# New Anthraquinones from a Marine *Streptomyces* sp. – Isolation, Structure Determination and Biological Activities*

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Z. Naturforsch. **61b,** 1450 – 1454 (2006); received July 21, 2006

Two new anthraquinones were isolated from the marine *Streptomyces* sp. B8000, in addition to the known metabolites 3,8-dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**), indole-3-carboxylic acid, 2-desoxythymidin, indole-3-acetic acid methyl ester, N-acetyltyramine, and nicotinic acid. The structures of the new compounds were established as 8-hydroxy-3-methoxy-1-propylanthraquinone (**2a**) and 3,8-dihydroxy-1-propylanthraquinone (**2c**) on the basis of extensive spectroscopic analyses. Some derivatives were prepared and their biological activities were studied.

*Key words:* 1-Propyl-anthraquinones, Marine Streptomycetes

## Introduction

Marine natural products provide a rich source of chemical diversity that can be used to design and develop new, potentially useful therapeutic agents. In the continuation of our screening and search of bioactive compounds from microorganisms we have investigated the crude extract of the marine *Streptomyces* sp. B8000, which exhibits biological activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Streptomyces viridochromogenes* (Tü 57); the chemical screening of this extract showed many yellow bands under day light, which turned red with sodium hydroxide, indicating *peri*-hydroxyquinones.

## Results and Discussion

The marine *Streptomyces* sp. isolate B8000 was cultivated in $M_2{}^+$ medium on a linear shaker for four days at 28 °C. The yellowish culture broth was filtered under pressure to deliver water phase and mycelium, which gave several new and known compounds on work-up by chromatography on silica gel and Sephadex.

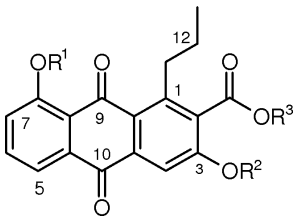
Compound **1a** was isolated as a yellow powder, which gave a violet to red colour reaction with 2 N NaOH indicating a *peri*-hydroxyquinone. The $^1$H NMR spectrum of **1a** showed a chelated hydroxyl signal at $\delta = 13.08$, the typical pattern of three adjacent aromatic protons, and a singlet at $\delta = 7.58$. The aliphatic region indicated only the presence of one methyl and two methylene groups at $\delta = 1.01$ (t), 1.60 (sext), and 3.30 (dd), respectively. The ESI mass spectrum showed a *pseudo*-molecule ion at $m/z = 325$ [M-H]$^-$, which afforded the molecular formula $C_{18}H_{14}O_6$by ESI HRMS data. In DMSO-$d_6$, the $^{13}$C NMR spectrum of **1a** showed 18 carbon signals, which – according to the DEPT spectrum – were due to four $sp^2$ methines, two methylenes, one methyl and eleven $sp^2$ quaternary carbon atoms, including three carbonyl signals at $\delta = 190.7$, 183.5 and 171.1. The first two were attributed to a quinone system and the latter to a carboxylic acid. According to AntiBase [1], these data are consistent with the structure of 3,8-dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**), an inhibitor of the activator protein-1 (AP-1) previously isolated from an *Actinomyces* sp. [2].

* Art. No. XXXIV on Marine Bacteria. For XXXIII, see C. B. Fondja Yao, M. Schiebel, E. Helmke, H. Anke, and H. Laatsch, Prefluostatin and New Urauchimycin Derivates Produced by Streptomycete Isolates, Z. Naturforsch. **61b**, 320 – 325 (2006).

