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DISIDEIN, A PENTACYCLIC SESTERTERPENE CONDENSED WITH AN HYDROXYHYDROQUINONE MOIETY, FROM THE SPONGE *DISIDEA PALLESCENS*

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Abstract—A novel pentacyclic saturated sesterterpene condensed with hydroxyhydroquinone moiety, which we named disidein (**1**), has been isolated from the marine sponge *Disidea pallescens* as disulfate sodium calcium salt. A minor accompaining compound, which seems a likely precursor of disidein, has been identified as 2-pentaprenylbenzoquinone (**7**).

COMPOUNDS of mixed biogenesis originating partly from mevalonate and partly from a benzoid precursor have been recently isolated from sponges.

Ircinia spinosula and *I. muscarum* were shown to contain 2-polyprenylbenzoquinones (mixture of isoprenologoues) and the corresponding quinols,[1] while *Halichondria panicea* yielded a group of 'triprenyl phenols', the paniceins, whose structures include on aromatic sesquiterpenoid moiety linked to a quinol or a quinone system.[2]

In our continuing search for constituents of marine sponges, we have examined the extracts of *Disidea pallescens*, collected in the bay of Naples, from which we have isolated in 4% yield a tri-hydric phenol as disulfate sodium and calcium salt, giving a green coloration with ferric chloride and a red-violet coloration with Pauly reagent. For the free phenol, named disidein, on the basis of the data shown below, we propose formula **1** as the most probable structure, which combine a pentacyclic sesterterpene saturated hydrocarbon and an hydroxyhydroquinone unit.

According to essentially the same procedure as reported in previous papers, the fresh tissues of *Disidea pallescens* were exhaustively extracted with acetone; solvent was removed and the aqueous residue was extracted with ether and then with n-butanol. Chromatography on silica gel of the n-butanol-soluble material gave disidein disulfate sodium calcium salt, as a colorless water-soluble solid, resistant to attempts at crystallization. It analyzed for $C_{31}H_{44}S_2O_9NaCa_{\frac{1}{2}}$.

The UV spectrum showed λ_{max} 279 nm, batochromically shifted to 296 nm in 2N KOH. Mild acid hydrolysis gave two moles of sulfuric acid per mole of compound and crystalline disidein (**1**), which was recrystallized from ether, $[\alpha]_D = +24°$, it decomposed at *ca* 260°, molecular formula $C_{31}H_{46}O_3$.

The IR (ν_{max} 3670, 3540, 1600 cm^{-1}) and UV (λ_{max} 287 nm bathochromically shifted to 291 by alkali) spectra indicated that **1** has phenolic structure, and NMR spectrum contained a single aromatic proton (δ 6·79).

Disidein gave a triacetate (**2**), $C_{37}H_{52}O_6$, m.p. 143–145°, $[\alpha]_D + 26·3°$, ν_{max} 1760 cm^{-1} and a trimethyl ether (**3**), m.p. 166–167°, $C_{34}H_{52}O_3$. The hydroxyhydroquinone nature of the chromophore in disidein was evident from its conversion on Ag_2O oxidation to an hydroxy-*p*-benzoquinone compound, dec. 300°, *m/e* 464 (M^+), δ Q–H 5·90, having absorption maxima at 280 and 391 nm (ϵ, 10,800, 260) in UV and IR bands at 3400 (sharp, H-bonded OH), 1655 (quinonoid CO), 1635 (H-bonded quinonoid CO) and 1595 (C = C)[3].

