# Synthesis of 2,2′-(ethane-1,1-diyl)bis(3,5,6,7,8-pentahydroxy-1,4-naphthoquinone), a metabolite of the sea urchins *Spatangus purpureus*, *Strongylocentrotus intermedius*, and *S. droebachiensis*

*D. N. Pelageev,[a]* M. N. Panchenko,[b] N. D. Pokhilo,[a] and V. F. Anufriev[a]*

[a] *Pacific Institute of Bioorganic Chemistry, Far-Eastern Branch of the Russian Academy of Sciences, 159 prosp. 100-letiya Vladivostoka, 690022 Vladivostok, Russian Federation. Fax: +7 (423) 231 4050. E-mail: pelageev@piboc.dvo.ru*

[b] *Institute of Chemistry and Applied Ecology of Far-Eastern State University, 27 ul. Oktyabr′skaya, 690600 Vladivostok, Russian Federation. Fax: +7 (423) 225 7609*

A key step in the synthesis of 2,2′-(alkane-1,1-diyl)bis(3,5,6,7,8-pentahydroxy-1,4-naphthoquinones) is an acid-catalyzed condensation of 2-hydroxynaphthazarins, the products of the retro aldol reaction of 2-hydroxy-3-(1-hydroxyalkyl)naphthazarins, with the corresponding aldehydes. This method is applicable, in particular, for the preparation of compound with the ethane-1,1-diyl bridge — a metabolite produced by the sea urchins *Spatangus purpureus, Strongylocentrotus intermedius*, and *S. droebachiensis*.

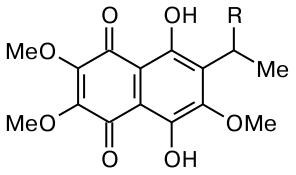
**Key words:** naphthazarins, aldehydes, condensation, metabolites, sea urchins.

Earlier, we have suggested and elaborated a preparative method for the preparation of polymethoxylated naphthazarins (5,8-dihydroxy-1,4-naphthoquinones)* from the corresponding chlorinated derivatives.[1,2] Methoxylated naphthazarins are convenient precursors in the synthesis of natural quinonoid compounds and their analogs.[3—5] This was demonstrated using synthesis of biologically active naphthazarins as an example, which possess high antioxidant and cardioprotecting activity,[6,7] or are already used as pharmaceutical drugs.[8,9]

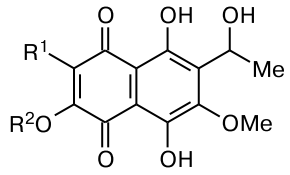
Recently, starting from echinochrome trimethyl ether **1a** we have obtained lomazarin (**1b**),[10] a pigment isolated earlier from the Australian plant *Lomandra hastilis*.[3,4] Alkaline hydrolysis of lomazarin gives norlomazarin (**2a**), a pigment from the same plant, and its isomer **2b** in low yields. However, the major product of this reaction is spinochrome D dimethyl ether **3a**. The latter is a result of retro aldol disintegration of 2-hydroxy-3-(1-hydroxyethyl)naphthazarin (**4a**) (Scheme 1).

The same products were obtained, when lomazarin bromo or acetoxy derivatives (**1c** and **1d**, respectively) were used instead of lomazarin (**1b**) itself, that indicates the readiness of conversion of compounds **1c**,**d** to (1-hydroxyethyl)naphthazarin **1b** under the reaction conditions.

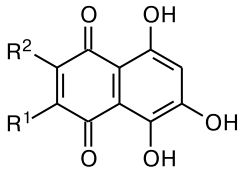
We found that under alkaline hydrolysis, substrates **5a**—**c** give mompain monomethyl ether **3b** (22% yield) and 6-hydroxy-2-(1-hydroxyethyl)-3-methoxynaphthazarin (**2c**, 40% yield), whereas substrates **5d**—**f** give rise to naphthopurpurin (**3c**). Compounds **3b**,**c**, similarly to dimethyl ether **3a**, are formed by the retro aldol disintegration of the corresponding 2-hydroxy-3-(1-hydroxyethyl)naphthazarins **4b**,**c**. The products obtained are either natural pigments (compound **3c**) or their methyl ethers (compounds **3a**,**b**).[3] It should be noted that some partially methylated polyhydroxynaphthazarins, includ-



