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Reaction of echinochrome trimethyl ether with aqueous ammonia

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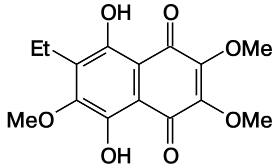
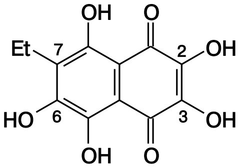
Reaction of 7-ethyl-2,3,6-trimethoxynaphthazarin with $NH_3 \cdot H_2O$ proceeds at the carbonyl groups at the C(4) atoms of the 1,4-naphthoquinonoid tautomeric forms. Methoxy group adjacent to ethyl group is the orienting substituent in this reaction.

Key words: 1,4-naphthoquinones, naphthazarins, echinochrome trimethyl ether, 8-aminojuglone derivatives, amination.

Chemistry of polymethoxylated naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) derivatives* is virtually unknown due to their low availability.[1] Previously, we developed convenient methods for the synthesis of these compounds,[2] which makes them attractive for the synthesis of other natural compounds and their analogs.[3–5] In this regard, echinochrome trimethyl ether (ETME) **1** is one of the promising compounds.[6,7]



1



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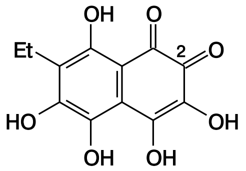
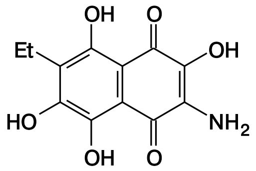


2 (A)



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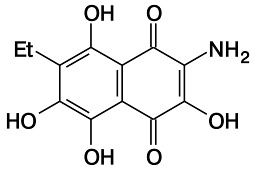

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It has previously been found[8] that reaction of 7-ethyl-2,3,6-trihydroxynaphthazarin (echinochrome, **2**) with aqueous ammonia followed addition—elimination mechanism,[9] the nucleophilic attack occurring at the C(2) atom of the corresponding 1,2-naphthoquinonoid tautomeric form **2** (**A**). The products of this reaction are amino derivatives **3** and **4**, echinamines A and B, respectively, which are the metabolites recently isolated from sea urchin *Scaphechinus mirabilis*.[10]

In continuation of this research, in the present work we studied the reaction of ETME **1** with 25% aqueous ammonia. In the solution, compound **1** can exist in two 1,4-naphthoquinonoid forms **A** and **B** (Scheme 1), consequently, the NH_3 molecule could attack positions 1, 4, 5 or 8 of the substrate to give four isomeric aminojuglones **5a**—**d**, respectively.

In fact, the reaction of compound **1** with aqueous ammonia gave only two products, which according to the spectral data (IR, NMR and mass spectroscopy) are isomeric 8-aminojuglones (the yields of the isolated products are 77 and 13%, respectively).

According to the HMBC experiment, the major reaction product has a structure of **5b**. Position of the hydroxy group at the C(5) atom was unambiguously determined from the HMBC spectrum from both total correlations of the hydroxy group proton and correlations between the protons of the methylene fragment of the ethyl group and the C(4) carbon atom as well (Table 1). Signals of the C(2) carbon atom and the OCH_3 group were unambiguously assigned using similar conclusions. When position of the hydroxy group is known (at the C(5) atom), one can easily assign the signals for the C(4a), C(5), and C(6) atoms by the HMBC correlations between these carbon atoms and the hydroxy group proton. The remaining signals could be attributed by the method of exclusion: the signals of the C(1) and C(8a) atoms appeared near the signals of the C(4) and C(4a), respectively. From signals of C(7) and C(8), the one shifted up-field should be attributed to the C(8) due to lower electronegativity of the nitro-

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* Hereinafter, unless othervise stated, only one of all possible tautomeric forms of naphthazarin derivatives is shown.