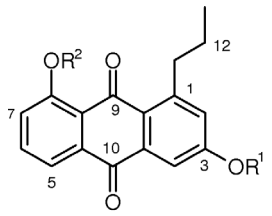
Table 1. $^{13}$C NMR and $^{1}$H NMR ($\delta$ in ppm, $J$ in Hz) in DMSO-$d_6$ of compounds **1a**, **2a** and **2c** at 600 MHz.

| Nr. | **1a** | | **2a** | | **2c** | |
|---|---|---|---|---|---|---|
| | C[a] | H | C[b] | H | C[b] | H |
| 1 | 147.4 | | 149.6 | | 149.8 | |
| 2 | 132.3 | | 123.1 | 7.28 (d, 2.8) | 124.2 | 7.03 (d, 2.6) |
| 3 | 163.4 | | 163.1 | | 163.1 | |
| 4 | 113.4 | 7.58 (s) | 110.1 | 7.59 (d, 2.8) | 112.5 | 7.48 (d, 2.6) |
| 4a | 138.5 | | 137.1 | | 137.3 | |
| 5 | 119.5 | 7.62 (dd, 1.2, 9.2) | 118.3 | 7.67 (dd, 1.3, 7.5) | 118.1 | 7.63 (dd, 1.3, 7.5) |
| 6 | 136.8 | 7.70 (t, 8.1) | 136.1 | 7.76 (dd,7.6, 8.1) | 135.8 | 7.71 (t, 7.8) |
| 7 | 125.5 | 7.33 (dd, 1.2, 9.0) | 124.3 | 7.35 (dd,1.3, 8.1) | 124.1 | 7.30 (dd, 1.3, 8.1) |
| 8 | 160.2 | 13.08 (s, 8-OH) | 161.5 | 12.90 (s, 8-OH) | 161.5 | 13.09 (s, 8-OH) |
| 8a | 118.1 | | 116.6 | | 116.6 | |
| 9 | 190.7 | | 189.3 | | 189.0 | |
| 9a | 123.7 | | 123.3 | | 121.4 | |
| 10 | 183.5 | | 182.1 | | 182.4 | |
| 10a | 133.8 | | 132.5 | | 132.5 | |
| 11 | 36.0 | 3.30 (dd, 7.5) | 37.1 | 3.19 (dd, ∼ 7.5) | 37.2 | 3.10 (dd, ∼ 7.5) |
| 12 | 25.1 | 1.60 (sext) | 23.4 | 1.62 (sext) | 23.3 | 1.61 (sext) |
| 13 | 15.1 | 1.01 (t, 7.3) | 14.1 | 1.00 (t, 7.3) | 14.1 | 0.99 (t, 7.3) |
| 14 | 171.1 | | 55.9 | 3.98 (s) | – | – |

[a] $^{13}$C measured at 75 MHz; [b] $^{13}$C measured at 125 MHz.



**1a:** $R^1$ = H, $R^2$ = H, $R^3$ = H
**1b:** $R^1$ = Ac, $R^2$ = H, $R^3$ = H
**1c:** $R^1$ = Ac, $R^2$ = $CH_3$, $R^3$ = $CH_3$



**2a**: $R^1 = CH_3$, $R^2 = H$
**2b**: $R^1 = CH_3$, $R^2 = Ac$
**2c**: $R^1 = H$, $R^2 = H$
**2d**: $R^1 = CH_3$, $R^2 = CH_3$

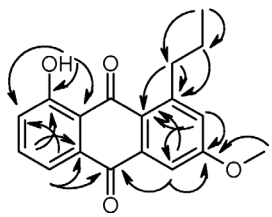
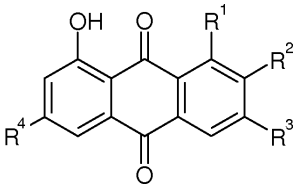


Fig. 1. HMBC correlation in compound **2a** and **2c**.

As our data showed some deviations from the published values, derivatives **1b** and **1c** were prepared by acetylation and methylation, which confirmed, however, the published structure by NMR measurements.