The molecular formula of disidein ($C_{31}H_{46}O_3$; nine formal unsaturations) and the absence of olefinic signals in the NMR spectrum led to consideration of a pentacyclic skeleton in addition to the hydroxyhydroquinone ring for disidein. Furthermore its NMR spectrum ($CD_3OH - CDCl_3$) displayed signals for two benzylic protons (m centered at *ca* δ 2·50) and also for six *t*-Me's [δ 1·30 (3H), 1·01 (3H) and 0·85 (12H); in the spectrum of **2** run in C_6D_6 the overlapping methyl signals at δ 0·85 were splitted into well separated singlets at δ 1·00 (6H) and 0·95 (6H) ppm]. In the spectrum of **3** the benzylic protons appear as a clear AB part of an ABX pattern with line positions at δ 2·69 and 2·37 ppm and J of 13 Hz (JAB), 7 Hz (JAX) and 13 Hz (JBX); irradiation a δ 1·95 changed the 7-line signal into a sharp AB quartet (J 13 Hz). This suggested the presence of a $-CH-CH_2-\phi$ grouping. The presence of six t-Me's, taken in conjunction with the above evidence, indicates that disidein is represented most favourably by formulae (**1** or **5**, part-structure), which are also well explained from the standpoint of biogenesis.

In fact, we may imagine that **6** undergoes an essentially synchronous process for the ring formation if H^+ is furnished at C-3. Notably, examination of the ether-soluble material has afforded in 0·1% yield 2-pentaprenylbenzoquinone (**7**), which seems a likely precursor of disidein.

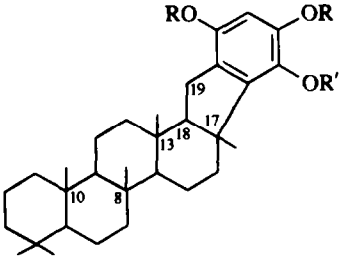
Its structure was suggested from spectral properties (Experimental) and comparison with isoprenologues described from two *Ircinia* sponges,[1] and was confirmed by synthesis. Condensation of quinol with farnesyl-linalool (*trans*) in the presence of boron trifluoride gave

2-pentaprenylquinol which was converted into the quinone with ferric chloride.

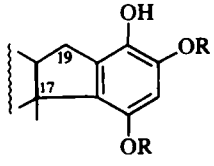
Coming back to disidein, the low field resonating angular Me signals in its NMR spectrum and in those of its derivatives (**2**, **3** and the hydroxy-*p*-benzoquinone) (δ 1·30 and 1·00 ppm *ca* in all spectra) can be assigned to 17-Me and 13-Me, respectively, deshielded by the neighbouring aromatic ring. In the spectrum of the model compound **8** the Me groups resonate at δ 1·30 and 1·22 ppm.[4]

Disidein (**1**), on $KMnO_4$ oxidation, furnished a carboxylic acid, characterized as the methyl ester (**9**), m.p. 151–153°, $C_{29}H_{48}O_4$, ν_{max} 1735 cm^{-1}, displaying in its NMR spectrum signals for 6-Me's at δ 1·04 (3H, 17-Me), 0·92 (3H), 0·85 (3H) and 0·80 (9H) ppm and for a $-CH_2-CO_2CH_3$ (δ 2·4, m). Its mass spectral fragmentation pattern is in full agreement with the proposed structure (**9**): the two major peaks occurring at *m/e* 259 (100%) and 191 (45%) originate by cleavage at the ring junction as indicated in **9** and loss of one hydrogen from the charged species.[5] A minor one occurs at *m/e* 205 (10%). The two major fragments were accurately mass measured.

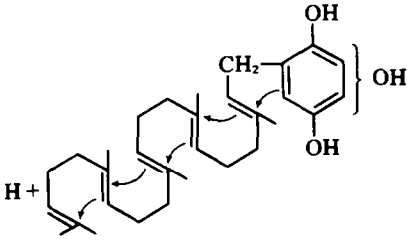
In contrast with the simplicity of the mass spectrum of **9**, the mass spectrum of disidein (**1**) includes a conspicuous number of ions, which can be assigned to the processes indicated in Fig 1, occurring with loss of an additional hydrogen from the charged species.[5] This offers a considerable substantial support to the structure of the C_{25} moiety of disidein. These assignments are substantiated partly by the high resolution mass spectrometry and



