Quinones and Related Compounds in Higher Plants. Part 16.[1] Naphthoquinones from *Radermachera sinica* Hemsl. (Bignoniaceae)

By **Kenichiro Inoue, Cheng-Chang Chen,** and **Hiroyuki Inouye,*** Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan
Kaoru Kuriyama, Shionogi Research Laboratory, Fukushima-ku, Osaka 553, Japan

Five new naphthoquinones, along with the known naphthoquinones lapachol (1), dehydro-α-lapachone (2), and dehydroiso-α-lapachone (3),† have been isolated from the wood of *Radermachera sinica* Hemsl. The structures of these new quinones were established as 3-hydroxy-6-methoxydehydroiso-α-lapachone (4), 3-hydroxydehydroiso-α-lapachone (5), 3,6-dimethoxydehydroiso-α-lapachone (6), 3,5-dihydroxy-6-methoxydehydroiso-α-lapachone (7), and 2-isopropenylnaphtho[2,3-*b*]furan-4,9-quinone (8). These quinones were found to be mixtures of both enantiomers in various proportions, *e.g.*, (3), 2*R*:2*S*, 4.5:1; (4), 2*R*,3*R*:2*S*,3*S*, 1:1; (5), 2*R*,3*R*:2*S*,3*S*, 4.2:1; (6), predominantly 2*R*,3*R*; and (7), predominantly 2*S*,3*S*.

We have previously elucidated the structures of the prenylnaphthoquinone congeners catalpalactone, catalponol, catalponone, deoxylapachol, and several α-lapachones and dehydroiso-α-lapachones isolated from the wood and callus tissues of *Catalpa ovata* G. Don.[2-4] We have also examined the biosynthesis of these substances.[5] As part of our study on the naphthoquinones of Bignoniaceae, to which *C. ovata* belongs, we have examined the constituents of the wood of *Radermachera sinica* Hemsl. and we now report the isolation and structural elucidation of eight prenylnaphthoquinones, including five new compounds, along with the isolation of four non-quinonoid compounds.

Dried wood of *R. sinica* was extracted with hot benzene, and the extract was worked up as described in the Experimental section to afford triacontanoic acid, 2-(4-hydroxyphenyl)ethyl triacontanoate,[3] vanillin, β-sitosterol, and three known naphthoquinonoids, lapachol (1), dehydro-α-lapachone (2), and dehydroiso-α-lapachone (3),[6]† along with five new naphthoquinonoids, 3-hydroxy-6-methoxydehydroiso-α-lapachone (4), 3-hydroxydehydroiso-α-lapachone (5), 3,6-dimethoxydehydroiso-α-lapachone (6), 3,5-dihydroxy-6-methoxydehydroiso-α-lapachone (7), and 2-isopropenylnaphtho[2,3-*b*]furan-4,9-quinone (8).

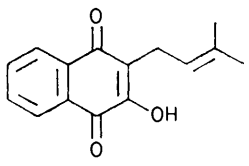
The quinone (4), obtained as optically inactive yellow needles, showed u.v. and i.r. spectral data indicative of a substituted naphthoquinone. The ^{1}H n.m.r. signals at δ 3.92, 7.10, 7.50, and 8.04 and the absence of signals in the quinonoid proton region (δ 5.8—6.8) indicated the compound to be a 6- or 7-methoxy-1,4-naphthoquinone substituted at the 2- and 3-positions.

The quinone (4) further showed in the i.r. spectrum an absorption for a hydroxy-group at 3 400 cm^{-1} and the ^{1}H n.m.r. spectrum showed signals at δ 3.03 and 5.39 assignable to a hydroxy-proton and a proton on the hydroxy-bearing carbon atom, respectively. In accordance with these findings, in the ^{1}H n.m.r. spectrum of its acetate (9) these signals were replaced by signals for an acetoxy-group and a proton on the acetoxy-bearing carbon atom at δ 2.14 and 6.32, respectively. Furthermore, (4) showed an i.r. band for a terminal methylene group at 895 cm^{-1} and n.m.r. signals for a vinyl methyl group at δ 1.79 and three protons in the region δ 4.92—5.19, suggesting the presence of an isopropenyl group. In fact, nuclear Overhauser experiments in the presence of Eu(fod)$_3$ revealed that the latter signals consisted of three signals at δ 5.03, 5.15 and 5.13, assigned to the methylene protons *cis* and *trans* to the vinyl methyl group and to the proton on the carbon atom adjacent to the isopropenyl group, respectively. Catalytic reduction of (4) over 5% palladium–charcoal yielded the dihydro-compound (10), in the ^{1}H n.m.r. spectrum of which the signals for the vinyl methyl and vinylic protons were absent and new signals for an isopropyl group appeared at δ 1.03 and 1.07 (each 3 H, d, *J* 7.0 Hz) and δ 1.85—2.35 (1 H, m). Signals for a proton attached to a hydroxy-bearing carbon and its vicinal proton were also observed at δ 5.38 (d, *J* 4.5 Hz) and 4.56 (dd, *J* 7.0 and 4.5 Hz), respectively. From the chemical shifts of these two protons, it could be assumed that the hydroxy-bearing carbon atom is adjacent to the quinone ring and the carbon atom bearing the latter proton has another oxygen function. As no signals for quinonoid protons were observed in the ^{1}H n.m.r. spectra of (4), (9), and (10), this oxygen atom should form an ether linkage between the quinone ring and the side-chain. Accordingly, (4) could be assigned structure A or B.

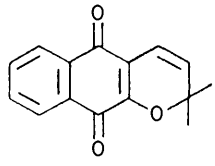
The ^{1}H n.m.r. spectra of (4) recorded in the presence of the shift reagent Eu(fod)$_3$ gave conclusive evidence for the location of the aromatic methoxy-group. Whereas proton H$_a$ attached to the hydroxy-bearing carbon atom showed the largest change in chemical shift among all the protons of (4), the shifts for the aromatic proton signals were in the following order: H$_c$ (d, *J* 3.0 Hz) > H$_e$ (d, *J* 8.5 Hz) > H$_d$ (dd, *J* 3.0 and 8.5 Hz). Accordingly, it was inferred that compound (4) should be 3-hydroxy-6-methoxydehydroiso-α-lapachone (structure A).

