Chemistry of naphthazarin derivatives
8.* Determination of structures of substituted 2-hydroxy-6(7)-methoxynaphthazarins and 7(8)-hydroxypyranonaphthazarins by IR spectroscopy

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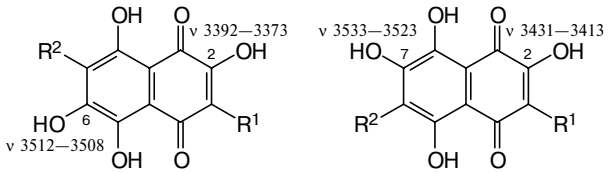
A set of substituted 2-hydroxy-6(7)-methoxynaphthazarins and 7(8)-hydroxypyranonaphthazarins were synthesized. The IR spectra of 2-hydroxy-6-methoxynaphthazarins and 7-hydroxypyranonaphthazarins, on the one hand, and of 2-hydroxy-7-methoxynaphthazarins and 8-hydroxypyranonaphthazarins, on the other hand, have the characteristic nonoverlapping intervals of stretching vibration frequencies of the β-hydroxy groups. These regularities confirm the structures of cristazarin and 6-methylcristazarin, which are metabolites of lichen *Cladonia cristatella*.

Key words: 5,8-dihydroxy-1,4-naphthoquinone, naphthazarin; 2,5,8-trihydroxy-6(7)-methoxy-1,4-naphthoquinone; 5,7(8),10-trihydroxy-2-methyl-2-(4-methyl-3-penten-1-yl)-2*H*-naphtho[2,3-b]pyran-6,9-dione; 3-ethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone, cristazarin, 3-ethyl-2,5,8-trihydroxy-7-methoxy-6-methyl-1,4-naphthoquinone, 6-methylcristazarin, stretching vibration frequencies of the β-hydroxy group; IR spectra of hydroxynaphthazarins, *Cladonia cristatella*.

The determination of the relative arrangement of the β-hydroxy groups in substituted 2,6(7)-dihydroxynapthazarins (2,5,6(7),8-tetrahydroxy-1,4-naphthoquinones) presents serious difficulties.[1] With the aim of overcoming these difficulties, we synthesized a set of substituted 2,6-dihydroxy- (**1a—e**) and 2,7-dihydroxynapthazarins (**2a—e**) and demonstrated that the stretching vibration frequencies ν(OH) of the β-hydroxy groups of the quinoid and aromatic moieties of the molecules are observed in the characteristic nonoverlapping intervals of the IR spectra. As a result of the present investigation, the structure of cuculoquinone, which has been identified previously as 7,7′-bis(3-ethyl-2,5,6,8-tetrahydroxynaphthalene-1,4-dione),[2] was revised. We established that this compound has the structure of 6,6′-bis(3-ethyl-2,5,7,8-tetrahydroxynaphthalene-1,4-dione).[3,4]



1a—e **2a—e**

	a	b	c	d	e
R^1	H	Et	Cl	Et	Et
R^2	H	H	H	Cl	Et

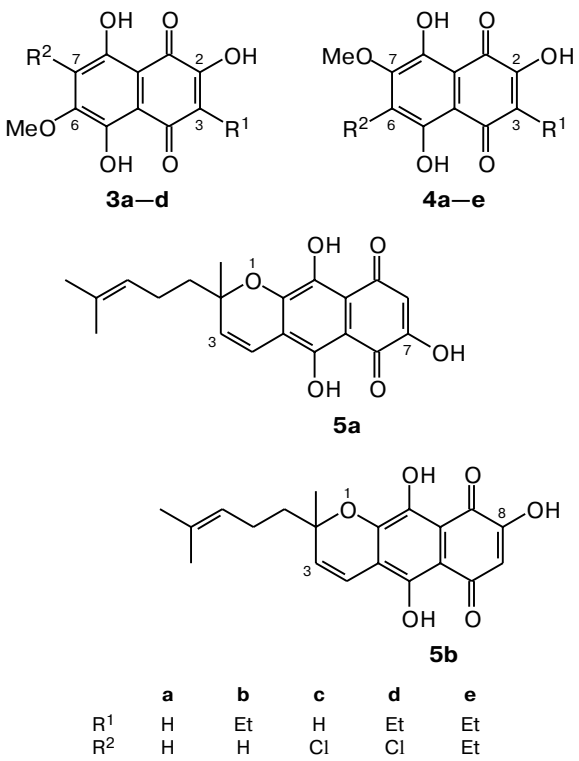
Analysis of the structures of monomethyl ethers of substituted 2,6(7)-dihydroxynapthazarins presents problems analogous to those that emerge in determining the structures of their O-demethylated analogs because the available physicochemical methods do not allow unambiguous conclusions about the relative arrangement of the substituents at the C(2), C(3), C(6), and C(7) atoms. The development of new procedures for investigation of the structures of monoalkyl ethers of 2,6(7)-dihydroxynaphthazarins is also of great importance in connection with the discovery of these compounds in nature.[3,5] To solve this problem, we synthesized several pairs of substituted 2-hydroxy-6(7)-methoxynaphthazarins **3a—d** and **4a—e** and 7(8)-hydroxypyranonaphthazarins **5a** and **5b**.