A second yellow *peri*-hydroxyquinone **2a** had the formula $C_{18}H_{16}O_4$ (by ESI HRMS). The $^{1}$H NMR data (Table 1) showed signals of a chelated hydroxy group at $\delta = 12.90$, a 1,2,3-trisubstituted aromatic ring and a propyl group as in **1a**. Instead of the H-4 singlet in **1a** at $\delta = 7.58$, *meta*-coupled doublets appeared at $\delta = 7.59$ and 7.28, suggesting a decarboxylation of **1a**; accordingly, the carboxyl signal of **1a** at $\delta = 171.1$ was missing, but a 3H singlet at $\delta = 3.98$ with a corresponding $^{13}$C NMR signal at $\delta = 55.9$ indicated an additional methoxy group. The benzylic methylene signal ($\delta = 3.19$) of the *n*-propyl moiety showed $^{2}J$ and $^{3}J$ correlations with C-1 ($\delta = 123.1$) and C-9a ($\delta = 123.3$); the *meta*-coupled proton signal at $\delta = 7.28$ (H-2) was correlated to C-9a ($\delta = 123.3$) and C-4 ($\delta = 110.1$). The signal of H-4 ($\delta = 7.58$), which showed *meta*-coupling with H-2, displayed interactions with C-3 (163.1) and C-10 (182.1). From the DEPT spectra and the foregoing data, the structure was established as the new 8-hydroxy-3-methoxy-1-propylanthraquinone (**2a**). Acetylation gave 8-acetoxy-3-methoxy-1-propylanthraquinone (**2b**).

The molecular formula of a third yellow quinone **2c** was established by ESI HRMS as $C_{17}H_{14}O_4$. The IR spectrum revealed the presence of hydroxyl and carbonyl groups by signals at 3500 and 1654 cm$^{-1}$, respectively. The $^{1}$H and $^{13}$C NMR spectra and the chemical and physical properties were similar to those of **1a** and 8-hydroxy-3-methoxy-1-propylanthraquinone (**2a**), including a highly deshielded signal of a chelated hydroxyl group at $\delta = 13.09$ and an AB system at $\delta = 7.03$ and 7.48 (d, $J = 2.6$ Hz). The spectroscopic data of **2a** and **2c** differed by the absence of the methoxy signal in **2c**. The NMR data (Table 1) and $^{1}$H-$^{1}$H COSY, HMQC and HMBC (Fig. 1) experiments were used to determine the structure as 3,8-dihydroxy-1-propylanthraquinone (**2c**), which is described here for the first time. Methylation of com-




**3a**: $R^1 = n$-Pr, $R^2 = H$, $R^3 = R^4 = OH$
**3b**: $R^1 = n$-Bu, $R^2 = COOH$, $R^3 = R^4 = H$
**3c**: $R^1 = CH_2CH_2$-*i*Pr, $R^2 = COOH$, $R^3 = R^4 = OH$

pound **2c** with diazo methane delivered the dimethoxy derivative **2d**.

Compounds **1a**, **2a** and **2c** belong to the rare group of naturally occurring $\alpha$-alkylanthraquinones like R1128-A (**3a**) [3], YT127A (**3b**), and YT128A (**3c**) [4]. Native compounds of this group became known first as insect pigments [5] and later as constituents of a few plants [6]. They exhibit various biological activities, *e. g.* as nonsteroidal estrogen receptor antagonists [3] or potent glucose-6-phosphate translocase inhibitors [4].

The antifungal and antibacterial activities of **1a**–**1c** and **2a**–**2d** were determined using the agar diffusion method with 9 mm paper disks loaded with 20 or 40 $\mu$g of each compound. Only 3,8-dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**) and 8-hydroxy-3-methoxy-1-propylanthraquinone (**2a**) showed moderated activities against *Staphylococcus aureus* and *Streptomyces viridochromogenes* (Tü 57) at 40 $\mu$g/disk with 14 mm and 12 mm inhibition diameter, respectively, and no activities against fungi.