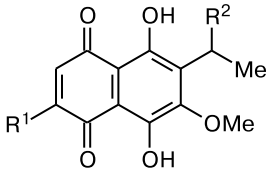
**1a—d**



**2a—c**



**3a—c**



**5a—h**

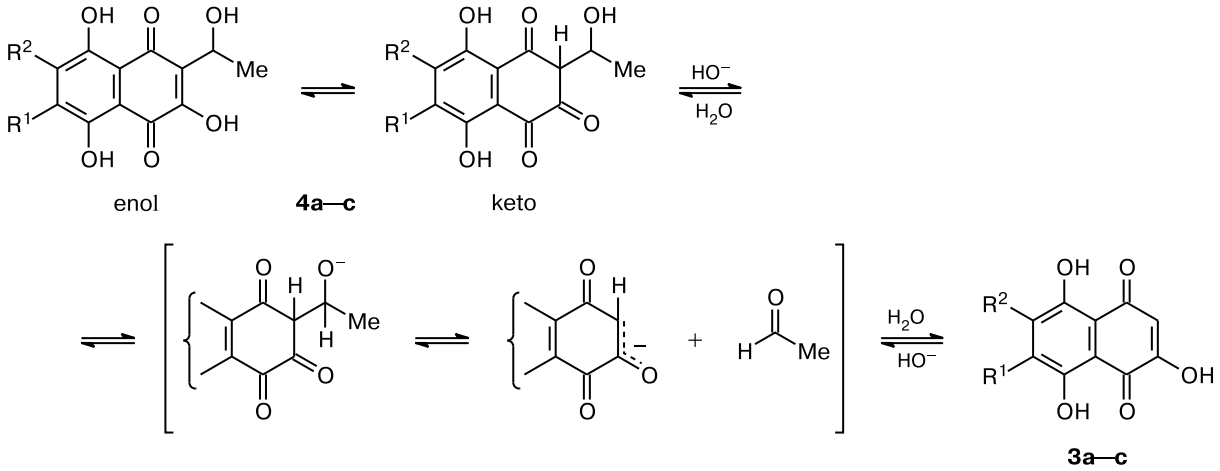
R = H (**1a**), OH (**1b**), Br (**1c**), OAc (**1d**)
$R^1$ = H (**2c**, **3c**, **5d—f**,**h**), OH (**2a**), OMe (**2b**, **3a**,**b**, **5a—c**,**g**)
$R^2$ = H (**2b**,**c**, **3b**,**c**, **5g**,**h**), OH (**5c**,**f**), Me (**2a**), OMe (**3a**), Br (**5a**,**d**), OAc (**5b**,**e**)

* The structures of naphthazarin derivatives in this work are given only in one of all possible tautomeric forms.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1439—1444, July, 2010.

1066-5285/10/5907-1472 

**Scheme 1**

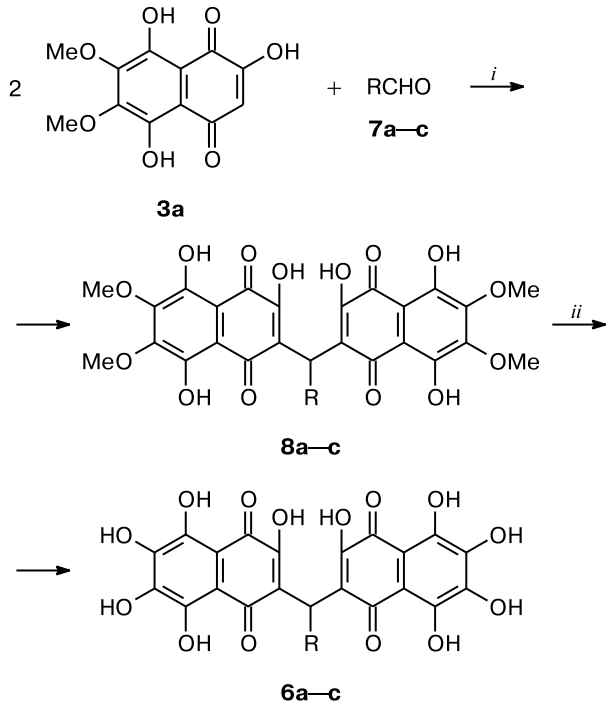



$R^1$ = H (**3c**, **4c**), OMe (**3a**,**b**, **4a**,**b**); $R^2$ = H (**3b**,**c**, **4b**,**c**), OMe (**3a**, **4a**)

ing diether **3a**, are poorly available compounds.[11] At the same time, they can be useful in the synthesis of a number of natural products.

