since XVIIb, XVIIIb and XXb showed nearly equal activities. The same test as already described[1a] on XVIIa, b and related compounds showed that dicarboxylic acid esters (XVIa, b, XXIVa, b) and 3′-demethyl compounds (XXIa, b) had the membrane-stabilizing activities nearly equal to, or slightly less than XVIIa, b, respectively, but dicarboxylic acids (XXIIIa, b, XXVa, b) labilized the membrane (Table II). From these results, it was concluded that the 3′-methyl group of XVIIa, b is not essential for the activity and introduction of a carboxyl group into XVIIa, b results in a loss of the stabilizing activity. A proper lipophilicity may be required for the membrane-stabilizing activity of these compounds.

Table II. Effect of XVIIa, b and Related Compounds on Release of Hydrolases from Lysosomal Fraction of Rat Liver

Compound	Concentration (M)	Hydrolase release (%)[a]		n[b]
		β-Glucuronidase	Acid phosphatase	
XVIIa	2×10^{-5}	98± 3[c]	99± 6	6
	2×10^{-4}	81± 4	73± 9	6
XXa	2×10^{-5}	89	89	1
	2×10^{-4}	78	77	1
XXIa	2×10^{-5}	95	92	2
	2×10^{-4}	83	71	2
XVIa	2×10^{-5}	93± 3	87± 4	3
	2×10^{-4}	82± 3	73± 6	3
XXIIIa	2×10^{-5}	115	146	2
	2×10^{-4}	129	208	2
XXIVa	2×10^{-5}	89	79	2
	2×10^{-4}	77	66	2
XXVa	2×10^{-5}	109± 2	121± 4	3
	2×10^{-4}	150± 4	266±24	3
XVIIb	2×10^{-5}	77± 4	65± 4	14
	2×10^{-4}	62± 4	50± 4	14
XXb	2×10^{-5}	68± 2	55± 2	6
	2×10^{-4}	66± 5	58± 6	6
XXIb	2×10^{-5}	84	84	2
	2×10^{-4}	72	70	2
XVIb	2×10^{-5}	80±10	65±14	3
	2×10^{-4}	60± 2	47± 6	3
XXIIIb	2×10^{-5}	110± 1	112	3
	2×10^{-4}	107± 2	113± 8	3
XXIVb	2×10^{-5}	68	52	2
	2×10^{-4}	63	45	2
XXVb	2×10^{-5}	112	116	2
	2×10^{-4}	118	143	2

a) Effect on membrane stability was assayed by determining the hydrolases released from the lysosomal fraction during incubation at 37° for 90 min as already described.[1a] % of control (Control: 100%). All the test compounds did not inhibit the lysosomal hydrolases.
b) Number of assays.
c) Standard error.

Experimental[16]

***trans,cis*-1,4-Dibromo-2-methyl-2-butene (*trans,cis*-II)**——To a well stirred solution of isoprene (I, 68 g) in CCl_4 (1 l), bromine (160 g) was added dropwise at 10° over a period of 5 hr and the mixture was

16) Melting points, measured with a Yanagimoto micro melting point apparatus are uncorrected. UV spectra were recorded in EtOH with a Hitachi EPS-3T spectrophotometer and IR spectra were with a Hitachi EPI-S2 spectrophotometer. NMR spectra were run on Varian HA-100 and T-60 spectrometers with TMS as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; t, triplet; q, quartet; b, broad; m, multiplet.

stirred at room temperature for 13 hr. After removal of the solvent, the residue was separated into four fractions by distillation under reduced pressure and each fraction was analyzed by GLC. GLC analysis was done with an Ohkura gaschromatograph (Model 2100) under the following conditions: Flow rate, N_2, 45 ml/min, H_2, 50 ml/min, air, 500 ml/min; column length and diameter, 200×0.2 cm; column temperature, 86°; column composition, 5% SE-30 on Gas Chrom Q (60—80 mesh). t_R (min): *trans*-II=7.2, *cis*-II=5.7.

Feaction	bp (mmHg)	g	% of II	Ratio *cis*-II/*trans*-II
1	60—77° (7)	15.1	72	1/ 4.7
2	78—79° (7)	44.8	91	1/ 5.8
3	80° (7)	75.6	100	1/ 7.3
4	76—80° (7)	50.9	100	1/12.4

Partial Acetylation of Dibromides (*trans,cis*-II)——To a well stirred mixture of anhydrous AcOK (8.6 g) in DMF (80 ml) was added dropwise a solution of *trans,cis*-II (20 g) in DMF (20 ml) over a period of 1.5 hr. After further stirring for 20 hr at 0°, the reaction mixture was diluted with water and extracted with petroleum ether. The extract was washed with water, dried over Na_2SO_4, and the solvent was evaporated *in vacuo* (usual manner hereafter), and the products were analyzed by GLC under the same condition as for II. t_R (min): *cis*-4-acetoxy-1-bromo-2-methyl-2-butene (*cis*-III)=10.6, *trans*-III=12.9, *cis*-1,4-diacetoxy-2-methyl-2-butene (*cis*-IV)=17.0, *trans*-IV=20.3.

