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Synthesis of Quinones having Carboxy- and Hydroxy-Alkyl Side Chains, and Their Effects on Rat-Liver Lysosomal Membrane

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In order to study the structure-activity relationship of metabolites of ubiquinone, α -tocopherol and phyloquinone (Ia, b, c, IIa, b, c), 3-carboxy-2-butenyl (IIIa, b, c), 6-hydroxy-3-methyl-2-hexenyl (IVa, b, c), 4-hydroxy-3-methylbutyl (Va, b), 4-hydroxy-3-methyl-2-butenyl (VIb, c), ω -carboxyalkyl (VIIa, b, c), and ω -hydroxyalkyl (VIIIa, b) side chains were introduced into the 6-position of 2,3-dimethoxy-5-methyl-1,4-benzoquinone and 2,3,5-trimethyl-1,4-benzoquinone, as well as the 3-position of 2-methyl-1,4-naphthoquinone. The effects of these quinones on the membrane stability of rat-liver lysosomes and on the activity of bovine heart phosphodiesterase were investigated. A good correlation was observed between these activities of the benzoquinone derivatives (VIIa, b).

Keywords—Ubiquinone metabolites; 1,4-benzoquinone derivatives; 1,4-naphthoquinone derivatives; rat-liver lysosomal membrane; bovine heart phosphodiesterase; structure-activity relationship

We previously found that ubiquinone homologs (Q-*n*), α -tocopherol and phyloquinone are metabolized into hexenoic acid derivatives (Ia, b, c, Chart 1) and butyric acid derivatives (IIa, b, c, Chart 1) in human and animal tissues.²⁾ These quinonyl acids and their derivatives have interesting effects on the lysosomal membrane of rat liver³⁾ and on humoral immune response in mice.⁴⁾ In this report, we describe the synthesis of 2',3'-dehydro compounds (IIIa, b, c) of II, hydroxy analogs (IVa, b, c, Va, b) of I and II, 2',3'-dehydro

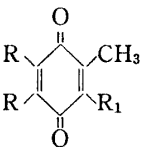
	No.	R ₁	R, R
	Ia, Ib, Ic	CH ₂ CH=CCH ₂ CH ₂ COOH CH ₃	a : H ₃ CO b : H ₃ C
	IIa, IIb IIc	CH ₂ CH ₂ CHCOOH CH ₃	c : 
	IIIa, IIIb, IIIc	CH ₂ CH=CCOOH CH ₃	
	IVa, IVb, IVc	CH ₂ CH=CCH ₂ CH ₂ CH ₂ OH CH ₃	
	Va, Vb	CH ₂ CH ₂ CHCH ₂ OH CH ₃	
	VIb, VIc	CH ₂ CH=CCH ₂ OH CH ₃	
	VIIa- <i>n</i> VIIb- <i>n</i> VIIc- <i>n</i>	(CH ₂) _{<i>n</i>-1} COOH	<i>n</i> 3, 4, 6, 8, 9, 10, 11, 13, 18, 22 3, 4, 5, 6, 7, 10 3, 4, 5, 6, 9
	VIIIa- <i>n</i> VIIIb- <i>n</i>	(CH ₂) _{<i>n</i>} OH	4, 6, 10, 13, 22 3, 6

Chart 1

compounds (VIb, c) of V, and related compounds (VIIa, b, c-*n*, VIIIa, b-*n*, *n*:3—22) (Chart 1), and the effects of these compounds (III—VIII) on the lysosomal membrane, as well as on phosphodiesterase activity. The structure-activity relationship is also discussed.

6-(3-Carboxy-2-butenyl)-5-methyl-1,4-benzoquinones (IIIa,b), 3-(3-Carboxy-2-butenyl)-2-methyl-1,4-naphthoquinone (IIIc), 6-(3-Carboxy-2-hydroxybutyl)-5-methyl-1,4-benzoquinones (XIVa, b) and 3-(3-Carboxy-2-hydroxybutyl)-2-methyl-1,4-naphthoquinone (XIVc) (Chart 2, Table I)

Condensation of 2,3-dimethoxy-5-methylhydroquinone (IXa) with cinnamyl alcohol, followed by oxidation with ferric chloride afforded phenylpropenylquinone (Xa). The reductive acetylation of Xa, followed by oxidation with osmium tetroxide-sodium periodate yielded an aldehyde (XIIa). Aldehydes (XIIb, c) were obtained in a similar way from 2,3,5-trimethyl hydroquinone (IXb) and 2-methyl-1,4-naphthohydroquinone (IXc), respectively. The aldehyde compounds XIIa, c have been obtained by ozone oxidation of the hydroquinone diacetates of Q-10 and menaquinones, respectively,⁵⁾ but we could more conveniently synthesize them by the method described above in good yields. XIIa was condensed with α -ethoxycarbonyl ethylidenetriphenylphosphorane to give ethyl 2-methyl-4-(2,5-diacetoxy-3,4-dimethoxy-6-methylphenyl)-2-butenate (XIIIa). In this reaction, the (*E*)-isomer of XIIIa was selectively obtained.⁶⁾ Similarly, XIIb, c were converted to (*E*)-isomers of XIIIb, c, respectively. Alkaline hydrolysis of XIIIa in the presence of sodium hydrosulfite, followed by oxidation with ferric chloride gave IIIa. XIVa was a minor product. The structure of IIIa was determined on the basis of the carboxy group (1690 cm^{-1}) and benzoquinone ($1660, 1645, 1615\text{ cm}^{-1}$) absorptions in the infrared (IR) spectrum, as well as the proton magnetic resonance (PMR) spectrum. XIVa showed a hydroxy group (3450 cm^{-1}) in the IR spectrum, and a broad peak at 3.98 ppm (1H, CH-O) instead of the methylene proton at the 2-position of the

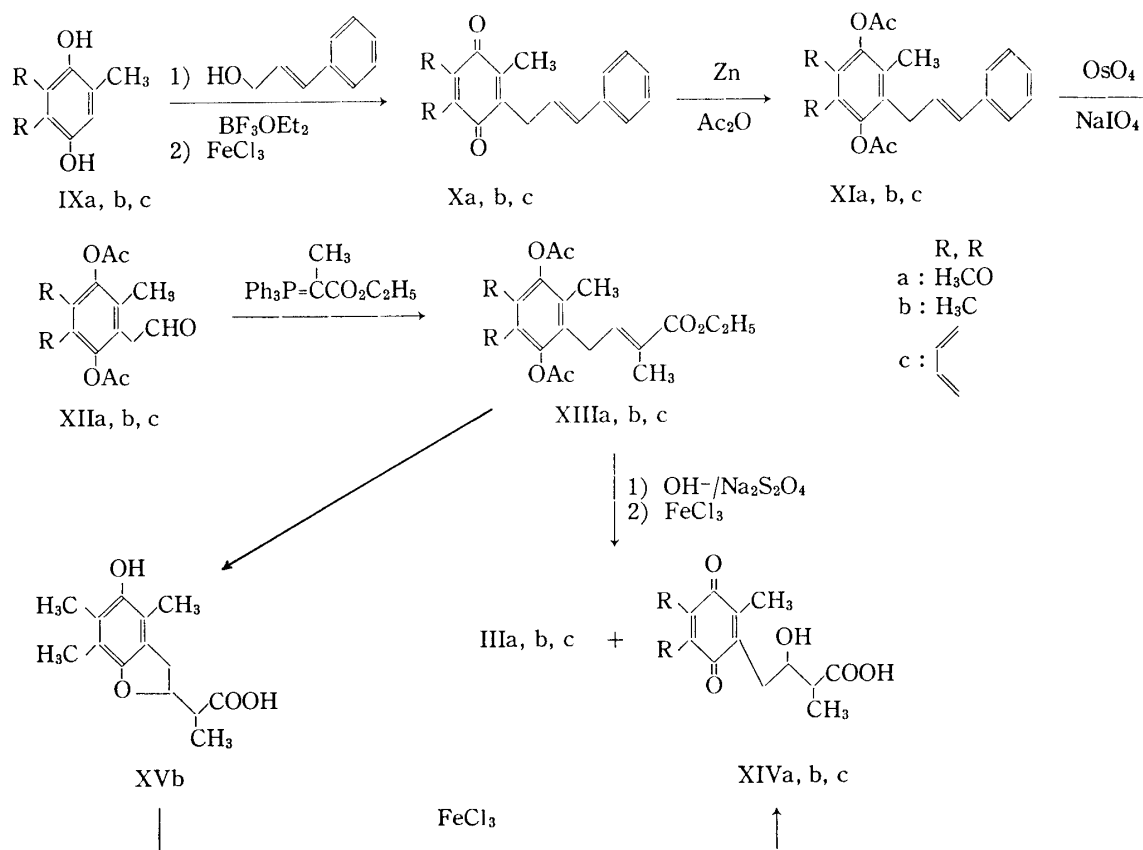


Chart 2

side chain of IIa in the PMR spectrum. The dihydrobenzofuran derivative (XVb) was obtained by the hydrolysis of XIIIb, XVb showed hydroxy (3420 cm^{-1}) and carboxy (1700 cm^{-1}) absorptions in the IR spectrum, and a doublet peak at 1.29 ppm (3H , $J=7\text{ Hz}$, CH_3) and multiplet peaks at $2.21\text{--}3.18\text{ ppm}$ (3H , CH_2 on the ring, CHCO) and $4.56\text{--}4.96\text{ ppm}$ (1H , CH-O) in the PMR spectrum, as well as absorption at 295 nm (substituted 2,3-dihydrobenzofuran) in the ultraviolet (UV) spectrum. XVb was oxidized with ferric chloride to XIVb. XVb was considered to be formed by the nucleophilic attack of the hydroxy group resulting from the hydrolysis of the acetyl group on the β -carbon in the side chain of XIIIb. Similarly, alkaline hydrolysis of XIIIb, c, followed by oxidation gave IIIb, c and XIVb, c.

TABLE I. Physicochemical Properties and Analytical Data of Quinone Compounds (III—VIII, XXXIX and LII)

Compound No.	Method ^{a)}	Yield (%)	mp ($^{\circ}\text{C}$) (Recyst. solv.)	Formula	Analysis (%)			
					Calcd		Found	
					C	H	C	H
IIIa	G	45	118.5—119.5 (Hexane—benzene) ^{b)}	$\text{C}_{14}\text{H}_{16}\text{O}_6$	59.99	5.75	60.13	5.63
IIIb	G	21	149—153 (Hexane—AcOEt)	$\text{C}_{14}\text{H}_{16}\text{O}_4$	67.73	6.50	67.39	6.44
IIIc	G	24	165—167 (dec.) (Hexane—benzene)	$\text{C}_{16}\text{H}_{14}\text{O}_4$	71.10	5.22	71.15	5.00
IVa	F	33	Oil	$\text{C}_{16}\text{H}_{22}\text{O}_5$	65.29	7.53	64.99	7.62
	I	72						
IVb	F	32	Oil	$\text{C}_{16}\text{H}_{22}\text{O}_3$	73.25	8.45	72.73	8.54
	I	58						
IVc	F	29	Oil	$\text{C}_{18}\text{H}_{20}\text{O}_3$	76.03	7.09	75.93	7.29
Va	I	67	Oil	$\text{C}_{14}\text{H}_{20}\text{O}_5$	62.67	7.51	62.69	7.57
Vb	I	96	Oil	$\text{C}_{14}\text{H}_{20}\text{O}_3$	71.16	8.53	71.24	8.57
VIb	I	11	Oil	$\text{C}_{14}\text{H}_{18}\text{O}_3$	^{c)}			
VIc	I	62	Oil	$\text{C}_{16}\text{H}_{16}\text{O}_3$	^{c)}			
VIIa-3	E	32	122—124 (Ether)	$\text{C}_{12}\text{H}_{14}\text{O}_6$	56.69	5.55	56.91	5.24
VIIa-4	A	82	74—75 (Hexane—ether)	$\text{C}_{13}\text{H}_{16}\text{O}_6$	58.20	6.01	58.03	5.77
VIIa-6	A	86	82—86 (Ether)	$\text{C}_{15}\text{H}_{20}\text{O}_6$	60.80	6.80	60.60	6.81
VIIa-8	A	78	62—63 (Hexane—ether)	$\text{C}_{17}\text{H}_{24}\text{O}_6$	62.95	7.46	63.23	7.49
VIIa-9	G	72	39—40.5 (Hexane—ether)	$\text{C}_{18}\text{H}_{26}\text{O}_6$	63.88	7.74	63.09	7.74
VIIa-10	A	97	59—60.5 (Hexane—ether)	$\text{C}_{19}\text{H}_{28}\text{O}_6$	64.75	8.01	64.69	8.11
VIIa-11	D	26	51—52.5 (Hexane—ether)	$\text{C}_{20}\text{H}_{30}\text{O}_6$	65.55	8.25	65.60	8.36
VIIa-13	G	75	62 (Hexane—ether)	$\text{C}_{22}\text{H}_{34}\text{O}_6$	66.98	8.69	67.15	8.77
VIIa-18	D	37	77—79 (EtOH)	$\text{C}_{27}\text{H}_{44}\text{O}_6$	69.79	9.55	69.86	9.78
VIIa-22	C	44	86—87 (Ether)	$\text{C}_{31}\text{H}_{52}\text{O}_6$	71.50	10.07	71.56	10.06
VIIb-3	G	75	112—114 (Hexane—ether)	$\text{C}_{12}\text{H}_{14}\text{O}_4$	64.85	6.35	64.84	6.32
VIIb-4	A	65	97—99 (Hexane—ether)	$\text{C}_{13}\text{H}_{16}\text{O}_4$	66.08	6.83	66.26	6.73
VIIb-5	A	69	67—69 (Hexane—ether)	$\text{C}_{14}\text{H}_{16}\text{O}_4$	67.18	7.25	67.26	7.23
VIIb-6	A	94	81—82 (Hexane—AcOEt)	$\text{C}_{15}\text{H}_{20}\text{O}_4$	68.16	7.63	68.19	7.61
VIIb-7	A	77	71—72 (Hexane—AcOEt)	$\text{C}_{16}\text{H}_{22}\text{O}_4$	69.04	7.97	69.08	8.04
VIIb-10	A	35	Oil	$\text{C}_{19}\text{H}_{28}\text{O}_4$	71.22	8.81	71.19	8.80
VIIc-5	G	70	103—108 (Hexane—ether)	$\text{C}_{16}\text{H}_{16}\text{O}_4$	70.58	5.92	69.82	5.75

(continued)