In the present work, we used dimethyl ether **3a** in the synthesis of 2,2′-(ethane-1,1-diyl)bis(3,5,6,7,8-pentahydroxy-1,4-naphthoquinone) (**6a**), a metabolite produced by the sea urchins *Spatangus purpureus, Strongylocentrotus intermedius*, *and S. droebachiensis*. Its methylene **6b** and benzylidene **6c** analogs were also obtained. To synthesize the target bisnaphthazarins **6a**—**c**, we used a described earlier method[12] for the condensation of 2-hydroxynaphthazarins with saturated aldehydes **7a**—**c** (Scheme 2).[12]

**Scheme 2**

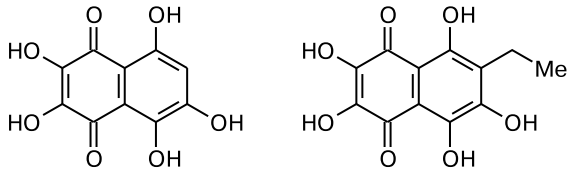



R = Me (**6a**, **7a**, **8a**), H (**6b**, **7b**, **8b**), 4-$HOC_6H_4$ (**6c**), 4-$MeOC_6H_4$ (**7c**, **8c**)

*i*. $MeNH_2 \cdot HCl$, EtOH, reflux, 4 h; *ii*. $AlCl_3$, $PhNO_2$, 70 °C, 12 h.

According to Scheme 2, compound **3a** reacts with aldehydes **7a**—**c** under acidic conditions giving the corresponding bisnaphthazarins **8a**—**c** containing four methoxy groups. Their demethylation leads to bis(trihydroxynaphthazarins) **6a**—**c** in good yields. Synthetic bisnaphthazarin **6a** has proved identical to the pigment isolated earlier from the sea urchins *Spatangus purpureus*, *Strongylocentrotus intermedius*, and *S. droebachiensis*[3].

Earlier, the authors of Ref. 13 have described an attempt to synthesize compound **6a** by the reaction of spinochrome D (**9**) with acetaldehyde in the presence of dilute HCl. A product with the melting point 155—157 °C was isolated from the reaction mixture in low yield (<5%), whose $R_f$ value, UV and IR spectra coincided with those for bisnaphthazarin **6a** (or were close to them).




It should be noted that the natural bisnaphthazarin **6a** does not melt, rather sublimes at 285—295 °C (see Ref. 4). It was also reported[14] that this product decomposes at temperatures >300 °C. In addition, UV and IR spectroscopy are not reliable enough at establishing structures of polyhydroxynaphthazarins even by comparison method.

For example, these methods cannot distinguish between bisnaphthazarin **6a**, spinochrome D (**9**), or echinochrome (**10**), which were mentioned in the previously cited work.[13] Thus, the synthesis of bisnaphthazarin **6a** has been in question until the present work.

## Experimental

Melting points were determined on a Boetius heating stage and not corrected. IR spectra were recorded on a Bruker Vector 22 spectrophotometer. $^1$H NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer in $CDCl_3$, DMSO-$d_6$, and $CD_3OD$, using TMS as an internal standard or residual signals of the corresponding solvent ($\delta_H$ 2.50, $\delta_C$ 39.5 for DMSO-$d_6$; $\delta_H$ 3.31, $\delta_C$ 49.6 for $CD_3OD$) as references. Mass spectra were obtained on a AMD-604S instrument (70 eV). Elemental analysis was performed on a Flash EA1112CHN/MAS200 C,H,N-analyser (Institute of Chemistry and Applied Ecology of Far-Eastern State University, Vladivostok). Reaction progress and individuality of compounds obtained were monitored by TLC on Merck Kieselgel 60F-254 plates activated with a 0.05% solution of tartaric acid in methanol and dried over 2—3 h at ~50 °C, using the *n*-hexane—acetone (3 : 1) solvent mixture as an eluent. Preparative TLC was performed on 20×20 cm plates with silica gel L (Chemapol®, Czechia), 5/40 μm, column chromatography was performed on silica gel of the same brand, the fractions 40/100 μm using the *n*-hexane—acetone solvent systems. The yields of compounds obtained were not optimized.

The starting compounds, *viz.*, 7-(1-bromoethyl)-5,8-dihydroxy-2,3,6-trimethoxy-1,4-naphthoquinone (**1c**), 7-(1-acetoxyethyl)-5,8-dihydroxy-2,3,6-trimethoxy-1,4-naphthoquinone (**1d**), 5,8-dihydroxy-7-(1-hydroxyethyl)-2,3,6-trimethoxy-1,4-naphthoquinone (lomazarin, **1b**), 2,5,8-trihydroxy-6,7-dimethoxy-1,4-naphthoquinone (**3a**),[10] 2-ethyl-5,8-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (**5g**),[15] and 2-ethyl-5,8-dihydroxy-3-methoxy-1,4-naphthoquinone (**5h**),[16] were obtained according to the procedures described earlier.

**Bromination of naphthazarins 5g,h (general procedure).** Bromine (1.2 g, 6.75 mmol) was added dropwise to a solution of the corresponding naphthazarin (4.5 mmol) in commercial $CCl_4$ (500 mL) with stirring, and the mixture was stirred in the light for 4 h at ~20 °C (TLC monitoring). After the reaction reached completion, the solvent was evaporated *in vacuo*. The corresponding bromo derivatives **5a**,**d** were isolated from the residue by column chromatography (*n*-hexane—acetone, 20 : 1) as red fine crystalline powders.

