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# A Facile Synthesis of 1,4-Benzoquinones Having a Hydroxyalkyl Side Chain

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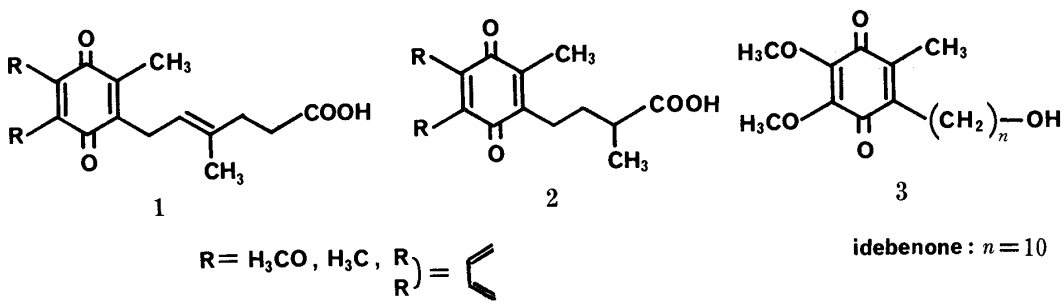
6-(ω-Hydroxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones (**3**) and 6-(ω-acetoxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones (**26**) having various carbon numbers (*n*) of the side chain were synthesized by the Friedel–Crafts coupling of 3,4,5-trimethoxytoluene (**4**) and ω-acetoxyalkanoyl chlorides (**5**) as a key step. The Fremy's salt oxidation or the salcomine-catalyzed oxidation of 6-(ω-hydroxyalkyl)-2,3-dimethoxy-5-methylphenols (**25**) and their acetates (**24**), the key intermediates of the process, gave rise to **3** and **26**, respectively, in good yields. The described method provides a good yield of the 1,4-benzoquinones and is suitable for the synthesis of other quinonyl analogs.

The effect on lipid peroxidation in canine brain homogenate of the 1,4-benzoquinones (**3**) having various carbon numbers (*n*) of the side chain was studied. Among the compounds tested, **3** having a carbon number in the range of $n=9$—13 showed rather strong antioxidant activity.

**Keywords**——1,4-benzoquinone; Friedel–Crafts reaction; ω-acetoxyalkanoyl chloride; Fremy's salt oxidation; salcomine-catalyzed oxidation; lipid peroxidation; antioxidant; structure–activity relationship

As an integral part of studies of ubiquinones and related compounds, we reported a series of new quinonyl acid metabolites (**1**, **2**) which were isolated from urine of rats and rabbits to which ubiquinone-7,α-tocopherol and phylloquinone had been administered.[1] These metabolites have interesting biological activities, such as lysosomal membrane-stabilizing effect,[2] immunoadjuvant activity,[3] and mitochondrial succinate and reduced nicotinamide adenine dinucleotide (NADH) oxidase activity.[4] These results prompted us to synthesize a series of 1,4-benzoquinones having a carboxy- or a hydroxy-alkyl side chain. Among the quinone derivatives synthesized previously,[5] 6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (idebenone) (**3**: $n=10$) was found to improve neurological symptoms in stroke-prone spontaneously hypertensive rats with experimental cerebral ischemia[6] and to show beneficial effects on physiological and neurological symptoms in patients with cerebral vascular diseases.[7] This report describes a facile synthesis of idebenone and related 1,4-benzoquinones having an ω-hydroxyalkyl side chain with various carbon numbers, as well as their effect on lipid peroxidation in canine brain homogenate.

From the synthetic point of view, an approach based on the Friedel–Crafts coupling[8] of 3,4,5-trimethoxytoluene (TMT) (**4**) with ω-acetoxyalkanoyl chlorides (**5**) as a side chain moiety looked promising for the synthesis of idebenone (**3**: $n=10$) and its homologs. We examined the coupling reactions of TMT (**4**) and 10-acetoxydecanoyl chloride (**5**: $n=10$) as a typical example in detail. The results are summarized in Table I. The Friedel–Crafts reaction proceeded smoothly with concomitant demethylation depending on the amount of aluminium chloride used, and gave a mixture of **6**, **7** and **8**. Among the products, a phenol (**7**) was quite suitable for transformation to the 1,4-benzoquinone structure.




1 2 3

Chart 1

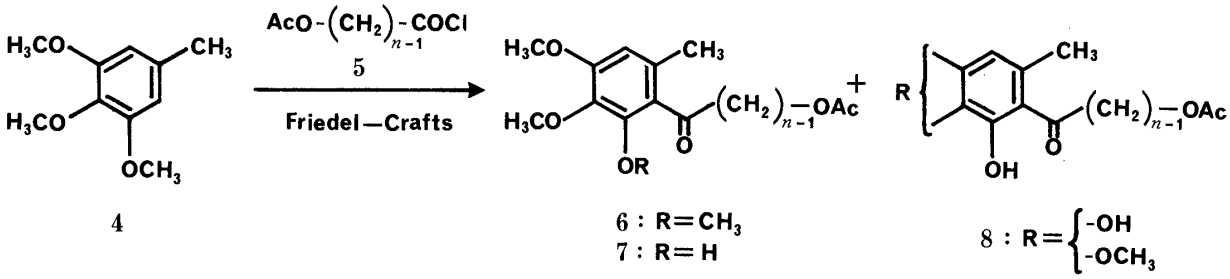



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Chart 2

TABLE I. Results of Various Friedel–Crafts Reaction of 3,4,5-Trimethoxytoluene (**4**) and 10-Acetoxydecanoyl Chloride (**5**: $n=10$) under Various Conditions

