Echinamines A and B, First Aminated Hydroxynaphthazarins from the Sea Urchin *Scaphechinus mirabilis*

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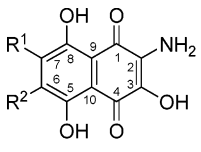
Received December 23, 2004

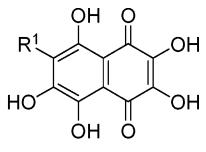
Two new spinochromes, echinamines A (**1**) and B (**2**), were isolated from the sea urchin *Scaphechinus mirabilis*. Compounds **1** and **2** represent the first examples of natural polyhydroxynaphthazarins with a primary amine group. The structures of **1** and **2** were established by analysis of spectroscopic data and synthesis of their dimethyl ethers.

From a large number of natural products containing a 1,4-naphthoquinone moiety, a group of 5,8-dihydroxy-1,4-naphthoquinones, known as naphthazarins, is of particular interest.[1−3] Hydroxynaphthazarins along with derivatives of juglone (5-hydroxy-1,4-naphthoquinones) were first isolated from sea urchins and named "spinochromes". Some spinochromes, such as echinochrome (**3**), and their synthetic analogues are known today as biologically active compounds that present antimicrobial,[4] antialgal,[5] cardioprotective,[6] and antioxidant[7] activities. Many polyhydroxyquinones of the spinochrome type have now been isolated from other marine sources: algae, sponges, and fungi.[3,8] Known quinonoid pigments have been reisolated many times from sea urchins, but new compounds of this series have not been identified in the last two decades.[8]

In the course of our search for new biologically active quinones from sea urchins, specimens of the sea urchin *Scaphechinus mirabilis* have been studied. Considering that sea urchin quinones generally occur in pigment granules associated with Ca^{2+}, Mg^{2+}, and proteins, EtOH containing 10% H_2SO_4 has been used for extraction. After evaporation of EtOH, the residue was partitioned between H_2O and $CHCl_3$. Pigments were extracted from the $CHCl_3$ phase with aqueous Na_2CO_3, and after acidification and extraction with $CHCl_3$, an organic layer containing quinones was obtained. Analysis by HPLC of the $CHCl_3$ extract indicated four major peaks. The peaks with retention times (t_R) of 5.7 and 11.1 min were identified by direct comparison with authentic samples of spinochrome D (**4**) and echinochrome A (**3**), respectively. The other two peaks (t_R 12.7 and 13.6 min) did not coincide with retention times of other known spinochromes. They were successfully separated by repeated low-pressure reversed-phase column chromatography of the quinonoid extract on a TSK gel Toyopearl HW-40 with 20−60% EtOH containing 0.6% HCOOH as eluent. Compound **3** was partially purified by Sephadex LH-20 chromatography using 7:1 $CHCl_3$/EtOH as eluent.



1: R^1 = OH, R^2 = Et
2: R^1 =Et, R^2 = OH



3: R^1 = Et
4: R^1 = H

The structures of known compounds **4** [2.5×10^{-4} % based on sea urchin wet weight (w/w)] and **3** (7.3×10^{-3} % w/w) were confirmed by comparison of their spectral data with literature data.[9] The structures of the new pigments **1** and **2** were elucidated by analysis of spectroscopic data and by comparison of t_R by HPLC analysis and spectroscopic data of dimethyl ethers of **1** and **2** with synthetic compounds 3-amino-7-ethyl-5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone and 2-amino-7-ethyl-5,8-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone, respectively.

Compound **1** (1.5×10^{-4} % w/w) was obtained as a dark brown powder, while **2** (4×10^{-4} % w/w) was obtained as dark brown needles. LREI mass spectra of **1** and **2** showed peaks of the molecular ion $[M]^+$ at *m/z* 265, one atomic mass unit less than the molecular ion of **3**. This molecular ion is in agreement with a molecular formula of $C_{12}H_{11}NO_6$ that was verified by HREIMS (found *m/z* 265.0598; calcd 265.0586). UV/vis spectra of **1** and **2** showed absorption maxima at λ_{max} 274, 345, and 479 nm, corresponding to those for polyhydroxynaphthazarines.[1,9] In alkaline EtOH, the absorption maximum at λ_{max} 345 nm shifted to 400 nm, as for echinochrome A.