Compound No.	Method ^{a)}	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%)			
					Calcd		Found	
					C	H	C	H
VIIc-6	G	65	103—105 (Hexane-ether)	C ₁₇ H ₁₈ O ₄	71.31	6.34	71.21	6.42
VIIa-4 Et	H	93	Oil	C ₁₅ H ₂₀ O ₆	60.80	6.80	61.26	7.12
VIIa-4 Bz	H	61	Oil	C ₂₀ H ₂₂ O ₆	67.02	6.19	66.84	6.05
VIIa-9 Et	E	25	Oil	C ₂₀ H ₃₀ O ₆	65.55	8.25	65.02	8.07
VIIa-10 Me	H	93	37—37.5 (Hexane-ether)	C ₂₀ H ₃₀ O ₆	65.55	8.25	65.44	8.36
VIIa-10 Et	H	74	Oil	C ₂₁ H ₃₂ O ₆	66.30	8.48	66.13	8.64
VIIa-10 Bz	H	69	Oil	C ₂₆ H ₃₄ O ₆	70.56	7.74	70.47	7.82
VIIa-10 Phenet	H	45	Oil	C ₂₇ H ₃₆ O ₆	71.02	7.95	70.83	8.11
VIIa-10 <i>t</i> -But	H	41	Oil	C ₂₃ H ₃₆ O ₆	67.62	8.88	67.49	8.91
VIIa-13 Me	E	36	54 (Hexane)	C ₂₃ H ₃₆ O ₆	67.62	8.88	67.52	8.59
VIIb-3 Me	E	35	Oil	C ₁₃ H ₁₆ O ₄	^{c)}			
VIIb-6 Et	A	70	Oil	C ₁₇ H ₂₄ O ₄	69.83	8.27	69.85	8.36
VIIb-6 Bz	H	71	Oil	C ₂₂ H ₂₆ O ₄	74.55	7.39	74.22	7.32
VIIIa-4	I	78	Oil	C ₁₃ H ₁₈ O ₅	61.64	7.14	61.47	7.32
VIIIa-6	I	62	Oil	C ₁₅ H ₂₂ O ₅	^{c)}			
VIIIa-10	A	67	52—53 (Hexane-AcOEt)	C ₁₉ H ₃₀ O ₅	67.43	8.94	67.41	8.94
VIIIa-13	I	65	65—66 (Hexane-ether)	C ₂₂ H ₃₆ O ₅	69.44	9.54	69.42	9.77
VIIIa-22	C	57	89—90.5 (EtOH)	C ₃₁ H ₅₄ O ₅	73.47	10.74	73.49	10.73
VIIIb-3	I	77	Oil	C ₁₂ H ₁₆ O ₃	^{c)}			
VIIIb-6	I	37	43—45 (Ether)	C ₁₅ H ₂₂ O ₃	71.97	8.86	72.33	8.58
XIVa	G	50	Oil	C ₁₄ H ₁₈ O ₇	56.37	6.08	56.19	6.43
XIVb	G	57	106—110 (Hexane-AcOEt)	C ₁₄ H ₁₈ O ₅	63.14	6.81	63.08	6.87
XIVc	G	55	144.5—150.5 (dec.) (Hexane-AcOEt)	C ₁₆ H ₁₆ O ₅	66.66	5.59	66.64	5.58
XXXIX	A	54	48—54 (Hexane-ether)	C ₁₅ H ₁₈ O ₇	58.06	5.85	57.89	5.90
LII	A	83	96.5—98.5 (Hexane-AcOEt)	C ₁₅ H ₁₈ O ₅	^{c)}			
LX		92	38 (Hexane)	C ₂₁ H ₃₂ O ₆	66.30	8.48	66.88	8.57

a) Methods: A, oxidation with Fremy's salt; B, oxidation with FeCl₃; C, oxidation with salcomine; D, Jones oxidation; E, condensation with diacylperoxide; F, condensation with BF₃ followed by oxidation with FeCl₃; G, hydrolysis of an ester compound followed by oxidation with FeCl₃; H, esterification of a carboxylic acid; I, reduction with LiAlH₄ followed by oxidation with FeCl₃.

b) AcOEt, ethyl acetate; ether, ethyl ether.

c) These compounds were determined by mass spectrometry.

Quinones having 6-Hydroxy-3-methyl-2-hexenyl (IVa, b, c), 4-Hydroxy-3-methylbutyl (Va, b) and 4-Hydroxy-3-methyl-2-butenyl (VIb, c) Side Chains (Chart 3, Table I)

ω -Hydroxy compounds (IVa, b, c, Va, b and VIb, c, Chart 1) were obtained from the corresponding esters (XVIa, b, c, XVIIa, b^{7,8)} and XIIIb, c, respectively) by reduction with lithium aluminum hydride, followed by oxidation of the resulting hydroquinones. An alternative synthetic route was sought for the synthesis of IVa, b, c. Methyl levulinate (XVIII) was condensed with α -ethoxycarbonylmethylidenetriphenylphosphorane to give a mixture of (Z),(E)⁹⁾ (1:3)-XIX. This mixture was reduced with lithium aluminum hydride at -20°C to (Z),(E)-XX, or at -78°C to (Z),(E)-XXI. XXI was reduced with lithium aluminum hydride at -20°C after protection of its hydroxy group as the tetrahydropyranylether (XXII) to obtain (Z),(E)-XXIII. A condensation of (Z),(E) mixture of XX or XXIII with the hydroquinone IXa, and subsequent oxidation with ferric chloride afforded (Z),(E) (1:3)-IVa. (E)-XX also gave (Z),(E) (1:3)-IVb upon condensation with the hydroquinone IXb, followed by oxidation of the condensed product, as suggested in the previous report.⁷⁾

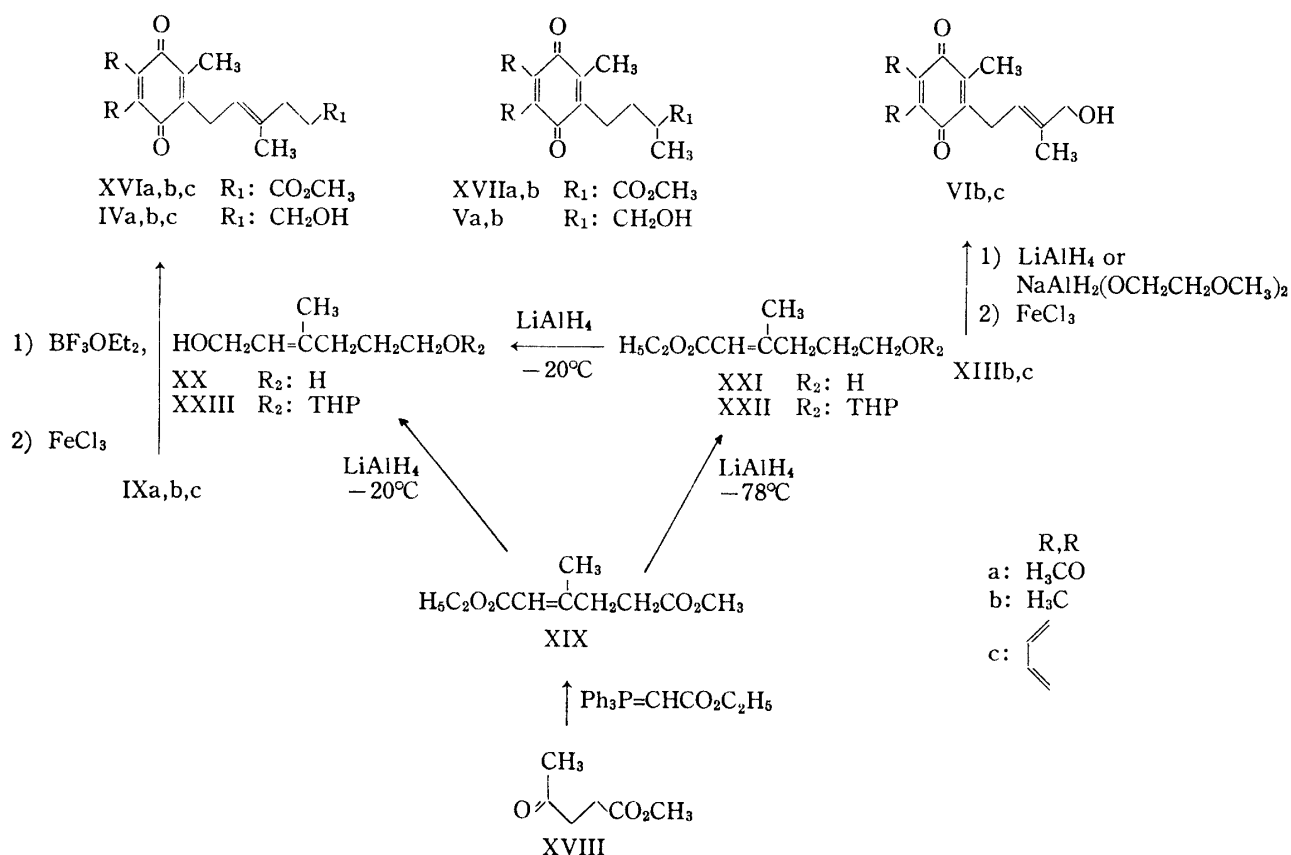


Chart 3

Quinones Having an ω -Carboxyalkyl Side Chain (VIIa, b, c)

According to the method described for the synthesis of metabolites (IIa, b, c),^{7,8)} 3,4,5-trimethoxytoluene (XXIV) was subjected to Friedel-Crafts reaction with succinic anhydride or chloroformylakanoate (XXV-*n*) to introduce the side chain (Chart 4). The reaction of XXIV with ethyl 9-chloroformylnonanoate (XXV-10 Et) was carried out in nitrobenzene under ice-cooling, and the mixture was hydrolyzed to give 2,3,4-trimethoxy-6-methylbenzoylnonanoic acid (XXVIII-10) and its 2-demethylated compound (XXVII-10). The compound XXVIII-10 was converted to XXVII-10 by treatment with aluminum chloride. Prolongation of the reaction time at room temperature generally resulted in the formation of the 2-demethylated

TABLE II. Physicochemical Data for ω -(2-Hydroxy-3,4-dimethoxy-6-methylbenzoyl)-alkanoic Acids (XXVII) and ω -(2,3,5-Trimethoxy-6-methylbenzoyl)alkanoic Acids (XXVIII) and Their Esters (XXVI)

Compound	mp (°C)	Formula	Analysis (%)				IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹ C=O
			Calcd		Found		
			C	H	C	H	
XXVI-10	49—53	C ₂₀ H ₃₀ O ₆	65.55	8.25	65.58	8.17	1620
XXVI-22	75—76	C ₃₂ H ₅₄ O ₆	71.87	10.18	71.73	10.24	1620
XXVII-4	145—147	C ₁₅ H ₁₆ O ₆	58.20	6.01	58.07	5.98	1610
XXVII-6	111—112	C ₁₅ H ₂₀ O ₆	60.80	6.80	60.69	6.75	1615
XXVII-8	97—98	C ₁₇ H ₂₄ O ₆	62.95	7.46	62.65	7.48	1610
XXVII-10	75—76.5	C ₁₉ H ₂₈ O ₆	64.75	8.01	64.87	8.06	1615
XXVII-22	103—105	C ₃₁ H ₅₂ O ₆	71.50	10.07	71.59	10.34	1650
XXVIII-10	40—43	C ₂₀ H ₃₀ O ₆	65.55	8.25	65.38	8.62	1695
XXVIII-22	88—90	C ₃₂ H ₅₄ O ₆	71.87	10.18	71.94	10.03	1690

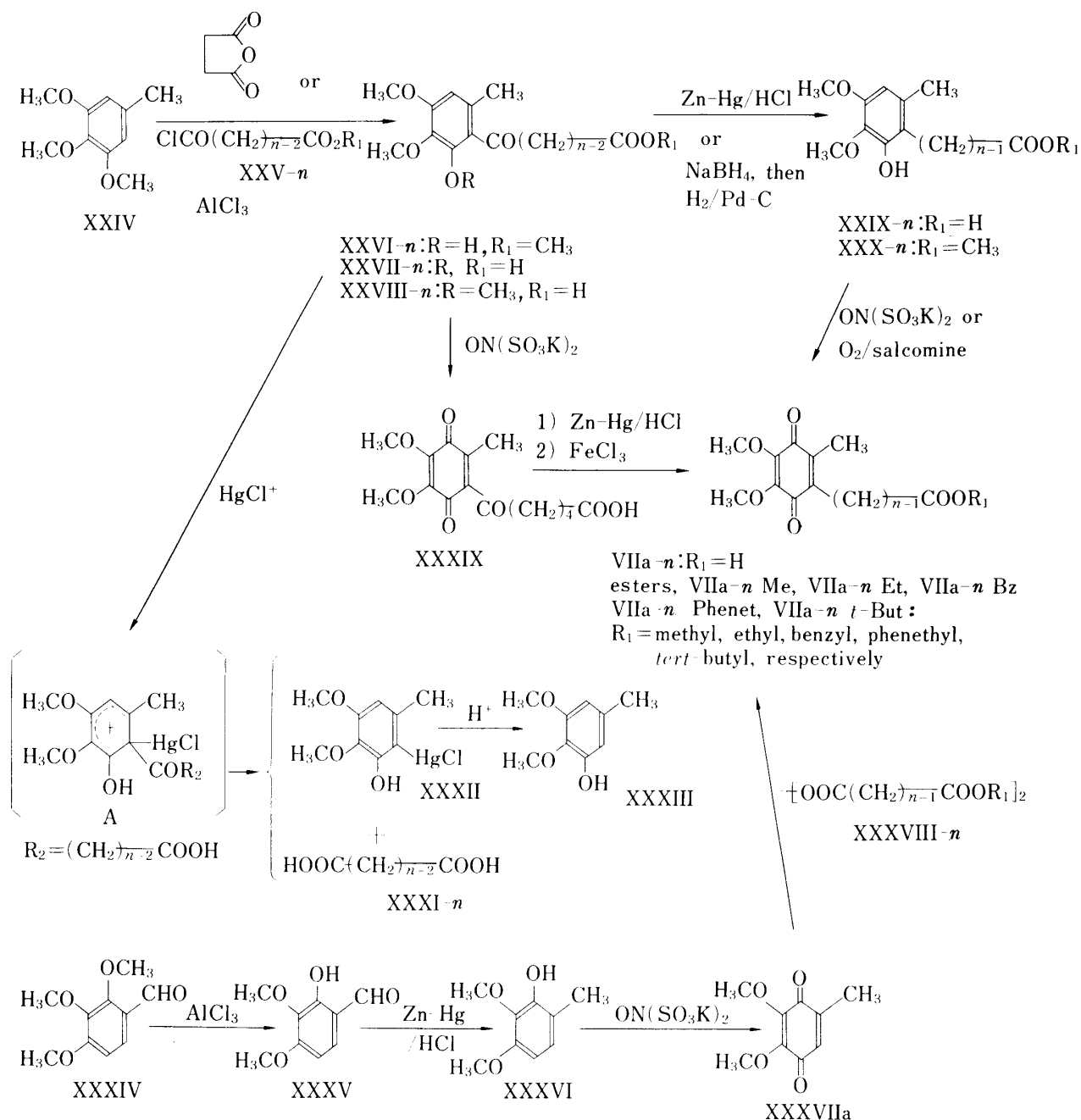


Chart 4

compound, XXVII- n . XXVI- n was obtained by the methylation of XXVII- n . In the similarly obtained arylketones (XXVI- n , XXVII- n), a shift of $\nu_{\text{C=O}}$ to lower wave numbers was observed in their IR spectra because of hydrogen bonding with the *ortho* hydroxy group (Table II). Reduction of XXVII- n (n : 4, 6, 8 and 10) was performed by Clemmensen reduction to obtain the corresponding XXIX-4, -6, -8 and -10 (Table III). A longer reaction time was required for the Clemmensen reduction of XXVII homologs having a side chain of larger carbon number (n). Sometimes, the Clemmensen reduction of XXVII- n was accompanied by deacylation at the 1-position to yield dicarboxylic acid (XXXI- n) and 2,3-dimethoxy-5-methylphenol (XXXIII). Such deacylation has been reported in the Clemmensen reduction of 2,6-dihydroxyvalerophenone,¹⁰⁾ as well as in the hydrolysis reaction of arylketones having an *ortho*-alkyl moiety with phosphoric acid.^{11,12)} Deacylation of XXVII-6 to adipic acid

TABLE III. Physicochemical Data for ω -(2-Hydroxy-3,4-dimethoxy-6-methylphenyl)-alkanoic Acids (XXIX) and Their Esters (XXX)

Compound	Yield (%)		mp (°C)	Formula	Analysis (%)			
	by Clemmensen reduction	by catalytic reduction			Calcd		Found	
					C	H	C	H
XXIX-4	67	—	98—100	C ₁₃ H ₁₈ O ₅	61.64	7.14	61.35	7.01
XXIX-6	42.3	90.7	38—44	C ₁₅ H ₂₂ O ₅	63.81	7.85	63.53	7.70
XXIX-8	24	66.5 ^{a)}	54—56	C ₁₇ H ₂₆ O ₅	65.78	8.44	66.06	8.58
XXIX-10	55.4	57.7	62.5—66	C ₁₉ H ₃₀ O ₅	67.43	8.74	67.50	8.89
XXIX-22	—	54	67—68	C ₃₁ H ₅₄ O ₅	73.47	10.74	73.76	10.78
XXX-10	—	78	Oil	C ₂₀ H ₃₂ O ₅	68.15	9.15	68.19	9.11
XXX-22	—	61.7	71—72.5	C ₃₂ H ₅₆ O ₅	73.80	10.84	74.06	11.06

a) See "Experimental."