| Run | Solvent[a] | Lewis acid (mol used)[b] | Reaction temp. (°C) | Reaction time (h) | Yield[c] (%) of products | | |
|---|---|---|---|---|---|---|---|
| | | | | | **6** | **7** | **8** |
| 1 | $EtNO_2$ | $AlCl_3$ (2.1) | 10 | 24 | 4 | 56 | 7 |
| 2 | $ClCH_2Cl$ | $AlCl_3$ (2.1) | 10 | 24 | — | 34 | 4 |
| 3 | $ClCH_2CH_2Cl$ | $AlCl_3$ (2.1) | 10 | 24 | 7 | 61 | — |
| 4 | $ClCH_2CH_2Cl$ | $ZnCl_2$ (2.1) | 10 | 72 | 2 | 41 | 8 |
| 5 | $ClCH_2CH_2Cl$ | $AlCl_3$ (1.1) | 20 | 72 | 43 | 29 | — |
| 6 | $ClCH_2CH_2Cl$ | $AlCl_3$ (1.5) | 20 | 72 | 32 | 40 | — |
| 7 | $ClCH_2CH_2Cl$ | $AlCl_3$ (2.1) | 20 | 72 | 3 | 79 | 6 |
| 8 | $ClCH_2CH_2Cl$ | $AlCl_3$ (2.1) | 30 | 72 | 2 | 77 | 9 |
| 9 | $ClCH_2CH_2Cl$ | $AlCl_3$ (2.1) | 40 | 72 | — | 71 | 2 |
| 10 | $ClCH_2CH_2Cl$ | $AlCl_3$ (3.1) | 20 | 72 | — | 44 | 35 |

*a*) All solvents used were dried over molecular sieves 3A. *b*) Freshly powdered aluminium chloride was used. *c*) Isolated yield.

$\omega$-Acetoxyalkanoyl chlorides (**5**) having various carbon numbers ($n$) and suitable for Friedel–Crafts coupling with TMT (**4**) were synthesized by the following methods, as shown in Chart 3. Sodium $\omega$-hydroxyalkanonates (**10**), obtained from the corresponding lactones (**9**), were treated with acetic anhydride in the presence of *p*-toluenesulfonic acid to give $\omega$-acetoxyalkanoic acids (**11**) in good yields. Methyl 10-hydroxydecanoate (**12**)[9] was hydrolyzed with sodium hydroxide and then acetylated with acetic anhydride to yield 10-acetoxydecanoic acid (**11**: $n=10$) in 97% yield. On the other hand, 9-bromononyl alcohol (**13**)[10] was converted to the acetate (**14**), which was treated with sodium cyanide[11,12] in dimethyl sulfoxide to afford 10-acetoxydecanenitrile (**15**) in 94% yield. Compound **15** was then transformed to **11** ($n=10$) by hydrolysis with sodium hydroxide followed by acetylation. 9-Acetoxynonyl aldehyde (**16**) was oxidized with potassium permanganate in the presence of magnesium sulfate hexahyd-

rate[13] in acetone to yield 9-acetoxynonanoic acid (**11**: $n=9$) in 93% yield. Treatment of **11** with phosphorus pentachloride in dichloromethane gave $\omega$-acetoxyalkanoyl chlorides (**5**) in high yields.

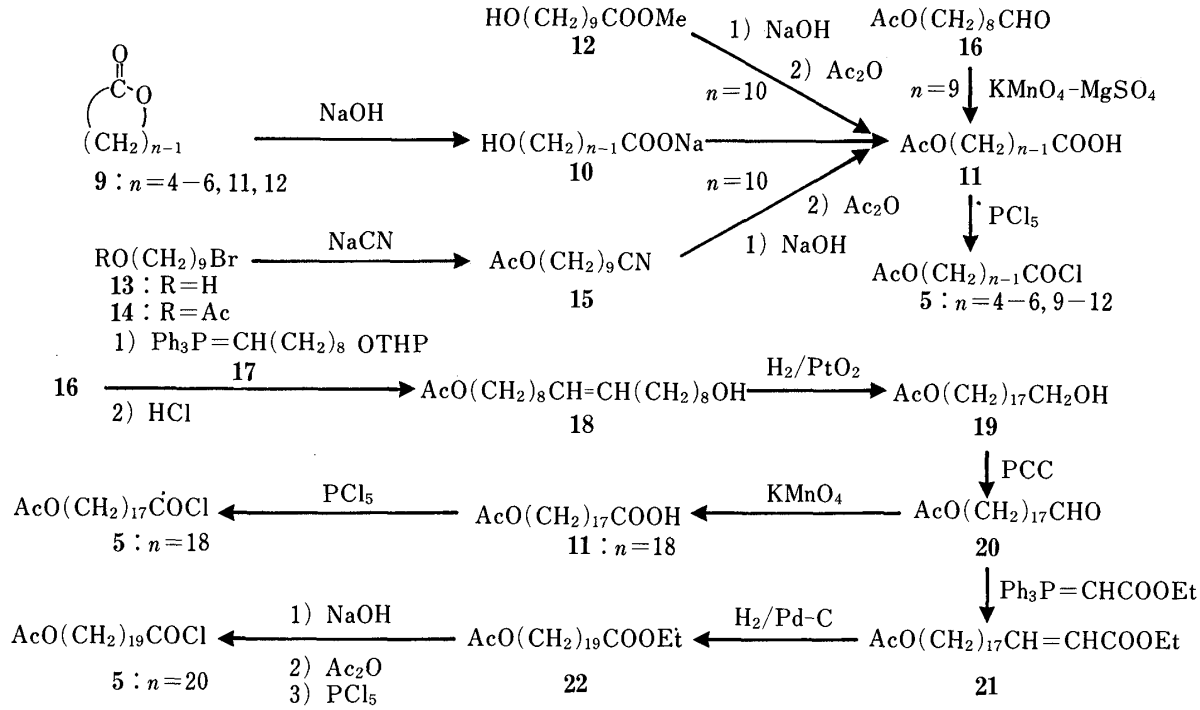


Chart 3

TABLE II. Physicochemical Data for $\omega$-Acetoxyalkanoyl Chlorides (**5**)