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Scheme 1

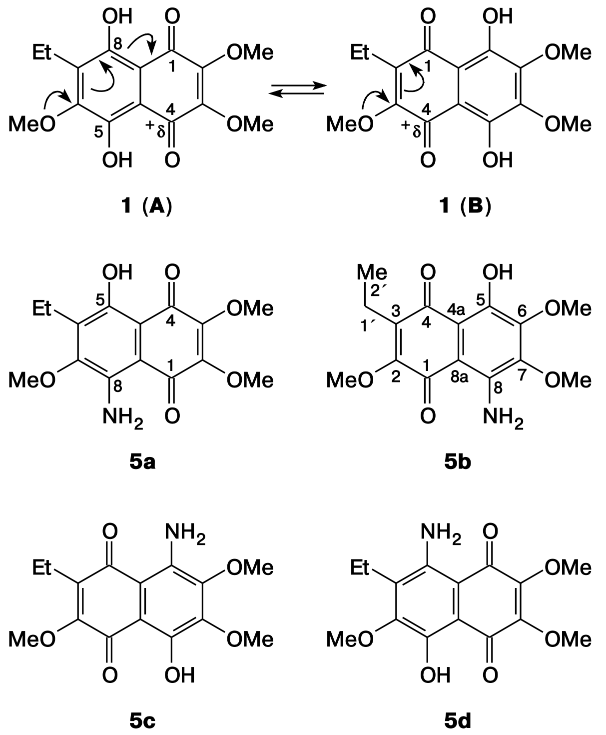


Table 1. Correlations of protons and atoms in HMBC spectra of aminojuglones **5a** and **5b**

Group	^{1}H NMR δ	HMBC
	Compound **5a**	
$CH_2C\underline{H}_3$	1.24	C(1´), C(6)
$C\underline{H}_2CH_3$	2.74	C(2´), C(6), C(7), C(5)
$C(7)OCH_3$	3.86	C(7)
$C(2)OCH_3$	4.04	C(2), C(8a), C(1)
$C(3)OCH_3$	4.13	C(3)
C(5)OH	13.99	C(4a), C(6), C(5), C(4)
$C(8)NH_2$	7.15	—
	Compound **5b**	
$CH_2C\underline{H}_3$	1.12	C(1´), C(3)
$C\underline{H}_2CH_3$	2.59	C(2´), C(3), C(2), C(4)
$C(6)OCH_3$	4.03	C(6)
$C(7)OCH_3$	4.08	C(7)
$C(2)OCH_3$	4.11	C(2)
C(5)OH	14.64	C(4a), C(6), C(5), C(4)
$C(8)NH_2$	5.00	—

gen atom with respect to the oxygen atom. Thus, compound **5b** resulted from the NH_3 molecule attack at the C(4) atom of the tautomeric form **A** of substrate **1**.

Based on the data from the HMBS experiment, the second reaction product has structure of **5a** (see Table 1). Aminojuglone **5a** was formed by attack of the NH_3 molecule at the C(4) atom of the tautomeric form **B** of the compound **1**.

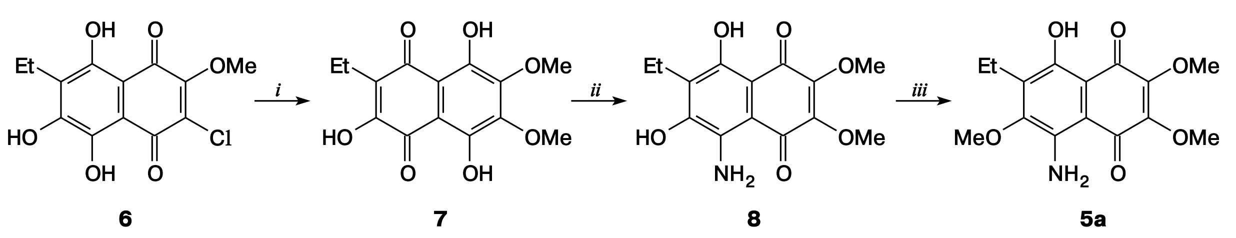
The structures of compounds **5a,b** synthesized were confirmed by counter synthesis. Aminojuglone **5a** was prepared from chlorohydroxynaphthazarin **6** according to the Scheme 2.

Replacement of the halogen atom by the methoxy group in the compound **6** by the action of the KF—MeOH—Al_2O_3 system at 120 °C resulted in echinochrome dimethyl ether **7** in the high yield. Amination of 2-hydroxynaphthazarin **7** with aqueous ammonia proceeded regiospecifically affording aminohydroxynaphthazarin **8**, which was methylated to give compound **5a**.