1; R=R'=H
2; R=R'=Me—CO—
3; R=R'=Me
4; R=Me, R'=H



5; R=H
12; R=Me



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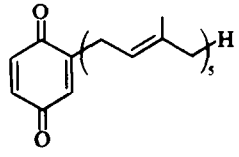

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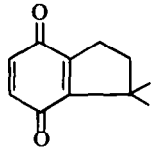

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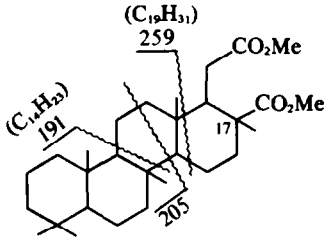

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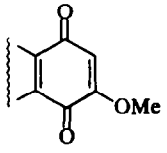

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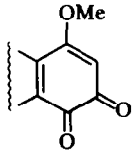

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partly by the spectrum of the dimethyl disidein (**4**; see below), in which analogous fragmentations (all accurately mass measured) are observed.

Information for the arrangement of the OH substituents on the benzenic ring was obtained from NMR data on dimethyl ether of disidein (**4**) in the presence of the deuteriated lanthanide shift reagent Eu (fod-d_9)$_3$, which favoured the substitution pattern indicated in **1**.

The dimethyl ether of disidein (**4**), p.f. 226–228°, was obtained on treatment of disidein with methanol-HCl. The two OMe groups are situated *meta* as shown by oxidation with DDQ in ethanol, which gave a yellow (main component) and a red compound.

The yellow compound appeared to be a methoxy-*p*-benzoquinone derivative (part-structure **10**), m.p. 202–204°, *m/e* 478 (M^+), having absorption maxima at 278 and 380 nm (ϵ 10,080 and 320) in the UV, IR bands at 1670, 1645 and 1590 cm^{-1}, and NMR signals at δ 5·68 (1H, s, Q–H) and 3·71 (3H, s, OCH_3). The minor compound, which was red, p.f. 198–200°, *m/e* 478 (M^+) showed an UV spectrum, λ_{max} 276, 442 and 550 (should) (ϵ 4,780; 1,650 and 82), typical of *o*-benzoquinones;[3] the IR showed bands at 1650, 1610 and 1575 cm^{-1} and in the NMR spectrum the quinonoid proton resonates at δ 5·56. The mass spectrum includes a very strong M+2 peak in agreement with an *o*-quinone structure[6] (part structure **11**).

As 1,2,4-trihydroxybenzene dimethyl ether yielded both a methoxy-*p*-benzoquinone and a methoxy-*p*-quinone, this is compatible only with a 2,4-dimethyl ether structure.

NMR data on disidein 2,4-dimethylether before and after the addition of 0·8 moles the europium shift reagent Eu (fod-d_9)$_3$ are listed in Table 1. Addition of 0·2–0·8 moles of Eu (fod)$_3$ per mole of **4** caused downfield shifts, which were approximately linear with respect to concentration of Eu (fod)$_3$.

The induced-shifts of benzylic (H_2-C-19) and 17-Me protons, which are about the same value, seem compatible with the arrangement of the substituents as shown in **4**. in the case of the alternative aromatic substitution patttern (part-structure **12**), the shift reagent would be expected to indice a shift for the benzylic methylene protons (*ortho*-situated in respect to the free OH) considerably further than the 17-Me signal. Furthermore in the 100 MHz NMR spectrum of **4** determined in $CDCl_3$ in the absence of a shift reagent the protons on C-18 and C-16 overlap and form a large broad multiplet centered around δ 2·0. Addition of 0·2–0·8 moles of Eu (fod)$_3$ per mole of **4** resulted in the separation of the signal into two multiplet integrating for 2H e 1H, respectively. They move about the same ppm as the 17-Me and the Ar–CH_2 protons and this also supports the aromatic substitution pattern as shown in **4**.