| Acid chloride (**5**) $n$ | bp (°C/mmHg) | IR (neat) cm$^{-1}$ COCl | IR (neat) cm$^{-1}$ OAc | $^1$H-NMR ($CDCl_3$) $\delta$ $CH_2COCl$ (2H, t, $J$=6 Hz) | $CH_2OAc$ (2H, t, $J$=7 Hz) | OAc (3H, s) | $-CH_2-$ (m) | Formula | Analysis (%) Calcd (Found) C | H |
|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 50—55/5 | 1795 | 1730 | 2.91 | 4.03 | 2.01 | 1.1—1.8 (2H) | $C_6H_9ClO_3$ | 43.78 (43.91 | 5.51 5.62) |
| 5 | 55—60/5 | 1795 | 1730 | 2.91 | 4.04 | 2.02 | 1.1—1.8 (4H) | $C_7H_{11}ClO_3$ | 47.07 (47.16 | 6.21 6.49) |
| 6 | 97—99/1 | 1795 | 1730 | 2.90 | 4.40 | 2.00 | 1.1—1.8 (6H) | $C_8H_{13}ClO_3$ | 49.88 (49.82 | 6.80 6.90) |
| 9 | 110—113/0.5 | 1800 | 1735 | 2.90 | 4.03 | 2.01 | 1.1—1.8 (12H) | $C_{11}H_{19}ClO_3$ | 56.28 (56.19 | 8.16 8.13) |
| 10 | 135—138/0.5 | 1795 | 1730 | 2.91 | 4.03 | 2.02 | 1.1—1.8 (14H) | $C_{12}H_{21}ClO_3$ | 57.94 (57.99 | 8.51 8.63) |
| 11 | 137—140/0.5 | 1795 | 1730 | 2.90 | 4.06 | 2.01 | 1.1—1.8 (16H) | $C_{13}H_{23}ClO_3$ | 59.42 (59.60 | 8.82 8.73) |
| 12 | 141—144/0.5 | 1795 | 1730 | 2.90 | 4.03 | 2.02 | 1.1—1.8 (18H) | $C_{14}H_{25}ClO_3$ | 60.75 (60.77 | 9.10 9.11) |
| 18 | Wax | 1800 | 1730 | 2.91 | 4.01 | 2.02 | 1.1—1.8 (30H) | $C_{20}H_{37}ClO_3$ | 66.55 (66.63 | 10.33 10.52) |
| 20 | Wax | 1800 | 1730 | 2.90 | 4.02 | 2.02 | 1.1—1.8 (34H) | $C_{22}H_{41}ClO_3$ | 67.92 (67.98 | 10.62 10.71) |

Wittig reaction of **16** with a phosphorane (**17**),[10] followed by deprotection with hydrochloric acid yielded *cis*-olefinic alcohol (**18**), which was hydrogenated over platinum oxide in methanol to afford 18-acetoxyoctadecanol (**19**) in 53% total yield. Oxidation of **19** with pyridinium chlorochromate[14] in dichloromethane gave 18-acetoxyoctadecanal (**20**) in 92% yield, and this was oxidized with potassium permanganate in the presence of magnesium sulfate hexahydrate[13] in acetone to afford 18-acetoxyoctadecanoic acid (**11**: $n=18$) in 90% yield. Compound **11** ($n=18$) was converted to the corresponding acid chloride (**5**: $n=18$) by the same procedure as described above in 94% yield. Reaction of **20** with 1.1 equivalents of ethoxycarbonylmethylenetriphenylphosphorane[15] in dry dimethoxyethane afforded an $\alpha,\beta$-unsaturated ester (**21**) as the (*E*)-isomer in 89% yield. Catalytic hydrogenation of **21** over 5% palladium on charcoal in methanol gave ethyl 20-acetoxyeicosanoate (**22**) in almost quantitative yield. Compound **22** was converted to 20-acetoxyeicosanoyl chloride (**5**: $n=20$) by hydrolysis with sodium hydroxide and then acetylation, followed by treatment with phosphorus pentachloride. The physicochemical data and elemental analyses of **5** are included in the Table II.

The Friedel–Crafts coupling of TMT (**4**) with $\omega$-acetoxyalkanoyl chlorides (**5**) under the reaction conditions shown in Table I (Run 7), followed by hydrolysis of the resulting acetates (**7**) with sodium hydroxide in methanol, provided 6-($\omega$-hydroxy-$\alpha$-oxoalkyl)-2,3-dimethoxy-5-methylphenols (**23**) in good yields. In the case of **5** ($n=4$ and 5), no coupling products could be isolated due to the ready lactonization of the acid chloride under the reaction conditions.

TABLE III. Catalytic Oxidation of the Phenols **24** and **25** Using Salcomine–Oxygen/Air

| Run | Phenol | *n* | $O_2$/air | % of salcomine[a] | Reaction time (d) | Additive[b] | Product | Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **24** | 10 | $O_2$ | 1 | 4 | Py | **26** | 76 |
| 2 | | 12 | $O_2$ | 4 | 3 | — | | 74 |
| 3 | **25** | 10 | $O_2$ | 2 | 3 | — | **3** | 87 |
| 4 | | 10 | $O_2$ | 4 | 2 | Py | | 82 |
| 5 | | 10 | Air | 7 | 5 | — | | 40 |
| 6 | | 12 | $O_2$ | 3 | 3 | — | | 77 |
| 7 | | 18 | $O_2$ | 1 | 3 | — | | 75 |
| 8 | | 20 | $O_2$ | 1 | 3 | — | | 80 |
| 9 | | 20 | Air | 7 | 6 | — | | 38 |

*a*) Weight % to the phenols used. *b*) J. H. Weber and D. H. Busch, *Inorg. Chem.*, **4**, 469 (1965); *idem*, *ibid.*, **4**, 472 (1965). *c*) Isolated yield.

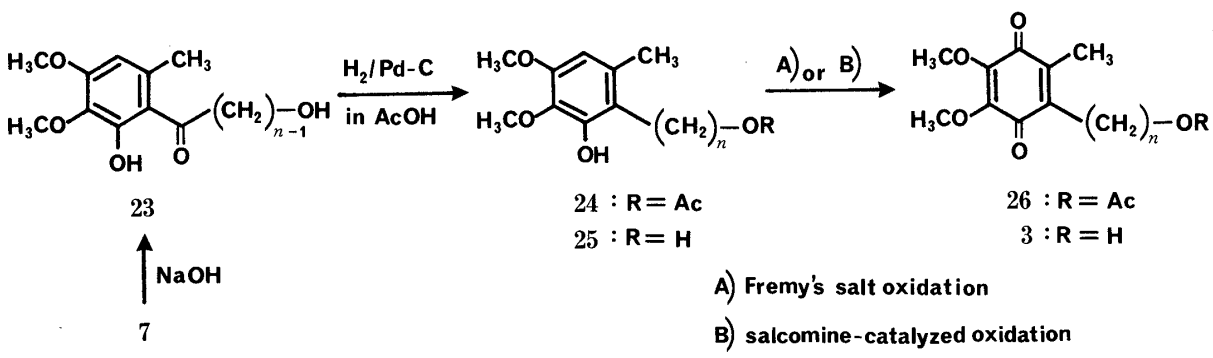


Chart 4

TABLE IV. Physicochemical Data for 6-(ω-Acetoxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones (**26**) and 6-(ω-Hydroxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones (**3**)