TABLE IV. Deacylation of Benzoyl Derivatives (XXVII, XXVIII, XLIII and XLVI)

Compound	Reaction conditions ^{a)}		Product	Yield (%)
	Reagent	Time (h)		
XXVII-6	HgCl ₂ -HCl	13	XXXIII	68.2
XXVII-6	HCl	23	XXXIII	22.0
XXVII-6	HgCl ₂	49	XXXII*, XXXIII**	1.0*, 19.0** ^{b)}
XXVIII-10	HgCl ₂ -HCl	7	XXIV	68.5
XLIII-7	HgCl ₂ -HCl	19	XL	48.6
XLVI-6	HgCl ₂ -HCl	27	—	— ^{c)}
XLVI-6	H ₃ PO ₄	11	XLIX	77.6

a) An aqueous solution of reagent was added to a solution of a compound in toluene except in the case of H₃PO₄. The reaction with H₃PO₄ was carried out without solvent.

b) Asterisks indicate products and corresponding yields.

c) Starting material was recovered.

(XXXI-6) and XXXIII (Table IV) with hydrochloric acid was slow, but was accelerated by the addition of mercuric chloride. Related compounds (XXVIII-10, XLIII-7) were also hydrolyzed as shown in Table IV. When XXVII-6 was heated with mercuric chloride, the chloromercury derivative (XXXII) was obtained in addition to XXXIII. Since XXVII-*n* has an electron-donating group on its *para*- as well as its *ortho*-position with respect to the acyl side chain, the carbonyl-attached carbon should be attacked more readily by an electrophile, HgCl⁺, as shown in A (Chart 4), and the product would be hydrolyzed to give XXXIII. XXVII-*n* (*n*: 6, 10 and 22) gave XXIX-*n* (*n*: 6, 10 and 22) upon catalytic reduction using palladium on carbon in acetic acid (Table III). XXIX-8 was also obtained in a shorter reaction time by reduction of the carboxyl group with sodium borohydride, followed by catalytic reduction with palladium on carbon (Table III). Oxidation of XXIX-*n* (*n*: 4, 6, 8 and 10) with potassium nitrosodisulfonate (Fremy's salt) gave the corresponding VIIa-*n* (*n*: 4, 6, 8 and 10) (Table I). Though phenols having an electron-withdrawing group on the ring were reported to resist oxidation with Fremy's salt,¹³⁾ XXVII-6 was oxidized with a large amount of Fremy's salt to give XXXIX (Table I). This was reduced by Clemmensen reduction, and oxidized with ferric chloride to VIIa-6. On the other hand, XXIX-22 could not be oxidized with Fremy's salt owing to its high lipophilicity, so it was oxidized by catalytic oxidation using salcomine¹⁴⁾ in *N,N*-dimethylformamide (DMF) under an atmosphere of oxygen to yield VIIa-22 (Table I).

Fieser *et al.*¹⁵⁾ reported the alkylation of naphthoquinone using diacylperoxide. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone (XXXVIIa) is a key intermediate for the synthesis of Q-metabolites *via* this reaction as well as for the synthesis of Q-*n*, and has been obtained from various starting materials.¹⁶⁾ Obol'nikova *et al.* obtained it by Fremy's salt-oxidation of

2,3-dimethoxy-6-methylphenol (XXXVI) derived from pyrogallol by partial methylation, subsequent formylation, and reduction of the resulting formyl group.¹⁷⁾ We modified this synthetic route because some difficulties were encountered in the partial methylation of pyrogallol (Chart 4). That is, XXXV was obtained by demethylation of 2,3,4-trimethoxybenzaldehyde (XXXIV)¹⁸⁾ with aluminum chloride in good yield, and subsequently reduced to XXXVI. XXXVIIa was condensed with diacylperoxides (XXXVIII-3, -9, -13), derived from succinic anhydride, 9-chloroformylnonanoate as well as 13-chloroformyltridecanoate, and hydrolyzed to give VIIa-3, -9 and -13 (Table I), respectively. Ester compounds, VIIa-*n* R₁ (R₁: methyl and ethyl) were obtained by heating VIIa-*n* in the corresponding alcohol with a small amount of *p*-toluenesulfonic acid. Esters, VIIa-*n* benzyl, phenethyl and *tert*-butyl were prepared from VIIa-*n* and benzyl bromide, phenethyl bromide and *tert*-butyl bromide, respectively, in the presence of silver oxide.

Compounds, VIIb-3—VIIb-10 were similarly prepared (Chart 5). The Friedel-Crafts reaction of 2,3,5-trimethylphenol (XL) with succinic anhydride or chloroformyalkanoates (XXV-*n*, *n*: 4, 5, 6, 7 and 10) gave the corresponding 2-hydroxy-3,4,6-trimethylbenzoyl compounds (XLII-*n*), their hydrolyzed products (XLIII-*n*) and dibenzoyl compounds (XLIV-*n*). Some of the physicochemical data were shown in Table V. When XL was reacted with XXV-10 in the presence of more than two equivalents of aluminum chloride in tetrachloroethane, unexpected compounds XLV-10 (52.1%), XLVI-10 (7.1%), XLVII-10 (1.4%) (Table VI) were obtained instead of XLII-10, XLIII-10 and XLIV-10. Similarly, condensation of XL with XXV-6 and -7 in the presence of more than two equivalents of aluminum chloride, followed by hydrolysis gave XLVI-6 (55.4%) and -7 (48.9%) (Table VI), respectively. The compounds, XLV-*n*, XLVI-*n* and XLVII-*n* obtained here showed a hydroxy proton similar to those for XLII-*n*, XLIII-*n* and XLIV-*n* (Table V), and an aromatic ring proton at a field lower than those of XLII-*n* and XLIII-*n* in their PMR spectra. In the IR spectra, the absorption due to the carbonyl group shifted to a lower wave number, and the compounds showed a negative color reaction with the ferric chloride-potassium ferricyanate reagent.¹⁹⁾ These results suggest the presence of a hydrogen bond between the hydroxy and the carbonyl groups. Further, compounds (XLVIII-6, -7) derived from XLVI-6 and -7 could not be oxidized with Fremy's salt. Deacylation of XLVI-6 with phosphoric acid gave 2,3,4-trimethylphenol (XLIX) (Table IV). Therefore, XLVI-*n* were concluded to be 2-hydroxy-3,4,5-trimethylbenzoyl

TABLE V. Physicochemical Properties of ω -(2-Hydroxy-3,4,6-trimethylbenzoyl)alkanoic Acids (XLIII), Their Esters (XLII) and 1, ω -Bis-(2-hydroxy-3,4,6-trimethylbenzoyl)alkanes (XLIV)

Compound	Yield(%) ^{a)}	mp (°C) ^{b)}	Formula	Analysis (%)				IR, $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹ C=O	PMR Spectra (δ in CDCl ₃)						
				Calcd		Found			CH ₃ on the ring	the ring proton	COOH	OH			
				C	H	C	H								
XLIII-4	30	168—171.5 ^a	C ₁₃ H ₁₆ O ₄	66.08	6.83	65.56	6.70	1610							
XLIII-5	19	155—157 ^a	C ₁₄ H ₁₈ O ₄	67.18	7.25	67.46	7.31	1610	2.12	2.23	2.51	6.51	—	—	
XLIV-5	Small	138	C ₂₃ H ₂₈ O ₄	74.97	7.66	75.03	7.65	1610	2.10	2.21	2.49	6.47	—	—	
XLII-6	63.5(51.5)	72—73 ^b	C ₁₇ H ₂₄ O ₄	69.83	8.27	69.78	8.44	1610	2.11	2.22	2.50	6.52	—	—	12.55
XLIII-6	Small	146—148 ^a	C ₁₅ H ₂₀ O ₄	68.16	7.63	67.95	7.92	1605	2.12	2.22	2.53	6.54	9.4	—	12.6
XLIV-6	Small	186—187.5 ^c	C ₂₄ H ₃₀ O ₄	^{c)}				1605	2.08	2.21	2.34	6.54	—	—	10.78
XLII-7	78.9	47—48 ^b	C ₁₈ H ₂₆ O ₄	70.56	8.55	70.23	8.72	1610	2.12	2.22	2.51	6.53	—	—	12.54
XLIII-7	2.2	119—125 ^b	C ₁₆ H ₂₂ O ₄	69.04	7.97	69.12	7.75	1610	2.14	2.25	2.53	6.54	9.40	—	12.6
XLII-10	52.6	48—50 ^d	C ₂₁ H ₃₂ O ₄	72.38	9.26	72.32	9.56	1610	2.12	2.22	2.51	6.53	—	—	12.54
XLIII-10	8.9	97—100 ^b	C ₁₉ H ₂₈ O ₄	71.22	8.81	71.10	8.97	1610	2.15	2.23	2.53	6.55	10.3	—	12.5
XLIV-10	3.4	125—129.5 ^c	C ₂₈ H ₃₈ O ₄	76.67	8.73	76.56	8.84	1610	2.22	2.33	2.53	6.56	—	—	12.56

a) Isolated yields of XLII, XLIII and XLIV in the same reaction. Number in parentheses represents isolated yields of the reaction in nitrobenzene.

b) Recrystallization solvent: a, AcOEt-hexane; b, EtOH; c, AcOEt; d, hexane.

c) This compound was determined by mass spectrometry.

compounds as shown in Chart 5. Auwers *et al.*¹¹⁾ reported that the Fries rearrangement of the acetate of XL with aluminum chloride gave a methyl-rearranged product, 2,3,4-trimethyl-6-acetylphenol in 86% yield. The methyl rearrangement of *o*-xylene to *m*-xylene was also observed in the Friedel-Crafts reaction.²⁰⁾ The Friedel-Crafts reaction of XL with XXV-10 at low temperature gave an ester compound (XLI) alone. Therefore, this reaction was considered to proceed *via* the Fries rearrangement of an ester compound (XLI), accompanied with the rearrangement of the methyl group.

TABLE VI. Physicochemical Properties of ω -(2-Hydroxy-3,4,5-trimethylbenzoyl)alkanoic Acids (XLVI), Its Ester (XLV) and 1, ω -Bis-(2-hydroxy-3,4,5-trimethylbenzoyl)alkanes (XLVII)

Compound	Yield (%) ^{a)}	mp(°C) ^{c)}	Formula	Analysis (%)				IR, ν_{max} cm ⁻¹ C=O	PMR Spectra (δ in CDCl ₃)					
				Calcd		Found			CH ₃ on the ring		the ring proton		COOH OH	
				C	H	C	H							
XLVI-6 ^{b)}	55.4	131—133 ^a	C ₁₅ H ₂₀ O ₄	60.16	7.63	67.94	7.64	1640	2.22	2.24	2.26	7.37	8.0	12.55
XLVII-6	Small	173—183 ^b	C ₂₄ H ₃₀ O ₄	^{d)}				1630	2.22	2.24	2.26	7.38	—	—
XLVI-7	48.9	101—104 ^b	C ₁₆ H ₂₂ O ₄	69.04	7.97	68.79	7.97	1625	2.20	2.23	2.25	7.38	9.3	12.6
XLV-10	52.1	64—65.5 ^b	C ₂₁ H ₃₂ O ₄	72.38	9.26	72.16	9.39	1635	2.21	2.26		7.40	—	12.67
XLVI-10	7.1	97—98 ^b	C ₁₉ H ₂₆ O ₄	71.22	8.81	71.21	9.00	1635	2.17	2.22		7.36	9.0	12.55
XLVII-10	1.4	135—142 ^b	C ₂₈ H ₃₈ O ₄	76.67	8.73	76.29	8.76	1635	2.22	2.26		7.38	—	12.66

a) Isolated yield.

b) Separated after hydrolysis of the reaction mixture.

c) Recrystallization solvent: a, AcOEt; b, AcOEt-hexane.

d) This compound was determined by mass spectrometry.

The Clemmensen reduction of XLII-6, XLIII-4, -5, -6, -7 and -10 gave L-6, LI-4, -5, -6, -7 and -10 (Table VII), respectively. Oxidation of these compounds with Fremy's salt gave the corresponding quinones (VIIb-*n* R₁, R₁: ethyl or H) (Table I) in 35—94% yields. XLIII-6 was oxidized with a large amount of Fremy's salt in a manner similar to the reaction of XXVII-6 to give a quinone compound (LII, Table I) in good yield, and this was converted into VIIb-6 by catalytic reduction, followed by oxidation with ferric chloride. VIIb-3 methyl (Table I) was obtained by the reaction of 2,3,5-trimethyl-1,4-benzoquinone (XXXVIIb) with the diacylperoxide (XXXVIII-3 Me), and it was hydrolyzed to VIIb-3 in the same manner as VIIa-13.

TABLE VII. Physicochemical Data for ω -(2-Hydroxy-3,4,5-trimethylphenyl)alkanoic Acids (XLVIII), ω -(2-Hydroxy-3,4,6-trimethylphenyl)alkanoic Acids (LI) and Their Esters (L)

Compound	Yield (%)	mp(°C) ^{a)}	PMR Spectra (δ in CDCl_3)				Formula	Analysis (%)			
			CH ₃ on the ring		the ring proton			Calcd		Found	
								C	H	C	H
XLVIII-6	62.2	99—115	2.18	2.20	2.21	6.75	C ₁₅ H ₂₂ O ₃	c)			
XLVIII-7	44.3	83—89	2.15	2.18		6.75	C ₁₆ H ₂₄ O ₃	c)			
L-6	70.5 ^{b)}	Oil	2.10	2.20		6.58	C ₁₇ H ₂₆ O ₃	c)			
LI-4	50.1	121—125	2.15	2.21		6.60	C ₁₃ H ₁₈ O ₃	70.24	8.16	70.37	8.17
LI-5	52.6	107	2.11	2.22		6.57	C ₁₄ H ₂₀ O ₃	71.16	8.53	71.26	8.61
LI-6	95.4	96—108	2.11	2.20		6.60	C ₁₅ H ₂₂ O ₃	71.97	8.86	71.67	9.02
LI-7	80.7	91—104	2.13	2.22		6.58	C ₁₆ H ₂₄ O ₃	72.69	9.15	72.48	9.03
LI-10	38.1	Oil	2.10	2.20		6.50	C ₁₉ H ₃₀ O ₃	c)			

a) Recrystallized from AcOEt-hexane.

b) LI-6 (19%) was also obtained through partial hydrolysis.

c) These compounds were determined by mass spectrometry.