The relative configuration of the 2- and 3-positions of (4) was concluded to be *cis*, because the protons H$_a$ and H$_b$ showed a nuclear Overhauser effect (n.O.e) in the ^{1}H n.m.r. spectrum of its acetate (9) in CDCl$_3$–[^{2}H$_5$]pyridine (2 : 1). It is known that, in the ^{1}H n.m.r. spectra of the

† Systematic names for compounds (1), (2), and (3) are 2-hydroxy-3-(3-methylbut-2-enyl)naphthalene-1,4-dione, 2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione, and 2,3-dihydro-2-(1-methylethenyl)naphtho[2,3-*b*]furan-4,9-dione, respectively.



(1)



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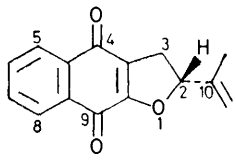
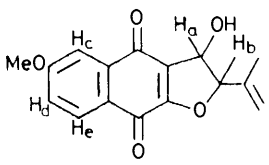
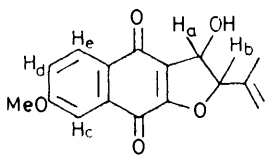


(3)

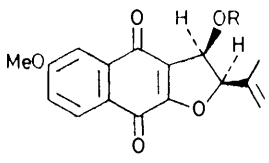
a mixture of the above substance and its enantiomer (4.5:1)



A



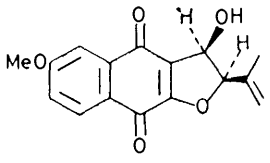
B



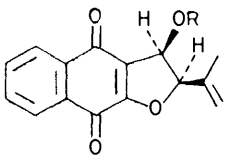
(4) R = H

a mixture of the above substance and its enantiomer (1:1)

(9) R = Ac

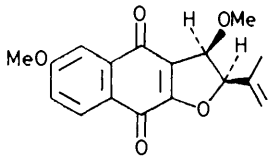


(10)

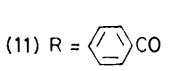


(5) R = H

a mixture of the above substance and its enantiomer (4.2:1)

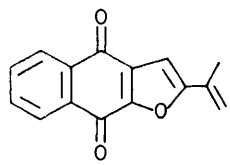


(6)



(11) R = CO

(16) R = Br CO



(8)

acetates of 2-alkyl-3-hydroxy-2,3-dihydrobenzofurans, the C-3 proton signal of the *cis*-form shifts 0.3 p.p.m. downfield from that of the *trans*-form to appear around δ 6.30.[7-9] The C-3 proton signal of (9) at δ 6.32 is in good accordance with this value supporting the *cis* configuration of the 2- and 3-positions. Thus, the structure of (4) has been established as 2,3-*cis*-3-hydroxy-6-methoxydehydroiso-α-lapachone.

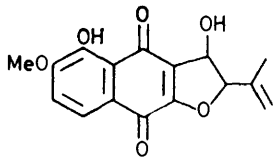
The quinone (5), obtained as yellow needles, gave a ^{1}H n.m.r. spectrum identical with that of (4) except for the absence of a methoxy-signal and accompanying differences in the aromatic proton region (see Experimental section). Accordingly, (5) was presumed to be 3-hydroxydehydroiso-α-lapachone. As the $J_{2,3}$ value (4.5 Hz) of (5) was the same as in the case of (4) and as an n.O.e was observed between the corresponding protons in the benzoate (11), it was established that compound (5) also has the 2,3-*cis*-configuration. Treatment of (5) with boron trifluoride afforded a dehydration product, which was also obtained as the sole product during attempted oxidation of the OH group of (5) with dimethyl sulphoxide (DMSO) and acetic anhydride or with Jones reagent. The ^{1}H n.m.r. spectrum of this substance showed signals at δ 2.14 (for the vinyl methyl protons), 5.35 and 5.94 (for the C=CH$_2$ protons), and 6.83 (for the β-H of a furan ring). Thus, it is evident that the dehydration product is 2-isopropenylnaphtho[2,3-*b*]furan-4,9-quinone. The quinone (8) isolated from this plant was found to be identical with this furanquinone.

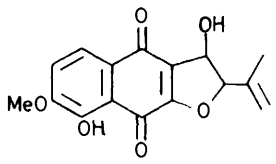
The quinone (6), obtained as a yellow powder, also showed u.v. and i.r. absorptions characteristic of 1,4-naphthoquinones. The ^{1}H n.m.r. spectral data (see Experimental section) suggested that compound (6) has a methoxy-group instead of the hydroxy-group of (4). In confirmation, methylation of (4) with MeI–Ag$_2$O gave a product whose ^{1}H n.m.r. spectrum was identical with that of (6). Thus, it was established that (6) is 2,3-*cis*-3,6-dimethoxydehydroiso-α-lapachone. The isolation of (6) involves no process that could have caused methylation. Besides, compound (6) is optically active, while (4) is inactive. Therefore, it is improbable that (6) is an artefact obtained from (4).

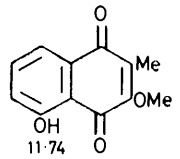
The quinone (7) was obtained as orange-red needles, $C_{16}H_{14}O_6$, m.p. 198—200 °C, $[\alpha]_D$ +2.6° (in chloroform). The u.v. and i.r. spectra of this substance were also characteristic of 1,4-naphthoquinones. The ^{1}H n.m.r. spectrum (see Experimental section) indicated (7) to be 3-hydroxydehydroiso-α-lapachone with a hydroxy-group at the *peri*-position of the quinone carbonyl group and also having a methoxy-group adjacent to the hydroxy-group. Thus, formula C or D could be assigned to this compound.