| Quinone | *n* | Oxidation method[a] | Yield[b] (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) C | H | IR (KBr) $cm^{-1}$ OH (OAc) | Quinone | $^1$H-NMR ($CDCl_3$) δ $OCH_3$ (6H, s) | $CH_3$ (3H, s) | Quinone-$CH_2$- (2H, t, $J$=7 Hz) | $-CH_2O-$ (2H, t, $J$=6 Hz) | OAc (3H, s) | $M^+$ | MS (*m/z*) Fragment[c] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **26** | 6 | A | 87 | 5 | $C_{17}H_{24}O_6$ | 62.95 | 7.46 | (1730) | 1660, 1640 | 3.97 | 2.00 | 2.47 | 4.02 | 2.02 | 324 | 282 | 195 | |
| | | B | 79 | | | (62.98 | 7.53) | | | | | | | | | | | |
| | 9 | A | 76 | 30 | $C_{20}H_{30}O_6$ | 65.55 | 8.25 | (1730) | 1660, 1640 | 3.97 | 2.00 | 2.43 | 4.02 | 2.02 | 366 | 324 | 195 | |
| | | | | | | (65.75 | 8.27) | | | | | | | | | | | |
| | 10 | A | 81 | 38 | $C_{21}H_{32}O_6$ | 66.30 | 8.48 | (1740) | 1660, 1640 | 3.97 | 2.00 | 2.44 | 4.03 | 2.03 | 380 | 324 | 195 | |
| | | B | 76 | | | (66.48 | 8.47) | | | | | | | | | | | |
| | 11 | A | 77 | 41 | $C_{22}H_{34}O_6$ | 66.98 | 8.69 | (1740) | 1660, 1640 | 3.96 | 1.99 | 2.43 | 4.02 | 2.02 | 394 | 352 | 195 | |
| | | | | | | (66.98 | 8.86) | | | | | | | | | | | |
| | 12 | A | 76 | 47 | $C_{23}H_{36}O_6$ | 67.62 | 8.88 | (1740) | 1660, 1640 | 3.97 | 2.00 | 2.45 | 4.03 | 2.02 | 408 | 366 | 195 | |
| | | B | 74 | | | (67.42 | 9.09) | | | | | | | | | | | |
| **3** | 6 | A | 84 | 15 | $C_{15}H_{22}O_5$ | 63.81 | 7.85 | 3400 | 1660, 1640 | 3.98 | 2.01 | 2.45 | 3.62 | | 282 | 264 | 252 | 195 |
| | | B | 76 | | | (63.79 | 7.88) | | | | | | | | | | | |
| | 9 | A | 82 | 45 | $C_{18}H_{28}O_5$ | 66.64 | 8.70 | 3550 | 1650, 1640 | 3.96 | 2.00 | 2.77 | 3.61 | | 324 | 306 | 294 | 195 |
| | | | | | | (66.54 | 8.69) | | | | | | | | | | | |
| | 10 | A | 79 | 55.5 | $C_{19}H_{30}O_5$ | 67.43 | 8.94 | 3550 | 1650, 1640 | 3.97 | 2.00 | 2.43 | 3.63 | | 338 | 320 | 308 | 195 |
| | | B | 87 | | | (67.40 | 8.92) | | | | | | | | | | | |
| | 11 | A | 76 | 57 | $C_{20}H_{32}O_5$ | 68.15 | 9.15 | 3550 | 1650, 1640 | 3.96 | 1.97 | 2.41 | 3.60 | | 352 | 334 | 322 | 195 |
| | | | | | | (68.22 | 9.19) | | | | | | | | | | | |
| | 12 | A | 77 | 63 | $C_{21}H_{34}O_5$ | 68.82 | 9.35 | 3550 | 1650, 1640 | 3.97 | 2.00 | 2.43 | 3.62 | | 366 | 348 | 336 | 195 |
| | | B | 77 | | | (68.83 | 9.42) | | | | | | | | | | | |
| | 18 | A | —[d] | 81 | $C_{27}H_{46}O_5$ | 71.95 | 10.29 | 3550 | 1650, 1640 | 3.96 | 2.00 | 2.45 | 3.63 | | 450 | 432 | 420 | 195 |
| | | B | 75 | | | (72.06 | 10.27) | | | | | | | | | | | |
| | 20 | A | —[d] | 85 | $C_{29}H_{50}O_5$ | 72.76 | 10.53 | 3550 | 1650, 1640 | 3.96 | 2.00 | 2.43 | 3.62 | | 478 | 460 | 448 | 195 |
| | | B | 80 | | | (72.81 | 10.67) | | | | | | | | | | | |

*a*) Method A, Fremy's salt oxidation; Method B, salcomine-catalyzed oxidation. *b*) Isolated yield after recrystallization from ether–hexane (1 : 3). *c*) The characteristic fragment peak at *m/z* = 195 was attributed to quinonylmethylium; H. Morimoto, T. Shima, I. Imada, M. Sasaki and A. Ouchida, *Justus Liebigs Ann. Chem.*, **702**, 137 (1962). *d*) Yields were below 5% after 72 h.

Catalytic hydrogenation of **23** over 5% palladium on charcoal in acetic acid in the presence of a catalytic amount of 70% perchloric acid gave 6-(ω-acetoxyalkyl)-2,3-dimethoxy-5-methylphenols (**24**) with concomitant acetylation of the terminal hydroxyl group in good yields. Compounds **24** were converted to the corresponding alcohols (**25**) by hydrolysis with sodium hydroxide. Both **24** and **25** were oxidized with Fremy's salt[16] in aqueous dimethylformamide in the presence of potassium phosphate (monobasic) under ice-water cooling to give 6-(ω-acetoxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones (**26**) and 6-(ω-hydroxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones (**3**), respectively, in good yields. Owing to the high hydrophobicity of the phenols (**24** and **25**) having a long alkyl side chain ($n=18$, 20), all attempts to oxidize them to the corresponding 1,4-benzoquinones with Fremy's salt in aqueous dimethylformamide or in aqueous methanol were unsuccessful.

