Chemistry of naphthazarin derivatives
9.* Direct observation of prototropic tautomerism of (poly)hydroxynaphthazarins by IR spectroscopy**

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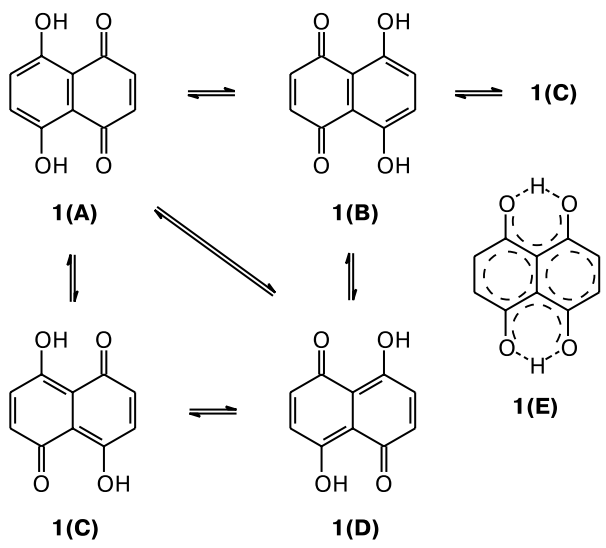
A series of substituted (poly)hydroxylated naphthazarins (5,8-dihydroxy-1,4-naphthoquinones) were synthesized. In general, (poly)hydroxynaphthazarins exist in organic aprotic solvents as mixtures of tautomeric 1,4-naphthoquinonoid forms (IR data). The ratio of tautomers was determined for the first time. The effects of the nature of substituents and the solvent polarity on the tautomeric equilibrium were qualitatively estimated.

Key words: naphthazarin, 5,8-dihydroxy-1,4-naphthoquinone, naphthopurpurin, hydroxydroseron, 3(6)-ethyl-2-hydroxynaphthazarin, cristazarin, aureoquinone, (poly)hydroxynaphthazarins; prototropic tautomerism; IR spectroscopy in solutions.

Prototropic tautomerism of naphthazarin (5,8-dihydroxy-1,4-naphthoquinone, **1**) and its derivatives has been known for a rather long time.[2] However, the high rate of tautomeric exchange makes this phenomenon difficult to study. According to the quantum-chemical data,[3,4] rapid (20—40 MHz) synchronous double tunneling of the OH protons occurs in naphthazarin tautomers **1(A)—(D)** (Scheme 1). The calculations showed that 1,4-naphthoquinonoid forms **1(A)** and **1(B)** are thermodynamically more stable by 25 kcal mol^{-1} than alternative 1,5-naphthoquinonoid forms **1(C)** and **1(D)** and by 29 kcal mol^{-1} than centrosymmetric structure **1(E)*****. ^{1}H, ^{13}C, and ^{17}O NMR studies in solutions revealed a rapid proton exchange in a naphthazarin molecule between the hydroxy and carbonyl groups, which averages the corresponding signals for the H, C, and O atoms in the quinonoid and benzenoid parts of the molecule on the NMR time scale.[6—8] Signals for the C atoms in positions 1 and 4, 5 and 8, 2 and 3, 6 and 7, and 9 and 10 are split only in the ^{13}C NMR spectrum of crystalline naphthazarin cooled to −160 °C.[7]

Earlier,[9—11] *O*-methylation of substituted naphthazarins followed by quantitative ^{1}H NMR analysis of a ratio of the resulting products was proposed for indirect estimation of the content of their tautomeric forms (Scheme 2). This estimation is only approximate since the original tautomers differ in reactivities and the tautomeric equilibrium can be affected by methylating agents.

Scheme 1



This approach cannot be applied to the study of hydroxynaphthazarins. For instance, the quantum-chemical calculations[12] show that the β-OH group in naphthopurpurin (**2a**) completely shifts the tautomeric equilib-

* For Part 8, see Ref. 1.

** In memory of Prof. O. B. Maximov (1911—2001).

*** When the present paper was prepared for publication, some doubt was cast on these calculations in a recent communication.[5]