The key intermediate in the synthesis of aminojuglone **5b** is diether **9** (Scheme 3). This compound can be synthesized by partial hydrolysis of ETME **1**. Acid hydrolysis is of low value for this purpose as it led to the complicated mixtures of mono and dimethyl ethers.[1] The most suitable reagent for this transformation is the alkali solution, whose action resulted in the cleavage of only one ether bond.[11]

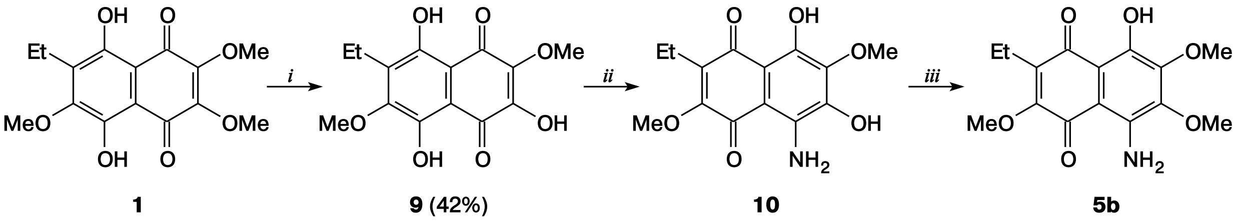
The treatment of compound **1** with 1% NaOH aqueous solution gave a mixture of products, dimethyl ether **9** was isolated from this mixture by chromatography in moderate yield.[1] The subsequent transformations **9**→**10**→**5b** (see Scheme 3) were carried out by the same methods as described for analogous transformations **7**→**8**→**5a** (see Scheme 2). From the mixture of products obtained by hydrolysis of **1**, compounds **7** (42%) and **11** (6%)[1]

Scheme 2



i. MeOH, F^-, Al_2O_3, 120 °C; *ii*. $NH_3 \cdot H_2O$; *iii*. CH_2N_2

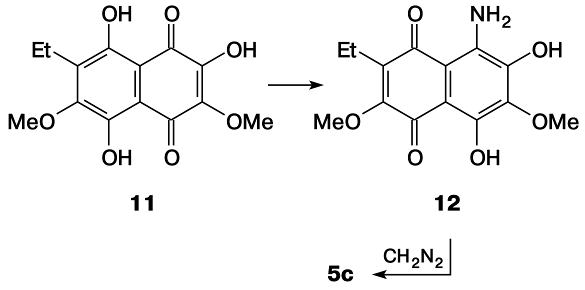
Scheme 3



i. 1% NaOH; *ii.* $NH_3 \cdot H_2O$; *iii.* CH_2N_2

were isolated along with diether **9**. Compound **11** was converted to the corresponding aminojuglone **12** followed by treatment with diazomethane to give compound **5c** (Scheme4).

Scheme 4



The position of the β-OH group of intermediate **7** is unequivocally provided by the structure of substrate **6** (see Scheme 2). The structures of compounds **9** and **11** were established based on ^{1}H and ^{13}C NMR spectroscopy and 2D NMR experiment (HMBC), and on comparison of the physicochemical parameters with published data. Thus, the position of the hydroxy group for compound **9** was unambiguously assigned from the HMBC spectra from both total correlations between the proton of the OH-group and couplings between the protons of the methylene group and the C(6) atom; the latter give also the position of the ethyl group. Arguing similarly, one can attribute the signals for C(7) and C(7)—O$\underline{C}H_3$. When the position of the hydroxy group at the C(5) atom is known, the assignment of the signals for the C(3), C(4), C(4a), C(5), and C(8) atoms is possible. Unambiguous assignment of the signals for the C(8a) and C(1) atoms can be done taking into account the couplings between the proton of hydroxy group at the C(8) atom and the listed above atoms. Correlation between the signals for the methoxy group protons (δ_H 4.19) and C(3) atom defines the position of this group. Broadened singlet at δ_H 6.82 in the ^{1}H NMR was attributed to the hydroxyl group at the C(2) atom.

In addition to the patterns established previously,[8] the positions of the amino groups in hydroxynaphthazarins **8**, **10**, and **12** can be found from 2D NMR experiment (HMBC) (Table 2).

Comparative analysis of the spectral data of the synthesized compounds **5a,b** with the corresponding products obtained by direct amination of echinochrome trimethyl ether **1** showed their complete identity. At the same time, TLC of the reaction mixture using an authentic sample as a reference detected no 8-aminojuglone of structure **5c**.