Therefore we studied a homogeneous catalytic oxidation[17] of the phenols (**24** and **25**) using salcomine[18] with molecular oxygen or air in dimethylformamide[19] at room temperature (Table III). Under the reaction conditions used (Runs 2, 3, and 8 in Table III), **24** and **25** gave **26** and **3**, respectively, in good yields together with small amounts (<5%) of by-products which were not investigated further. This homogeneous oxidation was not affected by the hydrophobicity of the phenols (**24** and **25**). The physicochemical data and elemental analyses of **26** and **3** are included in the Table IV.

The effects on lipid peroxidation[20] in canine brain homogenate of 1,4-benzoquinones (**3**) having various carbon number ($n$) of the alkyl side chain synthesized here and previously[5] were determined by measuring the formation of thiobarbituric acid-reactive substances (TBARS).[21] The quinones (**3**) having carbon numbers of $n=9$ to 13 showed rather strong antioxidant activity (80—90% inhibition at $1\times10^{-4}$ M), whereas compounds with a longer ($n=18$, 22) or a shorter ($n=4$, 6) chain had weak antioxidant activity. In this measurement, α-tocopherol showed weak antioxidant activity.

## Experimental

All melting points were determined on a micro hot stage apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a Varian EM-390 (90 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as $\delta$ values (ppm): s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Mass spectra (MS) were measured on a Hitachi RMU-6D mass spectrometer equipped with a direct inlet system.

**Friedel–Crafts Reaction of 4 with 5 ($n=10$) (Table I)**——Freshly powdered $AlCl_3$ (or $ZnCl_2$) was added to a solution of **4** (10 mmol) and 10-acetoxydecanoyl chloride (**5**: $n=10$) (11 mmol) in dry $ClCH_2CH_2Cl$ (30 ml) under ice-water cooling and the mixture was stirred at 5 °C for 2 h and then at 10—40 °C for 22—70 h. The mixture was poured into ice-water and the products were extracted with $CH_2Cl_2$. The extracts were washed with water, then dried over $Na_2SO_4$, and the solvent was evaporated off to give an oil. The oil was purified by column chromatography on silica gel using $CH_2Cl_2$–MeOH (20:1) as an eluent. The first effluent yielded 2-(10-acetoxy-1-oxodecyl)-3,4,5-trimethoxytoluene (**6**: $n=10$) as a colorless oil. *Anal.* Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.84; H, 8.62. IR $\nu_{max}^{neat}$ cm$^{-1}$: 1730, 1670, 1605. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.9 (14H, m, $CH_2$), 2.03 (3H, s, OAc), 2.24 (3H, s, Ar-$CH_3$), 2.84 (2H, t, $J=7$ Hz, $COCH_2$), 3.81, 3.84, 4.13 (each 3H, s, $OCH_3$), 4.02 (2H, t, $J=7$ Hz, $CH_2OAc$), 6.27 (1H, s, Ar-H). MS $m/z$: 394 [M$^+$], 352, 209 (benzoylium).

Further elution with the same eluent gave 6-(10-acetoxy-1-oxodecyl)-2,3-dimethoxy-5-methylphenol (**7**: $n=10$) as a colorless oil. *Anal.* Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.31; H, 8.50. IR $\nu_{max}^{neat}$ cm$^{-1}$: 3500, 1730, 1670, 1605. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.9 (14H, m, $CH_2$), 2.02 (3H, s, OAc), 2.41 (3H, s, Ar-$CH_3$), 2.84 (2H, t, $J=7$ Hz, $COCH_2$), 3.83, 3.86 (each 3H, s, $OCH_3$), 4.03 (2H, t, $J=7$ Hz, $CH_2OAc$), 6.27 (1H, s, Ar-H), 9.92 (1H, s, Ar-OH). MS $m/z$: 380 [M$^+$], 338, 195 (benzoylium).

The elution was continued with $CH_2Cl_2$–MeOH (10:1) to afford a mixture (**8**: $n=10$) of 6-(10-acetoxy-1-oxodecyl)-2-hydroxy-3-methoxy-5-methylphenol and 6-(10-acetoxy-1-oxodecyl)-3-hydroxy-2-methoxy-5-methylphenol as a colorless oil. IR $\nu_{max}^{neat}$ cm$^{-1}$: 3500—3400, 1730, 1670, 1605. MS $m/z$: 366 [M$^+$ for $C_{20}H_{30}O_6$], 324, 181 (benzoylium).

**Sodium ω-Hydroxyalkanoate (10: $n=4$—6, 11, and 12)**——A solution of a lactone (**9**) and NaOH (1.2 eq) in MeOH was refluxed for 5 h. The cooled solution was concentrated to dryness, giving **10** as a glassy powder which was used without purification. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3400—3200, 2800—2600, 1680—1660.

**ω-Acetoxyalkanoic Acids (11: $n=4$—6, 11, and 12)**——A solution of **10** in excess $Ac_2O$ was heated to 60 °C for 4—6 h. The excess $Ac_2O$ was removed and the residue was poured into ice-water. The product was extracted with ether and the extracts were washed with water, then dried over $Na_2SO_4$. The solvent was evaporated off to give **11** as a colorless oil, which was used directly for the next step. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 2800—2600, 1730, 1690.

**9-Acetoxydecanenitrile (15)**——A cooled solution of **13** (13.3 g) and $Ac_2O$ (50 ml) was stirred for 4 h and then at 25 °C for an additional 4 h. The solvent was removed and the residue was extracted with AcOEt. The extracts were washed with 5% $CuSO_4$ solution, then dried over $Na_2SO_4$, and the solvent was evaporated off to give **14** (15.8 g) as a colorless oil. Without purification, **14** (1.65 g) was added to a solution of NaCN (0.59 g) in dimethylsulfoxide (DMSO) (20 ml). The mixture was heated to 80 °C for 15 h, water was added, and the product was extracted with ether. The extracts were washed with saturated NaCl solution, then dried over $Na_2SO_4$, and the solvent was evaporated off to give **15** (1.98 g, 95%) as a colorless oil. *Anal.* Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.48; H, 10.23; N, 6.44. IR $\nu_{max}^{neat}$ $cm^{-1}$: 2250, 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (14H, m, $CH_2$), 2.01 (3H, s, OAc), 2.30 (2H, t, $J=6$ Hz, $CH_2CN$), 4.02 (2H, t, $J=7$ Hz, $CH_2OAc$).