Methylation of 2,6-dihydroxynapthazarins (**1a—d**) and 2,7-dihydroxynapthazarins (**2a—e**) with diazomethane under controlled conditions afforded the corresponding 2-hydroxy-6-methoxy (**3a—d**) and 2-hydroxy-7-methoxy derivatives (**4a—e**). The direction of methylation of 2,6-dihydroxy- (**1c,d**) and 2,7-dihydroxynaphthazarins (**2c,d**) at position 2 is affected by the chlorine atom at the C(3) atom, which increases the acidity of the corresponding β-hydroxy group (products **3c,d** and **4c,d**, respectively).[6] The reaction is accompanied by the formation of substantial amounts of dimethyl ethers (see Experimental). In the case of isomompain **1a** and mompain **2a**, these ethers predominate due to the tautomerism resulting in the equalization of the acidity

* For Part 7, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 92—97, January, 2001.

1066-5285/00/5001-0095 $25.00



	a	b	c	d	e
R^1	H	Et	H	Et	Et
R^2	H	H	Cl	Cl	Et

of the β-hydroxy groups in the quinoid and aromatic moieties in the case of the identical spatial environment about these groups.[7] Hydroxypyranonaphthazarins **5a** and **5b** were prepared by the acid-catalyzed reactions of dihydroxynaphthazarins **1a** and **2a**, respectively, with citral.[8] The resulting compounds were studied by IR spectroscopy in chloroform solutions. In the IR spectra (KBr), the absorption region for the β-hydroxy groups of the compounds under study (3300—3600 cm^{-1}) is poorly informative.[1]

It is known that naphthazarins in solutions undergo rather rapid prototropic tautomerism.[9] The β-hydroxy group in substituted hydroxynaphthazarins has a pronounced effect on the tautomeric equilibrium by shifting it to the isomer containing the OH group in the quinoid moiety[10] (Scheme 1). This fact was also confirmed by IR spectral data. Thus, the IR spectrum of naphthopurpurin **6** in $CHCl_3$ has a ν(OH) stretching absorption band at 3412 cm^{-1} belonging to the β-hydroxy group linked to the carbonyl group at the C(1) atom (structure **6**(**B**)) through an intramolecular hydrogen bond.[1] In the IR spectrum of monomethyl ether of mompain **4a** in $CHCl_3$, the ν(OH) absorption band of the β-hydroxy group is also observed in the "quinoid" region (at 3422 cm^{-1}). The spectra in chloroform solutions measured at different concentrations (from $4 \cdot 10^{-2}$ to $2 \cdot 10^{-3}$ mol L^{-1}) and the results of the change of the polar solvent $CHCl_3$ for nonpolar CCl_4 demonstrated that this band at 3422 cm^{-1} belongs to the β-hydroxy group linked to the carbonyl group at the C(1) atom (structure **4a**(**B**)) through an intramolecular hydrogen bond. The low-

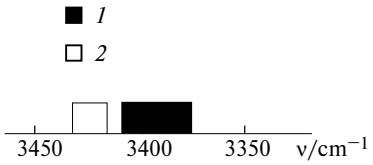
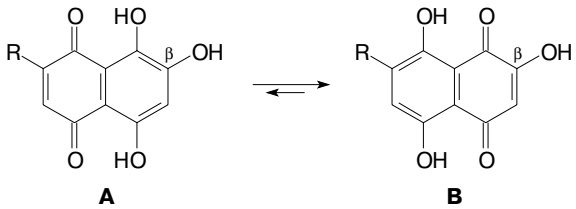


Fig. 1. Ranges of stretching vibration frequencies of the β-hydroxy group in the IR spectra of chloroform solutions of 2-hydroxy-6-methoxynaphthazarins **3a—d** (*1*) and 2-hydroxy-7-methoxynaphthazarins **4a—e**, **7**, and **8** (*2*).

intensity (the intensity is approximately 3—4 times smaller than that of the band at 3422 cm^{-1}) broad diffuse absorption band at 3400—2200 cm^{-1} with the maximum at ~3000 cm^{-1} belongs to the stretching vibration of the α-hydroxy group.[1]*

Scheme 1



6: R = H, **4a:** R = OMe

More detailed examination of the IR spectra of 2-hydroxy-6(7)-methoxynaphthazarins (**3a—d** and **4a—e**) revealed the dependence of the stretching vibration frequency of the β-hydroxy group in the quinoid moiety of the molecule on the position (6 or 7) of the methoxy group in the aromatic nucleus. Thus, the ν(OH) frequencies of the β-hydroxy group in 2-hydroxy-6-methoxynaphthazarins **3a** (3392 cm^{-1}), **3b** (3397 cm^{-1}), and **3d** (3381 cm^{-1}) (Fig. 1, Table 1) confirm that these compounds are derivatives of 2,6-dihydroxynaphthazarins **1a—e** (3394 $cm^{-1} \geq \nu(OH) \geq 3373$ cm^{-1} for the quinoid β-hydroxy group).[1] In the spectrum of monomethyl ether of chloromompain **3c**, the stretching vibration frequency of the β-hydroxy group (3409 cm^{-1}) is shifted by 15 cm^{-1} to the high-frequency region, but this band also does not overlap with the region of the ν(OH) frequencies for 2-hydroxy-7-methoxynaphthazarins **4a—e**. However, the IR spectra of 2-hydroxy-7-methoxynaphthazarins **4a—e** have the absorption bands of the β-hydroxy groups in the region of 3424—3417 cm^{-1} and the ν(OH) frequencies fall totally in the corresponding range found previously for the initial 2,7-dihydroxynaphthazarins **2a—e** (3431 $cm^{-1} \geq \nu(OH) \geq 3413$ cm^{-1} for the quinoid β-hydroxy group).[1]

The stretching vibration frequencies of the β-hydroxy groups in the IR spectra of hydroxypyranonaphthazarins

* This poorly informative absorption band is observed in the IR spectra of all compounds under study and is not reported in the Experimental section.