In summary, the reaction of echinochrome trimethyl ether **1** with $NH_3 \cdot H_2O$ involves the carbonyl groups at

Table 2. Correlations of protons and atoms in HMBC spectra of aminohydroxyjuglones **8**, **10**, and **12**

Compound **8**			Compound **10**			Compound **12**		
Group	^{1}H NMR δ	HMBC	Group	^{1}H NMR δ	HMBC	Group	^{1}H NMR δ	HMBC
$CH_2C\underline{H}_3$	1.22	C(6)	$CH_2C\underline{H}_3$	1.12	C(1′), C(3)	$CH_2C\underline{H}_3$	1.12	C(1′), C(2)
$C\underline{H}_2CH_3$	2.69	C(6), C(7), C(5)	$C\underline{H}_2CH_3$	2.59	C(2′), C(3), C(2), C(4)	$C\underline{H}_2CH_3$	2.62	C(2′), C(2), C(3), C(1)
C(2)OCH_3	4.05	C(2)	C(2)OCH_3	4.10	C(2)	C(3)OCH_3	4.04	C(3)
C(3)OCH_3	4.11	C(3)	C(6)OCH_3	4.12	C(6)	C(6)OCH_3	4.10	C(6)
C(7)OH	5.69	—	C(7)OH	6.42	—	C(7)OH	6.56	—
C(5)OH	13.99	C(4a), C(6), C(7), C(5), C(4)	C(5)OH	14.77	C(4a), C(6), C(5), C(4)	C(5)OH	14.20	C(4a), C(5), C(4)
C(8)NH_2	7.34	—	C(8)NH_2	7.22	—	C(8)NH_2	7.20	—

the C(4) atoms of the tautomers **A** and **B** and proceeds mainly at the carbonyl group of tautomer **A** (see Scheme 1). The orienting substituent in this reaction is the methoxy group adjacent to the ethyl group, the former reduced the electrophilicity of the carbonyl C(1) atom with respect to the carbonyl C(4) atom of the tautomers **A** and **B** of triether **1**.

Experimental

Melting points of the compounds synthesized were determined on Boetius apparatus and are uncorrected. IR spectra were run on a Bruker Vector 22 Fourier spectrophotometer in $CDCl_3$. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300, Bruker Avance 500, and Bruker Avance III-700 in $CDCl_3$, chemical shifts are given in the δ scale relative to Me_4Si (internal standard). The 2D HMBC experiments were performed by the standard procedure at room temperature on a KB-9000S mass spectrometer (electron impact, ionization energy 70 eV, direct inlet). Elemental analysis was performed on a Flash EA-1112 CHN-analyzer at the Institute of Chemistry and Applied Ecology of the Far Eastern Federal University, Vladivostok. The course of the reaction and purity of the products were monitored by TLC on Merck 60F-254 plates. Individual compounds were isolated from reaction mixtures by preparative TLC on silica gel plates (20×20 cm, H^+ form, 5—40 μm).[12] Starting hydroxychloronaphthazarin **6** (see Ref. 13) and echinochrome trimethyl ether **1** (see Ref. 2, 14) were synthesized by the known procedures.

3-Ethyl-2,5,8-trihydroxy-6,7-dimethoxy-1,4-naphthoquinone (7). A mixture of 3-chloro-7-ethyl-5,6,8-trihydroxy-2-methoxy-1,4-naphthoquinone (**6**) (0.3 g, 1 mmol, well-dried prior to use), anhydrous KF (0.35 g, 6 mmol), anhydrous neutral Al_2O_3 (1.2 g), and anhydrous MeOH* (24 mL) were stirred in autoclave for 12 h at 120±5 °C. The reaction mixture was cooled to room temperature, the precipitate was filtered off, and washed with small amount of acetone acidified with 10% HCl (3×1 mL). The combined filtrates were concentrated *in vacuo*, diluted with water (10 mL), and extracted with $CHCl_3$. The extracts were dried with Na_2SO_4 and the solvent was removed *in vacuo*. The solid residue was subjected to column chromatography (silica gel L 40/100 μm), elution with a mixture hexane—acetone. Yield 75%, R_f 0.41, m.p. 151—153 °C (*cf.* Ref 1: m.p. 153—154 °C). ^1H NMR, δ: 1.15 (t, 3 H, CH_3, J = 7.4 Hz); 2.62 (q, 2 H, CH_2, J = 7.4 Hz); 4.05 (s, 3 H, C(6)OCH_3); 4.13 (s, 3 H, C(7) OCH_3); 7.21 (br.s, 1 H, C(2)OH); 12.14 (s, 1 H, C(8)OH); 13.49 (s, 1 H, C(5)OH). ^{13}C NMR, δ: 12.6 (CH_3), 16.3 (CH_2), 61.58 (C(6)OCH_3), 61.63 (C(7)OCH_3), 106.5 (C(4a)), 106.6 (C(8a)), 126.6 (C(3)), 146.1 (C(2)), 150.2 (C(7)), 153.3 (C(6)), 158.8 (C(5)), 159.5 (C(8)), 175.2 (C(4)), 183.2 (C(1)). MS (EI, 18 eV), m/z (I_{rel} (%)): 296 $[M + 2]^+$ (7), 295 $[M + 1]^+$ (25), 294 $[M]^+$ (100), 279 (35), 251 (16), 233 (14).

