Three New Heptaprenylhydroquinone Derivatives from the Sponge Ircinia fasciculata

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THREE NEW HEPTAPRENYLHYDROQUINONE DERIVATIVES FROM THE SPONGE *IRCINIA FASCICULATA*[1]

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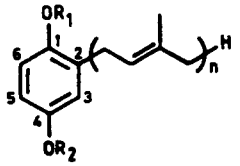
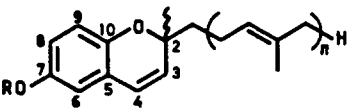
ABSTRACT.—2-Heptaprenylhydroquinone [**3**], its sulfate [**6**], 2-(hexaprenylmethyl)-2-methylchromenol [**10**], and 2-(hexaprenylmethyl)-2-methylchromanol [**14**] have been isolated from the sponge *Ircinia fasciculata*. Three of these compounds [**6**, **10**, **14**] are novel. Their structures have been established by spectral methods and chemical transformations.

In the course of our search for bioactive metabolites from Indian marine invertebrates (1–3), we investigated the sponge *Ircinia fasciculata* Pallas (Spongillidae) collected on the coast of the Gulf of Mannar, India. In previous reports the genus *Ircinia* has been shown to produce furanosesterterpenes (4–6) and polyprenylated hydroquinones (7–8) [**1–4**]. Recently, sulfated derivatives of polyprenylated hydroquinones [**5**, **7–9**] and the chromenols **11–13** have been isolated from a *Dysidea* species (9) and *Sarcotragus spinulosus* (10). These sulfated metabolites have been shown to inhibit H^+,K^+ and Na^+,K^+-ATPase. Chromatographic separation of the crude extract of *I. fasciculata* afforded the three new compounds 2-heptaprenylhydroquinone-1-sulfate [**6**], 2-(hexaprenylmethyl)-2-methylchromenol [**10**], 2-(hexaprenylmethyl)-2-methylchromanol [**14**], and the known heptaprenylhydroquinone, **3**.



1 R_1,R_2=H, n=4
2 R_1,R_2=H, n=6
3 R_1,R_2=H, n=7
4 R_1,R_2=H, n=8
5 R_1=SO_3Na, R_2=H, n=6
6 R_1=SO_3Na, R_2=H, n=7
6a R_1=SO_3Na, R_2=Me, n=7
7 R_1=H, R_2=SO_3Na, n=6
8 R_1=H, R_2=SO_3Na, n=7
9 R_1=H, R_2=SO_3Na, n=8

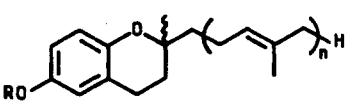


10 R=H, n=6
10a R=Me, n=6
11 R=SO_3Na, n=5
12 R=SO_3Na, n=6
13 R=SO_3Na, n=7

The MeOH-$CHCl_2$ (1:1) extract of the lyophilized sponge *Ircinia fasciculata* was partitioned between EtOAc and H_2O. The EtOAc extract was subjected to Si gel chromatography eluting with hexane, hexane/EtOAc mixtures, and C_6H_6/Me_2CO mixtures, and afforded three less polar compounds, **3**, **10**, **14**, and one highly polar compound, **6**.

Compound **3** was obtained as an oil, eims $[M]^+$ *m/z* 586, and analyzed for $C_{41}H_{62}O_3$. The study of its uv, ir, ^1H- and ^{13}C-nmr spectral data (7,11) led to its identification as 2-heptaprenyl-1,4-hydroquinone, which has previously been isolated from *Ircinia spinosula* (7) and *Hippospongia communis* (11).

Compound **10** was obtained as a viscous oil, $[\alpha]_D$ +3.6° (*c*=1, $CHCl_3$), eims $[M]^+$ *m/z* 584, and analyzed for



14 R=H, n=6
14a R=Me, n=6
15 R=H, n=1–6

[1]IICT Communication No. 3341.