**10-Acetoxydecanoic Acid (11: $n=10$)**——From **12**: A mixture of **12** (21.4 g) and NaOH (4.8 g) in MeOH (100 ml) was refluxed for 3 h. The cooled solution was evaporated to dryness, giving a glassy powder, which was dissolved in $Ac_2O$ (20.5 ml) in the presence of *p*-TsOH (400 mg). The mixture was heated to 60 °C for 2 h. After removal of the excess $Ac_2O$, the residue was poured into ice-water and the product was extracted with ether. The extracts were washed with water, then dried over $Na_2SO_4$, and the solvent was evaporated off to give **11** ($n=10$) (22.3 g, 97%) as a colorless oil. *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.71; H, 9.66. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 2800—2600, 1725, 1680.

From **15**: A mixture of **15** (1.6 g) and NaOH (0.4 g) in EtOH (10 ml) was refluxed for 19 h. The cooled solution was acidified with 3 N HCl and the product was extracted with ether. The extracts were washed with water, then dried over $Na_2SO_4$, and the solvent was evaporated off to give 10-hydroxydecanoic acid (1.3 g, 86%) as colorless needles, mp 74—76 °C. *Anal.* Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.82; H, 10.68. The acid was acetylated by the same procedure above to give **11** ($n=10$).

**9-Acetoxynonanoic Acid (11: $n=9$)**——A mixture of **16** (134 g), $KMnO_4$ (110 g), and $MgSO_4 \cdot 7H_2O$ (110 g) in acetone (2 l) was stirred at room temperature for 4 h. Then 6 N HCl (5 ml) was added to the reaction mixture and the resulting precipitates were filtered off. The filtrates were evaporated to give **11** ($n=9$) (134.6 g, 93%) as a colorless oil. *Anal.* Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.21; H, 9.39. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3300, 2800—2600, 1730, 1690.

**ω-Acetoxyalkanoyl Chlorides (5)**——$PCl_5$ (1.2 eq) was carefully added to a solution of **11** in $CH_2Cl_2$. The mixture was stirred for 2 h at 25 °C. After removal of the solvent, the acid chlorides (**5**) were purified by distillation (Table II).

**(*Z*)-18-Acetoxy-9-octadecen-1-ol (18)**——A mixture of **16** (61 g) and **17** (140 g) in dry DMSO (240 ml) was stirred at 5 °C for 2 h under an $N_2$ atmosphere. The mixture was poured into water and the product was extracted with ether. The extracts were washed with water, then dried over $Na_2SO_4$, and the solvent was evaporated off to give an oil (198 g). The oil was dissolved in hexane and the resulting crystals (triphenylphosphine oxide) were filtered off. The filtrates were evaporated to afford a colorless oil. The oil (89 g) was dissolved in MeOH (300 ml) containing 6 N HCl (10 ml) and the solution was kept at 25 °C for 1 h. The excess solvent was removed and the resulting residue was purified by column chromatography on silica gel using hexane–ether (1 : 2) as an eluent to give **18** (52.5 g, 53%) as a colorless oil. *Anal.* Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.61; H, 11.85. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 1730, 1650. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.8 (28H, m, $CH_2$), 2.01 (3H, s, OAc), 3.60 (2H, t, $J=6$ Hz, $CH_2OH$), 4.00 (2H, t, $J=7$ Hz, $CH_2OAc$), 5.32 (2H, t, $J=6$ Hz, CH=CH). MS *m/z*: 326 [$M^+$], 308, 284.

**18-Acetoxyoctadecanol (19)**——**18** (50 g) was hydrogenated over $PtO_2$ (1 g) in MeOH (250 ml) at room temperature under atmospheric pressure for 3 h. The catalyst was filtered off and the filtrate was evaporated to give crystals. Recrystallization from hexane–ether (2 : 1) gave **19** (50 g, quantitative) as colorless needles, mp 69 °C. *Anal.* Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.16; H, 12.39. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3400, 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.8 (32H, m, $CH_2$), 2.01 (3H, s, OAc), 3.60 (2H, t, $J=6$ Hz, $CH_2OH$), 4.01 (2H, t, $J=6$ Hz, $CH_2OAc$). MS *m/z*: 328 [$M^+$], 310, 250.

**18-Acetoxyoctadecanal (20)**——Pyridinium chlorochromate (PCC) (12 g) was added to a solution of **19** (12 g) in $CH_2Cl_2$ (300 ml) and the mixture was stirred for 3 h at room temperature. The $CH_2Cl_2$ phase was washed with 5% $NaHCO_3$ solution, then dried over $Na_2SO_4$, and the solvent was evaporated off to give **20** (11 g, 92%) as a colorless oil. *Anal.* Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.42; H, 11.78. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1730, 1720. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.8 (32H, m, $CH_2$), 2.01 (3H, s, OAc), 4.02 (2H, t, $J=7$ Hz, $CH_2OAc$), 9.21 (1H, t, $J=2$ Hz, CHO). MS *m/z*: 326 [$M^+$], 284.

**18-Acetoxyoctadecanoic Acid (11: $n=18$)**——A mixture of **20** (12 g), $KMnO_4$ (7.5 g), and $MgSO_4 \cdot 7H_2O$ (7.5 g) in acetone (200 ml) was stirred for 3 h at room temperature. Then 6 N HCl (2 ml) was added to the reaction mixture and the resulting precipitates were filtered off. The filtrate was evaporated to give crude crystals. Recrystallization from hexane gave **11** ($n=18$) (11.3 g, 90%) as colorless needles, mp 64 °C. *Anal.* Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.02; H, 11.26. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2800—2600, 1730, 1700. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.8 (32H, m, $CH_2$), 2.02 (3H, s, OAc), 4.02 (2H, t, $J=7$ Hz, $CH_2OAc$), 10.01 (1H, br s, COOH). MS *m/z*: 342 [$M^+$], 300.