Basic hydrolysis of 7-ethyl-5,8-dihydroxy-2,3,6-trimethoxy-1,4-naphthoquinone (1). A mixture of compound **1** (0.108 g, 0.35 mmol) and 1% aqueous NaOH (50 mL) was refluxed for 3 h. The reaction mixture was cooled to room temperature, acidified with 5% HCl to pH 3, extracted with AcOEt, the extract was dried with Na_2SO_4, and the solvent was removed *in vacuo*. Compounds **7** (R_f 0.41), **11** (R_f 0.35), and **9** (R_f 0.23) were separated by column chromatography (silica gel), elution with hexane—acetone, 3 : 1.

7-Ethyl-3,5,8-trihydroxy-2,6-dimethoxy-1,4-naphthoquinone (9). Yield 42%, m.p. 152—153 °C (*cf.* Ref. 1: m.p. 152—154 °C). ^1H NMR, δ: 1.17 (t, 3 H, CH_3, J = 7.5 Hz); 2.74 (q, 2 H, CH_2, J = 7.5 Hz); 4.04 (s, 3 H, C(6)OCH_3); 4.19 (s, 3 H, C(2)OCH_3); 6.82 (br.s, 1 H, C(3)OH); 12.09 (s, 1 H, C(5)OH); 13.11 (s, 1 H, C(8)OH). ^{13}C NMR, δ: 13.5 ($\underline{C}H_3CH_2$), 17.4 ($CH_3\underline{C}H_2$), 60.8 (C(2)$O\underline{C}H_3$), 61.4 (C(6)$O\underline{C}H_3$), 105.4 (C(8a)), 108.1 (C(4a)), 137.8 (C(7)), 140.9 (C(2)), 142.7 (C(3)), 153.4 (C(5)), 153.9 (C(6)), 159.6 (C(8)), 182.0 (C(4)), 182.7 (C(1)).

7-Ethyl-2,5,8-trihydroxy-3,6-dimethoxy-1,4-naphthoquinone (11). Yield 6%, m.p. 115—116 °C (*cf.* Ref. 1: m.p. 116 °C). ^1H NMR, δ: 1.16 (t, 3 H, CH_3, J = 7.5 Hz); 2.73 (q, 2 H, CH_2, J = 7.5 Hz); 4.07 (s, 3 H, C(6)OCH_3); 4.17 (s, 3 H, C(3)OCH_3); 6.99 (br.s, 1 H, C(2)OH); 12.17 (s, 1 H, C(5)OH); 13.10 (s, 1 H, C(8)OH).

Synthesis of aminonaphthoquinones 5a,b, 8, 10, and 12. A solution of the substrate (0.1 mmol) in 25% $NH_3 \cdot H_2O$ (5 mL, 83 mmol) was stirred for 10 min at room temperature (TLC monitoring, hexane—acetone, 3 : 1). After reaction was completed, the excess of ammonia was removed keeping the mixture under reduced pressure at 50 °C for 30 min. The mixture was cooled and a solution of potassium hydrogen phthalate (10 mL, 0.05 mol L^{-1}, pH 4.01) was added to the residue. The precipitate that formed was filtered off, dried under vacuum over $CaCl_2$, and purified by preparative TLC (elution with hexane—acetone, 3 : 1).