Acetylation of *trans*-III——The acetylation of *trans*-III (210 mg) was done in the same manner as the acetylation of *trans,cis*-II. The raw product was chromatographed on silica gel eluted with hexane–ether as the eluent giving *trans*-IV as a colorless oil. Yield 145 mg (77%). NMR (CCl_4): 1.73 (3H, s, $=CCH_3$), 1.98 (3H, s, $COCH_3$), 2.01 (3H, s, $COCH_3$), 4.44 (2H, s, $=CCH_2$), 4.57 (2H, d, $C\underline{H}_2CH=$), 5.57 (1H, t, CH=).

***trans*-Diethyl 4-Hydroxy-2-methyl-2-butenylmalonate (*trans*-VI), *cis*-VI and *trans*-Diethyl 4-Acetoxy-2-methyl-2-butenylmalonate (*trans*-V)**——1) Reaction in EtOH: Diethyl malonate (10.2 g) was added to a solution of Na (1 g) in EtOH (15.5 ml). The solution was diluted with benzene (5.3 ml), then *trans*-III (10.5 g) was added to this solution at room temperature. After being stirred for 1 hr, the reaction mixture was diluted with water and extracted with ether. The ether extract was worked up in the usual manner and the product was chromatographed on silica gel (450 g) with $CHCl_3$ (4.3 l) then $CHCl_3$–EtOH (49: 1, 1.2 l) as eluents. The fraction eluted with $CHCl_3$ was evaporated *in vacuo* giving *trans*-V as a colorless oil. Yield 6.17 g (50%). IR ν_{max}^{film} cm^{-1}: 1740 ($OCOCH_3$, $COOC_2H_5$). NMR ($CDCl_3$): 1.25 (6H, t, $COOCH_2C\underline{H}_3$), 1.73 (3H, s, $=CCH_3$), 1.96 (3H, s, $COCH_3$), 2.55 (2H, d, $=CCH_2$), 3.42 (1H, t, $CH<^{CO}_{CO}$), 4.12 (4H, q, $COOC\underline{H}_2CH_3$), 4.26 (2H, d, $=CCH_2O$), 5.32 (1H, t, =CH). *Anal.* Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.69; H, 7.74.

The fraction eluted with $CHCl_3$–EtOH (49: 1) was evaporated *in vacuo* giving *trans*-VI as a colorless oil. Yield 2.55 g (24%). IR ν_{max}^{film} cm^{-1}: 3430 (OH), 1735 ($COOC_2H_5$). NMR ($CDCl_3$): 1.25 (6H, t, $COOCH_2C\underline{H}_3$), 1.68 (3H, s, $=CCH_3$), 1.78 (1H, s, OH), 2.60 (2H, d, $=CCH_2$), 3.52 (1H, t, $CH<^{CO}_{CO}$), 4.01—4.25 (6H, m, $COOC\underline{H}_2CH_3$, $=CC\underline{H}_2OH$), 5.42 (1H, t, =CH).

A similar reaction starting from *trans,cis*-III (2.15 g) gave *trans*-VI (1.08 g, 43%) and *cis*-VI (0.37 g, 15%).

cis-VI: IR ν_{max}^{film} cm^{-1}: 3430 (OH), 1735 ($COOC_2H_5$). NMR ($CDCl_3$): 1.25 (6H, t, $COOCH_2C\underline{H}_3$), 1.73 (3H, s, $=CCH_3$), 1.95 (1H, s, OH), 2.68 (2H, d, $=CCH_2$), 3.56 (1H, t, $CH<^{CO}_{CO}$), 4.01—4.28 (6H, m, $COOC\underline{H}_2CH_3$, $=CC\underline{H}_2OH$), 5.54 (1H, t, =CH).

2) Reaction in Benzene: To a solution of diethyl malonate (2.83 g) in benzene (6 ml) was added Na (0.122 g). The mixture was refluxed for 5 hr then a solution of *trans*-III (1.02 g) in benzene (5 ml) was added dropwise. After being stirred for 5 hr, the mixture was diluted with water and extracted with ether. The extract was worked up in the usual manner. The residue was chromatographed on silica gel with hexane–ether (9: 1) as the eluent giving *trans*-V. Yield 0.97 g (69%).