$C_{41}H_{60}O_2$ by microanalysis. The peaks at 3420, 1580, and 1485 cm^{-1} in its ir spectrum indicated the presence of hydroxyl groups and an aromatic moiety in the molecule, which was further confirmed by formation of a monomethyl ether [**10a**] (CH_3I/K_2CO_3). Its uv spectrum is typical of a chromene (12), and this structure was supported by ^{13}C-nmr signals at δ 149.3 s (C-10), 146.6 s (C-7), 130.6 d (C-3), 122.6 d (C-4), 121.8 s (C-5), 116.5 d (C-6), 115.4 d (C-9), 112.9 d (C-8), and 78.0 s (C-2), as well as a base peak in its mass spectrum at *m/z* 161 corresponding to the 2-methyl-7-hydroxychromene ion. In the ^1H-nmr spectrum of compound **10**, the signals at δ 6.24 (d, J=10 Hz) and 5.57 (d, J=10 Hz) were assigned to olefinic protons of the chromene system. The signals at δ 6.61 (d, J=9 Hz), 6.53 (dd, J=9 and 3 Hz), and 6.42 (d, J=3 Hz) were due to aromatic protons. Further, the ^1H-nmr spectrum of **10** showed signals integrating for six olefinic protons at δ 5.10 and eight methyls at δ 1.66 (s, CH_3), 1.58 (br s, 6×CH_3), and 1.35 (s, CH_3). From the foregoing spectral data, the structure of compound **10** was established as 2-(hexaprenylmethyl)-2-methylchromenol [**10**]. An all-trans polyprenylic side-chain was recognized by comparison with previously reported data (7). Recently, the sulfate derivative [**12**] of compound **10** was isolated from *Sarcotragus spinulosus* (10).

Compound **14** was obtained as an oil, $[\alpha]_D$ +8° (c=0.11, $CHCl_3$), eims $[M]^+$ *m/z* 586, and analyzed for $C_{41}H_{62}O_2$ by microanalysis. Its ir spectrum showed peaks at 3410, 1665, 1620, and 1500 cm^{-1} consistent with the presence of phenolic hydroxyl and aromatic moieties. On methylation (CH_3I/K_2CO_3), compound **14** formed a monomethyl ether [**14a**], thus confirming the presence of a phenolic hydroxyl group. The ^1H-nmr spectrum of compound **14** was almost identical with that of **10**, except for the absence of the olefinic protons of the chromene moiety. It was evident from the mass spectrum that compound **14** is a dihydro derivative of **10**, which was supported by a fragment ion in the mass spectrum at *m/z* 163, corresponding to the 7-hydroxy-2-methylbenzopyran ion. Compound **14** was previously isolated as part of a mixture of chromanols [**15**] from the digestive glands of a dorid nudibranch, *Dendrodoris grandiflora* (13), but was not fully characterized.

Compound **6** was obtained as a colorless gum, positive fabms $[M+Na]^+$ *m/z* 711, and analyzed for $C_{41}H_{61}O_5SNa$ by microanalysis. The uv, ir, and ^1H- and ^{13}C-nmr spectra were almost similar to those of compound **5**, which was isolated from *Dysidea* sp. (9). However, compound **6** was a higher homologue of one isoprene unit and found to be a new compound. Further, it was observed that compound **6**, on standing for long periods in $CHCl_3$ or when in contact with Si gel, converted into compounds **3** and **14** in a 2:1 ratio, suggesting that compounds **3** and **14** may be artifacts obtained during the isolation process.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^1H-Nmr (200 MHz) and ^{13}C-nmr (50 MHz) spectra were recorded on a Varian Gemini spectrometer using TMS as internal standard. Chemical shifts are reported in ppm values and coupling constants (J) are expressed in Hz. Elemental analysis was carried out on a Perkin-Elmer 240C instrument. Optical rotations were measured with a Jasco Dip-370 polarimeter. Uv and ir spectra were recorded on Shimadzu and Perkin-Elmer 1310 spectrophotometers, respectively. Eims and fabms were recorded on Finnigan MAT 1020 and JEOL SX 102/DA-6000 instruments, respectively.

COLLECTION, EXTRACTION AND ISOLATION.—The sponge *Ircinia fasciculata* was collected in April 1993 at a depth of 40 feet by scuba diving, near Tuticorin in the Gulf of Mannar, India. A voucher specimen (IIC-124) has been lodged at the museum of the National Institute of Oceanography, Goa, India. The specimens were cut into thin slices and soaked in MeOH at the site of collection until work up. After the removal of MeOH, the sponge (500 g dry wt) was lyophilized and extracted with MeOH-CH_2Cl_2 (1:1) (2 liters). After evaporation of solvent under reduced pressure, the crude extract was partitioned between EtOAc and H_2O. Concentration of the organic layer resulted

in a gummy crude extract (16 g), which was subjected to Si gel (100–200 mesh) cc, eluting with hexane, hexane/EtOAc mixtures and C_6H_6/Me_2CO mixtures, to give four compounds, **3** (60 mg), **6** (400 mg), **10**, (500 mg), and **14** (28 mg).