Table 1. Stretching vibration frequencies of the β-OH groups in the IR spectra of the compounds synthesized

Compound	ν/cm^{-1}	Compound	ν/cm^{-1}
3a	3392	**4d**	3421
3b	3397	**4e**	3417
3c	3409	**5a**	3395
3d	3381	**5b**	3414
4a	3422	**7**	3417
4b	3424	**8**	3419
4c	3418		

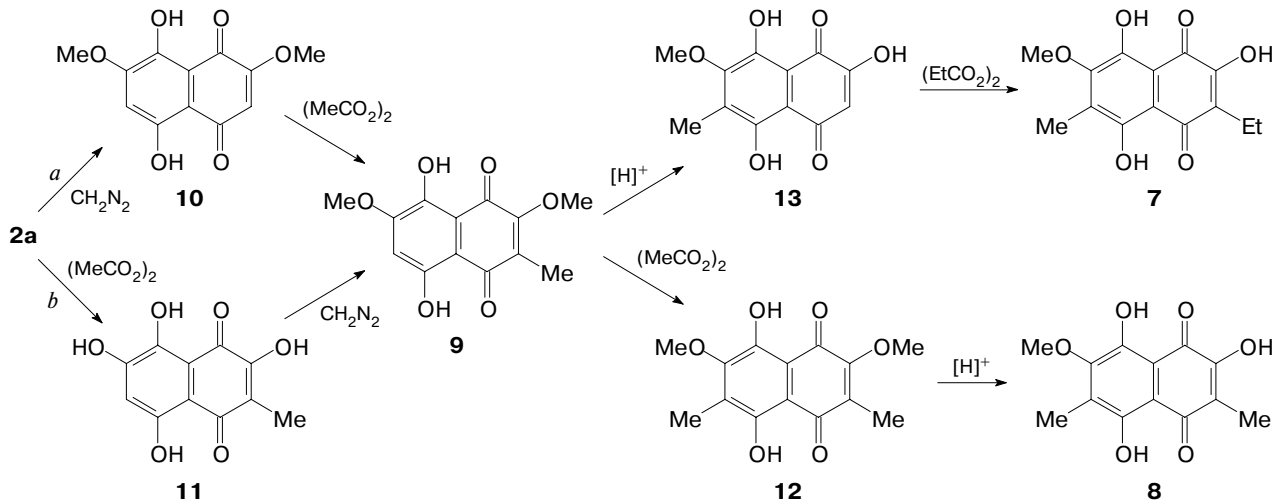
are also in good agreement with the ranges of the corresponding values found for the series of 2,6- and 2,7-dihydroxynaphthazarins and their monomethyl ethers. Thus, the ν(OH) absorption band of the β-hydroxy group in pyranonaphthazarin **5a** is observed at 3395 cm^{-1}, which indicates that this compound belongs to 2,6-dihydroxynaphthazarin derivatives. The IR spectrum of pyranonaphthazarin **5b**, which is an isomer of compound **5a**, has the stretching absorption band of the β-hydroxy group at 3414 cm^{-1} (see Table 1), which indicates that this compound belongs to 2,7-dihydroxynaphthazarin derivatives.

The regularity revealed for the stretching vibration frequencies of the β-hydroxy group in the IR spectra allows one to unambiguously identify substituted 6- and 7-alkoxy-2-hydroxynaphthazarins. In addition to cristazarin **4b**, this possibility was demonstrated using another pigment of lichen *Cladonia cristatella*, *viz.*, 6-methylcristazarin **7**, and its homolog **8** as examples (see Fig. 1, Table 1). It should be mentioned that compound **7** has been previously assigned to the series of 2,7-dihydroxynaphthazarin derivatives based on the biosynthesis of 6-methylcristazarin enriched with ^{13}C atoms and on a comparison of its ^{13}C NMR spectrum with that of the standard product.[5] Our investigation demonstrated that the absorption band of the β-hydroxy group in the IR spectrum of a chloroform solution of compound **7** is observed at 3417 cm^{-1}, which is typical of 2-hydroxy-7-methoxynaphthazarin derivatives. The stretching vibration frequency of the β-hydroxy group in the IR spectrum of compound **8** (3419 cm^{-1}) also falls in the range found for derivatives of monomethyl ether of mompain **4a—e**. We synthesized 6-methylcristazarin **7** and its homolog **8** starting from mompain **2a** according to Scheme 2.[11]

Of two paths presented in Scheme 2 (*a* and *b*), which give rise to the key substrate **9** in the synthesis of pigment **7**, the first path proved to be practically more convenient due to the fact that the purification of intermediates of conversion **2a**→**10**→**9** is less a problem than that associated with the purification of intermediates of conversion **2a**→**11**→**9**, the total yield of the target product **9** being the same (~25%). Free-radical C-methylation of dimethoxynaphthazarin **10** with acetyl peroxide gave rise to product **12** along with compound **9**. Under particular conditions, the former compound was obtained as the major product. Mild acid hydrolysis of dimethyl ethers **9** and **12** afforded 2-hydroxy-7-methoxynaphthazarin (**13**) and its methyl analog **8**, respectively. Pigment **7** was prepared by free-radical C-ethylation of hydroxynaphthazarin **13** under the action of propionyl peroxide.