The ^{13}C NMR spectra of **1** and **2** exhibited 12 carbon signals: two aliphatic carbons (δ 12.9, 16.3 in **1** and 12.9, 16.6 in **2**), three quaternary carbons (δ 102.6, 108.6, 126.5 and 103.9, 107.6, 124.4, respectively), two carbonyl carbons (δ 177.4, 181.7 and 176.6, 178.7, respectively), and seven quaternary oxygen- or nitrogen-bonded carbons (Table 1). The ^1H NMR spectra of **1** and **2** showed signals due to two chelated hydroxy groups and two rapidly D_2O exchangeable hydroxyl groups. The IR spectra of **1** and **2** showed an absorption band at 1603 cm^{-1}, which confirmed the presence of chelated carbonyl groups. Moreover, the ^1H NMR spectra of **1** and **2** showed resonance signals at δ 5.36 (2H) and 5.81 (2H), respectively, which were attributed to the protons of a primary amino group.[10] Thus, both **1** and **2** are isomeric 5,8-dihydroxy-1,4-naphthoquinones having an ethyl radical, an amino, and two β-hydroxyl groups located in different positions.

In the HMBC spectra of **1** and **2**, the amino group protons at δ 5.36 and 5.81 showed J_{C-H} long-range connectivities with corresponding carbonyl carbon atoms C-4 and C-1, while methylene protons of the ethyl group at δ 2.69 and 2.67 were coupled with the carbon atoms C-5 and C-8, respectively. These data unequivocally indicated that the amino group was attached to the quinonoid moiety and the ethyl group was located in the benzenoid ring of molecules **1** and **2**.

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10.1021/np049585r CCC: $30.25 © 2005 American Chemical Society and American Society of Pharmacognosy
Published on Web 08/20/2005

Table 1. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and HMBC Data of Echinamines A (**1**) and B (**2**) and Echinochrome (**3**)[a]

	1		**2**			**3**	
atom no.	δ_H (*J* Hz)	δ_C	δ_H (*J* Hz)	δ_C	HMBC[b] (H→C)	δ_H (*J* Hz)	δ_C
1		181.7		176.6			178.3[d]
2		137.0		134.8			141.8
3		132.4		135.1			139.8
4		177.4		178.7			176.8[d]
5		154.0		154.0			154.4
6		152.3		151.4			153.9
7		126.5		124.4			126.0
8		161.0		163.2			164.6
9		102.6		103.9			103.3
10		108.6		107.6			107.7
11	2.69 q (*7.5*) 2H	16.3	2.67 q (*7.5*) 2H	16.6	C-6, C-7, C-8, C-12	2.69 q (*7.5*) 2H	16.7
12	1.14 t (*7.5*) 3H	12.9	1.13 t (*7.5*) 3H	12.9	C-7, C-11	1.14 t (*7.5*) 3H	12.8
NH_2-2			5.81 br s 2H				
NH_2-3	5.36 br s 2H						
OH-2	8.49 br s					9.05 br s[c]	
OH-3			8.36 br s			9.05 br s[c]	
OH-5	12.62 br s		13.02 s			12.47 br s	
OH-6	9.20 br s		9.44 br s			9.05 br s[c]	
OH-8	13.03 s		13.02 s		C-7, C-8, C-9	13.02 s	

[a] Recorded in acetone-d_6. Assignments were supported by a combination of COSY, HMQC, and HMBC experiments. [b] Measured at 500 MHz. [c] Overlapped signal. [d] Signals are interchangeable with each other.

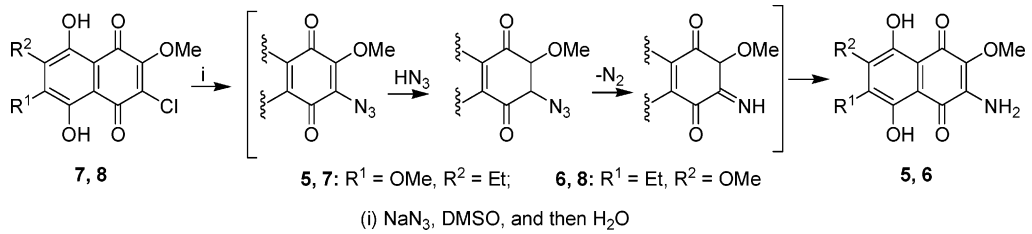

Figure 1. Synthesis of compounds **5** and **6**.

Therefore, we have concluded that structures of two new pigments were 3-amino-7-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone and 2-amino-7-ethyl-3,5,6,8-tetrahydroxy-1,4-naphthoquinone. However, the analysis of only spectroscopic data did not allow us to unambiguously assign which isomeric structure corresponded to either **1** or **2**.