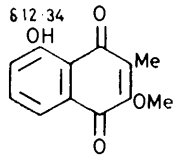
Owing to the very small amount of (7) we had at hand, we attempted to presume the substitution pattern of the aromatic ring with the aid of a spectroscopic method.

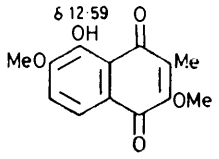
Recently, Musgrave *et al.*[10] found that the chemical shift of the 5-hydroxy-proton of 5-hydroxy-1,4-naphthoquinones (juglone-type naphthoquinones) is generally independent of sample concentration but is influenced by substituents such as hydroxy, methyl, chloro, and bromo groups, and that the effects caused by these substituents are additive. These findings have been applied for the structure elucidation of some naphthoquinones. We therefore attempted to locate the *peri*-hydroxy group in the quinone (7) by an extension of these findings. For

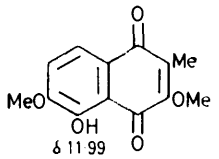

C

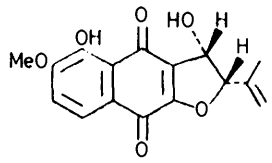

D


E


F


G


H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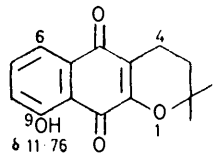
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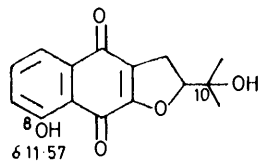
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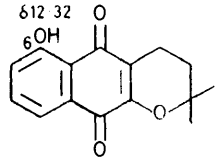
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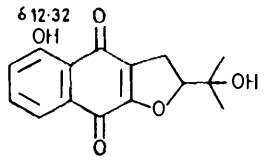
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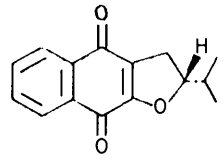
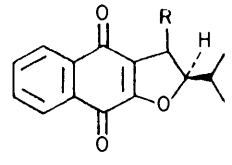

(17a)


(17b) R = H

(18) R = OH

this purpose, α-lapachones and dehydroiso-α-lapachones bearing a *peri*-hydroxy-group could be assumed to be juglone derivatives having an alkyl (or alkoxy) group at C-2 and an alkoxy (or an alkyl) group at C-3, which for calculation of the chemical shifts could be considered equivalent to methyl and methoxy-groups. Musgrave *et al.* calculated the chemical shift of the 5-hydroxy-group using that of the hydroxy-group of juglone (δ 11.87) as the base value to obtain the contributions of the methyl group at C-2, C-3, and C-6 as +0.06, +0.14, and +0.35 respectively. By extending their method, we assumed the observed differences between the chemical shift of juglone and its 2-, 3-, or 6-methoxy-derivatives (2-position: +0.33, 3-position: −0.19, and 6-position: +0.25) to be the contribution of each methoxy-group. The calculated chemical shifts of the 5-hydroxy-group of the model compounds E and F using these values are δ 11.74 and 12.34, respectively.

As expected, the value for E is consistent with the chemical shifts of the phenolic hydroxy-groups of the known 9-hydroxy-α-lapachone (12) (δ 11.76) and 8,10-dihydroxyiso-α-lapachone (13) (δ 11.57), and that for F with those of 6-hydroxy-α-lapachone (14) (δ 12.32) and 5,10-dihydroxyiso-α-lapachone (15) [11] (δ 12.13), respectively. Thus, the validity of the extended method for the prediction of the structure of juglone derivatives was proved.

Regarding the structure of (7), the calculated chemical shifts of the phenolic hydroxy-proton of the model compounds G and H are δ 12.59 and 11.99, respectively. As the chemical shift (δ 12.72) for the corresponding proton of (7) is very close to that of the model compound G, it is most likely that the structure of (7) is C rather than D. From the biogenetic viewpoint also, the co-occurrence of (4) bearing a methoxy-group at C-6 and -7 in this plant appears to favour this structure.

The relative stereochemistry at C-2 and C-3 of (7) seems to be *cis* as the ^{1}H n.m.r. signal pattern of the dihydrofuran moiety of this compound closely resembles those of (4) and (5). Accordingly, substance (7) is assigned to be 2,3-*cis*-3,5-dihydroxy-6-methoxy-dehydroiso-α-lapachone.

The quinone (3), mentioned at the beginning as a known compound, was obtained as light yellow needles. Its u.v. and i.r. spectra were characteristic of 1,4-naphthoquinones (see Experimental section). On the basis of these and ^{1}H n.m.r. data, it was identified as dehydroiso-α-lapachone.

Previously, Sandermann *et al.* had isolated a naphthoquinone, m.p. 104—105.5 °C, $[\alpha]_D$ −37.55° (in benzene) from *Paratecoma peroba* Kuhlm. (Bignoniaceae), to which the same structure (3) was assigned without providing detailed data.[6] Recently, Joshi *et al.* have also assigned the same structure to a quinone, m.p. 108—109 °C, isolated from *Tabebuia rosea* DC. of the same family but the $[\alpha]_D$ value was not given and no stereochemical assignment was made.[12]