***trans*-Ethyl 6-Hydroxy-4-hexenoate (*trans*-XI)**——To a well stirred solution of diethyl malonate (3.7 g) in THF (10 ml) and HMPA (2 ml) was added NaH (50% in mineral oil, 1.1 g). After stirring at room temperature for 30 min, a solution of *trans*-4-acetoxy-1-bromo-2-butene (*trans*-IX)[17] (3.7 g) in THF (10 ml) was added dropwise and the mixture was stirred at room temperature for 2 hr. The mixture was diluted with water and extracted with ether. The ether extract was worked up in the usual manner to give *trans*-diethyl 4-acetoxy-2-butenylmalonate (X, 2.6 g), bp 135—137° (0.7 mmHg). This was hydrolyzed with K_2CO_3

17) Y. Bahurel, F. Collonges, A. Menet, F. Pautet, A. Poncet, and G. Descotes, *Bull. Soc. Chim. France*, 1971, 2203.

(1.3 g) in EtOH at 75° for 2 hr. The precipitates were filtered off and the filtrate was evaporated *in vacuo*. The resulting oil was dissolved in ether and heated with 3,4-dihydro-α-pyran under reflux for 4 hr in the presence of *p*-toluenesulfonic acid. K_2CO_3 was added to the reaction mixture, which was then stirred at room temperature for 30 min. The precipitates were filtered off and the filtrate was evaporated *in vacuo*. A solution of the resulting oil in DMSO (10 ml) was heated at 160° for 4 hr in the presence of NaCN (0.56 g). The reaction mixture was poured into water and the aqueous solution was extracted with pentane. After removal of the solvent, the residue was dissolved in THF (2 ml) and the solution was heated with 3 N HCl at 50° for 30 min. The mixture was extracted with AcOEt, and the extract was worked up in the usual manner to give an oil. The oil was chromatographed on silica gel with $CHCl_3$ as the eluent giving a colorless oil. Yield 230 mg (8%). NMR (CCl_4): 1.24 (3H, t, $COOCH_2C\underline{H}_3$), 2.33 (4H, s, CH_2CH_2COO), 2.97 (1H, b, OH), 3.95 (2H, b, $C\underline{H}_2OH$), 4.08 (2H, q, $COOC\underline{H}_2CH_3$), 5.60 (2H, m, CH=).

γ-Vinyl-γ-butyrolactone (XII)——A mixture of 1,3-butadiene (VII) (14 g), bromoacetic acid (10.4 g), ferrous chloride (0.47 g) and acetonitrile (35 ml) in a sealed tube was heated at 115° for 12 hr. After cooling, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was distilled under reduced pressure to give a colorless oil. Yield 2.5 g (30%). bp 66° (0.5 mmHg) [lit.,[18] bp 75° (2 mmHg)]. IR ν_{max}^{film} cm^{-1}: 1770 (γ-lactone). NMR ($CDCl_3$): 1.82—2.70 (4H, m, CH_2), 4.95 (1H, q, CH–O), 5.15—6.22 (3H, m, CH_2=CH).

Methyl 4-Hydroxy-5-hexenoate (XIII)——XII (1.7 g) was hydrolyzed with 25% KOH (10 ml) at room temperature. The aqueous solution was washed with ether to remove the neutral substance and then acidified with cold dil. HCl and extracted with AcOEt. The extract was washed with saturated aqueous NaCl solution and treated with ethereal solution of CH_2N_2. The solvents were removed *in vacuo* giving a colorless oil. Yield 1.1 g (46%). The crude product was subjected to the next step without further purification. NMR ($CDCl_3$): 1.62—2.06 (2H, m, CH_2), 2.30—2.60 (2H, m, CH_2COO), 3.68 (3H, s, $COOCH_3$), 4.14 (1H, q, CH), 5.00—6.20 (3H, m, CH_2=CH).