To establish unequivocally the structures of **1** and **2**, we prepared the methyl ethers **5** and **6** from chloroethyldimethoxynaphthazarins **7** and **8**. The nucleophilic substitution of the chlorine atom by an azido group in both **7** and **8** in the presence of NaN_3 (excess) in DMSO, followed by treatment with H_2O, gave the expected 3-amino-7-ethyl-5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone (**5**) and 2-amino-7-ethyl-5,8-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (**6**), respectively, in moderate yield (Figure 1). The products **5** and **6** are the result of the reduction of the corresponding azido-1,4-naphthoquinone (derived from **7** and **8**) with hydrazoic acid that has arisen in the course of the treatment of the reaction mixture with water.[10]

The structures of **1** and **2** were rigorously established by comparison of methylated **1** and **2** with the synthetic compounds **5** and **6**, including their ^{1}H NMR spectra, t_R in HPLC analysis, R_f in TLC analysis, and mp.

The structures of both echinamines A and B were confirmed by treating echinochrome A (**3**) with a solution of concentrated ammonia. Reaction of **3** with NH_3 (excess) in EtOH resulted in a 1:1 mixture of **1** and **2** in 95% yield. Most likely, the conversion of **3** (in tautomeric 1,2-quinonoid forms) into **1** and **2** may be explained by an addition−elimination mechanism.[11]

Naturally occurring quinones with a primary amino group are rare. Only a few compounds having a primary amino group attached to a quinonoid skeleton have been isolated from marine sponges,[12] mushrooms,[13] and higher plants.[14] Aminoquinones **1** and **2** differ from the above-mentioned aminoquinones by the presence of several hydroxyl groups in a naphthoquinonoid skeleton. In contrast with other brightly colored pigments of sea urchins, compounds **1** and **2** have a toneless dun color similar to the color of spinochrome salts. Column chromatography zones and TLC R_f of compounds **1** and **2** overlapped and coincided with echinochrome A, and HPLC analysis allowed only to make distinctions between these pigments.

In the sea urchin crude extract, compounds **1** and **2** were detected in a 1:4 ratio (HPLC), and their content was from 1 to 4% of the total quinone amount. In addition, aminoquinones **1** and **2** can be converted into echinochrome on acid hydrolysis, like simple aminonaphthaquinone into lawsone.[3] In our hands, a 1:1 mixture of **1** and **2** reacted with EtOH + 10% H_2SO_4 for 1 day, giving a mixture of **1** (45%), **2** (40%), and **3** (15%). This implies that both **1** and **2** could serve as an additional source of compound **3** during isolation. However, extraction of urchins with fresh acid-free EtOH yielded a crude extract with **1**, **2**, and **3** in 15:40:45% ratio, respectively. This result obviously indicated that aminohydroxyhaphthazarins **1** and **2** were naturally occurring naphthoquinones produced by the sea urchin *S. mirabilis* and not artifacts of isolation.

Compounds **1**−**4** were tested for their ability to scavenge the stable 1,1-diphenyl-2-picrylhydrazyl radical (DPPH).[15] Echinamines A and B, echinochrome A, and spinochrome D were shown to have 50% radical scavenging ability (EC50) at a concentration of 0.01 mM against 0.1 mM DPPH in ethanol. The DPPH scavenging assay not only reveals antiradical properties of polyphenols but also estimates the reactivity of hydroxyl and amino groups. The rate and the activation parameters between DPPH and polyphenol at the early stage of the reaction are known to

be dependent on the number of phenolic hydroxyl and amino groups. Hence, **1** and **2** as well as echinochrome can donate five electrons/hydrogens easily and reveal high antiradical ability.

Experimental Section

General Experimental Procedures. Melting points were determined with a Boetius apparatus and are uncorrected. UV spectra were recorded on a Cecil CE 7250 spectrophotometer. IR spectra were recorded on a Bruker Vector-22 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX-300 or DRX-500 NMR spectrometers at ^{1}H and ^{13}C frequencies of 300 and 75 MHz, or 500 and 125 MHz, respectively. Chemical shifts were referenced to TMS (δ = 0.0 ppm). HMBC spectra were optimized for 10 Hz coupling. EIMS were measured on a LKB-9000S mass spectrometer at 70 eV. HREIMS were measured on an AMD-604S spectrometer at 70 eV. Elemental analyses were performed with the Flash EA1112 CHN/MAS200. Reversed-phase TSK gel Toyopearl HW-40 (TOSOH, Japan) and Sephadex LH-20 (Pharmacia Fine Chemicals) were used for column chromatography. Merck Kieselgel 60F-254 plates preliminarily treated with 0.05 M tartaric acid in MeOH and dried at ~50 °C for 2−3 h were used for TLC. Preparative TLC was performed on silica gel L (Chemapol, Czechia), 5/40 μm. The Agilent Technologies 1100 Series HPLC system (Agilent Technologies Deutschland GmbH, Waldbronn, Germany) with the QuatPump G1311A, the DEGASSER G1322A, the manual injector G1328B, the detector VWD G1314A, and the column described below were used for analytical HPLC. All solvents were distilled prior to use. Compounds **7** and **8** were prepared according to the earlier described procedure.[16]