Of the six quinones described above, (4), (5), (6), and (7) have two asymmetric carbon atoms and (3) has one. Therefore, the next problem was the elucidation of their absolute structures. Especially, the presence of the optically inactive compound (4) prompted us to examine

the optical purity of these substances. For this purpose, we chose the method of ^{1}H n.m.r. determination in the presence of a chiral shift reagent, namely, tris[3-trifluoroacetyl-(+)-camphorato]europium(III) [Eu(tfac)$_3$].[13] However, compounds (6) and (7) could not be studied by this method, as the former, a very minor component bearing no hydroxy-group, has three ethereal oxygens to which the reagent may co-ordinate at random, whereas the latter has a phenolic hydroxy-group which decomposes the shift reagent. In compounds (4) and (5), the largest difference between the chemical shifts of corresponding protons of both enantiomers is expected to be observed on C-3 protons because of the strongest co-ordination of the reagent to the hydroxy-group. Actually, in the spectrum of (4) in $CDCl_3$ solution, the signals of the C-3 proton of the two enantiomers were completely separated into two signals of equal intensity when the molar ratio of the shift reagent to the substrate was 0.04 : 1. As the configuration of (4) at C-2 and C-3 is *cis*, (4) must be an equimolar mixture of the 2*R*,3*R*- and 2*S*,3*S*-compounds. In the case of (5), the signals of the corresponding protons of both enantiomers were fully resolved in the presence of 0.08 equivalents of the shift reagent, demonstrating that (5) is a mixture of the (+)- and (−)-forms in the ratio 1 : 4.2. Finally, the spectrum of (3) was determined in the same way. As this substance has no hydroxy-group, it is likely that Eu(tfac)$_3$ co-ordinates between the quinonoid carbonyl group and the ethereal oxygen atom. Consequently, the olefinic proton oriented *trans* to the methyl group would be closest to the reagent. When the shift reagent and (3) were in the molar ratio 0.64 : 1, the signals of the C-3 protons of the two enantiomers were completely separated to indicate that 3 is a mixture of the (+)- and (−)-forms in the ratio 4.5 : 1.

It has already been mentioned that the hydroxy-group in the quinone (5) is oriented *cis* to the isopropenyl group. As the c.d. spectrum (in MeOH) of the *p*-bromobenzoate (16) derived from (5) showed positive first and negative second Cotton effects at 285 and 252 nm, respectively, the chirality between the naphthoquinone skeleton and the *p*-bromobenzoyl group is positive,[14] and this led to the establishment of *R*-configurations for both the C-3 and C-2 positions. Accordingly, it was concluded that the predominant (−)-enantiomer of (5) is (2*R*,3*R*)-3-hydroxydehydroiso-α-lapachone.

The absolute structure of the predominant enantiomer of (3) was established in the following way. Catalytic reduction of (3) over 5% Rh–C yielded the dihydro-compound (17a), m.p. 127 °C. On the other hand, the dihydro-compound (18) obtained by catalytic reduction of (5) over 5% Rh–C on hydrogenolysis over 10% Pd–C afforded (17b), which showed identical i.r. and ^{1}H n.m.r. spectra with those of (17a) and had the same melting point. However, the $[\alpha]_D$ value of (17b) was +20.0°, while that of 17a was −25.5° (in chloroform). Furthermore, the c.d. spectra of both substances were almost mirror images of each other. It was thus concluded that both substances are enantiomers; strictly speaking, the predominant enantiomers of the two substances are antipodes of each other. As the predominant enantiomer of (5) has the 2*R* configuration as described above, C-2 of (17b) and (17a) must have *S* and *R* configurations, respectively. Thus, it could be concluded that the absolute structure of the predominant enantiomer of 3 is (2*R*)-dehydroiso-α-lapachone.*

The absolute structures of (6) and (7) were assigned from the comparison of their c.d. spectra with that of (5). Although the c.d. curve of (6) shifts slightly to the longer wavelength than that of (5), they are essentially the same. Therefore, the absolute structure of (6) is assumed to be the same as that of (5). On the other hand, the c.d. curve of (7) is the mirror image of that of (6), indicating that the two substances have opposite configurations. Thus, (6) is a 2*R*,3*R*-compound, while (7) is a 2*S*,3*S*-compound. However, considering the optical inhomogeneity of other naphthoquinones of this plant, the possibility that (6) and (7) also contain minor amounts of their enantiomers cannot be excluded.

Considering the structural features of these quinones, the isolation procedure and findings on related quinones such as 4,9-dihydroxy-α-lapachone in the wood of *Catalpa ovata* [2] or dehydroiso-α-lapachones in callus cultures of the same plant,[4] the possibility that these mixtures of optical isomers are artefacts formed during the isolation process can be ruled out.

It is noteworthy that these dehydroiso-α-lapachones (3)—(7), in spite of the similarity of their structures, occur in only one case as the racemate and in other cases as mixtures of enantiomers in various proportions, the predominant enantiomers sometimes being of opposite chirality. This phenomenon underlines the complexity of the biosynthetic pathway of these quinones.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus. Optical rotations were measured with a Union PM 201 automatic digital polarimeter. U.v. spectra were recorded for solutions in methanol with a Hitachi 200-20 spectrophotometer, and i.r. spectra with a Hitachi 215 grating spectrophotometer. Unless otherwise stated, ^{1}H n.m.r. spectra were taken for solutions in $CDCl_3$ using Me_4Si as an internal standard on a Varian A-60 spectrometer. C.d. spectra were taken with a JASCO ORD/UV-6 optical rotatory dispersion spectrometer with c.d. attachment or a JASCO J-40 dichroism dispersion spectrometer. Mass spectra were obtained on a Hitachi RMU 6D spectrometer or JEOL-01SG-2 spectrometer. Unless designated otherwise, the eluant for column chromatography on silica gel (Mallinckrodt AR-100) was benzene. T.l.c. experiments were conducted with silica gel (Merck 60 GF_{254}). Preparative t.l.c. was performed using plates (20 × 20 cm, 1 mm in thickness) of silica gel (Merck 60 PF_{254}) with benzene–ethyl acetate (4 : 1 v/v) as the developing solvent. Spots on t.l.c. were detected by the yellow colour of the substances or under u.v. light. The ratios of the solvents for chromatography

* From the comparison of the $[\alpha]_D$ values, dehydroiso-α-lapachone obtained by Sandermann *et al.*[6] seems to be of higher optical purity than the one obtained by us. However, the predominant enantiomer of both preparations should have the same absolute configuration.

are given by volume. G.l.c. was carried out with a Shimadzu GC-6AM gas chromatograph equipped with a flame ionization detector (carrier gas: nitrogen).