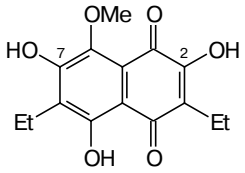
The IR spectra of the resulting compounds always have the stretching absorption band of the β-hydroxy group in the benzoid region[1] along with the stretching absorption band of the β-hydroxy group adjacent to the carbonyl quinoid group, which indicates that the tautomeric equilibrium actually occurs (see Scheme 1). In the spectra of different compounds, the intensity of the absorption band of the β-hydroxy group in the benzoid fragment changes from weak (~5%) to strong (~35%) with respect to that of the quinoid fragment. Investiga-

Scheme 2



tion of this interesting phenomenon is beyond the scope of the present study and will be reported elsewhere.

Unlike the IR spectra of 2-hydroxy-6(7)-methoxynaphthazarins **3a—d**, **4a—e**, **7**, and **8**, the spectrum of the 8-methoxy derivative of 2,7-dihydroxynaphthazarin **14**, which is one of the products of methylation of substrate **2e** with diazomethane, has the stretching absorption bands of the β-hydroxy groups at the C(2) and C(7) atoms at 3385 and 3498 cm^{-1}, respectively. Their ν(OH) frequencies fall in the ranges, which overlap with those found for the stretching absorption bands of the β-hydroxy group in the spectra of 2-hydroxy-6-methoxynaphthazarin derivatives **3a—d**. The determination of the structures of products of type **14** occurring in nature[3,12] by IR spectroscopy requires investigation of the corresponding series of model compounds.



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Experimental

The melting points were determined on a Boetius heating stage and were not corrected. The IR spectra were measured on a Bruker Vector 22 Fourier spectrometer (the resolution was 2.0 cm^{-1}) in $CDCl_3$ and $CHCl_3$ using cells with CaF_2 windows and polyethylene gaskets (the thickness of the layer was 0.40—1.50 mm). The stretching vibration frequencies of the β-hydroxy groups were measured after "leveling" of the spectrum. The reproducibility of the results of measurements was not worse than ±0.5 cm^{-1}. The concentrations of solutions of compounds **3a—d**, **4a—e**, **5a,b**, **7**, and **8** were $(2—5) \cdot 10^{-3}$ mol L^{-1}. The ^1H NMR spectra were recorded on a Bruker AC-250 spectrometer (250.13 MHz) in $CDCl_3$, DMSO-d_6, and acetone-d_6 (Me_4Si as the internal standard). The mass spectra (EI) were obtained on an LKB-9000S instrument with direct introduction of the samples; the energies of ionizing electrons were 18 and 70 eV. The course of the reactions and the purities of the compounds were monitored by TLC on Merck 60F-254 plates using the 2 : 1 hexane—acetone system as the eluent. The individual compounds were isolated from mixtures of the reaction products by preparative TLC on plates (20×20 cm) with a nonfixed silica gel layer (H^+ form;[11] 5—40 μm) in the 2 : 1 hexane—acetone system. The yields of the resulting compounds were not optimized. Compounds **1a** and **2a** were prepared according to a procedure reported previously.[11] Compounds **1b—d** and **2b—e** were synthesized according to a known procedure.[1]

2-Hydroxy-6(7)-methoxynaphthazarins 3a—d and 4a—e. The compounds were prepared by treatment of an ethereal solution of the corresponding 2,6(7)-dihydroxynaphthazarin (0.3 mmol) with a solution of diazomethane in diethyl ether.[13] The course of the reaction was monitored by TLC.

Methylation of isomompain (2,5,6,8-tetrahydroxy-1,4-naphthoquinone, **1a**) afforded **2,5,8-trihydroxy-6-methoxy-1,4-naphthoquinone (3a)** in a yield of 11 mg (16%), R_f 0.28, m.p. 224—226 °C (*cf.* lit. data:[7] m.p. 265—267 °C). IR ($CDCl_3$), ν/cm^{-1}: 3512 m, 3392 m (β-OH), 1628 m, 1602 s (C=O), 1582 sh.s (C=C). ^1H NMR ($CDCl_3$), δ: 4.00 (s, 3 H, OCH_3); 6.41 and 6.47 (both s, 1 H each, H(7), H(3)); 12.25 and 13.30 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 236 $[M]^+$ (100), 222 (57), 218 (16), 207 (32), 194 (16). In addition to product **3a**, **5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 44 mg (58%), R_f 0.34, m.p. 275—280 °C (*cf.* lit. data:[7] m.p. 295—296 °C). ^1H NMR ($CDCl_3$), δ: 3.98 (s, 6 H, 2 OCH_3); 6.37 (s, 2 H, H(3), H(7)); 13.09 (s, 2 H, C(8)—OH, C(5)—OH).