Naphthoquinone derivatives, VIIc-5 and -6 (Table I) were obtained by reaction of 2-methyl-1,4-naphthoquinone (XXXVIIc) with the diacylperoxides (XXXVIII-5 Et and -6 Et, respectively), followed by hydrolysis of the ester group (Chart 6). Previously, we reported that the condensation of 3-methylnaphthol (LIII) with methylsuccinic anhydride by the Friedel-Crafts reaction under some experimental conditions did not give the desired 2-acyl-3-methylnaphthol (LIV, mp 191—192°C) but an unknown product (LV, mp 159—161°C).⁸⁾ We studied the IR and PMR spectra of LV and its Clemmensen reduction-product (LVI) in detail, and they were found to be consistent with the structures shown in Chart 6. Further, LVI was recovered without being oxidized with Fremy's salt. Hence, LV and LVI were assigned as α -methyl- β -[2-(1-hydroxy-4-methylnaphthoyl)] propionic acid and α -methyl- γ -[2-(1-hydroxy-4-methylnaphthyl)] butyric acid, respectively.

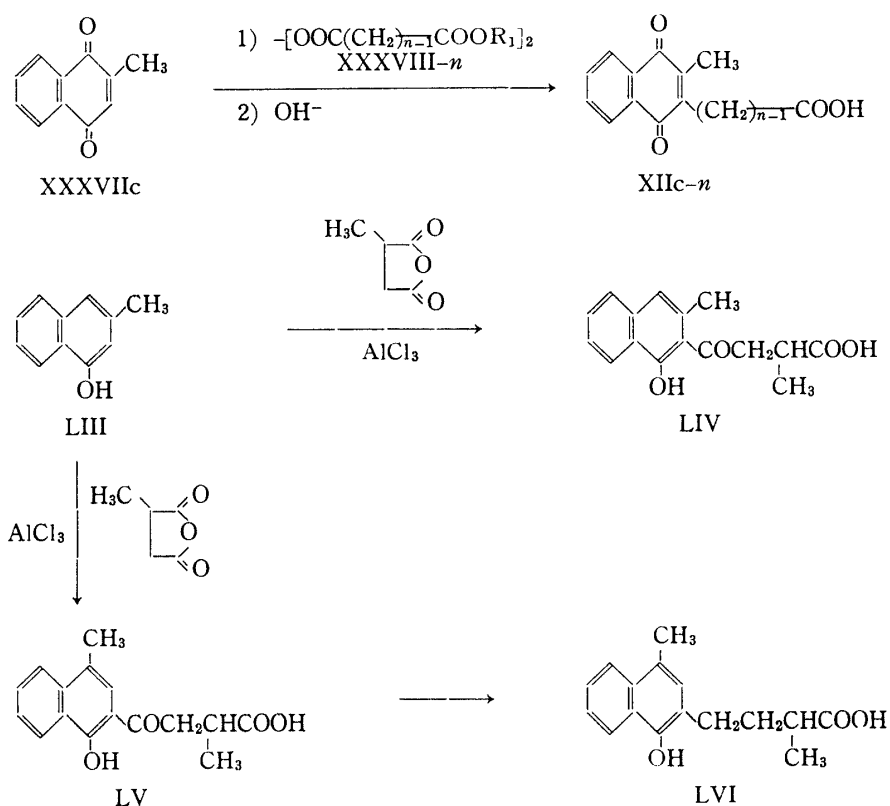


Chart 6

Quinones having an ω -Hydroxyalkyl Side Chain (Chart 7)

Reduction of the methyl or ethyl esters of VIIa-n (n : 4, 6, 10 and 13) and VIIb-6 with lithium aluminum hydride, followed by oxidation with ferric chloride gave the corresponding alcohols (VIIIa-n and VIIIb-6, Table I). XXX-10 and -22 were reduced to alcohols (LVII-10 and -22) with lithium aluminum hydride, then oxidized with Fremy's salt or oxygen in the presence of salcomine to give VIIIa-10 and -22 (Table I), respectively. The compound VIIIa-10 was acetylated with acetic anhydride to LX (Table I). VIIIb-6 was also obtained by the reduction of XLII-6 to LVIII with lithium aluminum hydride, followed by catalytic reduction, and oxidation of the resulting phenol (LIX) with Fremy's salt. 6-(2-Carboxyvinyl)-2,3,5-trimethyl-1,4-benzoquinone (LXIII) was obtained by condensation of LXI²¹⁾ with α -ethoxycarbonylmethylidenetriphenylphosphorane, followed by hydrolysis and oxidation. Reduction of its ethyl ester (LXIV) with lithium aluminum hydride, followed by oxidation with ferric chloride gave VIIIb-3 (Table I). VIIIa-11 and -18 were oxidized with Jones reagent to give VIIa-11 and -18, respectively (Table I).

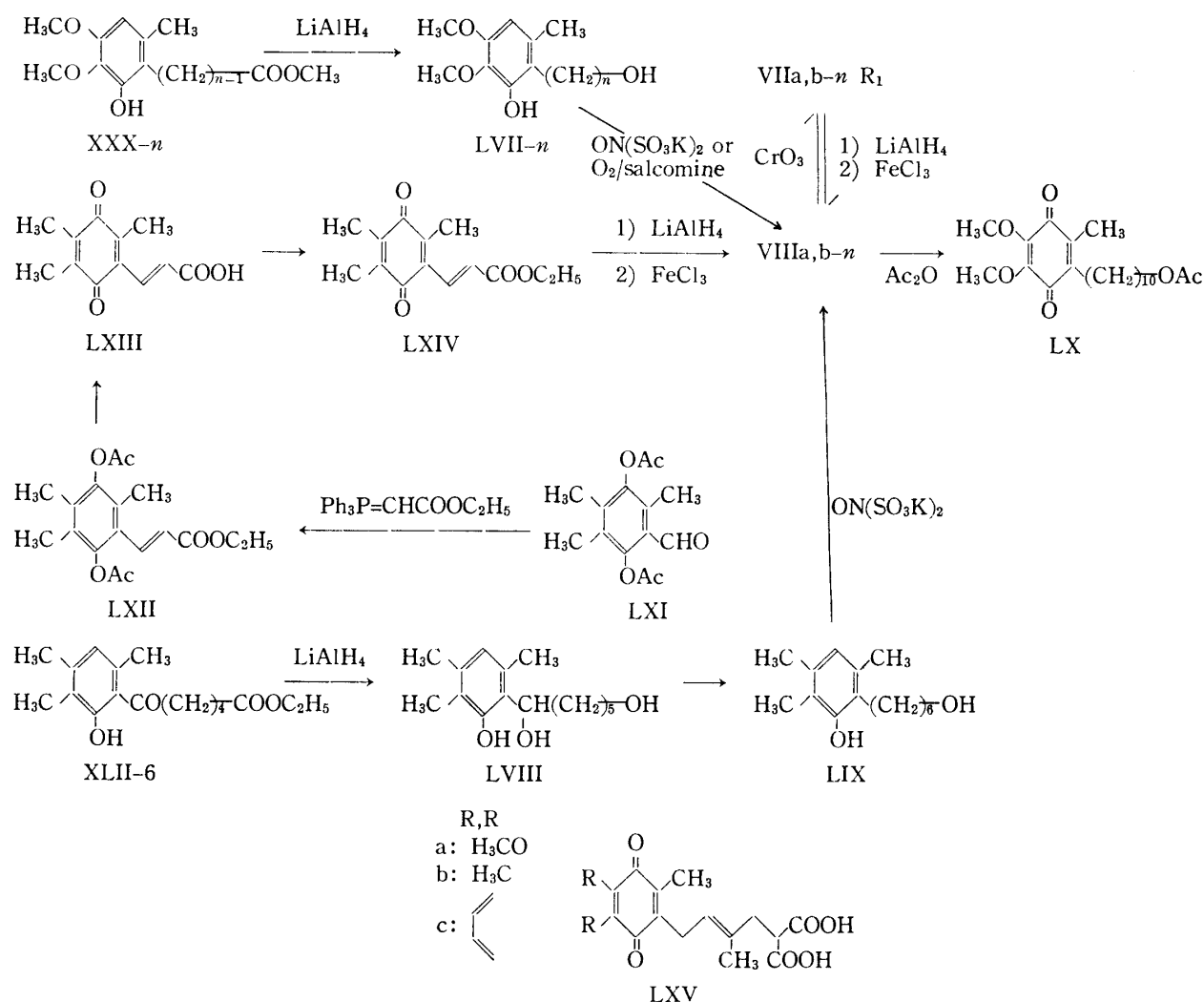


Chart 7

Effects on Rat-Liver Lysosomal Membrane

The lysosomes of tissue cells include various hydrolases, whose activities have been reported to be latent as long as the lysosomal membrane remains intact.²²⁾ The effects of some physiologically active compounds on the stability of the lysosomal membrane were correlated with their *in vivo* activities.²³⁾ Further, some of these compounds affected the tissue concentration of cyclic nucleotides, and the relationship of this effect to the membrane-stabilizing activity has been discussed.²⁴⁾ We found that the structure of the side chain of Ia, b, c, IIa, b, c and related compounds affected the lysosomal membrane-stabilizing activity.³⁾ That is, it was found that the 2',3'-double bond and 3'-methyl group in the side chain were not essential for the activity, and an appropriate lipophilicity was required because of the low activities of dicarboxylic acids (LXV, Chart 7) in comparison with those of the corresponding monocarboxylic acids. Compounds which were synthesized in this report were assayed as described previously.³⁾ Test compounds were dissolved in DMF, the concentration of which was adjusted to become 0.2% in the final incubation mixture, throughout this study. Since none of the test compounds inhibited the lysosomal hydrolases, their effects on the rat-liver lysosomal membrane were determined from the hydrolase activities released from the lysosomal fraction, and the following results were obtained. 1) In comparison with metabolites (Ia, b, c, IIa, b), the hydroxy analogs (IVa, b, c, Va, b) showed no difference (b and c series) or an increase in stabilizing activity, or a reversal of labilization to stabilization (a series) (Table

VIII). 2) Introduction of a 2',3'-double bond (IIIa, b, c) or a 2'-hydroxy group (XIVa, b, c) into IIa, b, c resulted in no difference (b and c series) or disappearance (a series) of labilizing activity (Table VIII). 3) The relation of the activity to the carbon number (n) of the side chain was investigated by using straight alkyl chain analogs (VIIa, b, c- n) which have a terminal carboxy group (Table IX). Among VIIa-6 through VIIa-10, VIIa-9 and -10 showed relatively strong stabilization. Homologs with a smaller carbon number than VIIa-4 exhibited

TABLE VIII. Effect of Compounds on Release of Hydrolases from Lysosomal Fraction and on Cyclic AMP Phosphodiesterase (I)

Compound	Concentration (M)	Effect on release of lysosomal hydrolases ^{a)}			Concentration (M)	Effect on phosphodiesterase ^{b)}			
		% hydrolases released				% inhibition			
		β -Glucuronidase	Acid phosphatase			Expt. I		Expt. II	
Ia	2×10^{-5}	$98 \pm 3^c)$	99 ± 6	(6) ^{d)}	5×10^{-4}	22 ± 1	(4)	38	(1)
	2×10^{-4}	81 ± 4	73 ± 9	(6)	1×10^{-3}	33 ± 5	(4)	54	(1)
IVa	2×10^{-5}	72 ± 2	67 ± 4	(3)	5×10^{-4}	60	(1)		
	2×10^{-4}	72 ± 5	63 ± 5	(3)	1×10^{-3}	84	(1)		
IIa	2×10^{-5}	116	131	(2)	5×10^{-4}	23	(2)		
	2×10^{-4}	121	162	(2)	1×10^{-3}	30	(2)		
Va	2×10^{-5}	70	69	(2)	5×10^{-4}	32	(1)		
	2×10^{-4}	62	57	(2)					
IIIa	2×10^{-5}	106 ± 9	96 ± 6	(3)	5×10^{-4}	49	(2)		
	2×10^{-4}	105 ± 4	99 ± 8	(3)	1×10^{-3}	67	(2)		
XIVa	2×10^{-5}	84	73	(2)	5×10^{-4}	47	(1)		
	2×10^{-4}	82	51	(2)	1×10^{-3}	60	(1)		
Ib	2×10^{-5}	77 ± 4	65 ± 4	(14)	5×10^{-4}	14 ± 4	(4)		
	2×10^{-4}	62 ± 4	50 ± 4	(14)	1×10^{-3}	32 ± 6	(4)	46	(1)
IVb	2×10^{-5}	77	66	(2)	5×10^{-4}				
					1×10^{-3}			47	(1)
IIb	2×10^{-5}	82 ± 2	73 ± 2	(6)	5×10^{-4}	8 ± 1	(3)		
	2×10^{-4}	63 ± 6	55 ± 6	(6)	1×10^{-3}	22 ± 2	(7)		
Vb	2×10^{-5}	78	82	(2)	5×10^{-4}	35	(1)		
	2×10^{-4}	71	79	(2)	1×10^{-3}	44	(1)		
IIIb	2×10^{-5}	84	86	(2)	5×10^{-4}	43	(2)		
	2×10^{-4}	64	56	(2)	1×10^{-3}	67	(2)		
XIVb	2×10^{-5}	93 ± 5	92 ± 5	(4)	5×10^{-4}	18	(2)		
	2×10^{-4}	71 ± 6	52 ± 6	(4)	1×10^{-3}	23	(2)		
Ic	2×10^{-5}	67 ± 4	49 ± 5	(15)	5×10^{-4}	51 ± 1	(4)	44	(1)
	2×10^{-4}	66 ± 3	54 ± 5	(13)	1×10^{-3}	68 ± 1	(3)	44	(1)
IVc	2×10^{-5}	75	64	(2)	5×10^{-4}	25	(1)	51	(1)
					1×10^{-3}	53	(1)	57	(1)
IIc	2×10^{-5}	76 ± 3	61 ± 4	(3)	5×10^{-4}	36	(1)		
	2×10^{-4}	57 ± 2	42 ± 7	(3)	1×10^{-3}	50	(1)		
IIIc	2×10^{-5}	72 ± 5	69 ± 6	(4)	5×10^{-4}	86	(2)		
	2×10^{-4}	74 ± 4	60 ± 5	(4)	1×10^{-3}	99	(2)		
XIVc	2×10^{-5}	90 ± 3	80 ± 3	(3)	5×10^{-4}	25	(1)		
	2×10^{-4}	85 ± 3	65 ± 4	(3)	1×10^{-3}	40	(1)		
Theophylline					5×10^{-4}			20 ± 3	(7)
					1×10^{-3}			40 ± 5	(7)

a) Effect on membrane stability was assayed by measuring the hydrolases released from the lysosomal fraction of rat liver during incubation at 37°C for 90 min as already described,³⁾ and values are given as % of control (control: 100%). None of the test compounds inhibited the lysosomal hydrolases.

b) Phosphodiesterase activity was determined by measuring inorganic phosphate after incubation for 30 min at 37°C, as already described (Butcher and Sutherland^{2b)}). The incubation mixture (1 ml) consisted of 0.5 M Tris-HCl, pH 7.5 (0.2 ml), 20 mM MgSO₄ (0.1 ml), 20 mM cyclic AMP (0.1 ml), 0.1 % 5'-nucleotidase (0.1 ml), 0.05% bovine heart phosphodiesterase (0.2 ml), a solution of a test compound in DMSO (5–10 μ l) and water. % inhibition with respect to the control is shown (control: 0%).