**2-(1-Bromoethyl)-5,8-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (5a)** was obtained from compound **5g**. The yield was 98%, m.p. 145—148 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 3033, 2943, 1609, 1476, 1456, 1424, 1403, 1302, 1277. $^1$H NMR ($CDCl_3$), δ: 2.09 (d, 3 H, Me, $J$ = 7.1 Hz); 3.94, 4.20 (both s, 3 H each, OMe); 5.75 (q, 1 H, CH, $J$ = 7.1 Hz); 6.28 (s, 1 H, H(7)); 12.66, 13.55 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 179.8, 174.1, 164.3, 161.6, 159.7, 155.6, 134.6, 111.8, 109.8, 105.9, 61.4, 56.8, 36.9, 23.6. MS, $m/z$ ($I_{rel}$ (%)): 356/358 [M]$^+$ (7), 277 (100), 261 (38), 249 (11), 233 (17). Found: $m/z$ 355.9876 [M]$^+$. $C_{14}H_{13}{}^{79}BrO_6$. Calculated: M = 355.98955.

**2-(1-Bromoethyl)-5,8-dihydroxy-3-methoxy-1,4-naphthoquinone (5d)** was obtained from compound **5h**. The yield was 98%, m.p. 118—121 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 3030, 2941, 1608, 1474, 1457, 1424, 1402, 1304, 1279. $^1$H NMR ($CDCl_3$), δ: 2.03 (d, 3 H, Me, $J$ = 7.0 Hz); 4.32 (s, 3 H, OMe); 5.63 (q, 1 H, CH, $J$ = 7.0 Hz); 7.21, 7.27 (both d, 1 H each, $J$ = 9.4 Hz); 12.25, 12.71 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 185.4, 183.2, 159.0, 158.1, 134.6, 130.9, 129.1, 128.9, 111.7, 110.6, 61.9, 36.2, 23.4. MS, $m/z$ ($I_{rel}$ (%)): 326/328 [M]$^+$ (9), 247 (100), 231 (18), 215 (20), 203 (12). Found: $m/z$ 325.9799 [M]$^+$. $C_{13}H_{11}{}^{79}BrO_5$. Calculated: M = 325.97898.

**Synthesis of acetoxy derivatives 5b,e (general procedure).** A solution of the corresponding 1-bromoethylnaphthazarin **5a**,**d** (3.4 mmol) and AcOK (1.67 g, 17 mmol) in the AcOH—$CHCl_3$ mixture (3 : 1, 60 mL) was refluxed for 2 h. The solvents were evaporated under reduced pressure, the residue was treated with water (100 mL) and extracted with AcOEt. The extracts were dried with $Na_2SO_4$ and concentrated *in vacuo*. The corresponding acetoxy derivatives **5b**,**e** were isolated from the residue by column chromatography (*n*-hexane—acetone, 20 : 1).

**2-(1-Acetoxyethyl)-5,8-dihydroxy-3,6-dimethoxy-1,4-naphthoquinone (5b)** was obtained from compound **5a**. The yield was 70%, m.p. 149—153 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 2984, 2942, 1729, 1607, 1476, 1456, 1427, 1405. $^1$H NMR ($CDCl_3$), δ: 1.62 (d, 3 H, Me, $J$ = 6.8 Hz); 2.07 (s, 3 H, OAc); 3.92, 4.11 (both s, 3 H each, OMe); 6.22 (s, 1 H, H(7)); 6.26 (q, 1 H, CH, $J$ = 6.8 Hz); 12.64, 13.42 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 181.5, 175.9, 170.5, 163.1, 160.0, 159.8, 155.1, 133.2, 111.7, 109.9, 106.1, 65.1, 61.5, 56.7, 21.1, 18.6. MS, $m/z$ ($I_{rel}$ (%)): 336 [M]$^+$ (23), 276 (79), 261 (100), 233 (27), 205 (14). Found: $m/z$ 336.0826 [M]$^+$. $C_{16}H_{16}O_8$. Calculated: M = 336.08452.

**2-(1-Acetoxyethyl)-5,8-dihydroxy-3-methoxy-1,4-naphthoquinone (5e)** was obtained from compound **5d**. The yield was 65%, m.p. 105—107 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 3037, 3005, 2952, 1730, 1610, 1573, 1458, 1408, 1292. $^1$H NMR ($CDCl_3$), δ: 1.61 (d, 3 H, Me, $J$ = 6.9 Hz); 2.07 (s, 3 H, OAc); 4.21 (s, 3 H, OMe); 6.13 (q, 1 H, CH, $J$ = 6.9 Hz); 7.19, 7.24 (both d, 1 H each, $J$ = 9.4 Hz); 12.24, 12.72 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 186.2, 183.2, 170.4, 159.2, 158.5, 158.4, 133.5, 130.9, 128.8, 111.8, 110.9, 64.8, 61.9, 21.0, 18.6. MS, $m/z$ ($I_{rel}$ (%)): 306 [M]$^+$ (24), 246 (100), 231 (92), 203 (37), 175 (17). Found: $m/z$ 306.0726 [M]$^+$. $C_{15}H_{14}O_7$. Calculated: M = 306.07395.