Isolation of Constituents.—Wood of *R. sinica*, collected at the Heng-Chun Tropical Botanical Garden, Taiwan, in April 1974, was used after drying followed by cutting into pieces. Dried wood (9.2 kg) was extracted with hot benzene (18 l × 2). The extract, after filtration, was concentrated *in vacuo* to give a dark brown residue (55 g), which was chromatographed on silica gel (906 g, 9 × 50 cm). The column was eluted successively with benzene–ethyl acetate (49 : 1) (1 l), (48 : 2) (2 l), (47 : 3) (2 l), (46 : 4) (5 l), and (9 : 1, all v/v) (3 l), collecting the following 200 ml fractions (frs.): Chr. 1–1 (frs. 1—19), Chr. 1–2 (frs. 20—25), Chr. 1–3 (frs. 26—30), Chr. 1–4 (frs. 31—33), Chr. 1–5 (frs. 34—37), Chr. 1–6 (frs. 38—46), Chr. 1–7 (frs. 48—63), Chr. 1–8 (frs. 65—75), Chr. 1–9 (frs. 76—80), and Chr. 1–10 (frs. 86—100). Each fraction was evaporated *in vacuo* and the resulting residue was submitted to further fractionation as described below.

Chr. 1–1. The waxy residue was not examined further.

Chr. 1–2. The residue (680 mg) was chromatographed on silica gel to afford triacontanoic acid (630 mg), m.p. 82—83 °C.

Chr. 1–3. The residue (245 mg) was chromatographed on silica gel (45 g, 3 × 14 cm) and the combined yellow eluates were concentrated *in vacuo*. Preparative t.l.c. of the residue (34 mg) showed three yellow bands, the middle of which was scraped off and extracted with chloroform. Evaporation of the extract *in vacuo* gave the naphthofuranquinone (8) (5 mg). This substance was identical with the dehydration product of (5) [^{1}H n.m.r. and g.l.c. (carrier gas 1.2 kg cm^{-2}; column temperature 200—240 °C at 2 °C min^{-1}; detector temperature 280 °C; retention time: 7.8 min (3% OV-1) and 10.4 min (1.5% OV-17)].

Chr. 1–4. The residue (900 mg) was chromatographed on silica gel to afford 2-(4-hydroxyphenyl)ethyl triacontanoate (750 mg), m.p. 83—83.5 °C.

Chr. 1–5. The residue (300 mg) was repeatedly crystallized from methanol to give *dehydroiso-α-lapachone* (3) as light yellow needles (80 mg), m.p. 98—99 °C, $[\alpha]_D^{23}$ −8.3° (*c*, 0.55 in methanol), +3.7° (*c*, 0.82 in chloroform), −31.3° (*c*, 0.80 in benzene) (Found: C, 75.15; H, 5.2. $C_{15}H_{12}O_3$ requires C, 75.02; H, 4.99%); $\lambda_{max.}$ 248, 254, 289, and 340 nm (log ε 4.25, 4.28, 4.00, and 3.32); $\nu_{max.}$ (Nujol) 1 675, 1 645, 1 635, 1 595, 1 585, and 900 cm^{-1}; δ 1.83br (s, vinyl methyl protons), 2.98 (dd, *J* 9.5 and 13.5 Hz, H-3), 3.40 (dd, *J* 10.5 and 13.5 Hz, H-3), 5.02br (s, $W_{\frac{1}{2}}$ 4.0 Hz, vinyl proton *cis* to Me), 5.16br (s, $W_{\frac{1}{2}}$ 2.0 Hz, vinyl proton *trans* to Me), 5.44 (dd, *J* 9.5 and 10.5 Hz, H-2), and 7.55—8.22 (A_2B_2 pattern, 4 ArH).

Chr. 1–6. The residue (2.5 g) was subjected to chromatography on silica gel (140 g, 4 × 25 cm), the eluate being collected in three fractions. The residue (600 mg) of the first fraction was recrystallized from methanol yielding orange-red scales (500 mg), m.p. 142—143 °C. This substance was identical with an authentic sample of lapachol (1) (mixed m.p., i.r. and ^{1}H n.m.r. spectra) (Found: C, 74.45; H, 6.1. Calc. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%); $\lambda_{max.}$ 253, 280, and 331 nm (log ε 4.39, 4.27, and 3.51); $\nu_{max.}$ (Nujol) 3 350, 1 655, 1 635, 1 590, 840, and 720 cm^{-1}; δ 1.70br (3 H, s, vinyl methyl protons), 1.80br (3 H, s, vinyl methyl protons), 3.31br [2 H, d, *J* 8.0 Hz, $CH_2CH{=}C(CH_3)_2$], 5.23 (1 H, deformed t, *J* 8.0 Hz, $CH_2CH{=}C$), 7.40br (1 H, s, OH, removed by addition of D_2O), and 7.50—8.23 (4 H, A_2B_2 pattern, ArH). The residue (33 mg) from the second fraction was subjected to preparative t.l.c. forming a yellow band around R_F 0.41 which was scraped off, extracted with chloroform, and concentrated *in vacuo* to give 3,6-dimethoxydehydroiso-α-lapachone (6) as a yellow syrupy residue (23 mg). This substance was found to be pure by t.l.c. (several solvent systems) and g.l.c. analyses (1.5% OV-17 and 3% OV-1); $[\alpha]_D^{24}$ −36.0° (*c*, 1.25 in chloroform); c.d. (methanol) θ (nm) 0 (500), −2 380 (425), 0 (348), +10 800 (309), 0 (292), −6 980 (278), 0 (247—230) and +28 700 (210) (Found: *m/e*, 300.1000. $C_{17}H_{16}O_5$ requires *M*, 300.0998); $\lambda_{max.}$ 265, 271, 305, 340, and 413 nm (log ε 4.32, 4.46, 4.30, 3.88, and 3.07); $\nu_{max.}$ (chloroform) 1 680, 1 655, 1 625, 1 595, and 890 cm^{-1}; δ 1.77 br (s, vinyl methyl protons), 3.58 (s, aliph. OMe), 3.96 (s, ArOMe), 4.88 (d, *J* 3.5 Hz, benzyl proton), 5.01br (s, $W_{\frac{1}{2}}$ 4.0 Hz, vinyl proton *cis* to Me), 5.13 (d, *J* 3.5 Hz, MeOCHC*H*O), and 5.13br (s, vinyl proton *trans* to Me). The residue from the third fraction was recrystallized from ethanol to give colourless needles (1.19 g), m.p. 138—139 °C, which were identical with an authentic sample of β-sitosterol in mixed m.p., ^{1}H n.m.r., and g.l.c. (Found: C, 84.3; H, 12.2. Calc. for $C_{29}H_{50}O$: C, 84.06; H, 12.05%).