Methylation of 3-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone (**1b**) afforded **3-ethyl-2,5,8-trihydroxy-6-methoxy-1,4-naphthoquinone (3b)** in a yield of 51 mg (65%), R_f 0.40, m.p. 198—201 °C. IR ($CDCl_3$), ν/cm^{-1}: 3515 w, 3397 m (β-OH), 1629 m, 1596 s (C=O), 1580 sh.m (C=C). ^1H NMR ($CDCl_3$), δ: 1.15 (t, 3 H, CH_3, J = 7.9 Hz); 2.62 (q, 2 H, CH_2, J = 7.9 Hz); 3.99 (s, 3 H, OCH_3); 6.50 (s, 1 H, H(7)); 7.46 (br.s, 1 H, β-OH); 12.09 and 13.60 (both s, 1 H each, α-OH). ^1H NMR (DMSO-d_6), δ: 1.03 (t, 3 H, CH_3, J = 7.9 Hz); 2.51 (q, 2 H, CH_2, J = 7.9 Hz); 3.93 (s, 3 H, OCH_3); 6.74 (s, 1 H, H(7)); 12.62 and 13.52 (both s, 1 H each, α-OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 265 $[M + 1]^+$ (17), 264 $[M]^+$ (100), 250 (9), 249 (22). In addition to product **3b**, **3-ethyl-5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 18 mg (22%), R_f 0.45, m.p. 139—142 °C. ^1H NMR ($CDCl_3$), δ: 1.15 (t, 3 H, CH_3, J = 7.6 Hz); 2.70 (q, 2 H, CH_2, J = 7.6 Hz); 3.95 and 4.12 (both s, 3 H each, OCH_3); 6.25 (s, 1 H, H(7)); 13.10 and 13.22 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 279 $[M + 1]^+$ (20), 278 $[M]^+$ (100), 264 (17), 263 (37).

Methylation of 3-chloro-2,5,6,8-tetrahydroxy-1,4-naphthoquinone (**1c**) afforded **7-chloro-2,5,8-trihydroxy-6-methoxy-1,4-naphthoquinone (3c)** in a yield of 47 mg (58%), R_f 0.41, m.p. 200—204 °C. IR ($CDCl_3$), ν/cm^{-1}: 3515 m, 3409 m (β-OH), 1661 w, 1624 sh.m, 1607 s (C=O), 1580 m, 1567 m (C=C). ^1H NMR ($CDCl_3$), δ: 4.26 (s, 3 H, OCH_3); 6.44 (s, 1 H, H(3)); 12.32 and 13.24 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 270/272 $[M]^+$ (100), 269/271 $[M - 1]^+$ (20), 252/254 (39), 241/243 (35), 235 (22), 224/226 (22). In addition to product **3c**, **7-chloro-5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 32 mg (38%), R_f 0.43, m.p. 190—194 °C. ^1H NMR ($CDCl_3$), δ: 3.97 and 4.26 (both s, 3 H each, OCH_3); 6.35 (s, 1 H, H(3)); 13.03 and 13.10 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 284/286 $[M]^+$ (100), 283/285 $[M - 1]^+$ (92), 266/268 (25), 255 (19), 249 (12), 236 (9).

Methylation of 7-chloro-3-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone (**1d**) afforded **7-chloro-3-ethyl-2,5,8-trihydroxy-6-methoxy-1,4-naphthoquinone (3d)** in a yield of 54 mg (60%), R_f 0.45, m.p. 137—139 °C. IR ($CDCl_3$), ν/cm^{-1}: 3503 w, 3381 m (β-OH), 1662 w, 1649 m, 1626 m, 1602 s (C=O), 1573 sh.m (C=C). ^1H NMR ($CDCl_3$), δ: 1.16 (t, 3 H, CH_3, J = 7.5 Hz); 2.73 (q, 2 H, CH_2, J = 7.5 Hz); 4.12 (s, 3 H, OCH_3); 7.82 (br.s, 1 H, β-OH); 12.15 and 13.20 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 298/300 $[M]^+$ (61), 297/299 $[M - 1]^+$ (100), 283/285 (19), 282/284 (23), 280 (8), 279 (9), 213 (10). In addition to product **3d**, **7-chloro-3-ethyl-5,8-dihydroxy-2,6-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 19 mg (20%), R_f 0.61, m.p. 136—138 °C (from acetone). ^1H NMR ($CDCl_3$), δ: 1.15 (t, 3 H, CH_3, J = 7.5 Hz); 2.69 (q, 2 H, CH_2, J = 7.5 Hz); 4.12 and 4.25 (both s, 3 H each, OCH_3); 13.10 and 13.15 (both s, 1 H each, α-OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 312/314 $[M]^+$ (100), 311/313 $[M - 1]^+$ (92), 297/299 (12), 296/298 (25), 294 (10), 293 (11), 256 (9).

Methylation of mompain (2,5,7,8-tetrahydroxy-1,4-naphthoquinone, **2a**) afforded **2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (4a)** in a yield of 25 mg (35%), R_f 0.28, m.p. 225—227 °C (*cf.* lit. data:[7] m.p. 240—241 °C). IR ($CDCl_3$), ν/cm^{-1}: 3525 m, 3422 m (β-OH), 1661 w, 1629 m, 1606 s (C=O), 1585 sh.w (C=C). ^{1}H NMR ($CDCl_3$), δ: 3.97 (s, 3 H, OCH_3); 6.48 and 6.53 (both s, 1 H each, H(6), H(3)); 12.08 and 13.11 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 236 [M]$^+$ (100), 223 (9), 218 (22), 208 (13), 206 (17), 205 (11), 193 (15), 190 (14). In addition to product **4a**, **5,8-dihydroxy-2,7-dimethoxy-1,4-naphthoquinone (10)** was isolated from the reaction mixture in a yield of 46 mg (61%), R_f 0.34, m.p. 270—272 °C (*cf.* lit. data:[7] m.p. 273—275 °C). ^{1}H NMR ($CDCl_3$), δ: 3.96 (s, 6 H, 2 OCH_3); 6.40 (s, 2 H, H(6) and H(3)); 12.73 and 13.15 (both s, 1 H each, C(8)—OH, C(5)—OH).