**Deacetylation of acetoxy derivatives 5b,e (general procedure).** A solution of the corresponding 1-acetoxyethylnaphthazarin **5b**,**e** (1.1 mmol) in the MeOH—$CF_3COOH$ mixture (2 : 1, 9 mL) was refluxed for 10 h. The solvents were evaporated under reduced pressure. The corresponding hydroxyethyl derivatives **5c**,**f** were isolated from the residue by column chromatography (*n*-hexane—acetone, 20 : 1).

**5,8-Dihydroxy-2-(1-hydroxyethyl)-3,6-dimethoxy-1,4-naphthoquinone (5c)** was obtained from compound **5b**. The yield was 87%, m.p. 140—142 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 3564, 2980, 2942, 1599, 1478, 1450, 1427, 1401. $^1$H NMR ($CDCl_3$), δ: 1.57 (d, 3 H, Me, $J$ = 6.0 Hz); 3.94, 4.12 (both s, 3 H each, OMe); 5.23 (q, 1 H, CH, $J$ = 6.0 Hz); 6.28 (s, 1 H, H(7)); 12.72, 13.46 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 179.2, 172.9, 166.2, 162.9, 159.8, 153.6, 136.7, 111.3, 109.4, 106.1, 64.5, 61.7, 56.8, 23.4. MS, $m/z$ ($I_{rel}$ (%)): 294 [M]$^+$ (85), 279 (100), 261 (82), 251 (22), 233 (37). Found: $m/z$ 294.0749 [M]$^+$. $C_{14}H_{14}O_7$. Calculated: M = 294.07395.

**5,8-Dihydroxy-2-(1-hydroxyethyl)-3-methoxy-1,4-naphthoquinone (5f)** was obtained from compound **5e**. The yield was 75%, m.p. 114—116 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 3540, 3040, 3007, 2982, 2860, 1711, 1604, 1567, 1456, 1409. $^1$H NMR ($CDCl_3$), δ:

1.54 (d, 3 H, Me, $J$ = 6.7 Hz); 4.22 (s, 3 H, OMe); 5.12 (q, 1 H, CH, $J$ = 6.7 Hz); 7.20, 7.25 (both d, 1 H each, $J$ = 9.5 Hz); 12.29, 12.58 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 188.8, 183.4, 158.7, 158.1, 156.6, 135.7, 130.7, 129.3, 111.4, 110.9, 64.2, 62.1, 23.4. MS, $m/z$ ($I_{rel}$ (%)): 264 $[M]^+$ (83), 249 (100), 231 (92), 221 (13), 203 (41). Found: $m/z$ 264.0645 $[M]^+$. $C_{13}H_{12}O_6$. Calculated: M = 264.06339.

**Alkaline hydrolysis of compounds 5a—f (general procedure).** The corresponding naphthazarin (1 mmol) was refluxed in 1% aqueous NaOH (10 mL) for 3 h, cooled, neutralized with conc. HCl, and extracted with AcOEt. The extract was dried with $Na_2SO_4$ and concentrated *in vacuo*. Products **3b**, **2c** in the case of compounds **5a—c** and product **3c** in the case of compounds **5d—f** were isolated from the residue by column chromatography (*n*-hexane—acetone, 10 : 1).

**2,5,8-Trihydroxy-6,7-dimethoxy-1,4-naphthoquinone (3a)** was obtained according to the known procedure[10] from compounds **1b—d**. The yield was 50%, m.p. 195—197 °C (from acetone) (*cf.* Ref. 11: m.p. 194—196 °C). IR ($CHCl_3$), ν/cm$^{-1}$: 3520, 3408, 2947, 1601, 1467, 1410, 1348, 1283, 1211. $^1$H NMR ($CDCl_3$), δ: 4.06, 4.16 (both s, 3 H each, OMe); 6.46 (s, 1 H, H(3)); 7.08 (br.s, 1 H, C(2)OH); 12.27, 13.12 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 177.5, 167.8, 167.0, 165.1, 156.4, 150.5, 146.1, 110.4, 108.0, 106.0, 61.7, 61.6.