## Experimental Section

NMR spectra were measured on Varian Unity 300 (300.145 MHz) and Varian Inova 500 (499.876 MHz) spectrometers. ESI MS were recorded on a Finnigan LCQ with quaternary pump Rheos 4000 (Flux Instrument). ESI HR mass spectra were measured on a Micromass LCT spectrometer coupled with a HP 1100 HPLC with a Diode Array Detector. EI MS were recorded on a Finnigan MAT 95 spectrometer (70 eV) with perfluorokerosine as reference substance for HREI MS. IR spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer from KBr pellets, and UV/vis spectra on a Perkin-Elmer Lamda 15 UV/vis spectrometer. Preparative HPLC was performed using an RP18 column (Eurochrom Eurospher RP 100-C18, 5 $\mu$m) with a 202 nm detector wavelength (JASCO variable wavelength monitor). Flash chromatography was carried out on silica gel 230–400 mesh. Thin layer chromatography (TLC) was performed on Polygram SIL G/$UV_{254}$ (Macherey-Nagel & Co.). $R_f$ values were measured on Polygram SIL G/UV254 (Macherey-Nagel & Co.) with $CH_2Cl_2$/MeOH when not stated otherwise. Size exclusion chromatography was done on Sephadex LH-20 (Pharmacia).

### *Taxonomic characteristics of strain B8000*

The *Streptomyces* strain B8000 has been derived from the sediment of the Laguna de Terminos at the Gulf of Mexico and was isolated on chitin medium [7] containing 50% natural seawater with incubation at 18 °C.

The almost complete 16S rRNA gene sequence of the strain B8000 shows 99% similarity to the gene sequence of *Streptomyces sindenensis*. The strain forms a yellow-brown substrate mycelium and a yellow greenish aerial mycelium with straight to flexuous (Rectiflexibiles) spore chains on yeast extract-malt extract agar. The reference culture of B8000 is maintained on yeast extract-malt extract agar in the Collection of Marine Actinomycetes at the Alfred-Wegener-Institute for Polar and Marine Research in Bremerhaven.

### *$M_2{}^+$ Medium*

Malt extract (10 g), yeast extract (4 g) and glucose (4 g) were dissolved in artificial seawater (0.5 L) and tap water (0.5 L). The medium was set to p$H = 7.8$ with 2 N NaOH and sterilized for 33 min at 121 °C. After sterilization, an end pH of 7.0 of the medium was attained.

### *Fermentation, extraction and isolation*

100 1-L-Erlenmeyer flasks each containing 250 mL of $M_2{}^+$ medium were inoculated with a 5 d old agar culture of *Streptomyces* sp. strain B8000. The flasks were kept at 28 °C for 120 h at 95 rpm. After harvesting, Celite ($\sim$ 1 kg) was added. By filtration using a filter press, the liquid phase was separated and extracted four times with ethyl acetate; the mycelium was extracted three times with acetone (5 L); the acetone was removed *in vacuo*. The aqueous phase was chromatographed on a XAD-16 column and the organic compounds were eluted with MeOH; after evaporation, the residue was extracted with ethyl acetate. Chromatography of this extract (3.2 g) on Sephadex LH-20 using $CH_2Cl_2$/50% MeOH delivered three fractions.

Fraction I was further separated on HPLC using MeCN/80% $H_2O$ and delivered 3,8-dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**, 18 mg) as a yellow powder. Fractions II and III delivered in a similar way indol-3-acetic acid methyl ester (4.3 mg) [8], indol-3-carboxylic acid (2.1 mg) [9], 2-desoxythymidin (1.7 mg) [10], and N-acetyltyramine (6.3 mg) [11].

Chromatography (see above) of the acetone extract of the mycelium (0.98 g) delivered 3,8-dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**, 3.5 mg), indol-3-carboxylic acid (1.8 mg), and indol-3-acetic acid methyl es-

ter (4.2 mg). The ethyl acetate extract of the mycelium (1.23 g) delivered 8-hydroxy-3-methoxy-1-propylanthraquinone **2a** (2.8 mg), 3,8-dihydroxy-1-propylanthraquinone (**2c**, 1.4 mg), and nicotinic acid (2.0 mg) [12].