***trans*-1-Acetoxy-4-hydroxy-2-methyl-3-(5′,5′-diethoxycarbonyl-3′-methyl-2′-pentenyl)naphthalene (XVc)**——1) To a well stirred mixture of XIVc (599 mg), BF_3-ether (0.76 ml), freshly fused $ZnCl_2$ (140 mg) and dioxane (10 ml), a solution of *trans*-V (571 mg) in dioxane (10 ml) was added dropwise over a period of 2 hr in a stream of N_2 at 70—85°. The reaction mixture was stirred for another 3 hr at 80°, then diluted with water and extracted with ether. The extract was worked up in the usual manner and the residue was chromatographed on silica gel (41 g) with $CHCl_3$ as the eluent. After the $CHCl_3$ had been evaporated, the resulting residue was crystallized from hexane–ether (1: 1) giving pale brown granules. mp 99—100°. Yield 580 mg (66%). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1760, 1735 ($COOC_2H_5$, $OCOCH_3$). NMR ($CDCl_3$): 1.12 (6H, t, $COOCH_2C\underline{H}_3$), 1.82 (3H, s, $=CCH_3$), 2.17 (3H, s, CH_3 on the ring), 2.43 (3H, s, $OCOCH_3$), 2.58 (2H, d, $=CCH_2$), 3.25 (2H, d, CH_2 on the ring), 3.50 (1H, t, $CH\langle^{CO}_{CO}$), 4.04 (4H, q, $COOC\underline{H}_2CH_3$), 5.17 (1H, t, =CH), 5.46 (1H, b, OH), 7.31—8.06 (4H, m, the ring H). *Anal.* Calcd. for $C_{25}H_{30}O_7$: C, 67.85; H, 6.83. Found: C, 67.80; H, 6.92.

2) Condensation of XIVc (1.5 g) with *trans*-VI (1.21 g) in a manner similar to 1) gave XVc. Yield 550 mg (25%).

***trans,cis*-2,3-Dimethoxy-5-methyl-6-(5′,5′-diethoxycarbonyl-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XVIa)**——To a solution of XIVa (364 mg) and *trans*-V (764 mg) in dioxane (15 ml) was added a solution of BF_3-ether (1.5 ml) in dioxane (12 ml). The mixture was stirred at 45—55° for 6 hr in a stream of N_2, then diluted with water and extracted with ether. The ether extract was shaken with 10% $FeCl_3$, then worked up in the usual manner and the residue was chromatographed on silica gel (40 g) with $CHCl_3$ as the eluent. The resulting product was purified by TLC using hexane–ether (1: 1) as the developing solvent to give an orange oil. Yield 312 mg (39%). UV λ_{max} nm ($E_{1cm}^{1\%}$): oxidized form 275 (359), reduced form 291 (131). IR ν_{max}^{film} cm^{-1}: 1750, 1735 ($COOC_2H_5$), 1665, 1650, 1615 (quinone). NMR ($CDCl_3$): 1.20, 1.25 (6H, t, *trans* and *cis* form of $COOCH_2C\underline{H}_3$), 1.65, 1.72 (3H, s, *cis*=CCH_3 and *trans*=CCH_3), 1.96, 1.99 (3H, s, *trans* and *cis* form of CH_3 on the ring), 2.53, 2.75 (2H, d, *trans*=CCH_2 and *cis*=CCH_2), 3.13, 3.18 (2H, s, *trans* and *cis* form of CH_2 on the ring), 3.46 (1H, t, $CH\langle^{CO}_{CO}$), 3.94 (6H, s, OCH_3), 4.10 (2H, q, $COOC\underline{H}_2CH_3$), 4.98 (1H, t, =CH). *Anal.* Calcd. for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.66; H, 6.92.

***trans,cis*-2,3,5-Trimethyl-6-(5′,5′-diethoxycarbonyl-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XVIb)**——XIVb (1.09 g) was condensed with *trans*-V (1.74 g) in a manner similar to that for XVIa. The resulting product was chromatographed on silica gel with hexane–ether (19: 1) as the eluent, giving a yellow oil. Yield 1.31 g (57%). UV λ_{max} nm ($E_{1cm}^{1\%}$): oxidized form 259 (448), 267 (456); reduced form 287 (108). IR ν_{max}^{film} cm^{-1}: 1755, 1740 ($COOC_2H_5$), 1650 (quinone). NMR ($CDCl_3$): 1.23 (6H, t, $COOCH_2C\underline{H}_3$), 1.65, 1.74 (3H, s, *cis* and *trans*=CCH_3), 1.98 (9H, s, CH_3 on the ring), 2.54, 2.76 (2H, d, *trans* and *cis*=CCH_2), 3.14 (2H, d, CH_2 on the ring), 3.26, 3.32 (1H, t, *trans* and *cis* $CH\langle^{CO}_{CO}$), 4.14 (4H, q, $COOC\underline{H}_2CH_3$), 5.00 (1H, t, =CH). *Anal.* Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.01; H, 7.62.

18) R.R. Russell and C.A. Vanderwerf, *J. Am. Chem. Soc.*, **69**, 11 (1947).