**2,5,8-Trihydroxy-7-methoxy-1,4-naphthoquinone (3b)** was obtained from compounds **5a—c**. The yield was 22%, m.p. 215—218 °C (*cf.* Ref. 11: m.p. 240—241 °C). IR ($CHCl_3$), ν/cm$^{-1}$: 3524, 3420, 2929, 2856, 1661, 1606, 1479, 1439, 1405, 1284. $^1$H NMR ($CDCl_3$), δ: 3.96 (s, 3 H, OMe); 6.47 (s, 1 H, H(3)); 6.53 (s, 1 H, H(6)); 7.03 (br.s, 1 H, C(2)OH); 12.07 (s, 1 H, C(8)OH); 13.10 (s, 1 H, C(5)OH). $^{13}$C NMR ($CDCl_3$), δ: 179.3, 173.0, 167.4, 160.1, 157.3, 155.7, 112.0, 110.9, 109.4, 104.3, 56.7. MS, $m/z$ ($I_{rel}$ (%)): 236 $[M]^+$ (100), 218 (20), 190 (11), 165 (14). Found: $m/z$ 236.0327 $[M]^+$. $C_{11}H_8O_6$. Calculated: M = 236.03209.

**5,6,8-Trihydroxy-2-(1-hydroxyethyl)-3-methoxy-1,4-naphthoquinone (2c)** was obtained from compounds **5a—c**. The yield was 40%, m.p. 165—167 °C. IR ($CHCl_3$), ν/cm$^{-1}$: 3562, 3525, 3416, 3020, 2979, 2933, 1605, 1459, 1408, 1364, 1328. $^1$H NMR ($CDCl_3$), δ: 1.58 (d, 3 H, Me, $J$ = 6.5 Hz); 4.10 (s, 3 H, OMe); 5.27 (q, 1 H, CH, $J$ = 6.5 Hz); 6.39 (s, 1 H, H(7)); 7.35 (br.s, 1 H, C(6)OH); 11.99, 13.59 (both s, 1 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 184.2, 177.6, 161.6, 157.7, 156.7, 152.5, 137.7, 111.5, 110.4, 106.6, 64.6, 61.7, 23.4. MS, $m/z$ ($I_{rel}$ (%)): 280 $[M]^+$ (63), 265 (100), 247 (62), 237 (17), 219 (27). Found: $m/z$ 280.0578 $[M]^+$. $C_{13}H_{12}O_7$. Calculated: M = 280.05830.

**2,5,8-Trihydroxy-1,4-naphthoquinone (naphthopurpurin, 3c)** was obtained from compounds **5d—f**. The yield was 25%, m.p. 220—225 °C (*cf.* Ref. 17: m.p. 200—210 °C). $^1$H NMR ($CDCl_3$), δ: 6.38 (s, 1 H, H(3)); 7.21 (d, 1 H, H(6), $J$ = 14.2 Hz); 7.34 (d, 1 H, H(7), $J$ = 14.2 Hz); 11.50, 12.75 (both s, 1 H each, α-OH).

**Condensation of hydroxynaphthazarin 3a with aldehydes 7a—c (general procedure).** A solution of naphthazarin **3a** (133 mg, 0.5 mmol), the corresponding aldehyde **7a—c** (1 mmol), and $MeNH_2 \cdot HCl$ (3 mg, 0.05 mmol) in ethanol (30 mL) was refluxed for 4 h. The solvent was evaporated under reduced pressure. Products **8a—c** were isolated from the residue by PTLC (*n*-hexane—acetone, 3 : 1).

**2,2′-(Ethane-1,1-diyl)bis(3,5,8-trihydroxy-6,7-dimethoxy-1,4-naphthoquinone) (8a)** was obtained by the reaction of naphthazarin **3a** with acetaldehyde (**7a**). The yield was 60%, m.p. 150—154 °C. Found (%): C, 55.92; H, 3.97. $C_{26}H_{22}O_{14}$. Calculated (%): C, 55.87; H, 4.07. IR ($CHCl_3$), ν/cm$^{-1}$: 3380, 2944, 2262, 1599, 1462, 1416, 1345, 1285. $^1$H NMR ($CDCl_3$), δ: 1.61 (d, 3 H, Me, $J$ = 7.4 Hz); 3.94, 4.02 (both s, 6 H each, OMe); 4.73 (q, 1 H, CH, $J$ = 7.4 Hz); 7.86 (br.s, 2 H, C(2)OH, C(2′)OH); 12.01, 13.33 (both s, 2 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 184.8, 177.5, 157.6, 156.9, 154.7, 150.4, 146.1, 125.1, 106.4, 106.37, 61.6, 61.5, 27.4, 16.5. MS, $m/z$ ($I_{rel}$ (%)): 558 $[M]^+$ (3), 292 (90), 266 (100), 251 (74).