Methylation of 3-ethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (**2b**) afforded **3-ethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (cristazarin, 4b)** in a yield of 54 mg (68%), R_f 0.40, m.p. 230—232 °C (*cf.* lit. data:[5] m.p. 154—157 °C, lit. data:[7] m.p. 230—232 °C). IR ($CDCl_3$), ν/cm^{-1}: 3526 w, 3424 m (β-OH), 1654 w, 1629 m, 1599 s (C=O), 1577 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.16 (t, 3 H, CH_3, J = 7.6 Hz); 2.64 (q, 2 H, CH_2, J = 7.6 Hz); 3.96 (s, 3 H, OCH_3); 6.57 (s, 1 H, H(6)); 7.13 (br.s, 1 H, β-OH); 12.04 and 13.34 (both s, 1 H each, C(8)—OH, C(5)—OH). ^{1}H NMR (DMSO-d_6), δ: 1.05 (t, 3 H, CH_3, J = 7.6 Hz); 2.50 (q, 2 H, CH_2, J = 7.6 Hz); 3.91 (s, 3 H, OCH_3); 6.76 (s, 1 H, H(6)); 11.11 (br.s, 1 H, β-OH); 12.27 and 13.50 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 264 [M]$^+$ (100). In addition to product **4b**, **3-ethyl-5,8-dihydroxy-2,7-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 27 mg (32%), R_f 0.45, m.p. 146—149 °C (*cf.* lit. data:[4,7,14] m.p. 145—147 °C). ^{1}H NMR ($CDCl_3$), δ: 1.16 (t, 3 H, CH_3, J = 7.6 Hz); 2.73 (q, 2 H, CH_2, J = 7.6 Hz); 3.94 and 4.06 (both s, 3 H each, OCH_3); 6.26 (s, 1 H, H(6)); 12.80 and 13.31 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 278 [M]$^+$ (100).

Methylation of 3-chloro-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (**2c**) afforded **6-chloro-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (4c)** in a yield of 50 mg (62%), R_f 0.32, m.p. 234—235 °C. IR ($CDCl_3$), ν/cm^{-1}: 3520 m, 3418 m (β-OH), 1663 w, 1620 m, 1606 s (C=O), 1575 m (C=C). ^{1}H NMR ($CDCl_3$), δ: 4.15 (s, 3 H, OCH_3); 6.45 (s, 1 H, H(3)); 11.97 and 13.37 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 270/272 [M]$^+$ (100), 269/271 [M − 1]$^+$ (36). In addition to product **4c**, **6-chloro-5,8-dihydroxy-2,7-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 25 mg (29%), R_f 0.40, m.p. 195—197 °C. ^{1}H NMR ($CDCl_3$), δ: 3.97 and 4.19 (both s, 3 H each, OCH_3); 6.35 (s, 1 H, H(3)); 12.69 and 13.27 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 284/286 [M]$^+$ (100), 283/285 [M − 1]$^+$ (89), 256 (57).

Methylation of 6-chloro-3-ethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (**2d**) afforded **6-chloro-3-ethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (4d)** in a yield of 68 mg (76%), R_f 0.42, m.p. 172—176 °C. IR ($CDCl_3$), ν/cm^{-1}: 3524 w, 3421 m (β-OH), 1654 w, 1626 m, 1603 s (C=O), 1566 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.15 (t, 3 H, CH_3, J = 7.5 Hz); 2.63 (q, 2 H, CH_2, J = 7.5 Hz); 4.12 (s, 3 H, OCH_3); 11.91 and 13.64 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 298/300 [M]$^+$ (100), 297/299 [M − 1]$^+$ (84), 283/285 (45), 282/284 (37). In addition to product **4d**, **6-chloro-3-ethyl-5,8-dihydroxy-2,7-dimethoxy-1,4-naphthoquinone** was isolated from the reaction mixture in a yield of 21 mg (22%), R_f 0.59, m.p. 129—131 °C. ^{1}H NMR ($CDCl_3$), δ: 1.15 (t, 3 H, CH_3, J = 7.5 Hz), 2.70 (q, 2 H, CH_2, J = 7.5 Hz); 4.10 and 4.21 (both s, 3 H each, OCH_3); 12.82 and 13.33 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 312/314 [M]$^+$ (100), 311/313 [M − 1]$^+$ (70), 297/299 (27), 296/298 (30), 278 (12), 223 (16).

Methylation of 3,6-diethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (**2e**) afforded **3,6-diethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (4e)** in a yield of 32 mg (36%), R_f 0.50, m.p. 115—117 °C. IR ($CDCl_3$), ν/cm^{-1}: 3519 m, 3417 m (β-OH), 1623 m, 1600 s (C=O), 1575 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.15 and 1.18 (both t, 3 H each, CH_3, J = 7.6 Hz); 2.62 and 2.76 (both q, 2 H each, CH_2, J = 7.6 Hz); 4.03 (s, 3 H, OCH_3); 12.01 and 13.54 (both s, 1 H each, C(8)—OH, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 292 [M]$^+$ (17), 291 [M − 1]$^+$ (16), 258 (37), 256 (100), 255 (15). In addition to product **4e**, **3,6-diethyl-2,5,7-trihydroxy-8-methoxy-1,4-naphthoquinone (14)** was isolated from the reaction mixture in a yield of 27 mg (31%), R_f 0.38, m.p. 180—185 °C. ^{1}H NMR ($CDCl_3$), δ: 1.14 and 1.18 (both t, 3 H each, CH_3, J = 7.6); 2.58 and 2.77 (both q, 2 H each, CH_2, J = 7.6 Hz); 3.94 (s, 3 H, OCH_3); 6.62 and 7.53 (both s, 1 H each, β-OH); 13.72 (s, 1 H, C(5)—OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 293 [M + 1]$^+$ (17), 292 [M]$^+$ (100), 291 [M − 1]$^+$ (97), 278 (18), 277 (24).