**18-Acetoxyoctadecanoyl Chloride (5: $n=18$)**——A mixture of **11** ($n=18$, 6.5 g) and $PCl_5$ (4.7 g) in $CH_2Cl_2$ (50 ml) was stirred at 25 °C for 2 h. The solvent and $POCl_3$ were evaporated off to leave **5** ($n=18$, 6.7 g) as a colorless wax (Table II).

**Ethyl (*E*)-20-Acetoxy-2-eicosenoate (21)**——A mixture of **20** (26 g) and ethoxycarbonylmethylenetriphenylphosphorane (31 g) in dry dimethoxyethane (DME) (150 ml) was stirred for 6 h at room temperature. The solvent was removed and the residue was dissolved in hexane (160 ml). The resulting crystals (triphenylphosphine oxide) were filtered off and the filtrate was evaporated to give **21** (28 g, 89%) as a colorless oil. *Anal.* Calcd for $C_{24}H_{44}O_4$: C, 72.68; H, 11.18. Found: C, 72.71; H, 11.23. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1730, 1720, 1650. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.8 (33H, m, $CH_3$ and $CH_2$), 2.02 (3H, s, OAc), 2.1—2.2 (2H, m, $CH_2CH=CHCOOEt$), 4.05 (2H, t, $J=7$ Hz, $CH_2OAc$), 4.16 (2H, t, $J=7$ Hz, $CH_2CH_3$), 5.77 (1H, dt, $J_1=16$ Hz, $J_2=1$ Hz, $CH=CHCOOEt$), 6.95 (1H, dt, $J_1=16$ Hz, $J_2=7$ Hz, $CH=CHCOOEt$). MS *m/z*: 369 [$M^+$], 350, 312, 308.

**Ethyl 20-Acetoxyeicosanoate (22)**——**21** (20 g) was hydrogenated over 5% Pd–C (1.2 g) in MeOH (200 ml) at room temperature under atmospheric pressure for 4 h. After removal of the catalyst, the solvent was evaporated off to give crystals. Recrystallization from hexane gave **22** (20 g, quantitative) as colorless needles, mp 53 °C. *Anal.* Calcd for $C_{24}H_{46}O_4$: C, 72.31; H, 11.63. Found: C, 72.39; H, 11.90. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.7 (37H, m, $CH_3$ and $CH_2$), 2.01 (3H, s, OAc), 2.27 (2H, t, $J=6$ Hz, $CH_2COOEt$), 4.05 (2H, t, $J=7$ Hz, $CH_2OAc$), 4.12 (2H, t, $J=7$ Hz, $CH_2CH_3$). MS *m/z*: 398 [$M^+$], 352, 338, 311, 298.

**20-Acetoxyeicosanoyl Chloride (5: $n=20$)**——A mixture of **22** (20 g) and NaOH (94.8 g) in MeOH (300 ml) was stirred for 4 h at room temperature. The solvent was removed to leave an amorphous powder, which was dissolved in $Ac_2O$ (30 ml) in the presence of *p*-TsOH (0.5 g). The solution was heated to 60 °C for 3 h. The excess $Ac_2O$ was removed and the residue was poured into water to give crystals. Recrystallization form hexane gave 20-acetoxyeicosanoic acid (18 g, 95%), mp 78 °C. *Anal.* Calcd for $C_{22}H_{42}O_4$: C, 71.30; H, 11.42. Found: C, 71.38; H, 11.61. The acid was converted to the acid chloride (**5**: $n=20$) by the same procedure as described above (Table II).

**6-(10-Hydroxy-1-oxodecyl)-2,3-dimethoxy-5-methylphenol (23: $n=10$)**——Freshly powdered $AlCl_3$ (28.1 g) was added to a solution of 10-acetoxydecanoyl chloride (**5**: $n=10$) (27.4 g) and **4** (18.2 g) in dry $ClCH_2CH_2Cl$ (300 ml) under ice-water cooling and the mixture was stirred at 5 °C for 2 h and then at 20 °C for an additional 70 h. The reaction mixture was poured into ice-water and the products were extracted with $CH_2Cl_2$. The extracts were washed with water, then dried over $Na_2SO_4$ and the solvent was evaporated off to give crude **7** ($n=10$) as a colorless oil. A solution of the crude **7** ($n=10$) (38.4 g) and NaOH (4.7 g) in MeOH (150 ml) was stirred for 2 h at room temperature. The excess solvent was removed and the residue was poured into water. The resulting crystals were recrystallized from ether–hexane (1 : 3) to give **23** ($n=10$, 26.7 g) as colorless needles. The elemental analysis and melting point are included in Table V. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3500, 3200, 1670, 1605. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.9 (14H, m, $CH_2$), 2.41 (3H, s, Ar-$CH_3$), 2.86 (2H, t, $J=7$ Hz, $COCH_2$), 3.61 (2H, t, $J=7$ Hz, $CH_2OH$), 3.84, 3.87 (each 3H, s, $OCH_3$), 6.27 (1H, s, Ar-H), 9.92 (1H, s, Ar-OH). MS *m/z*: 338 [$M^+$], 320, 195 (benzoylium).

**6-(10-Acetoxydecyl)-2,3-dimethoxy-5-methylphenol (24: $n=10$)**——**23** ($n=10$, 17 g) was hydrogenated over 5% Pd–C (2 g) in AcOH (150 ml) in the presence of 70% $HClO_4$ (0.3 ml) at room temperature under atmospheric pressure for 24 h. The catalyst was filtered off and the filtrate was concentrated to give an oil, which was extracted with $CH_2Cl_2$. The extracts were washed with 5% $NaHCO_3$, and dried over $Na_2SO_4$. The solvent was evaporated off to afford **24** ($n=10$, 18.4 g) as a colorless oil. The elemental analysis data are listed in Table V. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3450, 1703, 1605. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.8 (16H, m, $CH_2$), 2.03 (3H, s, OAc), 2.23 (3H, s, Ar-$CH_3$), 2.57 (2H, t, $J=7$ Hz, Ar-$CH_2$), 3.81, 3.85 (each 3H, s, $OCH_3$), 4.03 (2H, t, $J=6$ Hz, $CH_2OAc$), 5.80 (1H, s, Ar-OH), 6.25 (1H, s, Ar-H). MS *m/z*: 366 [$M^+$], 324, 181 (benzylium).