**2,2′-Methylenebis(3,5,8-trihydroxy-6,7-dimethoxy-1,4-naphthoquinone) (8b)** was obtained by the reaction of naphthazarin **3a** with paraformaldehyde (**7b**). The yield was 98%, m.p. 208—211 °C. Found (%): C, 55.09; H, 3.78. $C_{25}H_{20}O_{14}$. Calculated (%): C, 55.15; H, 3.70. IR ($CHCl_3$), ν/cm$^{-1}$: 3517, 3400, 3004, 2947, 1598, 1463, 1417, 1340, 1292. $^1$H NMR ($CDCl_3$), δ: 3.87 (s, 2 H, $CH_2$); 4.05, 4.12 (both s, 6 H each, OMe); 8.63 (br.s, 2 H, C(2)OH, C(2′)OH); 12.43, 13.26 (both s, 2 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 183.1, 175.5, 160.0, 158.9, 155.5, 149.9, 146.7, 120.9, 106.9, 106.1, 61.7, 61.6, 17.4. MS, $m/z$ ($I_{rel}$ (%)): 544 $[M]^+$ (26), 526 (16), 511 (6), 266 (100), 251 (88).

**2,2′-[(4-Methoxyphenyl)methylene]bis(3,5,8-trihydroxy-6,7-dimethoxy-1,4-naphthoquinone) (8c)** was obtained by the reaction of naphthazarin **3a** with 4-methoxybenzaldehyde (**7c**). The yield was 65%, m.p. 133—136 °C. Found (%): C, 59.01; H, 4.09. $C_{32}H_{26}O_{15}$. Calculated (%): C, 59.08; H, 4.03. IR ($CHCl_3$), ν/cm$^{-1}$: 3380, 3006, 2945, 2840, 1598, 1511, 1462, 1417, 1344, 1293. $^1$H NMR ($CDCl_3$), δ: 3.79 (s, 3 H, OMe); 4.05, 4.12 (both s, 6 H each, OMe); 6.20 (s, 1 H, CH); 6.83, 7.15 (both d, 2 H each, Ar, $J$ = 8.7 Hz); 7.88 (br.s, 2 H, C(2)OH, C(2′)OH); 12.21, 13.33 (both s, 2 H each, α-OH). $^{13}$C NMR ($CDCl_3$), δ: 183.5, 176.3, 159.1, 158.6, 158.3, 155.6, 150.5, 146.4, 129.2, 129.1, 122.9, 114.0, 106.8, 106.3, 61.7, 61.6, 55.2, 36.0. MS, $m/z$ ($I_{rel}$ (%)): 389 (100), 368 (62), 344 (52), 322 (46), 266 (32), 251 (25).

**Demethylation of methoxy groups of bisnaphthazarins 8a—c (general procedure).** The corresponding bisnaphthazarin **8a—c** (0.15 mmol) was added to a saturated solution of $AlCl_3$ in $PhNO_2$ (2 mL). The reaction mixture was stirred for 12 h at 70 °C, then cooled, and treated with 5% aq. HCl (100 mL), $PhNO_2$ was extracted with $CHCl_3$. The aqueous layer was refluxed for 1 h, cooled, and extracted with AcOEt. The extract was dried with $Na_2SO_4$ and concentrated *in vacuo*. Products **6a—c** were isolated from the residue by PTLC (*n*-hexane—acetone, 2 : 1).

**2,2′-(Ethane-1,1-diyl)bis(3,5,6,7,8-pentahydroxy-1,4-naphthoquinone) (6a)** was obtained from compound **8a**. The yield was 80%, m.p. >300 °C (*cf.* Ref. 3: m.p. >300 °C). Found (%): C, 52.56; H, 2.84. $C_{22}H_{14}O_{14}$. Calculated (%): C, 52.60; H, 2.81. $^1$H NMR (DMSO-$d_6$), δ: 1.62 (d, 3 H, Me, $J$ = 7.0 Hz); 4.78 (q, 1 H, CH, $J$ = 7.0 Hz); 10.31 (br.s, 6 H, OH); 12.70, 13.56 (both br.s, 2 H each, α-OH). $^{13}$C NMR (DMSO-$d_6$), δ: 170.7, 170.2, 169.4, 161.0, 155.4, 142.6, 139.5, 124.7, 105.9, 101.9, 27.6, 17.5. MS, $m/z$ ($I_{rel}$ (%)): 502 $[M]^+$ (3), 266 (12), 238 (54), 210 (100).

**2,2′-Methylenebis(3,5,6,7,8-pentahydroxy-1,4-naphthoquinone) (6b)** was obtained from compound **8b**. The yield was 55%, m.p. >300 °C. Found (%): C, 51.61; H, 2.54. $C_{21}H_{12}O_{14}$. Calculated (%): C, 51.65; H, 2.48. $^1$H NMR (DMSO-$d_6$), δ: 3.85 (s, 2 H, $CH_2$); 10.06, 10.20, 10.45, 12.72, 13.31 (all br.s, 2 H each, OH). $^{13}$C NMR (DMSO-$d_6$), δ: 172.4, 170.9, 168.2, 158.9, 154.7, 142.2, 139.7, 120.6, 106.1, 101.8, 17.2. MS, $m/z$ ($I_{rel}$ (%)): 488 $[M]^+$ (16), 251 (10), 238 (10).