5,8-Dihydroxy-2,7-dimethoxy-3-methyl-1,4-naphthoquinone (9). A solution of acetyl peroxide in ether[15] was added portionwise to a boiling solution of substrate **10** (175 mg, 0.7 mmol), which was prepared from compound **2a** according to the above-described procedure, in Bu^{t}OH (70 mL). The course of the reaction was monitored by TLC. The reaction was terminated when the degree of conversion reached ~60%. The mixture was concentrated. Chromatography of the residue by preparative TLC afforded product **9** in a yield of 68 mg (37%), R_f 0.42, m.p. 193—195 °C. ^{1}H NMR ($CDCl_3$), δ: 2.22 (s, 3 H, CH_3); 3.94 and 4.04 (both s, 3 H each, OCH_3); 6.26 (s, 1 H, H(6)); 12.78 and 13.29 (both s, 1 H each, α-OH). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 264 [M]$^+$ (100), 263 [M − 1]$^+$ (86), 250 (22), 249 (13), 234 (11). In addition to product **9**, **5,8-dihydroxy-2,7-dimethoxy-3,6-dimethyl-1,4-naphthoquinone (12)** was isolated from the reaction mixture in a yield of 53 mg (27%), R_f 0.66, m.p. 168—171 °C. ^{1}H NMR ($CDCl_3$), δ: 2.19 (s, 6 H, 2 CH_3); 4.06 (s, 6 H, 2 OCH_3); 12.86 and 13.39 (both s, 1 H each, α-OH). MS (EI, 18 eV), *m/z* (I_{rel} (%)): 278 [M]$^+$ (75), 277 [M − 1]$^+$ (100), 263 (53), 262 (52), 235 (36).

2,5,8-Trihydroxy-7-methoxy-6-methyl-1,4-naphthoquinone (13). Concentrated HCl (30 mL) was added dropwise to a boiling solution of dimethyl ether **9** (53 mg, 0.2 mmol) in methanol (30 mL) during 3 min. The reaction mixture was refluxed for 60 min, cooled, diluted with H_2O (50 mL), extracted with chloroform (2×20 mL), washed with a saturated solution of NaCl (2×20 mL), dried with anhydrous Na_2SO_4, and concentrated. Separation by preparative TLC afforded compound **13** in a yield of 20 mg (40%), R_f 0.39, m.p. 228—233 °C. ^{1}H NMR ($CDCl_3$), δ: 2.25 (s, 3 H, CH_3); 4.02 (s, 3 H, OCH_3); 6.38 (s, 1 H, H(3)); 7.29 (br.s, 1 H, β-OH); 13.04 and 13.37 (both s, 1 H each, α-OH). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 250 [M]$^+$ (100), 249 [M − 1]$^+$ (97), 235 (36), 234 (40), 207 (27), 206 (35).

3-Ethyl-2,5,8-trihydroxy-7-methoxy-6-methyl-1,4-naphthoquinone (6-methylcristazarin, 7). Free-radical C-ethylation of substrate **13** (13 mg, 0.05 mmol) in Bu^{t}OH (2 mL) under the action of an ethereal solution of propionyl peroxide[15] according to the procedure used for **9** afforded 6-methylcristazarin **7** in a yield of 6 mg (44%), R_f 0.90, m.p. 152—155 °C (*cf.* lit. data:[5] m.p. 148—151 °C). IR ($CHCl_3$), ν/cm^{-1}: 3518 w, 3417 m

(β-OH), 1658 w, 1623 m, 1598 s (C=O), 1577 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.14 (t, 3 H, CH_3, J = 7.8 Hz); 2.25 (s, 3 H, CH_3); 2.62 (q, 2 H, CH_2, J = 7.8 Hz); 3.99 (s, 3 H, OCH_3); 11.97 and 13.52 (both s, 1 H each, α-OH). ^{1}H NMR (DMSO-d_6), δ: 1.03 (t, 3 H, CH_3, J = 7.7 Hz); 2.14 (s, 3 H, CH_3); 2.48 (q, 2 H, CH_2, J = 7.7 Hz); 3.91 (s, 3 H, OCH_3); 11.28 (br.s, 1 H, β-OH); 12.27 (br.s, 1 H, α-OH); 13.64 (s, 1 H, α-OH). MS (EI, 70 eV), m/z (I_{rel} (%)): 278 $[M]^+$ (53), 277 $[M - 1]^+$(100), 252 (15), 251 (28), 250 (22), 224 (18), 223 (77), 222 (67).