2-HEPTAPRENYLHYDROQUINONE-1-SULFATE [**6**].—Compound **6** has obtained as a colorless gum; *anal.*, found C 71.49%, H 8.98%, S 4.70%, required for $C_{41}H_{61}O_5SNa$, C 71.47%, H 8.92%, S 4.65%; uv λ max ($CHCl_3$) nm (ε) 275 (3200), 241 (4900) nm; ir ν max (neat) 3440, 2910, 1660, 1610, 1580, 1480, 1440, 1255, 1040, 850, 735 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.11 (1H, d, J=9 Hz), 6.60 (1H, br s), 6.52 (1H, br d, J=9 Hz), 5.20 (1H, br s), 5.10 (6H, m), 3.36 (2H, br s), 1.9–2.15 (24H, m, 12×CH_2), 1.66 (3H, s, CH_3), 1.58 (21H, br s, 7×CH_3); ^{13}C nmr ($CDCl_3$) δ 153.9 s, 147.7 s, 137.4 s, 136.3 s, 135.2 s, 134.8 s (4C), 131.1 s, 124.0 d (6C), 123.0 d, 121.3 d, 116.5 d, 113.4 d, 39.7 t (7C), 28.2 t, 26.5 t (5C), 25.8 q, 17.8 q, 16.0 q (6C); fabms *m/z* 711 [(M+Na)$^+$].

Methylation of compound **6**.—Compound **6** (10 mg) was refluxed in dry Me_2CO (8 ml) with K_2CO_3 (300 mg) and methyl iodide (1 ml) for 12 h. After the usual workup, the product **6a** (8 mg) was purified by Si gel cc. *Anal.*, found C 71.81%, H 9.20%, S 4.57%, required for $C_{42}H_{63}O_5SNa$, C 71.76%, H 9.03%, S 4.56%; uv λ max ($CHCl_3$) (ε) 276 (3200), 241 (4800) nm; ir ν max (neat) 2910, 1650, 1600, 1470, 1440, 1250, 1040, 850, 730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.28 (1H, d, J=9 Hz), 6.63 (1H, br d, J=9 Hz), 6.62 (1H, br s), 5.25 (1H, br t, J=7 Hz), 5.1 (6H, m), 3.61 (3H, s, OCH_3), 3.38 (2H, br d, J=7 Hz), 1.9–2.15 (24H, m, 12×CH_2), 1.66 (3H, s, CH_3), 1.58 (21H, br s, 7×CH_3); fabms *m/z* 725 [(M+Na)$^+$].

2-(HEXAPRENYLMETHYL)-2-METHYLCHROMENOL [**10**].—Compound **10** was obtained as a colorless oil, [α]D +3.6° (c=1, $CHCl_3$); *anal.*, found C 84.24%, H 10.48%, required for $C_{41}H_{60}O_2$, C 84.19%, H 10.34%; uv λ max ($CHCl_3$) (ε) 330 (3800), 264 (5100), 243 (13,800) nm; ir ν max (neat) 3420, 2920, 1580, 1485, 1450, 1220 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.61 (1H, d, J=9 Hz), 6.53 (1H, dd, J=9 and 3 Hz), 6.42 (1H, d, J=3 Hz), 6.24 (1H, d, J=10 Hz), 5.57 (1H, d, J=10 Hz), 5.1 (6H, m), 1.9–2.15 (24H, m, 12×CH_2), 1.66 (3H, s, CH_3), 1.58 (18H, br s, 6×CH_3), 1.35 (3H, s, CH_3); ^{13}C nmr ($CDCl_3$) δ 149.3 s, 146.6 s, 135.1 s, 134.7 s (5C), 131.0 s, 130.6 d, 124.2 d (5C), 123.9 d, 122.6 d, 121.8 s, 116.7 d, 115.4 d, 112.9 d, 78.6 s, 40.7 t, 39.6 t (4C), 26.5 t (5C), 25.8 q, 25.6 q, 22.5 t, 17.5 q, 15.9 q (5C); eims *m/z* 584 (M^+), 515, 447, 379, 311, 243, 175, 161 (base peak), 69.