c) Mean value $\pm$ SE.

d) Number of assays.

an increase of labilizing activity in proportion to the decrease of n . In VIIb-3 through VIIb-10, the increase of stabilization paralleled the increase of n . The stabilizing activity of VIIc-3 through VIIc-9 decreased in proportion to the increase of n . 4) The stabilizing activities of the straight alkyl chain analogs having a terminal hydroxy group (VIIIa, VIIIb) were almost equal to those of the corresponding carboxy compounds except for VIIIa-4 and VIIIa-6, whose rather strong stabilizing activities were in contrast to those of the corresponding carboxylic

TABLE IX. Effect of Compounds on Release of Hydrolases from Lysosomal Fraction and on Cyclic AMP Phosphodiesterase (II)

Compound	Concentration (M)	Effect on release of lysosomal hydrolases ^{a)}						Effect on phosphodiesterase ^{b)}			
		% hydrolases released						Concentration (M)	% inhibition		
		Expt. I			Expt. II				Expt. I		Expt. II
		β -Glucur.	Acid phosph.		β -Glucur.	Acid phosph.					
VIIa-3	2×10^{-5}	129 $\pm$ 1 ^{c)}	159 $\pm$ 2	(3) ^{d)}				5×10^{-4}	20	(1)	
	2×10^{-4}	204 $\pm$ 20	518 $\pm$ 13	(3)				1×10^{-3}	43	(1)	
VIIa-4	2×10^{-5}	119 $\pm$ 1	142 $\pm$ 7	(3)	117	108	(2)	5×10^{-4}	33	(1)	
	2×10^{-4}	141 $\pm$ 9	293 $\pm$ 12	(3)	168 $\pm$ 10	149 $\pm$ 5	(4)	1×10^{-3}	39	(1)	
VIIa-6	2×10^{-5}	102 $\pm$ 6	100 $\pm$ 9	(3)				5×10^{-4}	27	(1)	
	2×10^{-4}	91 $\pm$ 7	91 $\pm$ 5	(3)				1×10^{-3}	44	(1)	
VIIa-8	2×10^{-5}				81	80	(2)				
	2×10^{-4}				67 $\pm$ 6	70 $\pm$ 17	(3)				
VIIa-9	2×10^{-5}	77 $\pm$ 1	72 $\pm$ 5	(3)				5×10^{-4}	51	(1)	
	2×10^{-4}	62 $\pm$ 5	63 $\pm$ 8	(3)				1×10^{-3}	72	(1)	
VIIa-10	2×10^{-5}	73 $\pm$ 4	79 $\pm$ 7	(3)	74 $\pm$ 3	73 $\pm$ 7	(3)	5×10^{-4}	74	(2)	
	2×10^{-4}	66 $\pm$ 6	74 $\pm$ 5	(3)	66 $\pm$ 8	62 $\pm$ 7	(3)				
VIIb-3	2×10^{-5}	93 $\pm$ 2	89 $\pm$ 5	(5)							
VIIb-4	2×10^{-5}				72	67		5×10^{-4}			15 (1)
								1×10^{-3}			25 $\pm$ 1 (5)
								2×10^{-3}			46 $\pm$ 2 (4)
								5×10^{-4}			19 (1)
VIIb-5	2×10^{-5}				73	72	(2)	5×10^{-4}			41 $\pm$ 3 (5)
								1×10^{-3}			55 $\pm$ 2 (4)
								2×10^{-3}			22 (2)
								5×10^{-4}			24 (2)
VIIb-6	2×10^{-5}	74 $\pm$ 3	63 $\pm$ 3	(6)	72 $\pm$ 6	74 $\pm$ 3	(3)	5×10^{-4}			
								1×10^{-3}			
VIIb-7	2×10^{-5}	70 $\pm$ 14	57 $\pm$ 10	(4)				5×10^{-4}	66	(1)	
								1×10^{-3}	83	(1)	
VIIb-10	2×10^{-5}	40 $\pm$ 5	34 $\pm$ 1	(3)				1.25×10^{-4}	48	(1)	
								2.5×10^{-4}	75	(2)	
								5×10^{-4}	95	(2)	
VIIc-3 ^{e)}	2×10^{-5}	65 $\pm$ 6	48 $\pm$ 6	(3)				5×10^{-4}			14 (1)
	2×10^{-4}	56 $\pm$ 1	50 $\pm$ 1	(3)				1×10^{-3}			38 (1)
VIIc-4 ^{e)}	2×10^{-5}	78 $\pm$ 4	65 $\pm$ 5	(3)				5×10^{-4}			28 (1)
	2×10^{-4}	67 $\pm$ 2	53 $\pm$ 7	(3)				1×10^{-3}			40 (1)
VIIc-5	2×10^{-5}	60	53	(1)				5×10^{-4}			26 (1)
	2×10^{-4}	70	69	(1)				1×10^{-3}			44 (1)
VIIc-6	2×10^{-5}	73	68	(1)				5×10^{-4}	72	(1)	
	2×10^{-4}	76	76	(1)				1×10^{-3}	88	(1)	
VIIc-9 ^{e)}	2×10^{-5}	85 $\pm$ 4	78 $\pm$ 8	(3)				2.5×10^{-4}	70	(2)	
	2×10^{-4}	111 $\pm$ 7	169 $\pm$ 26	(3)				5×10^{-4}	86	(1)	76 (2)
								1×10^{-3}	95	(1)	88 (2)

a) Assayed as described in the legend to Table VIII. Values are shown as % of control (control: 100%). β -Glucur.: β -glucuronidase. Acid phosph.: acid phosphatase.

b) Assayed as described in the legend to Table VIII.

c) Mean value $\pm$ SE.

d) Number of assays.

e) See ref. 14.

acids (VIIa-4, VIIa-6) (Table X). From these results, it was concluded that, in addition to the metabolites (Ia, b, c, IIb, c) which have already been reported, marked membrane-stabilizing activity was shown by the ω -hydroxy (IVa, b, VIIa, b-6, VIIa-10) and ω -carboxy (VIIa-8—VIIa-10, VIIb-10, VIIc-3—VIIc-5) analogs, especially by the hydroxy analogs.

TABLE X. Effect of Compounds on Release of Hydrolases from Lysosomal Fraction and on Cyclic AMP Phosphodiesterase (III)

Compound	Concentration (M)	Effect on release of lysosomal hydrolases ^{a)} % hydrolases released						Effect on phosphodiesterase ^{b)}		
		Expt. I			Expt. II			Concentration (M)	% inhibition	
		β -Glucur.	Acid phosph.		β -Glucur.	Acid phosph.				
VIIa-4	2×10^{-5}	88 ± 4^c	88 ± 4	(4) ^{d)}	75	65	(2)	5×10^{-4}	26	(1)
	2×10^{-4}	78 ± 7	73 ± 8	(4)	60	56	(2)	1×10^{-3}	39	(1)
VIIa-6	2×10^{-5}				71	67	(2)			
	2×10^{-4}				70	62	(2)			
VIIa-10	2×10^{-5}	76	64	(1)	72 ± 5	73 ± 7	(3)	2.5×10^{-4}	47	(1)
	2×10^{-4}	76	60	(1)				5×10^{-4}	61	(2)
								1×10^{-3}	64	(2)
VIIb-6	2×10^{-5}	80 ± 5	81 ± 5	(4)				5×10^{-4}	45	(2)
	2×10^{-4}	79 ± 8	87 ± 7	(4)				1×10^{-3}	60	(2)
Theophylline								5×10^{-4}	12 ± 2	(5)
								1×10^{-3}	24 ± 2	(11)
								2×10^{-3}	42	(1)

a) Assayed as described in the legend to Table VIII. Values are shown as % of control (control: 100%). β -Glucur.: β -glucuronidase. Acid phosph.: acid phosphatase.

b) Assayed as described in the legend to Table VIII.

c) Mean value $\pm$ SE.

d) Number of assays.

Phosphodiesterase is one of the enzymes which regulate the tissue level of cyclic nucleotides. In order to investigate the role of cyclic nucleotides in membrane stability, we determined the effects of these quinonyl compounds on the activity of bovine heart phosphodiesterase as already described.²⁵⁾ Since dimethylsulfoxide (DMSO) at levels below 5% did not show any inhibitory effect on the enzyme activity, a solution of test compounds in DMSO was added to the reaction mixture prior to the incubation. Under these conditions, these quinonyl compounds had an inhibitory effect on the activity of cyclic AMP phosphodiesterase (Table VIII—X). Among the metabolites (Ia, b, c, IIa, b, c), stronger inhibition was observed with naphthoquinone derivatives (Ic, IIc) than benzoquinone derivatives (Ia, b, IIa, b) (Table VIII). In straight alkyl chain analogs having a terminal carboxy group, inhibitory activity was correlated with n (Table IX). The 2',3'-double bond and 3'-methyl group in the metabolites were not essential for the activity. Among the compounds of the a and b series which showed rather strong membrane-stabilizing effects, a good correlation was observed between the activity and the inhibitory effect on cyclic AMP phosphodiesterase. The inhibitory effect of the c series compounds, in contrast to their membrane-stabilizing activity, increased in proportion to the increase of carbon number of the side chain. In general, the inhibitory effect of ω -hydroxy compounds was stronger than that of the corresponding carboxylic acids. The discrepancy between the inhibitory effect on phosphodiesterase and the membrane-stabilizing activity in compounds of the c series obscures the role of cyclic nucleotides in the stabilization of lysosomal membranes, and further studies are necessary.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus, and are uncorrected. UV spectra were recorded in EtOH with a Hitachi EPS-3T spectrophotometer, IR spectra were obtained

with Hitachi EPI-S2 and 215 spectrophotometers, and mass spectra with a Hitachi RMU-6D and a JMS-01SC mass spectrometer (Japan Electron Optics Co.). PMR spectra were run on Varian HA-100, T-60 and A-60A spectrometers with TMS as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Phosphodiesterase from beef heart in glycerol (Boehringer Mannheim), 5'-cyclic AMP (Boehringer Mannheim) and venom snake (Sigma) were purchased.

2,3-Dimethoxy-5-methyl-6-(3-phenyl-2-propenyl)-1,4-benzoquinone (Xa)—2,3-Dimethoxy-5-methylhydroquinone (IXa) [obtained from 2,3-dimethoxy-5-methyl-1,4-benzoquinone (XXXVIIa, 6.0 g, see Chart 4)] and cinnamyl alcohol (6.0 g) were dissolved in dioxane (60 ml). $\text{BF}_3\text{-Et}_2\text{O}$ (25 g) was added dropwise to this solution under N_2 gas at room temperature and the mixture was stirred for 90 min. A solution of FeCl_3 (61 g) in 83% MeOH (72 ml) was added to the reaction mixture, and the whole was stirred for 10 min, then diluted with H_2O and extracted with AcOEt. The extract was worked up in the usual manner and chromatographed on silica gel (200 g) with $\text{CCl}_4\text{-AcOEt}$ (10:1) as the eluent. Orange needles from EtOH, mp 74.5–76°C. Yield 4.1 g (42%). PMR (CDCl_3) δ : 2.05 (3H, s, CH_3), 3.34 (2H, d, $J=6$ Hz, CH_2), 3.96 (6H, s, OCH_3), 5.96 (1H, dd, $J=6$ and 16 Hz, $=\text{CH}$), 6.45 (1H, d, $J=16$ Hz, $=\text{CH}$ on the ring), 7.24 (5H, s, the ring H). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_4$: C, 72.46; H, 6.08. Found: C, 72.29; H, 6.03.

Xb and Xc were similarly obtained as follows.

2,3,5-Trimethyl-6-(3-phenyl-2-propenyl)-1,4-benzoquinone (Xb)—Xb was obtained from trimethylhydroquinone (7.0 g) as yellow needles, mp 119–120°C. Yield 9.4 g (78%). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2$: C, 81.17; H, 6.81. Found: C, 81.18; H, 6.75.

2-Methyl-3-(3-phenyl-2-propenyl)-1,4-naphthoquinone (Xc)—Xc was obtained from 2-methyl-1,4-naphthohydroquinone (4.3 g) as yellow plates, mp 125.5–127°C. Yield 2.0 g (28%). Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{O}_2$: C, 83.31; H, 5.59. Found: C, 83.19; H, 5.67.

1,4-Diacetoxy-2,3-dimethoxy-5-methyl-6-(3-phenyl-2-propenyl)benzene (XIa)—A suspension of Xa and Zn (2 g) in pyridine (20 ml) and Ac_2O (80 ml) was stirred for 30 min at room temperature. The precipitates were filtered off. The filtrate was diluted with H_2O and acidified with conc. HCl (20 ml). The crystals that precipitated were recrystallized from EtOH to give XIa as colorless needles, mp 114–115°C. Yield 4.5 g (89%). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_6$: C, 68.73; H, 6.29. Found: C, 68.63; H, 6.11.

Similarly, XIb and XIc were obtained as follows.

1,4-Diacetoxy-2,3,5-trimethyl-6-(3-phenyl-2-propenyl)benzene (XIb)—XIb was obtained from Xb as colorless needles, mp 128–129°C. Yield 10.6 g (85%). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_4$: C, 74.97; H, 6.86. Found: C, 74.99; H, 6.91.

1,4-Diacetoxy-2-methyl-3-(3-phenyl-2-propenyl)benzene (XIc)—XIc was obtained from Xc as colorless needles, mp 166–169°C. Yield 2.1 g (85%). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{O}_4$: C, 76.98; H, 5.92. Found: C, 77.05; H, 5.70.

2,5-Diacetoxy-3,4-dimethoxy-6-methylphenylacetaldehyde (XIIa)— OsO_4 (38.1 mg) was added to a solution of XIa (4.25 g) in dioxane- H_2O (3:1, 96 ml) at room temperature with stirring. After 10 min, NaIO_4 (12.5 g) was added portionwise to the mixture. After being stirred for 1 h, the mixture was diluted with H_2O and extracted with AcOEt. The extract was worked up in the usual manner and chromatographed. The fraction eluted with $\text{CCl}_4\text{-acetone}$ (10:1) was subjected to preparative thin layer chromatography with $\text{CCl}_4\text{-AcOEt}$ (5:1) to give XIIa as a colorless oil. Yield 2.75 g (80%). PMR (CDCl_3) δ : 2.04 (3H, s, CH_3), 2.28 (3H, s, COCH_3), 2.32 (3H, s, COCH_3), 3.54 (2H, d, $J=2$ Hz, CH_2), 3.84 (6H, s, OCH_3), 9.52 (1H, t, $J=2$ Hz, CHO). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_7$: C, 58.06; H, 5.85. Found: C, 58.29; H, 5.77.

XIIb and XIIc were similarly obtained as follows.

2,5-Diacetoxy-3,4,6-trimethylphenylacetaldehyde (XIIb)—XIIb was obtained from XIb (0.69 g). Colorless needles from AcOEt-hexane, mp 129.5–130°C. Yield 0.443 g (81%). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.73; H, 6.52. Found: C, 64.78; H, 6.36.

1,4-Diacetoxy-3-methylnaphthylacetaldehyde (XIIc)—XIIc was obtained from XIc (4.0 g). Colorless needles from AcOEt-hexane, mp 119–121°C (lit.^{5b}) mp 118–121°C. Yield 2.3 g (72%).