2,5,7,8-Tetrahydro-3-methyl-1,4-naphthoquinone (11). Free-radical C-methylation of mompain **2a** (100 mg, 0.45 mmol) in Bu^{t}OH (50 mL) under the action of acetyl peroxide afforded 2,5,7,8-tetrahydroxy-3-methyl-1,4-naphthoquinone (**11**) in a yield of 46 mg (43%), R_f 0.32, m.p. 238—241 °C. ^{1}H NMR (acetone-d_6), δ: 2.15 (s, 3 H, CH_3); 6.66 (s, 1 H, H(6)); 10.03 (br.s, 1 H, β-OH); 12.15 (br.s, 1 H, OH); 13.40 (s, 1 H, OH). MS (EI, 70 eV), m/z (I_{rel} (%)): $[M]^+$ (100), $[M - 1]^+$ (86).

Methylation of 3-methylmompain **11** (45 mg, 0.19 mmol) with a solution of diazomethane gave rise to dimethyl ether **9** in a yield of 45 mg (89%).

2,5,8-Trihydroxy-7-methoxy-3,6-dimethyl-1,4-naphthoquinone (8). Partial hydrolysis of dimethyl ether **12** (36 mg, 0.13 mmol) under the above-described conditions gave rise to 2,5,8-trihydroxy-7-methoxy-3,6-dimethyl-1,4-naphthoquinone (**8**) in a yield of 9 mg (25%), R_f 0.47, m.p. 206—210 °C. IR ($CDCl_3$), ν/cm^{-1}: 3523 w, 3419 m (β-OH), 1662 w, 1623 m, 1599 s (C=O), 1577 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 2.10 and 2.25 (both s, 3 H each, CH_3); 4.01 (s, 3 H, OCH_3); 7.25 (br.s, 1 H, β-OH); 11.98 and 13.49 (both s, 1 H each, α-OH). MS (EI, 70 eV), m/z (I_{rel} (%)): 264 $[M]^+$ (100), 263 $[M - 1]^+$ (98), 249 (30), 248 (28), 234 (13), 233 (13), 221 (16), 220 (14), 218 (18), 217 (17).

5,7,10-Trihydroxy-2-methyl-2-(4-methyl-3-penten-1-yl)-2*H*-naphtho[2,3-*b*]pyran-6,9-dione (5a). A solution of isomompain **1a** (0.3 mmol), freshly distilled citral (0.3 mmol), and $MeNH_2 \cdot HCl$ (0.4 mmol) in ethanol (10 mL) was kept at ~20 °C for 2 days. The reaction mixture was concentrated to 1—2 mL *in vacuo* at ~20 °C. Then H_2O (10 mL) was added and the mixture was extracted with diethyl ether (3×5 mL). The combined extracts were washed with H_2O and dried with Na_2SO_4. The solvent was removed and the residue was thoroughly dried *in vacuo*. Isolation by preparative TLC with the 3 : 1 hexane—acetone system as the eluent afforded compound **5a** in a yield of 33 mg (32%), R_f 0.38. IR ($CDCl_3$), ν/cm^{-1}: 3520 m, 3395 m (β-OH), 1667 m, 1642 m, 1615 sh.s, 1596 s (C=O), 1560 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.54 (s, 3 H, C(2)—CH_3); 1.56 and 1.69 (both br.s, 3 H each, C(4)—CH_3); 1.68—1.78 (m, 1 H, H_aC(1)); 1.84—2.01 (m, 1 H, H_bC(1)); 2.06—2.23 (m, 2 H, H(2)); 5.09 (br.t, 1 H, H(3), J = 6.3 Hz); 5.69 (d, 1 H, H(3), J = 10.2 Hz); 6.35 (s, 1 H, H(8)); 6.71 (d, 1 H, H(4), J = 10.2 Hz); 12.39 and 13.20 (both s, 1 H each, C(5)—OH, C(10)—OH).

5,8,10-Trihydroxy-2-methyl-2-(4-methyl-3-penten-1-yl)-2*H*-naphtho[2,3-*b*]pyran-6,9-dione (5b). A solution of mompain **2a** (0.3 mmol), freshly distilled citral (0.3 mmol), and $MeNH_2 \cdot HCl$ (0.4 mmol) in ethanol (10 mL) was kept at ~20 °C for 2 days. The reaction mixture was worked up as described for compound **5a**. Product **5b** was obtained in a yield of 36 mg (34%), R_f 0.40. IR ($CDCl_3$), ν/cm^{-1}: 3523 m, 3413 m (β-OH), 1663 m, 1602 s (C=O), 1560 sh.m (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.52 (s, 3 H, C(2)—CH_3); 1.56 and 1.69 (both br.s, 3 H each, C(4)—CH_3); 1.68—1.78 (m, 1 H, H_aC(1)); 1.84—1.99 (m, 1 H, H_bC(1)); 2.06—2.20 (m, 2 H, H(2)); 5.09 (br.t, 1 H, H(3), J = 6.3 Hz); 5.75 (d, 1 H, H(3), J = 10.2 Hz); 6.40 (s, 1 H, H(7)); 6.76 (d, 1 H, H(4), J = 10.2 Hz); 7.14 (br.signal, 1 H, β-OH); 12.00 and 13.36 (both s, 1 H each, C(10)—OH, C(5)—OH). MS (EI, 70 eV), m/z (I_{rel} (%)): 356 (34) $[M]^+$, 273 (100), 272 (46).

This work was partially supported by the Russian Foundation for Basic Research (Project No. 96-15-97316), the USA Civilian Research and Development Foundation (Grant REC-003), and the Ministry of Education of the Russian Federation.

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Received June 15, 2000;
in revised form August 4, 2000