Animal Material. Sea urchins were collected by scuba at a depth of 5 m off Peter the Great Bay of the Japan Sea, Russian Federation, in September 2002. Animal material was stored in a −20 °C freezer prior to extraction. The voucher specimen of *S. mirabilis* Agassiz (order Clypeasteroida, family Dendrasteridae) is under storage in the Pacific Institute of Bioorganic Chemistry, Vladivostok (LCQS-SU-012). Taxonomic identification was provided by one of us (N.P.M.).

Extraction and Isolation. The defrosted sea urchins (2 kg, wet wt) were extracted with EtOH containing 10% H_2SO_4 (3 × 3 L) at room temperature. The combined EtOH extracts were concentrated in vacuo. The residue was partitioned between H_2O (0.3 L) and $CHCl_3$ (3 × 0.3 L). Quinonoid pigments as sodium salts were extracted from $CHCl_3$ with 1% Na_2CO_3 solution (0.3 L, under argon). The solution of pigment sodium salts was acidified to pH 2, and quinones were extracted with $CHCl_3$ (2 × 0.2 L) and EtOAc (2 × 0.2 L). The combined organic extracts were evaporated, and the residue (406 mg, 2 × 10^{-2} % yield of sea urchin wet weight) was sequentially separated by low-pressure reversed-phase column chromatography (20 × 2 cm column) on a Toyopearl column using 20−50% EtOH containing 0.6% HCOOH gradient elution to obtain three fractions. Fraction 1 was purified on a Toyopearl (40 × 2 cm) column with 20% EtOH containing 0.6% HCOOH as eluent to give **4** (5 mg). Fraction 2 containing echinochrome A was purified in the same manner, followed by column chromatography (50 × 1 cm) on a Sephadex LH-20 column, using 7:1 chloroform/ethanol, to give **3** (145 mg). Fraction 3 contained most of compounds **1** and **2** as assessed by HPLC analysis. This fraction was separated by chromatograraphy on a Toyopearl column (40 × 2 cm) using 40−60% EtOH containing 0.6% HCOOH, giving 3 mg of echinamine A (**1**) and 8 mg of echinamine B (**2**).

HPLC Analysis. For the analysis of fractions, a ZORBAX Eclipce XDB-C_8 column (150 × 4.6 mm i.d., 5 μm) was used. The mobile phase was 1% aqueous acetic acid (A) and acetonitrile containing 1% acetic acid (B) with a gradient elution of 10−30% B (6 min), 30−70% B (20 min), and 70−30% B (25 min). The flow rate was 1.0 mL/min at 30 °C and monitored by UV at 254 nm. The data obtained were analyzed with the ChemStation program var. 09 (Agilent Technologies Deutschland GmbH, Waldbronn, Germany). The retention time (t_R) values for **4**, **3**, **1**, and **2** were 5.7, 11.1, 12.7, and 13.6 min, respectively.

Echinamine A (1): dark brown powder (acetone); mp 245−246 °C; UV (EtOH) λ_{max} (log ϵ) 217 (4.33), 233 (4.41), 274 (4.11), 345 (3.29), 479 (3.30) nm; IR ($CHCl_3$) ν_{max} 3522 m, 3445 w, 3379 m (NH_2, β-OH), 1650 m, 1603 m (C=O), 1589 s, 1562 s (NH_2, C=C) cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 266 [M + 1]$^+$ (44), 265 [M]$^+$ (100), 264 (15), 223 (12), 222 (40); HREIMS *m/z* 265.0598 (calcd for $C_{12}H_{11}NO_6$, 265.0586).

Echinamine B (2): dark brown needles (acetone); mp 265−267 °C; UV (EtOH) λ_{max} (log ϵ) 217 (4.33), 275 (4.41), 343 (3.19), 480 (3.30) nm; IR ($CHCl_3$) ν_{max} 3518 m, 3460 w, 3398 m (NH_2, β-OH), 1664 m, 1603 m (C=O), 1580 m, 1560 s (NH_2, C=C) cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 266 [M + 1]$^+$ (32), 265 [M]$^+$ (77), 250 (25), 237 (17), 222 (100); HREIMS *m/z* 265.0598 (calcd for $C_{12}H_{11}NO_6$, 265.0586).