***trans,cis*-2,3-Dimethoxy-5-methyl-6-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XVIIa) and 2,3-Dimethoxy-5-methyl-6-(5′-carboxy-3′-hydroxy-3′-methylpentyl)-1,4-benzoquinone Lactone (XVIIIa)**——A solution of XVIa (90 mg) in ether (2 ml) was stirred with 10% aqueous $Na_2S_2O_4$ (4 ml) in a stream of N_2 for reduction to XVa. To this solution, 30% KOH was added and the mixture was stirred for 1 hr, then acidified with dil. HCl and extracted with AcOEt. The extract was worked up in the usual manner to give powder. The resulting powder was heated at 130—140° for 1 hr to decarboxylate. The residue was dissolved in ether and the solution was shaken with 10% $FeCl_3$ (4 ml). The ether layer was worked up in the usual manner to give an orange oil. The oil was subjected to preparative TLC using $CHCl_3$–EtOH (19: 1) as the developing solvent. The band of $R_f=0.39$ was extracted with ether and the extract was evaporated *in vacuo* giving XVIIa as an orange oil (21 mg, 31%). This was identified with the authentic sample (XVIIa)[5a] by UV, IR and NMR spectra. A similar treatment of the band of $R_f=0.78$ gave XVIIIa (4.8 mg, 7%) as an orange oil which was identified with the authentic sample[5a] by UV, IR and NMR spectra.

***trans*-2,3,5-Trimethyl-6-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XVIIb) and 2,3,5-Trimethyl-6-(5′-carboxy-3′-hydroxy-3′-methylpentyl)-1,4-benzoquinone Lactone (XVIIIb)**——Hydrolysis and decarboxylation of XVIb (374 mg) followed by oxidation were carried out in a manner similar to that for XVIIa and XVIIIa. The products were separated into three fractions by column chromatography with $CHCl_3$ as the eluent. The residue obtained from the third fraction was recrystallized from hexane–ether giving XVIIb as yellow needles, mp 102—103° (lit.,[5b] mp 103—104°). Yield 97 mg (35%). Recrystallization of the residue obtained from the second fraction from hexane–ether gave XVIIIb as yellow granules. mp 62—64° (lit.,[5b] mp 64—66°). Yield 25 mg (9%).

***trans*-2-Methyl-3-(5′-carboxy-3′-methyl-2′-pentenyl)-1,4-naphthoquinone (XVIIc)**——*trans*-XVc (519 mg) was treated in a manner similar to that for XVIIa and the product was recrystallized from hexane–ether giving yellow needles, mp 127—129° (lit.,[5b] mp 130—131.5°). Yield 109 mg (31%).

1-Acetoxy-4-hydroxy-2-methyl-3-(5′,5′-diethoxycarbonyl-3′-methylpentyl) naphthalene (XIXc)——XVc (884 mg) was hydrogenated over PtO_2 in dioxane (13 ml) at room temperature. The catalyst was filtered off then the filtrate was concentrated *in vacuo* and the residue was recrystallized from hexane–ether giving colorless needles, mp 94—97°. Yield 520 mg (59%). *Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.41; H, 7.19.

2,3-Dimethoxy-5-methyl-6-(5′-carboxy-3′-methylpentyl)-1,4-benzoquinone (XXa)——1) XVIa (103 mg) was hydrogenated over PtO_2 in EtOH (16 ml) at room temperature. After H_2 absorption had ceased, the catalyst was filtered off and the filtrate was evaporated *in vacuo* giving 2,3-dimethoxy-5-methyl-6-(5′,5′-diethoxycarbonyl-3′-methylpentyl)hydroquinone (XIXa) which was hydrolyzed, decarboxylated then oxidized in a manner similar to that for XVIIa. The product was subjected to preparative TLC using $CHCl_3$–EtOH (95: 5) as the developing solvent giving an orange oil. Yield 37 mg (48%). UV λ_{max} nm ($E^{1\%}_{1cm}$): oxidized form 278 (532), reduced form 290 (175). IR ν^{film}_{max} cm^{-1}: 2500, 1740, 1708 (COOH), 1665, 1650, 1615 (quinone). NMR ($CDCl_3$): 0.98 (3H, d, CH_3), 1.20—1.73 (5H, m, CH_2CHCH_2), 2.00 (3H, s, CH_3 on the ring), 2.25—2.58 (4H, m, CH_2 on the ring, CH_2COO), 3.97 (6H, s, OCH_3), 8.73 (1H, b, COOH). *Anal.* Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.72; H, 7.21.

2) XVIIa (65 mg) was hydrogenated over PtO_2 in EtOH (17 ml) at room temperature. After H_2 absorption had ceased, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The resulting hydroquinone compound was dissolved in ether and the solution was shaken with 10% $FeCl_3$ (7 ml). The ether layer was separated and worked up in the usual manner. The resulting oil was subjected to preparative TLC using $CHCl_3$–EtOH (95: 5) as the developing solvent to give an orange oil. Yield 53 mg (81%).