(E)-Ethyl 4-(2,5-Diacetoxy-3,4-dimethoxy-6-methylphenyl)-2-methyl-2-butenolate (XIIIa)—A solution of XIIa (1.57 g) and α -ethoxycarbonyl ethylidene triphenylphosphorane (2.0 g) in benzene (50 ml) was refluxed for 1 h. The mixture was evaporated to dryness *in vacuo*. The resulting residue was purified by column chromatography with $\text{CCl}_4\text{-AcOEt}$ (5:1) to give XIIIa as a colorless oil. Yield 1.8 g (90%). PMR (CDCl_3) δ : 1.25 (3H, t, OCH_2CH_3), 1.96 (3H, s, CH_3), 2.06 (3H, s, CH_3 on the ring), 3.38 (2H, d, $J=7$ Hz, CH_2), 3.83 (6H, s, OCH_3), 4.15 (2H, q, OCH_2), 6.57 (1H, t, $=\text{CH}$). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_8$: C, 60.90; H, 6.64. Found: C, 60.96; H, 6.80.

XIIIb and XIIIc were similarly obtained as follows.

(E)-Ethyl 4-(2,5-Diacetoxy-3,4,6-trimethylphenyl)-2-methyl-2-butenolate (XIIIb)—XIIIb was obtained from XIIb (3.0 g). Colorless needles from EtOH, mp 118–119°C. Yield 3.6 g (92%). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_6$: C, 66.28; H, 7.23. Found: C, 66.41; H, 7.16.

(E)-Ethyl 4-(1,4-Diacetoxy-3-methylnaphthyl)-2-methyl-2-butenolate (XIIIc)—XIIIc was obtained from XIIc (1.04 g). Colorless needles from EtOH, mp 144–144.5°C. Yield 1.2 g (90%). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_6$: C, 68.73; H, 6.29. Found: C, 68.62; H, 6.07.

(*E*)-6-(3-Carboxy-2-butenyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (IIIa) and 6-(3-Carboxy-2-hydroxybutyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (XIVa)—1) 10% KOH (30 ml) was added to a solution of XIIIa (0.68 g) and $\text{Na}_2\text{S}_2\text{O}_4$ (2.1 g) in acetone (7 ml) under N_2 gas at room temperature, and the mixture was stirred for 30 min. The reaction mixture was diluted with H_2O , acidified with cold 3 *N* HCl (20 ml) and extracted with AcOEt. The extract was worked up in the usual manner. The residue was dissolved in 83% MeOH (36 ml) and oxidized with FeCl_3 (35 g) in 83% MeOH (48 ml). The mixture was worked up in the usual manner. The resulting oil was separated into two fractions by column chromatography with CCl_4 -AcOEt-AcOH (100:30:1) as the eluent. The first fraction gave IIIa as orange needles from benzene-hexane. Yield 0.217 g (45%). PMR (CDCl_3) δ : 1.98 (3H, s, CH_3), 2.04 (3H, s, CH_3 on the ring), 3.39 (2H, d, $J=7$ Hz, CH_2), 4.00 (6H, s, OCH_3), 6.64 (1H, t, $J=7$ Hz, (*E*)=CH). The second fraction was subjected to preparative TLC with CCl_4 -acetone-AcOH (50:20:1) as the developing solvent to give XIVa as an orange oil. Yield 0.063 g (12%). PMR (CDCl_3) δ : 1.31 (3H, d, $J=7$ Hz, CH_3), 2.08 (3H, s, CH_3 on the ring), 2.48—2.82 (1H, m, CHCOO), 2.68 (2H, d, $J=7$ Hz, CH_2), 3.98 (7H, s, OCH_3 and CHOH), 7.08 (2H, br, COOH and OH).

2) 10% KOH (20 ml) was added to a solution of XIIIa (0.4 g) and $\text{Na}_2\text{S}_2\text{O}_4$ (1.5 g) in acetone (6 ml) under N_2 gas at room temperature, and the mixture was refluxed for 8 h. A solution of FeCl_3 (30 g) in 83% MeOH (72 ml) was then added, and the mixture was stirred for 1 h. The mixture was extracted with AcOEt and the extract was worked up in the usual manner to give IIIa (0.006 g, 2%) and XIVa (0.149 g, 50%).

(*E*)-6-(3-Carboxy-2-butenyl)-2,3,5-trimethyl-1,4-benzoquinone (IIIb), 6-(3-Carboxy-2-hydroxybutyl)-2,3,5-trimethyl-1,4-benzoquinone (XIVb), (*E*)-3-(3-Carboxy-2-butenyl)-2-methyl-1,4-naphthoquinone (IIIc) and 3-(3-Carboxy-2-hydroxybutyl)-2-methyl-1,4-naphthoquinone (XIVc)—1) A similar reaction starting from XIIIb gave IIIb and XIVb, and that from IIIc gave IIIc and XIVc.

IIIb: Yellow needles. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2400—2650, 1690 (COOH), 1640 (quinone).

XIVb: Yellow needles. PMR (CDCl_3) δ : 1.30 (3H, d, $J=6.5$ Hz, CH_3), 2.01 (6H, s, CH_3 on the ring), 2.06 (3H, s, CH_3 on the ring), 2.48—2.80 (1H, m, CHCOO), 2.69 (2H, d, $J=6.5$ Hz, CH_2), 3.92 (1H, br, CHOH), 6.74 (2H, br, COOH and OH).

IIIc: Yellow needles. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2350—2650, 1690 (COOH), 1660 (quinone). PMR (CDCl_3) δ : 2.03 (3H, s, CH_3), 2.20 (3H, s, CH_3 on the ring), 3.57 (2H, d, $J=7.5$ Hz, CH_2), 6.74 (1H, t, $J=7.5$ Hz, (*E*)=CH), 7.70 (2H, m, the ring H), 8.12 (2H, m, the ring H).

XIVc: Yellow needles. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2300—2600, 1700 (COOH), 1660 (quinone). PMR (CDCl_3) δ : 1.33 (3H, d, $J=7$ Hz, CH_3), 2.20 (3H, s, CH_3 on the ring), 2.54—2.97 (1H, m, CHCOO), 2.83 (2H, d, $J=7$ Hz, CH_2), 3.93—4.32 (1H, m, CHOH), 6.22 (2H, br, COOH and OH), 7.65 (2H, m, the ring H), 8.03 (2H, m, the ring H).

2) A solution of FeCl_3 (0.2 g) in 83% MeOH (2.4 ml) was added to a solution of 2-[2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl)]propionic acid (XVb, 20 mg) in MeOH (2 ml) at room temperature, and the mixture was stirred for 30 min. The mixture was diluted with cold H_2O and extracted with AcOEt. The extract was worked up in the usual manner to give XIVb. Yield 15 mg (70%).

2-[2-(2,3-Dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl)]propionic Acid (XVb)—10% KOH (6.2 ml) was added to a solution of XIIIb (0.135 g) and $\text{Na}_2\text{S}_2\text{O}_4$ (0.388 g) in acetone (1.5 ml), and the mixture was refluxed for 3 h, then cooled. Cold 3 *N* HCl was added to the mixture and the whole was extracted with AcOEt. The extract was worked up in the usual manner. The residue was subjected to column chromatography with CCl_4 -AcOH (10:1) as the eluent to give XVb. Colorless needles (from benzene), mp 168—171°C. Yield 0.065 g (71%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420 (OH), 1710, 1695 (COOH). PMR (CD_3OD) δ : 1.29 (3H, d, $J=7$ Hz, CH_3). Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.30; H, 7.18. MS m/z : 250 (M^+), 189 (M^+-61), 176 (M^+-74). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 295 (3670).

(*Z*), (*E*)-6-(Hydroxy-3-methyl-2-hexenyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (IVa)—1) A solution of the hydroquinone derived from (*Z*), (*E*)-2,3-dimethoxy-6-(5-methoxycarbonyl-3-methyl-2-pentenyl)-5-methyl-1,4-benzoquinone⁷⁾ (XVIa, 1.49 g) in dry Et_2O (200 ml) was added to a suspension of LiAlH_4 (1 g) in Et_2O under ice-cooling. After being stirred for 3 h, the mixture was worked up in the usual manner and oxidized with FeCl_3 . The product was purified by column chromatography with CCl_4 -AcOEt (3:1) to give IVa as an orange oil. Yield 1.05 g (72%). PMR (CDCl_3) δ : 1.62—1.84 (2H, m, CH_2), 1.69, 1.77 (3H, s, (*Z*) and (*E*)= CCH_3), 1.92—2.16 (2H, m, = CCH_2), 2.04 (3H, s, CH_3 on the ring), 2.42 (1H, br, OH), 3.20 (2H, d, CH_2 on the ring), 3.59, 3.67 (2H, t, (*E*) and (*Z*) CH_2O), 4.02 (6H, s, OCH_3), 5.00 (1H, t, =CH).

2) A solution of BF_3 - Et_2O (3 ml) in dioxane (3 ml) was added to a solution of 2,3-dimethoxy-5-methylhydroquinone (IXa) [derived from 2,3-dimethoxy-5-methyl-1,4-benzoquinone (XXXVIIa, 0.313 g)] and XX (0.318 g) in dioxane (6 ml) at room temperature with stirring. After 90 min of stirring, a solution of FeCl_3 (3 g) in 83% MeOH (18 ml) was added to the mixture. The whole was stirred for 30 min and diluted with cold H_2O . The extract with AcOEt was worked up in the usual manner, and subjected to column chromatography on silica gel (20 g) with CCl_4 -AcOEt (3:1) as the eluent as well as preparative TLC with CCl_4 -AcOEt (3:1) as the developing solvent to give IVa as an orange oil. Yield 0.164 g (33%).

(*Z*), (*E*)-6-(Hydroxy-3-methyl-2-hexenyl)-2,3,5-trimethyl-1,4-benzoquinone (IVb), (*Z*), (*E*)-3-(Hydroxy-3-methyl-2-hexenyl)-2-methyl-1,4-naphthoquinone (IVc), 6-(4-Hydroxy-3-methylbutyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (Va) and 6-(4-Hydroxy-3-methylbutyl)-2,3,5-trimethyl-1,4-benzoquinone (Vb)—IVb, c,

Va and Vb were obtained by reduction with LiAlH_4 by a method similar to that used for IVa.

IVb: PMR (CDCl_3) δ : 1.62—1.80 (2H, m, CH_2), 1.69, 1.77 (3H, s, (Z) and (E)= CCH_3), 1.94—2.16 (2H, m, = CCH_2), 2.03 (9H, s, CH_3 on the ring), 2.80 (1H, br, OH), 3.21 (2H, d, CH_2 on the ring), 3.58, 3.68 (2H, t, (E) and (Z) CH_2O), 5.01 (1H, t, =CH).

IVc: PMR (CDCl_3) δ : 1.62—1.80 (2H, m, CH_2), 1.68, 1.80 (3H, s, (Z) and (E)= CCH_3), 1.97—2.14 (2H, m, = CCH_2), 2.20 (3H, s, CH_3 on the ring), 3.36 (2H, d, CH_2 on the ring), 3.58, 3.70 (2H, t, (E) and (Z) CH_2O), 5.07 (1H, t, =CH), 7.68 (2H, m, the ring H), 8.06 (2H, m, the ring H).

Va: PMR (CDCl_3) δ : 1.00 (3H, d, $J=6$ Hz, CH_3), 1.10—1.80 (3H, m, CH and CH_2), 1.94 (1H, br, OH), 2.04 (3H, s, CH_3 on the ring), 2.50 (2H, t, CH_2 on the ring), 3.54 (2H, d, $J=6$ Hz, CH_2O), 4.00 (6H, s, OCH_3).

Vb: PMR (CDCl_3) δ : 0.99 (3H, d, $J=6$ Hz, CH_3), 1.10—1.80 (3H, m, CH and CH_2), 2.00 (9H, s, CH_3 on the ring), 2.50 (2H, t, CH_2 on the ring), 3.52 (2H, d, $J=6$ Hz, CH_2O).

Other data for these quinones are shown in Table I.

6-(4-Hydroxy-3-methyl-2-butenyl)-2,3,5-trimethyl-1,4-benzoquinone (VIb)—A solution of 4% $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in benzene (15.9 ml) was added to a solution of XIIIb (203 mg) in benzene (20 ml) at room temperature with stirring. After 2 h, cold H_2O was added to the mixture to decompose the excess $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$. A solution of FeCl_3 (8 g) in 83% MeOH (24 ml) was then added, and the mixture was stirred for 30 min and extracted with AcOEt . The extract was worked up in the usual manner and purified by column chromatography with CCl_4 -acetone (10:1) as the eluent to give VIb as a yellow oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3500 (OH), 1640 (quinone). PMR (CDCl_3) δ : 1.26 (1H, br, OH), 1.80 (3H, s, CH_3), 2.02 (9H, s, CH_3 on the ring), 3.25 (2H, d, CH_2 on the ring), 3.98 (2H, s, CH_2O), 5.36 (1H, t, $\text{CH}=\text{CH}$).

3-(4-Hydroxy-3-methyl-2-butenyl)-2-methyl-1,4-naphthoquinone (VIc)—VIc (46.5 mg) was obtained by reduction of XIIfc (112 mg) with LiAlH_4 as described for IVa. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3500 (OH), 1660 (quinone). PMR (CDCl_3) δ : 1.66 (1H, br, OH), 1.85 (3H, s, CH_3), 2.20 (3H, s, CH_3 on the ring), 3.41 (2H, d, CH_2 on the ring), 4.00 (2H, s, CH_2O), 5.34 (1H, t, $\text{CH}=\text{CH}$), 7.50—8.20 (4H, m, the ring H).

(Z),(E)-Ethyl 5-Methoxycarbonyl-3-methyl-2-pentenoate (XIX)—A solution of methyl levulinate (XVIII, 3.0 g) and ethoxycarbonylmethylidenetriphenylphosphorane (10 g) in xylene (100 ml) was refluxed for 24 h. The reaction mixture was worked up in the usual manner. Hexane was added to the resulting residue and an insoluble material was filtered off. The filtrate was evaporated to dryness and the residue was subjected to column chromatography on silica gel (200 g) with CCl_4 - AcOEt (10:1) as the eluent to give XIX as a colorless oil. Yield 3.9 g (85%). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4$: C, 59.98; H, 8.05. Found: C, 60.02; H, 8.10.

(Z),(E)-3-Methyl-2-hexene-1,6-diol (XX)—A solution of XIX (6.0 g) in Et_2O (60 ml) was added to a suspension of LiAlH_4 (2.0 g) in Et_2O (100 ml) at -20°C with stirring. After 70 min, a small portion of cold H_2O and saturated aqueous NaHCO_3 solution were added. The aqueous solution was extracted with AcOEt . The extract was worked up in the usual manner and the residue was subjected to column chromatography on silica gel (150 g) with CHCl_3 -MeOH (15:1) as the eluent to give XX as a colorless oil. Yield 3.365 g (86%). MS m/z : 130 (M^+), 112 ($\text{M}^+ - 18$).

(Z),(E)-Ethyl 6-Hydroxy-3-methyl-2-hexenoate (XXI)—A solution of XIX (3.0 g) in Et_2O (30 ml) was added to a suspension of LiAlH_4 (1 g) in Et_2O (50 ml) at -78°C with stirring. After 30 min, the mixture was worked up as described for XX to give XXI as a colorless oil. Yield 1.85 g (70%). Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}_3$: C, 62.76; H, 9.36. Found: C, 62.76; H, 9.45.