Significantly the terpenoid skeleton of disidein (**1**) has been already encountered in scalarin, deoxoscalarin and scalaradial, sesterterpenes recently isolated from sponges.[7,8]

Also interesting is the occurrence of the free hydroxyhydroquinone in the sponge *Axinella polypoides*.[9]

EXPERIMENTAL

Sponges (*Disidea pallescens*) were collected in the Bay of Naples. Columns chromatography was carried on silica gel 0·05–0·2 mm (Merck). TLC and PLC were carried out on precoated silica gel plates (Merck). NMR spectra were determined on a Varian XL-100 spectrometer (TMS as internal reference). Mass spectra were measured on an A.E.I. MS-30 instrument at 70 eV. UV and IR spectra were measured on Baush and Lomb Spectronic 505 and Perkin-Elmer 257 Infracord spectrophotometers.

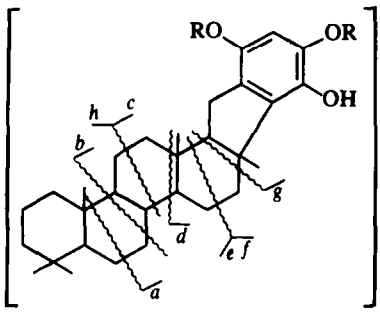
Extraction of Disidea pallescens. Fresh material (68 g, dry after extraction) was extracted (×3) with acetone at room temp for 3 days. The combined extracts (1 l) were concentrated and the remaining aqueous soln was extracted with ether and subsequently with n-BuOH. After removal of solvents, the ethereal extracts gave 3·1 g of an oily residue and the n-BuOH-extracts yielded 4·1 g of a solid residue.

Butanol-soluble material. This was applied to a silica gel column (200 g), which was eluted with $CHCl_3$ and increasing amounts of MeOH. Disidein as disulfate sodium calcium salt (2·7 g) was recovered on the $CHCl_3$–MeOH, 7:3 fractions. (Found: C, 54·9; H, 6·9; S, 8·9, Na, 32,000 ppm, Ca, 30,500 ppm; $C_{31}H_{44}S_2O_9$ $NaCa_{\frac{1}{2}}$ requires: C, 55·8; H, 6·6; S, 9·6%; Na, 34,480 ppm; Ca, 29,980. Sodium and Calcium were determined by

Table 1. NMR data on disidein dimethylether (**4**) before and after addition of the europium shift reagent Eu (fod-d_9)$_3$

Signal identification	δ ($CDCl_3$)[a]	δ (Eu-$CDCl_3$)[b]	$\Delta\delta$
Ar–H	6·3	11·7	5·4
orto–OMe	3·77 or 3·85	8·6	4·83–4·75
para–OMe	3·85 or 3·77	5·4	1·55–1·63
H_2 at C-19	2·62	4·12	1·50
H at C-18, H_2 at C-16	2·0 broad	2·95 (1H) 3·56 (2H)	0·95 1·56
Me at C-17	1·31	2·61	1·30
Me at C-13	1·01	1·54	0·53
Me's at C-8, C-9	0·85	1·00 0·95	0·15 0·10
Me's at C-4	0·85	0·85	0

[a] Relative to TMS in the absence of Eu(fod)$_3$.
[b] Relative to TMS after the addition of 0·8 moles of Eu(fod)$_3$ per mole of **4**.