8-Amino-6-ethyl-5-hydroxy-2,3,7-trimethoxy-1,4-naphthoquinone (5a). Yield 13%, R_f 0.42 (hexane—acetone, 2 : 1), m.p. 143—148 °C. MS, m/z (I_{rel} (%)): 307 $[M]^+$ (100), 291 (75), 278 (11), 249 (11), 234 (8). Found (%): C, 58.67; H, 5.60; N, 4.59. $C_{15}H_{17}NO_6$. Calculated (%): C, 58.63; H, 5.58; N, 4.56. IR, ν/cm^{-1}: 3486, 3310, 2942, 1601, 1584, 1519, 1459. ^1H NMR, δ: 1.24 (t, 3 H, $C\underline{H}_3CH_2$, J = 7.5 Hz); 2.74 (q, 2 H, $CH_3C\underline{H}_2$, J = 7.5 Hz); 3.86 (s, 3 H, C(7)OCH_3); 4.04 (s, 3 H, C(2)OCH_3); 4.13 (s, 3 H, C(3)OCH_3); 5.00 (br.s, 2 H, NH_2); 13.99 (s, 1 H, C(5)OH). ^{13}C NMR, δ: 13.6 ($\underline{C}H_3CH_2$), 17.7 ($CH_3\underline{C}H_2$), 61.3 (C(7)$O\underline{C}H_3$), 61.4 (C(2)$O\underline{C}H_3$, C(3)$O\underline{C}H_3$), 105.8 (C(8a)), 107.8 (C(4a)), 134.6 (C(6)), 141.7 (C(8)), 146.1 (C(2)), 149.9 (C(3)), 154.3 (C(7)), 158.6 (C(5)), 180.6 (C(1)), 184.5 (C(4)).

8-Amino-3-ethyl-5-hydroxy-2,6,7-trimethoxy-1,4-naphthoquinone (5b). Yield 77%, R_f 0.54 (hexane—acetone, 2 : 1), m.p. 112—114 °C. MS, m/z (I_{rel} (%)): 308 $[M + 1]^+$ (19), 307 $[M]^+$ (80), 293 (18), 292 (100), 277 (14), 274 (11), 259 (8), 249 (10), 234 (10). Found (%): C, 58.58; H, 5.65; N, 4.65. $C_{15}H_{17}NO_6$. Calculated (%): C, 58.63; H, 5.58; N, 4.56. IR, ν/cm^{-1}: 3486, 3307, 1599, 1590, 1523. ^1H NMR, δ: 1.12 (t, 3 H, CH_3, J = 7.5 Hz); 2.59 (q, 2 H, CH_2, J = 7.5 Hz); 4.03 (s, 3 H, C(6)OCH_3); 4.08 (s, 3 H, C(7)OCH_3); 4.11 (s, 3 H, C(2)OCH_3); 14.64 (s, 1 H, C(5)OH). ^{13}C NMR, δ: 13.5 ($\underline{C}H_3CH_2$), 16.6 ($CH_3\underline{C}H_2$), 61.1 (C(7)$O\underline{C}H_3$), 61.3 (C(6)$O\underline{C}H_3$), 61.4 (C(2)$O\underline{C}H_3$), 104.4 (C(8a)), 108.6 (C(4a)), 136.0 (C(3)), 142.9 (C(8)), 145.3 (C(6)), 146.0 (C(7)), 154.9 (C(5)), 159.6 (C(2)), 179.3 (C(1)), 187.4 (C(4)).

8-Amino-6-ethyl-5,7-dihydroxy-2,3-dimethoxy-1,4-naphthoquinone (8). Yield 98%, R_f 0.68 (hexane—acetone, 1 : 1), m.p. 203—205 °C. MS, m/z (I_{rel} (%)): 294 $[M + 1]^+$ (18), 293 $[M]^+$ (100), 279 (15), 278 (92), 275 (11), 263 (20), 260 (26), 250 (11),

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* Anhydrous starting reagents were prepared according to the known procedure.[2]

245 (12), 232 (14). Found (%): C, 57.30; H, 5.18; N, 4.75. $C_{14}H_{15}NO_6$. Calculated (%): C, 57.34; H, 5.16; N, 4.78. IR, ν/cm^{-1}: 3587, 3493, 3308, 2876, 1600, 1582, 1522, 1461, 1202. ^{1}H NMR, δ: 1.21 (t, 3 H, CH_3, J = 7.6 Hz); 2.69 (q, 2 H, CH_2, J = 7.6 Hz); 4.05 (s, 3 H, C(2)OCH_3); 4.11 (s, 3 H, C(3)OCH_3); 5.69 (br.s, 1 H, C(7)OH); 7.34 (br.s, 2 H, NH_2); 14.38 (s, 1 H, C(5)OH). ^{13}C NMR, δ: 12.7 (CH_3), 16.4 (CH_2), 61.2, 61.3 (C(3)O$\underline{C}H_3$, C(2)O$\underline{C}H_3$), 105.6 (C(4a)), 105.8 (C(8a)), 122.4 (C(6)), 138.6 (C(8)), 146.8, 149.6 (C(2), C(3)), 149.2 (C(7)), 159.0 (C(5)), 180.7 (C(1)), 183.3 (C(4)).