Methylation of 1 and 2. Treatment of **1** and **2** with an ethereal solution of CH_2N_2 quantitatively yielded dimethyl ethers **5** and **6**, respectively.

Compound 5: yellow-brown needles ($CHCl_3$); mp 300 °C (dec); IR ($CHCl_3$) ν_{max} 3514 m, 3398 m (N*H*$_2$), 1684 w, 1641 m, 1616 m (C=O), 1593 s, 1556 s (NH_2, C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (3H, t, J = 7.6, C*H*$_3$), 2.74 (2H, q, J = 7.6, C*H*$_2$), 4.00 and 4.01 (3H each, both s, OC*H*$_3$), 5.06 (2H, br s, N*H*$_2$), 12.52 and 13.48 (1H each, both s, α-O*H*); EIMS *m/z* 293 [M]$^+$ (100), 292 (30), 278 (76), 263 (22), 250 (31), 248 (36), 235 (26), 221 (26); *anal.* C 57.25%, H 5.25%, calcd for $C_{14}H_{15}NO_6$, C 57.32%, H 5.16%.

Compound 6: yellow-brown needles ($CHCl_3$); mp 118−120 °C; IR ($CHCl_3$) ν_{max} 3514 m, 3396 m (N*H*$_2$), 1639 m, 1618 m (C=O), 1590 s, 1555 (NH_2, C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (3H, t, J = 7.5, C*H*$_3$), 2.70 (2H, q, J = 7.5, C*H*$_2$), 3.99 and 4.06 (3H each, both s, OC*H*$_3$), 5.16 (2H, br s, N*H*$_2$), 12.67 and 13.55 (1H each, both s, α-O*H*); EIMS *m/z* 293 [M]$^+$ (100), 292 (86), 279 (22), 278 (86), 263 (25), 250 (23), 248 (24); *anal.* C 57.27%, H 5.22%, calcd for $C_{14}H_{15}NO_6$, C 57.32%, H 5.16%.

Reaction of Chloronaphthazarins 7 and 8 with NaN_3. Solid NaN_3 (65 mg, 1.0 mmol) was added to a stirred solution of the corresponding naphthazarin **7** or **8** (80 mg, 0.26 mmol) in 5 mL of DMSO. The reaction mixture was stirred at 60−70 °C and monitored by TLC. After completion, the reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated, and the product was isolated by preparative TLC (*n*-hexane/acetone, 3:1).

3-Amino-7-ethyl-5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone (5): brown powder from **7**, 32.5 mg (43%); mp 300 °C (dec); R_f 0.32; HPLC analysis, mp, and ^{1}H NMR spectrum were identical to that of the dimethyl ether **5**.

2-Amino-7-ethyl-5,8-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (6): brown powder from **8**, 32.9 mg (45%); mp 118−120 °C; R_f 0.36; HPLC analysis, mp, and ^{1}H NMR spectrum were identical to that of the dimethyl ether **6**.

Reaction of the Echinochrome with Ammonia to Form 1 and 2. A 25% aqueous NH_3 solution (5 mL, 73 mmol) was added to 10 mL of an ethanolic solution of echinochrome A (**3**, 100 mg, 0.39 mmol) with stirring. The reaction mixture was acidified by HCl. The precipitate formed was carefully washed with H_2O. The product of the reaction was separated by reversed-phase HPLC (Toyopearl HW-40, 40% EtOH containing 0.6% HCOOH) to yield echinamines A (**1**) (48 mg, 48%) and B (**2**) (47 mg, 47%).

DPPH Scavenging Assay. The antiradical activity of the quinones **1**−**4** was determined using the stable l,l-diphenyl-2-picrylhydrazyl radical (DPPH) and the procedures described by Senba et al.[15] DPPH was obtained from Fluka. The ethanolic 0.1 mM solution of DPPH had an absorption band at 517 nm with optical density 1.0, which disappears upon reduction by an antiradical compound. A 3 mL sample of DPPH solution was first put into the UV cell, and then a 6 μL aliquot of the ethanolic solution (10 mM) of each sample was

added and mixed vigorously for 10 s. The absorbance change at 517 nm was recorded during 15 min.

Acknowledgment. This research was supported by Grant No. 03-04-49515 from the RFBR, grant SSh. 1237.2003.3 of the President of the Russian Federation of Support of Leading Scientific Schools, the Integration Project of Far-Eastern and Siberian Branches of RAS (No. 05-II-0-00-002), the Program Grants of the Presidium of RAS "Molecular and Cell Biology" (No. 05-I-05-005), and "Fundamental sciences for medicine".

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NP049585R