(Z),(E)-Ethyl 3-Methyl-6-(α -tetrahydropyranyloxy)-2-hexenoate (XXII)—Conc. HCl (0.04 ml) was added to a mixture of XXI (2.6 g) and 3,4-dihydro- α -pyran (5.2 g) at 0°C with stirring. After 3 h, saturated aqueous NaHCO_3 solution was added to the reaction mixture and the whole was extracted with AcOEt . The extract was worked up in the usual manner and the residue was subjected to column chromatography on silica gel (100 g) with CCl_4 - AcOEt (10:1) as the eluent to give XXII as a colorless oil. Yield 3.7 g (96%). Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_4$: C, 65.59; H, 9.44. Found: C, 65.43; H, 9.32.

(Z),(E)-3-Methyl-6-(α -tetrahydropyranyloxy)-2-hexenol (XXIII)—A solution of XXII (3.5 g) in Et_2O (50 ml) was added to a suspension of LiAlH_4 (1.0 g) in Et_2O (100 ml) at -78°C with stirring. After being stirred for 1 h at -20°C , the reaction mixture was diluted with cold H_2O and saturated aqueous NaHCO_3 solution, and extracted with AcOEt . The extract was worked up in the usual manner and the residue was subjected to column chromatography on silica gel (70 g) with CCl_4 - AcOEt (3:1) as the eluent to give XXIII as a colorless oil. Yield 2.45 g (78%). MS m/z : 196 ($\text{M}^+ - 18$), 130 ($\text{M}^+ - 84$), 112 ($\text{M}^+ - 102$).

ω -Chloroformylalkanoate (XXV-4, -6, -7, -8, -10, -14 and -22)—Monoesters of succinic acid, adipic acid, pimelic acid, suberic acid, sebacic acid, 1,14-tetradecanedioic acid and 1,22-docosanedioic acid²⁶⁾ were obtained by heating succinic anhydride or these dicarboxylic acids with alcohol (MeOH or EtOH), followed by fractional distillation (n : 4, 6, 7, 8 and 10), or by partial hydrolysis of these diesters with $\text{Ba}(\text{OH})_2$ ²⁷⁾ (n : 14 and 22). XXV-4, -6, -7, -8, -10 and -14 were obtained by heating the corresponding monoester with thionyl chloride, followed by distillation *in vacuo*. XXV-22 was prepared by the reaction of the corresponding monoester with PCl_5 for 12 h in dichloromethane.

5-(2-Hydroxy-3,4-dimethoxy-6-methylbenzoyl)valeric Acid (XXVII-6, Table II)— AlCl_3 (3.72 g, 28.0 mmol) was added in small portions to a solution of ethyl 5-chloroformylpentanoate (XXV-6 Et, 2.66 g, 12.8 mmol) and 3,4,5-trimethoxytoluene (2.09 g, 11.5 mmol) in nitrobenzene (12 ml) under ice-cooling with stirring.

The mixture was stirred at 0°C for 6 h and at room temperature for an additional 64 h. The reaction mixture was diluted with cold dil. HCl and extracted with Et₂O. The extract was evaporated to dryness and the resulting residue was hydrolyzed with 12% KOH in MeOH (20 ml). The mixture was worked up in the usual manner and recrystallized from benzene to give XXVII-6 as pale brown needles. Yield 1.97 g (58%). PMR (CDCl₃) δ : 1.72 (4H, m, CH₂), 2.37 (2H, t, CH₂COO), 2.39 (3H, s, CH₃ on the ring), 2.88 (2H, t, COCH₂), 3.81 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 6.26 (1H, s, the ring H), 9.70 (2H, br, OH and COOH).

XXVII-4, -8 and -22 were prepared in a similar manner.

9-(2-Hydroxy-3,4-dimethoxy-6-methylbenzoyl)nonanoic Acid (XXVII-10) and 9-(2,3,4-Trimethoxy-6-methylbenzoyl)nonanoic Acid (XXVIII-10)—AlCl₃ (4.08 g) was added in small portions to a solution of ethyl 9-chloroformylnonanoate (XXV-10 Et, 3.52 g) and 3,4,5-trimethoxytoluene (XXIV, 2.21 g) in nitrobenzene (20 ml) at 0°C with stirring. The mixture was stirred at 0°C for 16 h and at room temperature for an additional 1.5 h. The mixture was diluted with cold dil. HCl and extracted with Et₂O. The extract was evaporated to dryness and the resulting residue was hydrolyzed with 25% KOH in MeOH (10 ml). The mixture was acidified with dil. HCl and extracted with AcOEt. The extract was worked up in the usual manner. The residue was dissolved in a small portion of AcOEt. The insoluble sebacic acid was filtered off and the filtrate was concentrated. The resulting residue was chromatographed on silicic acid (60 g) to provide two fractions. The first fraction eluted with benzene-Et₂O (9:1) was concentrated *in vacuo*, giving XXVIII-10 (1.82 g, 41.2%) as a colorless oil which crystallized on standing. PMR (CDCl₃) δ : 1.20—1.87 (12H, m, CH₂), 2.15 (3H, s, CH₃ on the ring), 2.42 (2H, t, CH₂COO), 2.72 (2H, t, COCH₂), 3.80 (9H, s, OCH₃), 3.40 (1H, s, the ring H), 9.32 (1H, br, COOH). The fraction eluted with benzene-Et₂O (5.7:1) was concentrated *in vacuo*, giving XXVII-10, which was recrystallized from hexane-Et₂O as colorless needles. Yield 0.67 g (13.0%). PMR (CDCl₃) δ : 1.17—1.90 (12H, m, CH₂), 2.34 (2H, t, CH₂COO), 2.40 (3H, s, CH₃ on the ring), 2.87 (2H, t, COCH₂), 3.83 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 6.27 (1H, s, the ring H), 10.21 (2H, br, OH and COOH).

10-(2-Hydroxy-3,4-dimethoxy-6-methylphenyl)decanoic Acid (XXIX-10)—1) A mixture of XXVII-10 (254 mg), Zn-Hg (prepared from 0.56 g of Zn and 0.056 g of HgCl₂), toluene (1 ml), conc. HCl (0.5 ml) and H₂O (one drop) was refluxed for 15 h. The toluene layer was separated and the aqueous layer was extracted with Et₂O. The toluene and Et₂O layers were combined and worked up in the usual manner. The residue was crystallized from ligroin to give XXIX-10 as colorless crystals. Yield 140 mg (55.4%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450 (OH), 2400—2700, 1695 (COOH). PMR (CDCl₃) δ : 1.20—1.87 (14H, m, CH₂), 2.22 (3H, s, CH₃ on the ring), 2.43 (4H, t, CH₂ on the ring and CH₂CO), 3.80 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 5.23 (1H, s, the ring H).

2) XXVII-10 (186 mg) was hydrogenated over 5% Pd-C in AcOH (17 ml) for 6.5 h at room temperature and then for 6.5 h longer at 50—60°C. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized from ligroin to give XXIX-10. Yield 103 mg (57.7%).

8-(2-Hydroxy-3,4-dimethoxy-6-methylphenyl)octanoic Acid (XXIX-8)—A solution of XXVII-8 (1 g) in MeOH (30 ml) was reduced with NaBH₄ (300 mg) and worked up in the usual manner. The residue was dissolved in AcOH (100 ml) and the solution was hydrogenated over 5% Pd-C for 70 min at room temperature. The reaction mixture was worked up in the usual manner to give XXIX-8 as pale brown crystals. Yield 636 mg (66.5%). Physicochemical data are given in Table III.

Compounds XXIX-4, -6 and -22 were prepared in a similar manner. Their physicochemical data are listed in Table III.

Deacylation of XXVII-6—1) A mixture of XXVII-6 (31 mg), HgCl₂ (11.3 mg), toluene (1 ml), conc. HCl (three drops) and H₂O (three drops) was refluxed for 13 h. After cooling, the reaction mixture was extracted with Et₂O and the extract was worked up in the usual manner. The resulting residue was chromatographed on silicic acid (1 g) with CHCl₃ as the eluent, giving 2,3-dimethoxy-5-methylphenol (XXXIII) as colorless crystals, mp 57°C (lit.²⁸) mp 57°C).

2) A mixture of XXVII-6 (32 mg), toluene (3 ml), conc. HCl (0.075 ml) and H₂O (three drops) was refluxed for 23 h. After cooling, the reaction mixture was extracted with Et₂O and the extract was worked up in the usual manner. The resulting residue was subjected to preparative TLC with CHCl₃-EtOH (19:1) as the developing solvent, giving XXXIII.

3) A mixture of XXVII-6 (102 mg), HgCl₂ (113 mg), toluene (8 ml) and H₂O (1 ml) was refluxed for 23 h. After the addition of HgCl₂ (344 mg), the mixture was refluxed for an additional 26 h and worked up in the usual manner. The resulting residue was subjected to preparative TLC with CHCl₃-EtOH (19:1) as the developing solvent and recrystallized from CHCl₃ to give 2,3-dimethoxy-5-methyl-6-chloromercuriphenol (XXXII) as colorless needles, mp 184—186°C. PMR (acetone-*d*₆) δ : 2.37 (3H, s, CH₃), 3.70 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 6.24 (1H, s, the ring H). MS *m/z*: 404, 402 (M⁺), 168 (M⁺ - HgCl + 1). XXXII was obtained from the mother liquor of the above recrystallization.

6-(5-Carboxypentyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-6)—1) A solution of ON(SO₃K)₂ (800 mg) in H₂O (10 ml) was added to a solution of XXIX-6 (84 mg) in 1% NaOH (1.43 ml) and the mixture was stirred for 1 h at room temperature, then acidified with dil. HCl and extracted with Et₂O. The extract was worked up in the usual manner and the resulting residue was crystallized from Et₂O to give VIIa-6 as orange needles. Yield 76 mg (86%). PMR (CDCl₃) δ : 1.27—1.80 (6H, m, CH₂), 2.03 (3H, s, CH₃ on the ring), 2.40 (4H, t, CH₂ on the ring and CH₂CO), 4.00 (6H, s, OCH₃), 9.45 (1H, br, COOH).

Compounds VIIa-4, -8 and -10 were prepared in a similar manner and their physicochemical data are

given in Table I.

2) XXXIX (12 mg) was subjected to the Clemmensen reduction as described in procedure 1) for XXIX-10. The resulting hydroquinone was oxidized with FeCl_3 in 83% MeOH and worked up in the usual manner to give VIIa-6 as orange needles. Yield 6.7 mg (58%).

6-(21-Carbonylhenicosyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-22)—A solution of XXIX-22 (300 mg) in DMF (20 ml) was stirred under an oxygen stream in the presence of bis(salicylidene) ethylenediaminocobalt (salcomine, 50 mg) at room temperature for 24 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting oil was dissolved in AcOEt, washed with H_2O and dried over Na_2SO_4 . The solvent was evaporated off and the residue was chromatographed on silica gel with CHCl_3 as the eluent. The solvent was evaporated off, and the resulting residue was crystallized from EtOH to give VIIa-22 as orange yellow needles. Yield 135 mg (43.8%).

6-(2-Carboxyethyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-3)—Disuccinoyl peroxide (XXXVIII-3, 2 g) was added portionwise to a solution of XXXVIIa (0.91 g) in AcOH (10 ml) at 90°C. The reaction mixture was heated for an additional 4 h and then diluted with H_2O . The mixture was extracted with Et_2O and the extract was worked up in the usual manner and recrystallized from Et_2O to give VIIa-3 as orange red crystals. Yield 0.4 g (32%).

6-(12-Carboxydodecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-13)—Solutions of 30% $\text{Na}_2\text{S}_2\text{O}_4$ (5 ml) and 30% KOH (3.5 ml) were added to a solution of the hydroquinone derived from VIIa-13 Me (1.5 g), and the mixture was stirred under a stream of N_2 at 50°C for 2.5 h. After cooling, the mixture was acidified with 3 N HCl and extracted with Et_2O . The extract was worked up in the usual manner and the residue was oxidized with FeCl_3 . The resulting product was recrystallized from Et_2O -hexane to give VIIa-13 as orange needles. Yield 1.09 g (75%). PMR (CDCl_3) δ : 1.16–1.80 (20H, br, CH_2), 2.03 (3H, s, CH_3 on the ring), 2.36 (4H, t, CH_2 on the ring and CH_2COO), 3.99 (6H, s, OCH_3).

VIIa-9 was obtained in a similar manner from VIIa-9 Et.

2-Hydroxy-3,4-dimethoxybenzaldehyde (XXXV)—A solution of AlCl_3 (4 g) in Et_2O (20 ml) was added to 2,3,4-trimethoxybenzaldehyde (XXXIV) and the mixture was stirred for 72 h at room temperature. The reaction mixture was diluted with ice- H_2O and acidified with cold 3 N HCl. The Et_2O layer was separated and extracted with 1% NaOH. The alkaline extract was acidified and extracted with Et_2O . The extract was worked up in the usual manner and the residue was distilled under reduced pressure to afford XXXV, bp 122°C (2 mmHg) (lit.,¹⁸) bp 120–121°C (2 mmHg). Yield 1.27 g (70.6%).

2-Hydroxy-3,4-dimethoxytoluene (XXXVI)—A mixture of XXXV (1.8 g), Zn-Hg (3.6 g), conc. HCl (4 ml), H_2O (2 ml) and toluene (10 ml) was refluxed for 14 h. The mixture was worked up in the usual manner and the residue was distilled under reduced pressure to afford XXXVI, bp 88°C (2 mmHg) (lit.,¹⁷) bp 79–80°C (1.5 mmHg). Yield 1.2 g (72.3%).

2,3-Dimethoxy-5-methyl-1,4-benzoquinone (XXXVII)—A solution of $\text{ON}(\text{SO}_3\text{K})_2$ (12 g) and AcONa (0.9 g) in H_2O (100 ml) was added to a solution of XXXVI (1.2 g) in acetone (60 ml) and the mixture was stirred for 2 h at room temperature. The reaction mixture was worked up in the usual manner and the residue was recrystallized from petroleum ether to give XXXVII as orange needles, mp 57–59°C (lit.,¹⁷) mp 59–60°C. Yield 1.3 g (quantitative).

Bis-13-methoxycarbonyltridecanoyl Peroxide (XXXVIII-13 Me)—XXV-14 Me (11.7 g) was dissolved in petroleum ether (200 ml). Ice- H_2O (60 ml) was added to the solution with ice-cooling under stirring, and then Na_2O_2 (5.2 g) was added dropwise to the mixture. After being stirred for 1 h, the reaction mixture was extracted with Et_2O . The extract was worked up in the usual manner to give XXXVIII-13 Me (7.6 g) as crude crystals. This product was used for the following reaction without purification. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1790, 1760 (C–O–O), 1730 (COOCH_3).



Compounds XXXVIII-3 Me, -5 Et, -6 Et, and -9 Et were prepared in a similar manner from XXV-4 Me, -6 Et, -7 Et, and -10 Et, respectively.

XXXVIII-3 was also obtained from succinic anhydride and H_2O_2 .

2,3-Dimethoxy-5-methyl-6-(1-oxo-5-carboxypentyl)-1,4-benzoquinone (XXXIX)—A solution of $\text{ON}(\text{SO}_3\text{K})_2$ (4.95 g) in 0.17 M KH_2PO_4 (4 ml) and H_2O (20 ml) was added to a solution of XXVII-6 (57 mg) in acetone (4 ml) and the mixture was stirred for 3 h at room temperature. The reaction mixture was worked up in the usual manner and recrystallized from Et_2O -hexane to give XXXIX as orange crystals. Yield 32 mg (53.6%). PMR (CDCl_3) δ : 1.69 (4H, m, CH_2), 1.93 (3H, s, CH_3), 2.37 (2H, m, CH_2COO), 2.65 (2H, m, COCH_2), 3.99 (6H, s, OCH_3).