2,3,5-Trimethyl-6-(5′-carboxy-3′-methylpentyl)-1,4-benzoquinone (XXb)——1) XVIb (372 mg) was treated in a manner similar to that for XXa and the resulting product was recrystallized from ligroin to give yellow needles, mp 58—61°. Yield 142 mg (52%). UV λ_{max} nm: 261, 268. IR ν^{KBr}_{max} cm^{-1}: 2600, 1710 (COOH), 1640 (quinone). NMR ($CDCl_3$): 0.99 (3H, d, CH_3), 1.18—1.80 (5H, m, CH_2CHCH_2), 1.96 (9H, s, CH_3 on the ring), 2.26—2.50 (4H, m, CH_2 on the ring, CH_2COO), 11.12 (1H, b, COOH). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.23; H, 8.18.

2) XVIIb (878 mg) was hydrogenated in a manner similar to that for XXa to give XXb. Yield 827 mg (94%).

2-Methyl-3-(5′-carboxy-3′-methylpentyl)-1,4-naphthoquinone (XXc)——XIXc (222 mg) was treated in a manner similar to that for XXa and the resulting product was recrystallized from hexane–ether giving yellow needles, mp 61—63°. Yield 55 mg (37%). UV λ^{KBr}_{max} in EtOH containing 0.01 volume of 1 M ammonium acetate (pH 5.0) nm ($E^{1\%}_{1cm}$): oxidized form 244 (560), 248 (570), 265 (552), 272 (580), 330 (87), reduced form 244 (1380), 323 (140), 333 (140). IR ν^{KBr}_{max} cm^{-1}: 1705 (COOH), 1655, 1620 (quinone). NMR ($CDCl_3$): 1.00 (3H, d, CH_3), 1.25—1.78 (5H, m, CH_2CHCH_2), 2.16 (3H, s, CH_3 on the ring), 2.30—2.75 (4H, m, CH_2 on the ring, CH_2COO), 7.70 (2H, m, the ring H), 8.06 (2H, m, the ring H), 10.67 (1H, b, COOH). *Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.96; H, 6.80.

2,3-Dimethoxy-5-methyl-6-(5′-carboxy-2′-pentenyl)-1,4-benzoquinone (XXIa) and 2,3-Dimethoxy-5-methyl-6-(3′-carboxy-1′-vinylpropyl)-1,4-benzoquinone (XXIIa)——XIVa (1.0 g) was condensed with XIII (1.0 g) in a manner similar to that for XVIa. The product was hydrolyzed with 30% KOH (9 ml) containing $Na_2S_2O_4$ (1 g) in a stream of N_2 at room temperature. The mixture was acidified with cold dil. HCl and ex-

tracted with ether. The ether solution was extracted with saturated aqueous $NaHCO_3$. The aqueous solution was acidified with cold dil. HCl and extracted with AcOEt. The extract was shaken with 10% $FeCl_3$ to oxidize the resulting hydroquinone and worked up in the usual manner. The resulting powder was recrystallized from ether–hexane to give XXIa as orange needles, mp 69—71°. Yield 186 mg (12%). NMR ($CDCl_3$): 2.00 (3H, s, CH_3 on the ring), 2.36 (4H, b, CH_2), 3.18 (2H, d, CH_2 on the ring), 4.00 (6H, s, OCH_3), 5.47 (2H, m, =CH), 7.14 (1H, b, COOH). *Anal.* Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.52; H, 6.03.

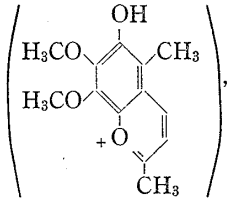
The residue obtained from the mother liquor was subjected to preparative TLC developing in hexane–ether–AcOH (6: 4: 1) and the upper yellow band was extracted with ether. After removal of the solvent, the residue was recrystallized from hexane–ether to give XXIIa as orange needles. mp 77—79.5°. Yield 216 mg (14%). NMR ($CDCl_3$): 2.06 (3H, s, CH_3 on the ring), 2.10—2.40 (4H, m, CH_2), 3.60 (1H, q, CH on the ring), 3.99 (6H, s, OCH_3), 4.90—5.25 (2H, m, $=CH_2$), 6.08 (1H, m, CH=), 8.50 (1H, b, COOH). *Anal.* Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 60.94; H, 6.13.

2,3,5-Trimethyl-6-(5′-carboxy-2′-pentenyl)-1,4-benzoquinone (XXIb) and 2,3,5-Trimethyl-6-(3′-carboxy-1′-vinylpropyl)-1,4-benzoquinone (XXIIb)——1) The products obtained by the reaction of XIVb (3.04 g) with XIII (1.4 g) in a manner similar to that for XXIa and XXIIa were recrystallized from hexane–ether to give XXIb as yellow needles, mp 91—93°. Yield 569 mg (22%). NMR ($CDCl_3$): 2.02 (9H, s, CH_3), 2.36 (4H, b, CH_2), 3.20 (2H, d, CH_2 on the ring), 5.48 (2H, m, =CH), 10.06 (1H, b, COOH). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: 68.37; H, 7.10.