Chr. 1–7. The residue (228 mg) was recrystallized from methanol yielding orange-red pillars (130 mg), m.p. 143 °C, which were identified as dehydro-α-lapachone (2) by comparison (mixed m.p., i.r., and ^{1}H n.m.r. spectra) with an authentic sample; $\lambda_{max.}$ 203, 253, 282, and 338 nm (log ε 4.36, 4.24, 4.16, and 3.26); $\nu_{max.}$ (Nujol) 1 665, 1 635sh, 1 625, 1 585, 1 565, and 870 cm^{-1}; δ 1.55 (6 H, s, geminal Me), 5.72 (1 H, d, *J* 10.0 Hz, 3-H), 6.65 (1 H, d, *J* 10.0 Hz, 4-H), and 7.58—8.18 (4 H, A_2B_2 pattern, ArH). The mother-liquor of the recrystallization of (2) contained, besides (2), vanillin (37 mg), m.p. 81—82 °C.

Chr. 1–8. The residue (950 mg) was recrystallized from methanol to give *3-hydroxydehydroiso-α-lapachone* (5) as yellow needles (900 mg), m.p. 164—165 °C; $[\alpha]_D^{24}$ −20.2° (*c*, 1.20 in methanol); (Found: C, 70.4; H, 4.75. $C_{15}H_{12}O_4$ requires C, 70.42; H, 4.69%); $\lambda_{max.}$ 246, 252, 285, 338 and 375 nm (log ε 4.27, 4.31, 4.06, 3.71, and 3.05); $\nu_{max.}$ 3 450, 1 670, 1 630sh, 1 625, 1 610, 1 580, 1 565, and 890 cm^{-1}; δ 1.80br (s, vinyl methyl protons), 3.20—3.55 (OH, disappeared under treatment with D_2O), 5.03br (s, vinyl proton *cis* to Me), 5.17br (s, vinyl proton *trans* to Me), 5.19 (d, *J* 4.5 Hz, HOCHC*H*O), 5.42 (d, *J* 4.5 Hz, a proton on a hydroxy-bearing carbon), and 7.64—7.88 and 7.93—8.20 (A_2B_2 pattern, 4 ArH).

Chr. 1–9. The residue (1.83 g) was recrystallized from methanol yielding *3-hydroxy-6-methoxydehydroiso-α-lapachone* (4) as orange-yellow needles (1.30 g), m.p. 126—127 °C. This substance showed no optical activity; (Found: C, 67.2; H, 4.8. $C_{16}H_{14}O_5$ requires C, 67.13; H, 4.93%); $\lambda_{max.}$ 264sh, 272, 299sh, 307, 343, and 406 nm (log ε 4.24, 4.27, 4.09, 4.12, 3.68, and 3.09); $\nu_{max.}$ (Nujol) 3 400, 1 670, 1 645, 1 625, 1 585, and 895 cm^{-1}; *m/e* 286 (M^+, 100%); δ 1.79br (s, vinyl methyl protons), 3.03br (s, OH, disappears on addition of D_2O); 3.92 (s, ArOCH_3), 5.39 (d, *J* 4.0 Hz, *H*COH), 7.10 (dd, *J* 8.5 and 3.0 Hz, 7-H), 7.50 (d, *J* 3.0 Hz, 5-H), and 8.04 (d, *J* 8.5 Hz, 8-H).

Chr. 1–10. The residue (800 mg) was chromatographed on silica gel (30 g, 2.8 × 13 cm) with benzene–ethyl acetate (9 : 1 v/v) as eluant. The combined orange eluates were concentrated *in vacuo* to give a residue (55 mg) which was subjected to preparative t.l.c. A reddish brown band around R_F 0.1 was scraped off and extracted with methanol. The extract was concentrated *in vacuo* and the residue was recrystallized from methanol yielding 3,5-*dihydroxy*-6-

methoxydehydroiso-α-lapachone (7) as reddish orange needles (30 mg), m.p. 198—200 °C; $[\alpha]_D^{24}$ +2.6° (*c*, 1.50 in chloroform); c.d. (methanol) θ (nm) 0 (530), +930 (445), +1 270 (430), +2 320 (405), +2 640 (390), 0 (337), −10 400 (311), 0 (292), +4 070 (275), +4 070 (245), 0 (230), −36 800 (208), and −16 300 (200); (Found *m/e*, 302.0794. $C_{16}H_{14}O_6$ requires *M*, 302.0790); $\lambda_{max.}$ 228, 248sh, 274, 310, and 440 nm (log ε 4.28, 4.14, 3.83, 3.90, and 3.65); $\nu_{max.}$ (Nujol) 3 530, 1 670, 1 640sh, 1 630, 1 610, and 900 cm^{-1}; δ 1.80br (s, vinyl methyl protons), 3.98 (s, ArOMe), 5.03br (s, vinyl proton *cis* to Me), 5.08—5.28 (m, CH_2=CMeCH), 5.38 (d, *J* 4.0 Hz, benzyl proton), 6.97 and 7.62 (each d, *J* 8.5 Hz, two adjacent ArH), and 12.72 (s, hydrogen-bonded ArOH, disappeared under treatment with D_2O).