*3,8-Dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**)*

Yellow powder, $R_f = 0.39$ ($CH_2Cl_2$/15% MeOH), – $R_t$ = 12.2 min (HPLC eluted with MeCN/80% $H_2O$). – $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 13.08$ (s, 1H, 8-OH), 7.70 (t, $J$ = 8.1 Hz, 1H, 6-H), 7.62 (dd, $J = 1.2$, 9.2 Hz, 1H, 5-H), 7.58 (s, 1H, 4-H), 7.33 (dd, $J = 1.2$, 9.0 Hz, 1H, 7-H), 3.30 (dd, $J = J' = 7.5$ Hz, 2H, 11-$H_2$), 1.60 (sext, 2H, 12-$H_2$), 1.01 (t, $J = 7.3$ Hz, 3H, 13-$H_3$). – $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 190.7$ ($C_q$-9), 183.5 ($C_q$-10), 171.1 (COOH), 163.4 ($C_q$-3), 160.2 ($C_q$-8), 147.4 ($C_q$-1), 138.5 ($C_q$-4a), 136.8 (CH-6), 133.8 ($C_q$-10a), 132.3 ($C_q$-2), 125.5 (CH-7), 123.7 ($C_q$-9a), 119.5 (CH-5), 118.1 ($C_q$-8a), 113.4 (CH-4), 36.0 ($CH_2$-11), 25.1 ($CH_2$-12), 15.1 ($CH_3$-13). – (-)-ESI MS: *m/z* (%) = 673 ([2M-2H+Na]$^-$, (44), 325 ([M-H]$^-$, 100). – (-)-ESI HRMS: 325.07176 ([M-H]$^-$, calcd. 325.07175 for $C_{18}H_{13}O_6$).

*8-Hydroxy-3-methoxy-1-propylanthraquinone (**2a**)*

Yellow solid, $R_f = 0.67$ ($CH_2Cl_2$). – UV/vis (MeOH): $\lambda_{max}$ $(\log\varepsilon)$ = 256 (3.56), 395 (3.01) nm. – IR (KBr): $\nu$ = 3443, 2927, 2855, 2361, 2343, 1669, 1633, 1596, 1458, 1353, 1317, 1245, 1214, 1138, 1028, 784, 756, 668 cm$^{-1}$. – $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 12.90$ (s br, 1H, 8-OH), 7.76 (dd, $J$ = 7.6, 8.1 Hz, 1H, 6-H), 7.67 (dd, $J = 1.3$, 7.5 Hz, 1H, 5-H), 7.59 (d, $J = 2.8$ Hz, 1H, 4-H), 7.35 (dd, $J = 1.3$, 8.1 Hz, 1H, 7-H), 7.28 (d, $J = 2.8$ Hz, 2-H), 3.98 (s, 3H, -$OCH_3$), 3.19 (dd, $J = J' = 7.5$ Hz, 2H, 11-$H_2$), 1.62 (sext, $J = 7.5$ Hz, 2H, 12-$H_2$), 1.00 (t, $J = 7.3$ Hz, 3H, 13-$H_3$). – $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 189.3$ ($C_q$-9), 182.1 ($C_q$-10), 163.1 ($C_q$-3), 161.5 ($C_q$-8), 149.6 ($C_q$-1), 137.1 ($C_q$-4a), 136.1 (CH-6), 132.5 ($C_q$-10a), 124.3 (CH-7), 123.3 ($C_q$-9a), 123.1 (CH-2), 118.3 (CH-5), 116.6 ($C_q$-8a), 110.1 (CH-4), 55.9 ($C_q$-O), 37.1 ($CH_2$-11), 23.4 ($CH_2$-12), 14.1 ($CH_3$-13). – EI MS (70 eV): *m/z* (%) = 296 ($M^+$, 84), 278 (100), 263 (20), 235 (8), 168 (12), 149 (10), 139 (18). – (+)-ESI MS: *m/z* (%) = 593 ([2M+H]$^+$, 80), 297 ([M+H]$^+$, 100). – (+)-ESI HRMS: 297.11214 ([M+H]$^+$, calcd. 297.11215 for $C_{18}H_{17}O_4$).