2,3-Dimethoxy-6-(12-methoxycarbonyldodecyl)-5-methyl-1,4-benzoquinone (VIIa-13 Me)—Bis-13-methoxycarbonyltridecanoyl peroxide (XXXVIII-13 Me, 7.6 g) and XXXVIIa (1.7 g) were reacted as described for VIIa-3 to give VIIa-13 Me. Yield 1.37 g (36%).

Esterification of VIIa-n—1) A solution of VIIa-10 (1 g) and *p*-toluenesulfonic acid (25 mg) in EtOH (50 ml) was heated at 60°C for 2 h. The solvent was evaporated off *in vacuo* and the residue was diluted with H_2O and extracted with AcOEt. The extract was worked up in the usual manner and the residue was purified by column chromatography on silica gel with CCl_4 -AcOEt (19:1) to give 6-(9-ethoxycarbonylnonyl)-

2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-10 Et) as an orange oil. Yield 800 mg (74.1%).

2) A mixture of VIIa-4 (1 g), benzyl bromide (1.44 g) and Ag₂O (1.34 g) in dry benzene (20 ml) was refluxed for 1 h. Insoluble materials were filtered off, and the filtrate was washed with H₂O, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CCl₄-AcOEt (4: 1) to give 6-(3-benzyloxycarbonylpropyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-4 Bz) as an orange oil. Yield 889 mg (60.5%).

Benzyl, phenethyl and *tert*-butyl esters of VIIa-10 were prepared in a similar manner from VIIa-10.

5-(2-Hydroxy-3,4,6-trimethylbenzoyl)valeric Acid (XLIII-6), Its Ester (XLII-6) and 1,4-Bis-(2-hydroxy-3,4,6-trimethylbenzoyl)butane (XLIV-6) (Chart 5)—1) Powdered AlCl₃ (3.5 g, 26 mmol) was added to a solution of 2,3,5-trimethylphenol (XL, 1.4 g, 10.3 mmol) in C₂H₂Cl₄ (10 ml) with stirring and ice-cooling under a stream of N₂, and a solution of ethyl 5-chloroformylpentanoate (XXV-6 Et, 3 g, 15.6 mmol) was added to the reaction mixture. The whole was heated at 110–120°C for 17 h. After cooling, the mixture was diluted with H₂O, acidified with 3 N HCl and extracted with CHCl₃. The extract was worked up in the usual manner and the residue was separated by column chromatography to give XLII-6, XLIII-6 and XLIV-6.

Compounds XLII-7, XLIII-7, XLII-10, XLIII-10 and XLIV-10 were obtained in a similar manner. Their physicochemical data are listed in Table V.

2) A solution of XL (155 mg, 1.1 mmol), XXV-6 Et (335 mg, 1.9 mmol) and AlCl₃ (500 mg, 3.8 mmol) in nitrobenzene (20 ml) was heated at 60–70°C for 18 h. The reaction mixture was worked up in the manner described in procedure 1) to give XLII-6.

9-(2-Hydroxy-3,4,5-trimethylbenzoyl)nonanoic Acid (XLVI-10), Its Ester (XLV-10) and 1,8-Bis(2-hydroxy-3,4,5-trimethylbenzoyl)octane (XLVII-10)—A solution of XL (1.5 g, 11.0 mmol), XXV-10 Et (3 g, 12.0 mmol) and AlCl₃ (3.5 g, 26.2 mmol) in C₂H₂Cl₄ (15 ml) was heated at 110°C for 13 h then treated in the manner described for XLII-6, XLIII-6 and XLIV-6 to give XLV-10, XLVI-10 and XLVII-10. Physicochemical data are listed in Table VI.

Compounds XLVI-6, -7, XLVII-6 and -7 were prepared analogously after hydrolysis of the products.

ω-(2-Hydroxy-3,4,6-trimethylphenyl)alkanoic Acid (LI-*n*), Its Ester (L-*n*) and ω-(2-Hydroxy-3,4,5-trimethylphenyl)alkanoic Acid (XLVIII-*n*)—L-*n*, LI-*n* and XLVIII-*n* were obtained by methods similar to those described for XXIX-10 from XLII-*n*, XLIII-*n* and XLV-*n*, respectively.

2,3,4-Trimethylphenol (XLIX)—A solution of XLVI-6 (20 mg) in H₃PO₄ (2 ml) was refluxed for 11 h. After cooling, the reaction mixture was diluted with H₂O and extracted with AcOEt. The extract was worked up in the usual manner and the residue was chromatographed on silicic acid (1 g) with CHCl₃ as the eluent, giving XLIX, which was recrystallized from petroleum ether to give colorless needles, mp 78–80.5°C (lit.²⁹ mp 81°C).

6-(5-Carboxy-1-oxopentyl)-2,3,5-trimethyl-1,4-benzoquinone (LII)—ON(SO₃K)₂ (0.1 g) was added to a solution of XLIII-6 (48 mg) in 0.5% NaOH (3 ml) and the mixture was stirred for 10 min at room temperature. The mixture was diluted with H₂O, acidified with 3 N HCl and extracted with Et₂O. The extract was worked up in the usual manner and the resulting residue was recrystallized from hexane-AcOEt to give LII as yellow crystals. Yield 42 mg (83.2%).

6-(5-Carboxypentyl)-2,3,5-trimethyl-1,4-benzoquinone (VIIb-6)—1) LII (9 mg) was hydrogenated over 5% Pd-C (10 mg) in AcOH (2 ml) at 65–70°C for 4 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt and shaken with 10% FeCl₃ (10 ml) to give VIIb-6.

2) ON(SO₃K)₂ (0.9 g) was added to a solution of LI-6 (0.111 g) in 1% NaOH (5 ml) and H₂O (3 ml), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with cold H₂O (50 ml) and then acidified with dil. HCl. The resulting yellow precipitate was recrystallized to give VIIb-6.

6-(2-Carboxyethyl)-2,3,5-trimethyl-1,4-benzoquinone (VIIb-3)—XXXVIIb (1 g) was treated with bis-2-methoxycarbonylpropionyl peroxide (XXXVIII-3 Me, 1.4 g) in a manner similar to that described for VIIa-3 to give VIIb-3 Me as a yellow oil. Yield 0.55 g (35%). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1740 (COOCH₃), 1640 (quinone). PMR (CDCl₃) δ : 1.98 (6H, s, CH₃ on the ring), 2.05 (3H, s, CH₃ on the ring), 2.47 (2H, t, CH₂COO), 2.82 (2H, t, CH₂ on the ring), 3.50 (3H, s, COOCH₃). VIIb-3 Me was hydrolyzed in a manner similar to that described for VIIa-13 to give VIIb-3.

6-(5-Benzyloxycarbonylpentyl)-2,3,5-trimethyl-1,4-benzoquinone (VIIb-6 Bz)—VIIb-6 Bz was obtained by a method similar to that described for VIIa-4 Bz.

3-(5-Carboxypentyl)-2-methyl-1,4-naphthoquinone (VIIC-5)—Bis-5-ethoxycarbonylpentanoyl peroxide (XXXVIII-5 Et, 1.36 g) and XXXVIIc (0.674 g) were treated in a manner similar to that described for VIIa-3 to give VIIC-5 Et (150 mg). It was hydrolyzed as described for VIIa-13 to give VIIC-5. Yield 95 mg.

VIIC-6 Et and VIIC-6 were prepared analogously.

6-(22-Hydroxydocosyl)-2,3-dimethoxy-5-methylphenol (LVII-22)—A solution of methyl 22-(2-hydroxy-3,4-dimethoxy-6-methylphenyl)docosanoate (XXX-22, 1.42 g) in THF (27 ml) was added to a suspension of LiAlH₄ (0.41 g) in Et₂O (10 ml) under ice-cooling. After being stirred at room temperature for 1 h, the mixture was acidified with 3 N HCl and extracted with AcOEt. The extract was worked up in the

usual manner to give crystals, which were recrystallized from EtOH to give LVII-22 as pale pink crystals, mp 78—81°C. Yield 1.3 g (quantitative). PMR (CDCl₃) δ : 1.26 (40H, br, CH₂), 2.23 (3H, s, CH₃ on the ring), 2.53 (2H, t, CH₂ on the ring), 3.61 (2H, t, CH₂O), 3.80 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 6.21 (1H, s, the ring H). Anal. Calcd for C₃₁H₅₄O₄: C, 75.87; H, 11.09. Found: C, 75.79; H, 11.38.

6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methylphenol (LVII-10)—LVII-10 was obtained in a manner similar to that described for LVII-22. PMR (CDCl₃) δ : 1.32 (16H, br, CH₂), 2.24 (3H, s, CH₃ on the ring), 2.57 (2H, t, CH₂ on the ring), 3.61 (2H, t, CH₂O), 3.81 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 6.25 (1H, s, the ring H). Anal. Calcd for C₁₉H₃₂O₄: C, 70.33; H, 9.94. Found: C, 70.07; H, 10.05.

1-(2-Hydroxy-3,4,6-trimethylphenyl)-1,6-hexanediol (LVIII)—LiAlH₄ (0.5 g) was added to a solution of ethyl 5-(2-hydroxy-3,4,6-trimethylbenzoyl)pentanoate (XLII-6, 0.4 g) in THF (100 ml), and the mixture was stirred for 1 h. The resulting mixture was worked up in the usual manner to give crystals, which were recrystallized from Et₂O to give LVIII as colorless needles, mp 135—136°C. Yield 0.32 g (93%). Anal. Calcd for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.54.

6-(2-Hydroxy-3,4,6-trimethylphenyl)-1-hexanol (LIX)—LVIII (543 mg) was hydrogenated over 5% Pd-C (479 mg) in AcOH (15 ml). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give an oil. The oil was chromatographed on silica gel (17 g) with CHCl₃-MeOH (100:1) as the eluent. The solvent was evaporated off to give LIX as colorless needles, mp 81—82°C. Yield 87 mg (17%). Anal. Calcd for C₁₅H₂₄O₂: C, 76.22; H, 10.24. Found: C, 76.08; H, 10.33.

6-(10-Acetoxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (LX)—Ac₂O (0.1 g) was added to a cooled, well-stirred solution of 6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-10, 0.3 g) in pyridine (1 ml). After being stirred for 1 h at room temperature, the mixture was diluted with H₂O. The extract was worked up in the usual manner to give crystals, which were recrystallized from EtOH to give LX as orange needles, mp 38°C. Yield 0.31 g (92%).

(E)-1,4-Diacetoxy-6-(2-ethoxycarbonylvinyl)-2,3,5-trimethylbenzene (LXII)—A suspension of 2,5-diacetoxy-3,4,6-trimethylbenzaldehyde (LXI, 1.2 g) and α -ethoxycarbonylmethylidenetriphenylphosphorane (2.5 g) in dioxane (150 ml) was refluxed for 16 h, then the solvent was removed *in vacuo*. The resulting white solid was triturated with AcOEt and filtered. The filtrate was purified by column chromatography on silica gel with CCl₄-acetone (10:1) as the eluent. Recrystallization of the residue from EtOH gave LXII as colorless needles, mp 117—119°C. Yield 1.6 g (96%). IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1750 (OCOCH₃), 1715 (COOEt). PMR (CDCl₃) δ : 6.15 (1H, d, $J=16$ Hz, CH=), 7.6 (1H, d, $J=16$ Hz, CH=). Anal. Calcd for C₁₈H₂₂O₆: C, 64.65; H, 6.63. Found: C, 64.52; H, 6.80.

(E)-6-(2-Carboxyvinyl)-2,3,5-trimethyl-1,4-benzoquinone (LXIII)—10% KOH in acetone-H₂O (1:5, 36 ml) was added dropwise to a solution of LXII (0.497 g) in acetone-H₂O (2:1, 15 ml) with stirring at room temperature. After being stirred for 1.5 h, the mixture was ice-cooled, acidified with cold dil. HCl, and extracted with AcOEt (300 ml). The AcOEt layer was treated with 3.3% FeCl₃ (300 ml) and worked up in the usual manner. The resulting residue was triturated with hexane-AcOEt (10:1) and recrystallized from AcOEt to give LXIII as yellow needles, mp 162—169°C. Yield 0.275 g (84%). PMR (CDCl₃) δ : 2.04 (6H, s, CH₃ on the ring), 2.22 (3H, s, CH₃ on the ring), 6.76 (1H, d, $J=16$ Hz, CH=), 7.72 (1H, d, $J=16$ Hz, CH=), 10.4 (1H, br, COOH). Anal. Calcd for C₁₂H₁₂O₄: C, 65.44; H, 5.49. Found: C, 65.18; H, 5.62.

(E)-6-(2-Ethoxycarbonylvinyl)-2,3,5-trimethyl-1,4-benzoquinone (LXIV)—LXIII was dissolved in EtOH saturated with HCl gas, and the solution was worked up in the usual manner. The resulting residue was recrystallized from Et₂O-hexane to give LXIV as yellow needles, mp 58°C. Anal. Calcd for C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.74; H, 6.49.

6-(ω -Hydroxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIIa-*n*) and 6-(ω -Hydroxyalkyl)-2,3,5-trimethyl-1,4-benzoquinone (VIIIb-*n*)—1) A solution of 6-(3-ethoxycarbonylpropyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-4 Et, 0.78 g) in Et₂O (10 ml) was added to a suspension of LiAlH₄ (0.5 g) in Et₂O under cooling in an ice bath. After being stirred for 1 h at room temperature, the mixture was acidified with 3 N HCl. The ethereal layer was separated and the remaining part was extracted with Et₂O. The combined ethereal layer and the extract were washed with H₂O, dried over Na₂SO₄ and concentrated *in vacuo* to give 6-(4-hydroxybutyl)-2,3-dimethoxy-5-methylhydroquinone. A solution of the hydroquinone in Et₂O was shaken with 16% FeCl₃ (10 ml) and the ethereal layer was worked up in the usual manner. The residue was subjected to column chromatography on silica gel with CHCl₃ to give VIIIa-4 as an orange oil. Yield 0.52 g (77.7%).

Compounds VIIIa-6, -10, -13 and VIIIb-6 were prepared in a similar manner from the corresponding esters (VIIa, b-*n* R₁).

2) VIIIa-10 was obtained by oxidation of LVII-10 with Fremy's salt in a manner similar to that described for VIIa-6. VIIIb-6 was similarly obtained from LIX.

3) VIIIa-22 was obtained by oxidation of LVII-22 using salcomine in a manner similar to that described for VIIa-22.

4) A solution of LXIV in Et₂O was treated in a manner similar to that described for VIIIa-4. The resulting residue was subjected to column chromatography on silica gel with CHCl₃-EtOH (9:1) to give VIIIb-3 as a yellow oil.

6-(17-Carboxyheptadecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (VIIa-18)—Jones reagent (0.5

ml) was added to a solution of VIIa-18³⁰⁾ (172 mg) in acetone (10 ml) under ice-cooling, and the mixture was stirred for 10 min. The reaction mixture was diluted with H₂O and extracted with CHCl₃. The extract was worked up in the usual manner to give VIIa-18 as orange needles. Yield 65 mg (37.1%).

VIIa-11 was prepared in a similar manner from VIIa-11.³⁰⁾

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