Acetylation of 3-Hydroxy-6-methoxydehydroiso-α-lapachone (4).—The quinone (4) (150 mg) was acetylated with acetic anhydride (1.5 ml) and pyridine (1.5 ml) in the usual manner and the product was recrystallized from methanol to give the *acetate* (9) as yellow needles (121 mg), m.p. 142—143 °C (Found: C, 65.7; H, 5.0. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.91%); $\lambda_{max.}$ 225, 266, 300, and 340 nm (log ε 4.17, 4.36, 4.12, and 3.74); $\nu_{max.}$ (Nujol) 1 735, 1 680, 1 625, 1 595, and 850 cm^{-1}; δ 1.85br (3 H, s, vinyl methyl protons), 2.14 (3 H, s, OAc), 3.96 (3 H, s, OCH_3), 5.00—5.22 (3 H, 2-H and terminal methylene), 6.32 (1 H, d, *J* 3.0 Hz, 3-H), 7.15 (1 H, dd, *J* 8.5 and 2.5 Hz, 7-H), 7.56 (1 H, d, *J* 2.5 Hz, 5-H), and 8.07 (1 H, d, *J* 8.5 Hz, 8-H).

Catalytic Reduction of 3-Hydroxy-6-methoxydehydroiso-α-lapachone (4).—The quinone (4) (50 mg) in ethanol (6 ml) was hydrogenated over Pd–C prepared from 5% palladium chloride (0.2 ml) and charcoal (Darco 60, 50 mg) in H_2 atmosphere for 30 min. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to give the *dihydroderivative* (10) as yellow needles (48 mg), m.p. 128—129 °C (Found: C, 66.7; H, 5.35. $C_{16}H_{16}O_5$ requires C, 66.66; H, 5.59%); $\lambda_{max.}$ 264, 270, 306, and 340 (log ε 4.35, 4.38, 4.21, and 3.79); $\nu_{max.}$ (Nujol) 3 400, 3 280, 1 670, 1 640, 1 620, 1 590, 1 565, and 850 cm^{-1}; δ 1.03 and 1.07 (each 3 H, d, *J* 7.0 Hz, geminal Me), 1.85—2.35 (1 H, m, MeCHMe), 3.49br (1 H, s, OH, removed by addition of D_2O), 3.94 (3 H, s, OCH_3), 4.56 (1 H, dd, *J* 7.0 and 4.5 Hz, 2-H), 5.38 (1 H, d, *J* 4.5 Hz, 3-H), 7.10 (1 H, dd, *J* 8.5 and 3.0 Hz, 7-H), 7.48 (1 H, d, *J* 3.0 Hz, 5-H), and 8.01 (1 H, d, *J* 8.5 Hz, 8-H).

Methylation of 3-Hydroxy-6-methoxydehydroiso-α-lapachone (4) *with* MeI–Ag_2O.—Freshly prepared Ag_2O (17.7 mg) and methyl iodide (0.1 ml) were added to a solution of (4) (20 mg) in chloroform (5 ml) and the mixture was stirred at room temperature for 20 h. After removal of Ag_2O by filtration, the filtrate was evaporated *in vacuo* and the residue was subjected to preparative t.l.c. A band around R_F 0.50 was scraped off and extracted with chloroform. The residue obtained after evaporation of the extract was redissolved in hot methanol. A yellow powder (5 mg) precipitated on cooling to room temperature, which was identical with compound (6) (i.r., ^1H n.m.r., and mass spectra).

Treatment of 3-Hydroxydehydroiso-α-lapachone (5) *with* BF_3.—BF_3–ether (0.2 ml) was added to a solution of (5) (40 mg) in dry methylene chloride (3 ml) and the solution was stirred at room temperature for 0.5 h. After dilution with water, the solution was extracted with chloroform. The extract was washed successively with 5% aqueous sodium hydrogencarbonate and water, dried, and evaporated *in vacuo*. The residue was subjected to preparative t.l.c. giving a yellow band around R_F 0.52, which was extracted with chloroform. After evaporation of the extract, the residue was recrystallized from ethanol to give *2-isopropenylnaphtho*[2,3-b]*furan-4,9-quinone* (8) as yellow needles (26 mg), m.p. 172—173 °C (Found: C, 75.4; H, 4.45. $C_{15}H_{10}O_3$ requires C, 75.62; H, 4.23%); $\lambda_{max.}$ 253, 264, 280, 340, and 410 nm (log ε 4.89, 4.84, 3.99, 3.82, and 3.57); $\nu_{max.}$ (Nujol) 1 660, 1 655sh, 1 640, 1 580, 1 500, and 895 cm^{-1}; δ 2.14br (3 H, s, vinyl methyl protons), 5.35br (1 H, s, vinyl H *cis* to Me), 5.94br (1 H, s, vinyl H *trans* to Me), 6.83 (1 H, s, 3-H), and 7.50—8.37 (4 H, A_2B_2 pattern, ArH).

Treatment of 3-Hydroxydehydroiso-α-lapachone (5) *with Oxidizing Agents*.—Acetic anhydride (0.3 ml) was added to a solution of (5) (30 mg) in dimethyl sulphoxide (0.5 ml) and the mixture was stirred at room temperature for 3 h. After dilution with water, the mixture was extracted with chloroform. The extract was washed successively with 5% aqueous sodium hydrogencarbonate and water, dried, and evaporated *in vacuo*. The residue was recrystallized from ethanol to give the quinone (8) (21 mg). Reaction of (5) with Jones reagent also afforded (8) as the sole product.

Benzoylation of 3-Hydroxydehydroiso-α-lapachone (5).—Compound (5) (30 mg) was treated with dry pyridine and benzoyl chloride and after the usual work-up the product was subjected to preparative t.l.c. and a yellow band of *ca.* R_F 0.38 was scraped off and extracted with chloroform. After evaporation of the chloroform extract, the residue was recrystallized from methanol to give the *benzoate* (11) as light yellow needles (10 mg), m.p. 159—161 °C, $[\alpha]_D^{24}$ −15.5° (*c*, 0.12 in methanol) (Found: C, 73.25; H, 4.4. $C_{22}H_{16}O_5$ requires C, 73.39; H, 4.47%); $\lambda_{max.}$ 243, 252, and 284 nm (log ε 4.22, 4.14, and 3.83); $\nu_{max.}$ (Nujol) 1 705, 1 685, 1 650, 1 630, 1 590, 1 570, and 885 cm^{-1}; δ 1.92br (3 H, s, vinyl methyl protons), 5.11br (1 H, s, vinyl H *cis* to Me), 5.21br (1 H, s, vinyl H *trans* to Me), 5.31br (1 H, d, *J* 3.0 Hz, 2-H), 6.58 (1 H, d, *J* 3.0 Hz, 3-H), and 7.37—8.27 (9 H, m, ArH).