*3,8-Dihydroxy-1-propylanthraquinone (**2c**)*

Yellow solid, $R_f = 0.70$ ($CH_2Cl_2$/5% MeOH). – UV/vis (MeOH): $\lambda_{max}$ $(\log\varepsilon)$ = 260 (3.89), 396 (3.44) nm. – IR (KBr): $\nu$ = 3406, 2967, 2927, 2856, 1654, 1633, 1603, 1473, 1456, 1371, 1323, 1285, 1239, 1215, 1157, 834, 810, 783, 756 cm$^{-1}$. – $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta = 13.09$ (s br, 1H, 8-OH), 7.71 (t, $J = 7.8$ Hz, 1H, 6-H), 7.63 (dd, $J = 1.3$, 7.5 Hz, 1H, 5-H), 7.48 (d, $J = 2.6$ Hz, 1H, 4-H), 7.30 (dd, $J = 1.3$, 8.1 Hz, 1H, 7-H), 7.03 (d, $J = 2.6$ Hz, 1H, 2-H), 3.10 (dd, $J = J' = 7.5$ Hz, 2H, 11-$H_2$), 1.63 (sext, $J = 7.5$ Hz, 2H, 12-$H_2$), 0.99 (t, $J = 7.3$ Hz, 3H, 13-$H_3$). – $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 189.0$ ($C_q$-9), 182.4 ($C_q$-10), 163.1 ($C_q$-3), 161.5 ($C_q$-8), 149.8 ($C_q$-1), 137.3 ($C_q$-4a), 135.8 (CH-6), 132.5 ($C_q$-10a), 124.2 (CH-2), 124.1 (CH-7), 121.4 ($C_q$-9a), 118.1 (CH-5), 116.6 ($C_q$-8a), 112.5 (CH-4), 37.2 ($CH_2$-11), 23.3 ($CH_2$-12), 14.1 ($CH_3$-13). – EI MS (70 eV): *m/z* (%) = 282 ([M]$^+$, 100), 264 (95), 249 (22), 247 (20), 221 (8), 127 (10). – (-)-ESI MS: *m/z* (%) = 562 ([2M-H]$^-$, 20), 281 ([M-H]$^-$, 100). – (-)-ESI HRMS: 281.08188 ([M-H]$^-$, calcd. 281.08191 for $C_{17}H_{13}O_4$).

*8-Acetoxy-3-hydroxy-1-propylanthraquinone-2-carboxylic acid (**1b**) and 8-acetoxy-3-methoxy-1-propylanthraquinone (**2b**)*

3,8-Dihydroxy-1-propylanthraquinone-2-carboxylic acid (**1a**, 3.17 mg) or 8-hydroxy-3-methoxy-1-propylanthraquinone (**2a**, 1.0 mg), respectively, were dissolved in pyridine (0.2 mL) and acetanhydride (0.5 mL). The solution was stirred for 4 h at 20 °C. Hydrolysis and work-up gave **1b** (3.0 mg, 84%) and **2b** (0.9 mg, 79%), respectively. – **1b**: Yellow solid, $R_f = 0.42$ ($CH_2Cl_2$/15% MeOH). – $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 8.60$ (s br, 1H, OH), 8.04 (dd, $J = 1.2$, 7.6 Hz, 1H, 5-H), 7.85 (t, $J = 7.8$ Hz, 1H, 6-H), 7.57 (dd, $J = 1.2$, 7.8 Hz, 1H, 7-H), 7.54 (s, 1H, 4-H), 2.98 (t, $J = 7.4$ Hz, 2H, 11-$H_2$), 2.38 (s, 3H, $CH_3$-COO), 1.55 (sext, 2H, 12-$H_2$), 0.99 (t, $J = 7.3$ Hz, 3H, 13-$H_3$); COO*H* not assigned. – (-)-ESI MS: *m/z* (%) = 757 ([2M-2H+Na]$^-$, 36), 734 ([2M-H]$^-$, 20), 367 ([M-H]$^-$, 84). – (-)-ESI HRMS: 367.08233 ([M-H]$^-$, calcd. 367.08234 for $C_{20}H_{15}O_7$).