Disidein; R = H[a]					*Disidein-dimethylether*; R = Me[a]				
		Obsvd.	Calcd.	Relative Intens. (%)			Obsvd.	Calcd.	Relative Intens. (%)
M^+/e	$C_{31}H_{46}O_3$	466·3440	466·3446	100	M^+/e	$C_{33}H_{50}O_3$	494·3752	494·3759	100
a	—	327	—	1·5	*a*	$C_{23}H_{31}O_3$	355·2273	355·2273	0·5
b	—	313	—	3	*b*	$C_{22}H_{29}O_3$	341·2113	341·2116	0·8
c	$C_{16}H_{19}O_3$	259·1334	259·1335	12	*c*	$C_{18}H_{23}O_3$	287·1645	287·1647	4·5
d	—	245	—	13	*d*	$C_{17}H_{21}O_3$	273·1487	273·1490	
e	—	273	—	3·5	*e*	$C_{20}H_{33}$	273·2583	273·2582	4·5
f	$C_{11}H_{11}O_3$	191·0713	191·0708	100	*f*	$C_{13}H_{15}O_3$	219·1023	219·1021	56
g	$C_{10}H_9O_3$	177·0554	177·0551	22	*g*	$C_{12}H_{13}O_3$	205·0862	205·0864	11
h	—	205	—	8	*h*	$C_{15}H_{25}$	205·1954	205·1956	

[a] In the spectra of disidein and its dimethyl ether there is one more significant peak at *m/e* 231 (9%) and 259 (3%), respectively and it may originate by the fragmentation *d* with loss of a Me group instead of an H atom. The peak *m/e* 259 was accurately mass measured: 259·1332; calcd. for $C_{16}H_{19}O_3$ 259·1334.

Fig. 1. MS spectral data of disidein and its dimethylether. All the fragmentation processes occur with loss of an additional hydrogen atom from the charged species.

flame emission). UV: $\lambda_{max}^{H_2O}$ 279 (ε, 1294) nm; $\lambda_{max}^{2N\text{-}KOH}$ 296 (ε, 2330) nm; NMR (CD_3OH) 6·80 (1H, s), 1·36 (3H, s, t-Me), 1·05 (3H, s, t-Me), 0·87 (12H, bs, t-Me's). The determination of sulfate by gravimetric method,[10] after hydrolysis with dil HCl, indicated the presence of two sufate groups per molecule.

Ether-soluble material. This was chromatographed on a column of silica gel impregnated with $AgNO_3$ (12 g $AgNO_3$–60 g SiO_2), which was washed with light petroleum and increasing amounts of benzene was to remove the furanosesquiterpenoid components,[11] and further eluted with benzene and increasing amounts of ether. Fractions eluted with benzene-ether, 8:2, were subjected to PLC on SiO_2 in C_6H_6–light petroleum (b.p. 40–70°), 1:1 to give *2-pentaprenylbenzoquinone* (7), (60 mg), λ_{max} (CH_3OH) 246, 311 (log ε 4·02, 2·50), ν_{max} (liquid film) 1660 and 1600 cm^{-1}, δ (CCl_4) 6·64 (2H, bs, Q–H), 6·43 (1H, bs, Q–H), 5·31 (1H, t, J 6 Hz, QCH_2CH=C), 5·08 (4H, bm, CH=C), 3·08 (2H, d, J 6 Hz, Q–CH_2–CH=C), 2·05 and 1·95 (16H, each bs, CH_2), 1·64 (6H, s, *cis*-Me of the ω-unit and *trans*-Me of the α-unit), 1·58 (12H, s, *trans*-Me), *m/e* (%) 448 (2, M^+), 379 (3), 311 (3), 243 (3), 175 (4), 161 (100), 123 (80), 121 (50).

Hydrolysis of disidein disulfate sodium calcium salt. The salt (2 g) was dissolved in dil 0·1N HCl (100 ml) and the soln was allowed to stand at room temp for 5 min and then extracted several times with ether to give *disidein* (1) as solid (1·3 g). The product was crystallized from ether (0·8 g) (*m/e* 446·3440; $C_{31}H_{46}O_3$ requires: 466·3446), dec. 260°, $[\alpha]_D$ + 24° (2·3 in dioxan); λ_{max} (MeOH) 287 nm (ε, 4,990); ν_{max} ($CHCl_3$) 3670, 3540, 1600, 1220, 1170, 1020 and 920 cm^{-1}; δ (CD_3OD–$CDCl_3$) 6·80 (1H, s, Ar–H), 2·60 (2H, m, $-CH_2$–Ar), 1·30 (3H, s, 17-Me), 1·00 (3H, s, 13-Me), 0·86 (12H, bs, t-Me's); the mass spectrum is described in Fig 1.