Catalytic Reduction of Dehydroiso-α-lapachone (3).—The quinone (3) (30 mg) in ethanol (4 ml) was subjected to catalytic reduction over 5% Rh–C (30 mg) in H_2 atmosphere for 20 min. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to yield (2R)-*iso-α-lapachone* (17a) as light yellow needles, 24 mg, m.p. 127 °C; $[\alpha]_D^{24}$ −25.5° (*c*, 0.92 in chloroform); c.d. (methanol) θ (nm) 0 (495), +1 430 (438), +1 510 (424), 0 (396), −910 (370), −310 (330), −7 680 (295), −7 960 (279), −1 890 (235), and −18 900 (210) (Found: C, 74.55; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.36; H, 5.82%); $\lambda_{max.}$ 248, 253, 288, and 335 nm (log ε 4.42, 4.45, 4.18, and 3.54); $\nu_{max.}$ (Nujol) 1 670, 1 640, 1 620, 1 590, and 1 570 cm^{-1}; δ 1.03 and 1.08 (each 3 H, d, *J* 7.5 Hz, geminal Me), 1.70—2.45 (1 H, m, MeCHMe), 2.87 (1 H, dd, *J* 10.0 and 17.0 Hz, 3-H), 3.24 (1 H, dd, *J* 9.5 and 17.0 Hz, 3-H), 4.83 (1 H, ddd, *J* 10.0, 9.5, and 6.5 Hz, 2-H), and 7.46—8.22 (4 H, A_2B_2 pattern, ArH).

Catalytic Reduction of 3-Hydroxydehydroiso-α-lapachone (5).—The quinone (5) (100 mg) in ethanol (12 ml) was subjected to catalytic reduction over 5% Rh–C (100 mg) in H_2 atmosphere for 10 min. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* and the residue was subjected to preparative t.l.c. A yellow band around R_F 0.25 was extracted with chloroform. The residue obtained by concentration of the chloroform extract was recrystallized from ethanol yielding *3-hydroxyiso-α-lapachone* (18) as light yellow needles, 67 mg, m.p. 122—124 °C; $[\alpha]_D^{20}$ +26.9° (*c*, 0.78 in chloroform) (Found: *m/e*, 258.0853.

$C_{15}H_{14}O_4$ requires *M*, 258.0892); $\lambda_{max.}$ 246, 251, 287, and 336 nm (log ε 4.26, 4.33, 4.04, and 3.16); $\nu_{max.}$ (chloroform) 3 550, 3 400, 1 680, 1 650, 1 645, 1 625, 1 595, and 1 570 cm^{-1}; δ 1.04 and 1.07 (each 3 H, d, *J* 7.0 Hz, geminal Me), 1.78—2.38 (1 H, m, MeC*H*Me), 3.17—3.78 (1 H, OH, removed by addition of D_2O), 4.58 (1 H, dd, *J* 4.5 and 7.0 Hz, 2-H), 5.40 (1 H, d, *J* 4.5 Hz, 3-H), and 7.42—8.42 (4 H, A_2B_2 pattern, ArH).

Hydrogenolysis of 3-*Hydroxyiso-α-lapachone* (18).—The quinone (18) (80 mg) in ethanol (5 ml) was subjected to catalytic reduction over Pd–C [from 10% palladium chloride (0.3 ml) and charcoal (Darco 60, 30 mg)] in H_2 atmosphere for 2 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol yielding (2S)-*iso-α-lapachone* (17b) as yellow needles (20 mg), m.p. 127 °C; $[\alpha]_D^{24}$ +20.0° (*c*, 0.30 in chloroform); c.d. (methanol) θ (nm) 0 (490), −830 (440), −900 (425), 0 (387), +140 (370), +70 (340), +3 360 (293), +3 100 (282), +290 (235), and +6 660 (215). The i.r. and ^1H n.m.r. spectra of this compound were identical with those of (16a).

p-*Bromobenzoate* (16) *of* 3-*Hydroxydehydroiso-α-lapachone* (5).—Compound (5) (30 mg) was benzoylated with pyridine and *p*-bromobenzoyl chloride under the usual conditions and the product was recrystallized from methanol to give the p-*bromobenzoate* (16) as light yellow needles (23 mg), m.p. 162—163.5 °C; c.d. (methanol) θ (nm) 0 (470), +920 (436), +740 (419), 0 (410.5), −5 760 (367), 0 (317), +21 000 (289), 0 (263), −51 600 (252.5), 0 (241), +6 900 (230), +5 200 (219), and +25 100 (210) (Found: C, 60.35; H, 3.55. $C_{22}H_{15}BrO_5$ requires C, 60.25; H, 3.44%); $\lambda_{max.}$ 239, 249sh, and 282 nm (log ε 4.19, 4.14, and 3.81); $\nu_{max.}$ (1 715, 1 680, 1 650, 1 645sh, 1 625, 1 585, 910, and 860 cm^{-1}; δ 1.92br (3 H, s, vinyl methyl protons), 5.12br (1 H, s, vinyl H *cis* to Me), 5.22br (1 H, s, vinyl H *trans* to Me), 5.30br (1 H, d, *J* 3.0 Hz, 2-H), 6.58 (1 H, d, *J* 3.0 Hz, 3-H), and 7.48—8.33 (8 H, A_2B_2 and $A'_2B'_2$ pattern, ArH).

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