After removal of the solvents, the mother liquor was subjected to preparative TLC with hexane–AcOH (9: 1) as the developing solvent. The upper yellow band was extracted with ether and the extract was evaporated *in vacuo* giving XXIIb as a yellow oil. Yield 631 mg (25%). NMR (CCl_4): 1.97 (6H, s, CH_3), 2.04 (3H, s, CH_3), 2.10—2.50 (4H, m, CH_2), 3.55 (1H, q, CH), 4.80—5.20 (2H, m, $=CH_2$), 6.05 (1H, m, =CH), 10.34 (1H, b, COOH). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.56; H, 6.93.

2) The reaction of XIVb (304 mg) with *trans*-XI (158 mg) in a manner similar to that for XXIa and XXIIa gave a mixture (6: 7) of XXIb and XXIIb (196 mg, 75%).

***trans,cis*-2,3-Dimethoxy-5-methyl-6-(5′,5′-dicarboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XXIIIa)**——XVIa (30 mg) was hydrolyzed with 30% KOH (3 ml) in the presence of $Na_2S_2O_4$ (70 mg). The resulting hydroquinone derivative was oxidized with $FeCl_3$. The product was chromatographed on silicic acid with $CHCl_3$–EtOH (49: 1) as the developing solvent to afford an orange oil. Yield 18 mg (70%). IR ν_{max}^{film} cm^{-1}: 2500, 1732, 1713 (COOH), 1645, 1615 (quinone). NMR ($CDCl_3$): 1.70, 1.86 (3H, s, *cis* and *trans*=CCH_3), 1.94 (3H, s, CH_3 on the ring), 2.56 (2H, d, $=CCH_2$), 3.14 (2H, d, CH_2 on the ring), 3.66 (1H, t, $CH\langle^{CO}_{CO}$), 3.92 (6H, s, OCH_3), 5.04 (1H, t, =CH), 8.26 (2H, b, COOH). MS *m/e*: 352 (M^+), 308 (M^+-CO_2), 235



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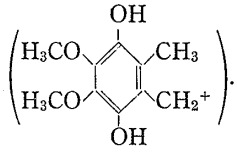

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***trans*-2,3,5-Trimethyl-6-(5′,5′-dicarboxy-3′-methyl-2′-pentenyl)-1,4-benzoquinone (XXIIIb)**——XVIb (139 mg) was treated in a manner similar to that for XXIIIa. The resulting product was recrystallized from hexane–ether giving pale yellow needles, mp 117—119°. Yield 101 mg (85%). UV λ_{max} nm ($E_{1cm}^{1\%}$): oxidized form 260 (572), 267 (587); reduced form 287 (133). IR ν_{max}^{KBr} cm^{-1}: 1710 (COOH), 1645 (quinone). NMR ($CDCl_3$): 1.78 (3H, s, $=CCH_3$), 1.97 (9H, s, CH_3 on the ring), 2.58 (2H, d, $=CCH_2$), 3.18 (2H, d, CH_2 on the ring), 3.60 (1H, t, $CH\langle^{CO}_{CO}$), 5.07 (1H, t, =CH), 10.03 (2H, b, COOH). *Anal.* Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.49; H, 6.26.

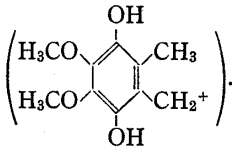
***trans*-2-Methyl-3-(5′,5′-dicarboxy-3′-methyl-2′-pentenyl)-1,4-naphthoquinone (XXIIIc)**——XVc (221 mg) was treated in a manner similar to that for XXIIIa. The resulting product was recrystallized from AcOEt yielding yellow needles, mp 155—157°. Yield 150 mg (88%). UV λ_{max} in EtOH containing 0.01 volume of 1 M ammonium acetate (pH 5.0) nm ($E_{1cm}^{1\%}$): oxidized form 244 (546), 249 (550), 263 (455), 270 (470), 330 (85); reduced form 245 (972), 320 (104). IR ν_{max}^{KBr} cm^{-1}: 2600, 1710 (COOH), 1665, 1620 (quinone). NMR (d_6-DMSO): 1.76 (3H, s, $=CCH_3$), 2.07 (3H, s, CH_3 on the ring), 2.40 (2H, d, $=CCH_2$), 3.24—3.40 (3H, m, $CH\langle^{CO}_{CO}$, CH_2 on the ring), 5.02 (1H, t, =CH), 7.76, 7.96 (4H, m, the ring H). *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.44; H, 5.23.