**6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methylphenol (25: $n=10$)**——A solution of **24** ($n=10$, 37 g) and NaOH (4.6 g) in MeOH (300 ml) was stirred at 5 °C for 24 h. The excess solvent was removed and the residue was extracted with $CH_2Cl_2$. The extracts were washed with water, and dried over $Na_2SO_4$. The solvent was evaporated off to give **25** ($n=10$, 32 g) as a colorless oil. The elemental analysis data are included in Table V. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 1605. $^1$H-NMR ($CDCl_3$) $\delta$: 1.2—1.8 (16H, m, $CH_2$), 2.23 (3H, s, Ar-$CH_3$), 2.57 (2H, t, $J=6$ Hz, $CH_2OH$), 3.61 (2H, t, $J=7$ Hz, Ar-$CH_2$), 3.80, 3.84 (each 3H, s, $OCH_3$), 5.86 (2H, s, Ar-OH), 6.24 (1H, s, Ar-H). MS *m/z*: 324 [$M^+$], 306, 294, 181 (benzylium).

The other phenols (**23**, **24**, and **25**) having a different carbon number ($n$) of the alkyl side chain were prepared by the same procedure as described above. The elemental analysis data and melting points of **23**, **24**, and **25** are given in Table V.

**6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (3: $n=10$)**——Method A: A mixture of Fremy's salt (16 g) and **25** ($n=10$, 7.3 g) in DMF–$H_2O$–MeOH (1 : 1 : 1) (100 ml) containing 0.17 M $KH_2PO_4$ solution (10 ml) was stirred at 5 °C for 72 h. Water (200 ml) was added to the mixture and the product was extracted with $CH_2Cl_2$. The extracts were washed with water, then dried over $Na_2SO_4$, and the solvent was evaporated off to give crude crystals. Recrystallization from hexane–ether (3 : 1) gave **3** ($n=10$, 6.1 g) as yellow needles.

Method B (Run 3 in Table III): A mixture of **25** ($n=10$, 4.3 g) and salcomine (200 mg) in DMF (100 ml) was stirred at room temperature under an oxygen atmosphere for 72 h. Water (300 ml) was added to the mixture and the products were extracted with $CH_2Cl_2$. The extracts were washed with water, then dried over $Na_2SO_4$, and the solvent

TABLE V. Elemental Analyses and Melting Points of the Phenols (**23**—**25**)

| Phenol | *n* | Yield[a] (%) | mp (°C) | Formula | Analysis (%) Calcd C | Calcd H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| **23** | 6 | 78 | 72 | $C_{15}H_{22}O_5$ | 63.81 | 7.85 | 64.10 | 7.88 |
| | 9 | 78 | 72 | $C_{18}H_{28}O_5$ | 66.64 | 8.70 | 66.34 | 8.70 |
| | 10 | 79 | 67 | $C_{19}H_{30}O_5$ | 67.43 | 8.94 | 67.41 | 8.83 |
| | 11 | 81 | 81 | $C_{20}H_{32}O_5$ | 68.15 | 9.15 | 68.27 | 9.30 |
| | 12 | 75 | 82 | $C_{21}H_{34}O_5$ | 68.82 | 9.35 | 69.00 | 9.46 |
| | 18 | 78 | 101 | $C_{27}H_{46}O_5$ | 71.96 | 10.29 | 72.08 | 10.51 |
| | 20 | 64 | 105 | $C_{29}H_{50}O_5$ | 72.76 | 10.53 | 72.95 | 10.68 |
| **24** | 6 | Quant. | Oil | $C_{17}H_{26}O_5$ | 65.78 | 8.44 | 65.79 | 8.46 |
| | 9 | Quant. | Oil | $C_{20}H_{32}O_5$ | 68.15 | 9.15 | 68.33 | 9.20 |
| | 10 | Quant. | Oil | $C_{21}H_{34}O_5$ | 68.82 | 9.35 | 68.90 | 9.38 |
| | 11 | Quant. | Oil | $C_{22}H_{36}O_5$ | 69.44 | 9.54 | 69.53 | 9.62 |
| | 12 | Quant. | Oil | $C_{23}H_{38}O_5$ | 70.01 | 9.71 | 70.21 | 9.83 |
| | 18 | Quant. | 53 | $C_{29}H_{50}O_5$ | 72.76 | 10.53 | 72.60 | 10.42 |
| | 20 | Quant. | 59 | $C_{31}H_{54}O_5$ | 73.47 | 10.74 | 73.46 | 10.74 |
| **25** | 6 | Quant. | Oil | $C_{15}H_{24}O_4$ | 67.13 | 9.02 | 67.26 | 9.03 |
| | 9 | Quant. | Oil | $C_{18}H_{30}O_4$ | 69.64 | 9.74 | 69.63 | 9.77 |
| | 10 | Quant. | Oil | $C_{19}H_{32}O_4$ | 70.33 | 9.94 | 70.52 | 9.90 |
| | 11 | Quant. | Oil | $C_{20}H_{34}O_4$ | 70.97 | 10.13 | 71.12 | 10.26 |
| | 12 | Quant. | Oil | $C_{21}H_{36}O_4$ | 71.55 | 10.30 | 71.70 | 10.38 |
| | 18 | Quant. | 68 | $C_{27}H_{48}O_4$ | 74.26 | 11.08 | 74.33 | 11.12 |
| | 20 | Quant. | 72 | $C_{29}H_{52}O_4$ | 74.95 | 11.28 | 75.19 | 11.30 |

*a*) Isolated yield after recrystallization from ether–hexane (1 : 2), where applicable.

was evaporated off to give a dark yellow oil. Purification by silica gel column chromatography using $CH_2Cl_2$–ether (10 : 1) as an eluent gave **3** ($n=10$, 3.9 g) as yellow needles (Table IV).

The other phenols (**24** and **25**) were also oxidized to the 1,4-benzoquinones (**26** and **3**, respectively) by method A or B described above (Table IV).

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