Disidein (1) on treatment with excess Ac_2O in pyridine (100 mg/2 ml/3 drops) at reflux for 1 hr, formed a *triacetate* (2), which was chromatographed on silica gel column (eluent: C_6H_6-ether, 95:5). The product was crystallized from MeOH, m.p. 143–145°, $[\alpha]_D$ + 26·3° (*c* 3 in $CHCl_3$) (Found: C, 74·7; H, 8·4. $C_{37}H_{52}O_6$ requires: C, 75·0; H, 8·5%), λ_{max} (CH_3OH) 220, 261 (ε 4,930; 295) *nm*, ν_{max} 1760 cm^{-1}, δ ($CDCl_3$) 6·79 (1H, s, Ar–H), 2·50 (2H, m, CH_2–Ar), 2·26 (6H, s, CH_3CO–), 2·21 (3H, s, CH_3CO–), 1·30 (3H, s, 17-Me), 1·01 (3H, s, 13-Me), 0·85 (12H, s, t-Me's), in C_6D_6 the acetyl protons were splitted into well separated singlets at δ 2·01, 1·92 and 1·89 ppm and the t-Me's resonate at δ 1·46 (3H), 1·05 (3H), 1·00 (6H) and 0·95 (6H) ppm, *m/e* 592 (2, M^+), 550 (22), 508 (63), 466 (100), 191 (45).

Disidein (1) formed a *trimethyl ether* (3), when it was allowed to react with dimethylsulfate and NaOH aq (both added portionwise to a solution of 1 in EtOH) at reflux for 3 hr.

This was purified by PLC [eluent: C_6H_6–light petroleum (b.p. 40–70°), 9:1] and, on crystallization from MeOH, yielded crystals, m.p. 166–167° (Found: C, 80·1; H, 10·0. $C_{34}H_{52}O_3$ requires: C, 80·3; H, 10·2%), δ ($CDCl_3$) 6·27 (1H, s, Ar–H), 3·82 (3H, s, OCH_3), 3·79 (6H, s, OCH_3), δ 2·50 (2H, 7-line signal. J 13 Hz, 7 Hz, CH_2–Ar), 1·30 (3H, s, 17-Me), 1·01 (3H, s, 13-Me), 0·85 (12H, bs, t-Me's), *m/e* 508 (M^+).

Disidein (1) formed a *dimethyl ether* (4), when it was allowed to react with MeOH saturated with HCl (48 hr at room temp). This derivative was purified by column chromatography on silica gel in C_6H_6 and it was crystallized from C_6H_6–MeOH, m.p. 226–228°,

(Found: C, 80·0; H, 9·9, $C_{33}H_{50}O_3$ requires: C, 80·2; H, 10·1%), λ_{max} (MeOH) 285 (ϵ 3,480) nm, ν_{max} 3540 (sharp), the NMR is reported in Table 1; the mass spectrum is reported in Fig 1.

Oxidation of disidein

(i) *With* Ag_2O. Disidein (**1**) (30 mg) in ether (5 ml) was treated with Ag_2O (100 mg) with stirring at room temp for 5 min. Filtn, evapn of the solvent and PLC on silica gel in C_6H_6-ether, 9:1, gave the *corresponding hydroxy-p-benzoquinone* (18 mg), which was crystallized from $CHCl_3$, dec 300° (*m/e* 464·3286; $C_{31}H_{44}O_3$ requires: 464·3290), λ_{max} ($CHCl_3$) 280, 391 (ϵ 10,830, 260) nm, ν_{max} ($CHCl_3$) 3400, 1655, 1635 and 1595 cm^{-1}, δ ($CDCl_3$) 5·90 (1H, s, Q–H), 1·30 (3H, s), 1·01 (3H, s); *m/e* 466 (18, $M^+ + 2$), 464 (10, M^+), 191 (100), 189 (18).