**2b**: Yellow solid, $R_f = 0.7$ ($CH_2Cl_2$). – $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 8.08$ (dd, $J = 1.3$, 7.8 Hz, 1H, 5-H), 7.84 (t, $J = 7.6$ Hz, 1H, 6-H), 7.59 (dd, $J = 1.3$, 7.6 Hz, 1H, 7-H), 7.52 (d, $J = 2.8$ Hz, 1H, 2-H), 7.22 (d, $J = 2.8$ Hz, 1H, 4-H), 3.95 (s, 3H, $CH_3$-O), 3.05 (dd, $J = J' = 7.5$ Hz, 2H, 11-$H_2$), 2.39 (s, 3H, $CH_3$-COO), 1.60 (sext, 2H, 12-$H_2$), 0.99 (t, $J = 7.4$ Hz, 3H, 13-$H_3$). – EI MS (70 eV): *m/z* (%) = 338 ([M]$^+$, 36), 296 (86), 278 (100), 218 (17), 139 (18). – (+)-ESI HRMS: 339.12276 ([M+H]$^+$, calcd. 339.12271 for $C_{20}H_{19}O_5$).

*8-Acetoxy-3-methoxy-1-propylanthraquinone-2-carboxylic acid methyl ester (**1c**) and 3,8-dimethoxy-1-propylanthraquinone (**2d**)*

Compounds **1b** (1.5 mg) and **2c** (0.5 mg), respectively, were dissolved in methylene chloride (2 ml) and an etherial diazomethane solution (2 ml) was added at −20 °C. Immediate evaporation to dryness gave **1c** (1.5 mg, 93%) and **2d**

(0.5 mg, 91%), respectively. – **1c**: Yellow solid, $R_f = 0.44$ ($CH_2Cl_2$/15% MeOH). – $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 8.08$ (dd, $J = 1.2$, 7.8 Hz, 1H, 5-H), 7.89 (t, $J = 7.9$ Hz, 1H, 6-H), 7.68 (s, 1H, 4-H), 7.60 (dd, $J = 1.2$, 8.0 Hz, 1H, 7-H), 4.00 (s, 3H, $CH_3$-O), 3.88 (s, 3H, $CH_3$-O), 2.88 (dd, $J = J' = 7.2$ Hz, 2H, 11-$H_2$), 2.38 (s, 3H, $CH_3$-COO), 1.52 (sext, 2H, 12-$H_2$), 0.99 (t, $J = 7.2$ Hz, 3H, 13-$H_3$). – (+)-ESI MS: *m/z* (%) = 814 ([2M+Na], 52), 419 ([M+Na]$^+$, 16). – (+)-ESI HRMS: 419.11012 ([M+Na]$^+$, calcd. 419.11014 for $C_{22}H_{20}O_7Na$).

**2d**: Yellow solid, $R_f = 0.76$ ($CH_2Cl_2$/5% MeOH). – $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 7.58$ (dd, $J = 1.2$, 7.5 Hz, 1H, 5-H), 7.52 (dd, $J = 1.2$, 7.6 Hz, 1H, 7-H), 7.50 (t, $J = 7.5$ Hz, 1H, 6-H), 7.18 (d, $J = 2.7$ Hz, 1H, 4-H), 7.16 (d, $J = 2.7$ Hz, 1H, 2-H), 3.85 (s, 3H, $CH_3$-O), 3.70 (s, 3H, $CH_3$-O), 2.81 (m, 2H, 11-$H_2$), 1.58 (sext, $J = 7.5$ Hz, 2H, 12-$H_2$), 0.98 (t, $J = 7.5$ Hz, 3H, 13-$H_3$). – EI MS (70 eV): *m/z* (%) = 310 ([M]$^+$, 37), 294 (76), 282 (80), 267 (68), 248 (38), 165.1 (16), 115.1 (18), 63 (20). – (+)-ESI HRMS: 311.12779 ([M+H]$^+$, calcd. 311.12781 for $C_{19}H_{19}O_4$).

*Acknowledgements*

We thank R. Machinek for the NMR spectra, H. Frauendorf for the mass spectra, and Mrs. F. Lissy for microbiological work. H. M. P. P. is thankful to the DAAD (Deutscher Akademischer Austauschdienst) for a research grant.

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Druck: AZ Druck und Datentechnik GmbH, Kempten