**2,2´-[(4-Hydroxyphenyl)methylene]bis(3,5,6,7,8-pentahydroxy-1,4-naphthoquinone) (6c)** was obtained from compound **8c**. The yield was 39%, m.p. >300 °C. Found (%): C, 55.71; H, 2.82. $C_{27}H_{16}O_{15}$. Calculated (%): C, 55.87; H, 2.78. $^1$H NMR ($CD_3OD$), δ: 6.24 (s, 1 H, CH); 6.67, 7.01 (both d, 2 H each, Ar, $J$ = 8.5 Hz). $^{13}$C NMR ($CD_3OD$), δ: 174.2, 172.8, 171.2, 161.5, 157.4, 157.3, 143.9, 141.2, 132.1, 130.9, 124.7, 116.5, 108.6, 104.3, 38.3. MS, $m/z$ ($I_{rel}$ (%)): 238 (50), 210 (100), 168 (24), 94 (86).

This work was partially financially supported by the Presidium of the Russian Academy of Sciences (Program "Molecular and Cell Biology", Grant 09-I-P22-06) and jointly by the Far-Eastern, Siberian, and Ural Branches of RAS (Interdisciplinary Integration Project, Grant 09-II-SU-05-001).

## References

1. V. Ph. Anufriev, V. L. Novikov, *Tetrahedron Lett.*, 1995, **36**, 2515.
2. V. F. Anufriev, S. G. Polonik, N. D. Pokhilo, N. N. Balaneva, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 2128 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 2247].
3. R. H. Thomson, *Naturally Occurring Quinones*, 2nd ed., Academic Press, London—New York, 1971, 734 pp.
4. R. H. Thomson, *Naturally Occurring Quinones*; 3rd ed., Chapman and Hall, London—New York, 1987, 732 pp.
5. R. H. Thomson, *Naturally Occurring Quinones*; 4th ed., Blackie Academic and Professional, London—New York, 1997, 746 pp.
6. V. Ph. Anufriev, V. L. Novikov, O. B. Maximov, G. B. Elyakov, D. O. Levitsky, A. V. Lebedev, S. M. Sadretdinov, A. V. Shvilkin, N. I. Afonskaya, M. Ya. Ruda, N. M. Cherpachenko, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 587.
7. N. D. Pokhilo, M. I. Shuvalova, M. V. Lebedko, G. I. Sopelnyak, A. Ya. Yakubovskaya, N. P. Mischenko, S. A. Fedoreyev, V. Ph. Anufriev, *J. Nat. Prod.*, 2006, **69**, 1125.
8. Pat. RF 98118370, 1998; *Byul. Isobret.* [*Invention Bull.*], 1998, 22; *Chem. Abstrs*, 2000, **132**, 284239b.
9. Pat. RF 98118369, 1998; *Byul. Isobret.* [*Invention Bull.*], 1998, 26; *Chem. Abstrs*, 2000, **132**, 284240v.
10. D. N. Pelageev, M. N. Panchenko, N. D. Pokhilo, V. A. Denisenko, V. F. Anufriev, *Khim. Prirod. Soedin.*, 2008, **44**, 581 [*Chem. Nat. Compd.* (*Engl. Transl.*), 2008, **44**, 719].
11. R. E. Moore, H. Singh, C. W. J. Chang, P. J. Scheuer, *Tetrahedron*, 1967, **23**, 3271.
12. V. F. Anufriev, A. Ya. Chizhova, V. A. Denisenko, V. L. Novikov, *Zh. Org. Khim.*, 1993, **29**, 2008 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 1993, **29**].
13. J. W. Mathieson, R. H. Thomson, *J. Chem. Soc.*, 1971, 153.
14. N. K. Utkina, A. P. Shchedrin, O. B. Maximumov, *Khim. Prirod. Soedin.*, 1976, 439; *Chem. Abstrs*, 1977, **85**, 156788d.
15. V. P. Glazunov, A. Ya. Tchizhova, N. D. Pokhilo, V. Ph. Anufriev, G. B. Elyakov, *Tetrahedron*, 2002, **58**, 1751.
16. A. Ya. Chizhova, T. Yu. Kochergina, V. F. Anufriev, V. A. Denisenko, V. P. Glazunov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 947 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1999, **48**, 938].
17. R. E. Moore, I. Singh, P. J. Scheuer, *J. Org. Chem.*, 1966, **31**, 3645.

*Received March 10, 2010*