(ii) *With* $KMnO_4$. To a solution of **1** (200 mg) in 2N K_2CO_3 (4 ml), 3% $KMnO_4$ aq (7 ml) was added portionwise in about 2 hr.

The excess of oxidant was destroyed with Na_2SO_3 and after filtration, the soln was acidified with 2N HCl and the acid was extracted with ether. After removal of the solvent the residue was methylated with diazomethane in MeOH in the usual way, followed by chromatography on silica gel in benzene, to give the *ester* **9** (mg 26) m.p. 151–155° (ETOH)(*m/e* 460·3548; $C_{29}H_{48}O_4$ requires: 460·3552, ν_{max} (liquid film) (1735 cm^{-1}), δ ($CDCl_3$) 3·62, 3·64 (6H together, each s, OCH_3), 2·45 (2H, m, CH_2–CO_2Me), 1·05 (3H, s), 0·92 (3H, s), 0·84 (3H, s), 0·80 (9H, s); *m/e* 460 (6, M^+), 259 (100), 205 (10), 191 (45); accurate mass measurements: 259·2430 (calcd. for $C_{19}H_{31}$ 259·2425), 191·1797 (calcd. for $C_{14}H_{23}$ 191·1799).

DDQ oxidation of the dimethyl ether (**4**). The ether **4** (50 mg) and DDQ (50 mg) were kept in EtOH (3 ml) at room temp for 5 min. PLC on silica gel of the mixture in C_6H_6-ether, 95:5 gave the *methoxy-p-benzoquinone derivative* (part-structure **10**) (R_f 0·7, 24 mg), recrystallized from cyclohexane, m.p. 202–204° (*m/e* 478·3442; $C_{32}H_{46}O_3$ requires: 478·3446), λ_{max} (CH_3OH) 278, 380 (ϵ 10,800, 320) nm, ν_{max} 1670, 1645 and 1590 cm^{-1}, δ ($CDCl_3$) 5·68 (1H, s, Q–H), 3·71 (3H, s, OCH_3), 1·27 (3H, s), 0·98 (3H, s), 0·82 (12H, s) ppm; *m/e* 480 (32, $M^+ + 2$), 478 (22, M^+), 205 (56), 203 (18), 191 (100), and the *methoxy-o-benzoquinone derivative* (part-structure **11**) (R_f 0·6; 7 mg), crystallized from cyclohexane, m.p. 198–200° (*m/e* 478·3449. $C_{32}H_{46}O_3$ requires: 478·3446), λ_{max} (CH_3OH) 276, 442, 550 (sh) (ϵ, 4·780, 1·650, 82), ν_{max} 1650, 1610 and 1575 cm^{-1}, δ ($CDCl_3$) 5·55 (1H, s, Q–H) 3·80 (3H, s, OCH_3), 1·29 (3H, s), 1·04 (3H, s), 0·88 (12H, s) ppm; *m/e* 480 (100, $M^+ + 2$), 478 (10, M^+), 205 (22), 203 (3), 191 (10).

Synthesis of 2-pentaprenylbenzoquinone (**7**). To hydroquinone (200 mg) and redistilled BF_3-etherate (0·05 ml) in dry dioxan (1 ml) at 60°, *all-trans* farnesyl-linalool (370 mg) in dioxan (0·5 ml) was added over a period of 5 min, and the soln stirred for 1 hr at 60° then for 4 hr at room temp.

The mixture was diluted with ether and extracted with $NaHCO_3$ aq. The organic phase was washed with water then shaken with ferric chloride (1·0 M, 2 ml) for 10 min.

The orange ether layer was dried ($MgSO_4$) and evaporated to give a yellow oil, which was chromatographed on silica gel in C_6H_6 to give 2-pentaprenylbenzoquinone (80 mg) as oil.

To spectral properties were identical to those of the natural sample, given above.

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