8-Amino-3-ethyl-5,7-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone (10). Yield 97%, R_f 0.26 (hexane—acetone, 2 : 1), m.p. 192—195 °C. MS, m/z (I_{rel} (%)): 293 $[M]^+$ (100), 278 (97), 263 (18), 260 (20), 232 (18). Found (%): C, 57.23; H, 5.20; N, 4.83. $C_{14}H_{15}NO_6$. Calculated (%): C, 57.34; H, 5.16; N, 4.78. ^{1}H NMR, δ: 1.12 (t, 3 H, CH_3, J = 7.5 Hz); 2.59 (q, 2 H, CH_2, J = 7.5 Hz); 4.10 (s, 3 H, C(2)OCH_3); 4.12 (s, 3 H, C(6)OCH_3); 6.42 (br.s, 1 H, C(7)OH); 7.22 (br.s, 2 H, NH_2); 14.77 (s, 1 H, C(5)OH). ^{13}C NMR, δ: 13.5 (CH_3), 16.6 (CH_2), 61.3 (C(6)O$\underline{C}H_3$), 61.4 (C(2)O$\underline{C}H_3$), 104.9 (C(8a)), 106.9 (C(4a)), 136.3 (C(3)), 138.4 (C(8)), 138.6 (C(6)), 143.1 (C(7)), 153.9 (C(5)), 159.2 (C(2)), 179.4 (C(1)), 187.3 (C(4)).

8-Amino-2-ethyl-5,7-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (12). Yield 97%, R_f 0.30 (hexane—acetone, 2 : 1). ^{1}H NMR, δ: 1.12 (t, 3 H, CH_3, J = 7.5 Hz); 2.62 (q, 2 H, CH_2, J = 7.5 Hz); 4.04 (s, 3 H, C(3)OCH_3); 4.10 (s, 3 H, C(6)OCH_3); 6.56 (br.s, 1 H, C(7)OH); 7.20 (br.s, 2 H, NH_2); 14.20 (s, 1 H, C(5)OH). ^{13}C NMR, δ: 13.7 (CH_3), 17.3 (CH_2), 61.26 (C(3)O$\underline{C}H_3$), 61.34 (C(6)O$\underline{C}H_3$), 104.6 (C(8a)), 107.6 (C(4a)), 137.5 (C(8)), 137.6 (C(6)), 140.7 (C(2)), 144.3 (C(7)), 154.1 (C(5)), 156.6 (C(3)), 182.9 (C(4)), 184.3 (C(1)).

Methylation of aminojuglones 8, 10 and 12. A solution of the substrate (0.07 mmol) in diethyl ether (5 mL) was treated with diazomethane solution at room temperature (TLC monitoring, hexane—acetone, 2 : 1).[15] The solvent was removed *in vacuo*, the products were isolated by preparative TLC (hexane—acetone, 2 : 1).

8-Amino-6-ethyl-5-hydroxy-2,3,7-trimethoxy-1,4-naphthoquinone (5a) was prepared by methylation of 8-amino-6-ethyl-5,7-dihydroxy-2,3-dimethoxy-1,4-naphthoquinone (**8**) in 98% yield.

8-Amino-3-ethyl-5-hydroxy-2,6,7-trimethoxy-1,4-naphthoquinone (5b) was prepared by methylation of 8-amino-3-ethyl-5,7-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone (**10**) in 95% yield.

8-Amino-2-ethyl-5-hydroxy-3,6,7-trimethoxy-1,4-naphthoquinone (5c) was prepared by methylation of 8-amino-2-ethyl-5,7-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (**12**) in 95% yield. ^{1}H NMR, δ: 1.12 (t, 3 H, CH_3, J = 7.5 Hz); 2.62 (q, 2 H, CH_2, J = 7.5 Hz); 4.01 (s, 3 H, C(6)OCH_3); 4.04 (s, 3 H, C(7)OCH_3); 4.09 (s, 3 H, C(3)OCH_3); 14.05 (s, 1 H, C(5)OH).

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