2,3-Dimethoxy-5-methyl-6-(5′,5′-diethoxycarbonyl-3′-methylpentyl)-1,4-benzoquinone (XXIVa)——XIXa (51 mg) obtained in the synthesis of XXa was oxidized with $FeCl_3$ and the product was purified by TLC developing in hexane–ether (1: 1) to give an orange oil. Yield 49 mg (95%). UV λ_{max} nm ($E_{1cm}^{1\%}$): oxidized form 278 (378); reduced form 291 (116). IR ν_{max}^{film} cm^{-1}: 1750, 1735 ($COOC_2H_5$), 1670, 1650, 1613 (quinone). NMR ($CDCl_3$): 0.97 (3H, d, CH_3), 1.24 (6H, t, $COOCH_2C\underline{H}_3$), 1.16—1.88 (5H, m, CH_2CHCH_2),

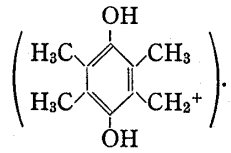
1.98 (3H, s, CH_3 on the ring), 2.43 (2H, t, CH_2 on the ring), 3.40 (1H, t, $CH\langle^{CO}_{CO}$), 3.95 (6H, s, OCH_3), 4.16 (4H, q, $COOC\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{21}H_{30}O_8$: C, 61.45; H, 7.37. Found: C, 61.33; H, 7.47.

2,3,5-Trimethyl-6-(5′,5′-diethoxycarbonyl-3′-methylpentyl)-1,4-benzoquinone (XXIVb)——XVIb (342 mg) was hydrogenated in a manner similar to that for XIXc and resulting XIXb was oxidized with $FeCl_3$ giving a yellow oil. Yield 310 mg (90%). UV λ_{max} nm ($E^{1\%}_{1cm}$): oxidized form 261 (491), 269 (504); reduced form 287 (136). IR ν^{film}_{max} cm^{-1}: 1750, 1730 ($COOC_2H_5$), 1640 (quinone). NMR ($CDCl_3$): 1.00 (3H, d, CH_3), 1.28 (6H, t, $COOCH_2C\underline{H}_3$), 1.20—2.00 (5H, m, CH_2CHCH_2), 2.03 (9H, s, CH_3 on the ring), 2.48 (2H, t, CH_2 on the ring), 3.48 (1H, t, $CH\langle^{CO}_{CO}$), 4.22 (4H, q, $COOC\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.46; H, 8.01.

2,3-Dimethoxy-5-methyl-6-(5′,5′-dicarboxy-3′-methylpentyl)-1,4-benzoquinone (XXVa)——XIXa (60 mg) obtained in the synthesis of XXa was treated in a manner similar to that for XXIIIa. The resulting product was chromatographed on silicic acid with $CHCl_3$–EtOH (49: 1) as the developing solvent to afford an orange oil. Yield 18 mg (35%). UV λ_{max} nm: oxidized form 278; reduced from 291. IR ν^{film}_{max} cm^{-1}: 2600, 1710 (COOH), 1660, 1650, 1615 (quinone). NMR ($CDCl_3$): 1.00 (3H, d, CH_3), 1.24—1.83 (5H, m, CH_2CHCH_2), 1.98 (3H, s, CH_3 on the ring), 2.45 (2H, t, CH_2 on the ring), 3.52 (1H, t, $CH\langle^{CO}_{CO}$), 3.93 (6H, s, OCH_3), 9.61 (2H, b, COOH). MS *m/e*: 354 (M^+), 310 (M^+-CO_2), 197



2,3,5-Trimethyl-6-(5′,5′-dicarboxy-3′-methylpentyl)-1,4-benzoquinone (XXVb)——XXIVb (226 mg) was treated in a manner similar to that for XXIIIa. The resulting product was recrystallized from hexane–ether (1: 1) to afford yellow needles, mp 110—112°. Yield 192 mg (quantitative). UV λ_{max} nm: 260, 268. IR ν^{KBr}_{max} cm^{-1}: 2650, 1715 (COOH), 1645 (quinone). NMR ($CDCl_3$): 1.00 (3H, d, CH_3), 1.16—1.90 (5H, m, CH_2CHCH_2), 1.98 (9H, s, CH_3 on the ring), 2.45 (2H, t, CH_2 on the ring), 3.53 (1H, t, $CH\langle^{CO}_{CO}$), 10.33 (2H, b, COOH). MS *m/e*: 322 (M^+), 278 (M^+-CO_2), 165



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