Methylation of compound **10**.—Compound **10** (50 mg) was refluxed in dry Me_2CO (10 ml) with K_2CO_3 (1 g) and methyl iodide (2 ml) for 12 h. After the usual workup, the product **10a** (50 mg) was purified by Si gel cc. *Anal.*, found C 84.31%, H 10.49%, required for $C_{42}H_{62}O_2$, C 84.22%, H 10.43%; [α]D +0.4° (c=1, $CHCl_3$); uv λ max ($CHCl_3$) (ε) 331 (3500), 263 (5400), 244 (11,800) nm; ir ν max (neat) 2920, 1580, 1490, 1450, 1260, 1040 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.68 (1H, d, J=9 Hz), 6.63 (1H, dd, J=9 and 3 Hz), 6.51 (1H, d, J=3 Hz), 6.30 (1H, d, J=10 Hz), 5.58 (1H, d, J=10 Hz), 5.10 (6H, m), 3.72 (3H, s, OCH_3), 1.9–2.15 (24H, m, 12×CH_2), 1.66 (3H, s, CH_3), 1.58 (18H, m, 6×CH_3), 1.37 (3H, s, CH_3); eims *m/z* 598 (M^+), 175 (base peak), 69.

2-(HEXAPRENYLMETHYL)-2-METHYLCHROMANOL [**14**].—Compound **14** was obtained as an oil, [α]D +8° (c=0.11, $CHCl_3$); *anal.*, found C 84.02%, H 10.74%, required for $C_{41}H_{62}O_2$, C 83.9%, H 10.65%; uv λ max ($CHCl_3$) (ε) 298 (4300), 242 (8500) nm; ir ν max (neat) 3410, 2920, 1665, 1620, 1500, 1450, 1380, 1220, 820 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.62 (1H, d, J=9 Hz), 6.55 (1H, dd, J=9 and 3 Hz), 6.51 (1H, d, J=3 Hz), 5.1 (6H, m), 2.71 (2H, t, J=7.5 Hz), 1.9–2.15 (24H, m, 12×CH_2), 1.78 (2H, t, J=7.5 Hz), 1.66 (3H, s, CH_3), 1.58 (18H, br s, 6×CH_3), 1.27 (3H, s, CH_3); ^{13}C nmr ($CDCl_3$) δ 148.5, 148.1, 135.3, 134.9 (4C), 131.4, 124.3 (5C), 122.0, 117.9, 115.4, 114.5, 75.6, 39.7 (4C), 39.4, 31.0, 26.7 (5C), 25.7, 24.2, 22.4, 22.2, 17.9, 15.0 (5C); eims *m/z* 586 (M^+), 517, 449, 381, 313, 245, 177, 163, 69 (base peak).

Methylation of compound **14**.—Compound **14** (8 mg) was refluxed in dry Me_2CO (8 ml) with K_2CO_3 (300 mg) and methyl iodide (1 ml) for 12 h. After the usual workup, the product **14a** (8 mg) was purified by Si gel cc. *Anal.*, found C 84.02%, H 10.78%, required for $C_{42}H_{64}O_2$, C 83.94%, H 10.73%; [α]D +0.6° (c=0.4, $CHCl_3$); uv λ max ($CHCl_3$) (ε) 297 (4,100), 241 (5,450) nm; ir ν max (neat) 2920, 1495, 1450, 1380, 1220, 1040 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.72 (1H, d, J=9 Hz), 6.66 (1H, d, J=9 and 3 Hz), 6.60 (1H, d, J=3 Hz), 5.10 (6H, m), 3.74 (3H, s, OCH_3), 2.73 (2H, t, J=7.5 Hz), 1.9–2.15 (24H, m, 12 × CH_2), 1.8 (2H, t, J=7.5 Hz), 1.66 (3H, s, CH_3), 1.58 (18H, br s, 6 × CH_3), 1.28 (3H, s, CH_3); eims m/z 600 (M^+), 531, 463, 395, 327, 259, 191, 177, 69 (base peak).

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