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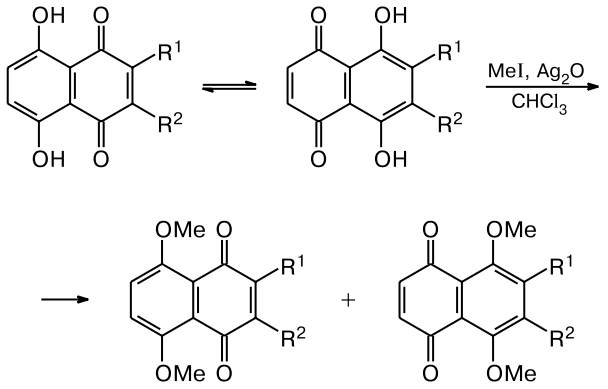
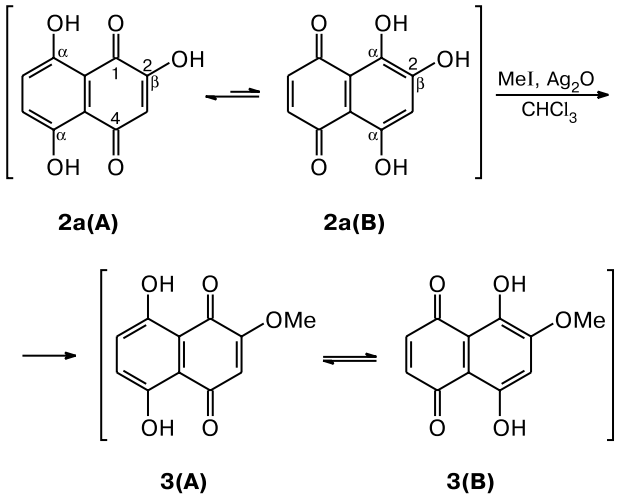
Scheme 2



R^1 = H, R^2 = COMe;
R^1 = R^2 = Cl, Br;
R^1 = H, R^2 = STol, SOTol, SO_2Tol

rium towards tautomer **A** (Scheme 3). However, the β-OH group is more reactive than the α-OH groups and thus is primarily methylated to give methoxy derivative **3**. Clearly, the equilibrium conditions for forms **3(A)** and **3(B)** will differ from those for the starting hydroxynaphthazarin **2a**.

Scheme 3



2a(A) **2a(B)**

3(A) **3(B)**

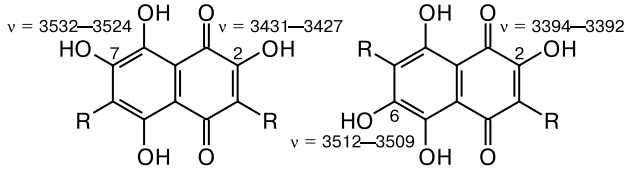
IR spectroscopy is a significantly "faster" method compared to NMR spectroscopy so that IR spectral parameters are not usually time-averaged. However, IR spectroscopy is not applied widely to the study of tautomerism of naphthazarins since the absorption bands of the C—H and C=O stretching vibrations are not very informative. Indeed, in the IR spectra of hydroxynaphthazarins, low-intensity absorption bands ν(C—H) at 3100—3000 cm^{-1} overlap with a broad band of the α-OH groups and a shift of the ν(C=O) bands for the tautomers is smaller than or comparable with the half-widths ($\Delta\nu_{1/2}$) of these bands, which complicates their interpretation. In addition, deuteration experiments showed that the C=O and α-OH stretching vibrations are mixed up in naphthazarin itself.

Moreover, the frequencies of the β-OH stretching vibrations (ν(OH)) in the IR spectra of hydroxynaphthazarins depend on their ability to form intramolecular hydrogen bonds (IMHB) and their strengths.[13] Thus, hydroxynaphthazarins are a convenient system for experimental investigations of prototropic tautomerism.[14]

Recently developed methods for the synthesis of different (poly)hydroxynaphthazarin derivatives have opened practical prospects for the study of their prototropic tautomerism.[1,13—18] To a considerable extent, the study has become possible due to Fourier transform infrared (FT-IR) spectrophotometers put into laboratory practice. Such instruments are more sensitive than common grating spectrophotometers and enable reliably recording and collecting quantitative spectral data for compounds sparingly soluble in low polar solvents; hydroxynaphthazarins are among such compounds. Here we present the results of the IR study of prototropic tautomerism of hydroxynaphthazarins in aprotic organic solvents.

Results and Discussion

As noted above, the ν(OH) vibration frequencies of hydroxynaphthazarins depend on the ability of β-OH group to form IMHB and on their strengths. The IR spectrum of 3,6-diethyl-2,7-dihydroxynaphthazarin (**4c**) in $CDCl_3$ contains two distinct narrow absorption bands at 3427 and 3532 cm^{-1} with $\Delta\nu_{1/2}$ = 46 and 37 cm^{-1} (Fig. 1, spectrum *1*), which were assigned to the stretching vibrations of the β-OH groups in the quinonoid (at the C(2) atom) and benzenoid parts (at the C(7) atom) of the molecule, respectively. The stretching vibrations of the α-OH groups appear as a broad diffuse band in the 3400—2200 cm^{-1} range.[13]



4a—c **5a,b**

4: R = H (**a**), Me (**b**), Et (**c**)
5: R = H (**a**), Et (**b**)

Dilution experiments and a study of the solvent polarity effect on the position of the ν(OH) band revealed a rather strong IMHB (~4.3 kcal mol^{-1}) between the β-OH

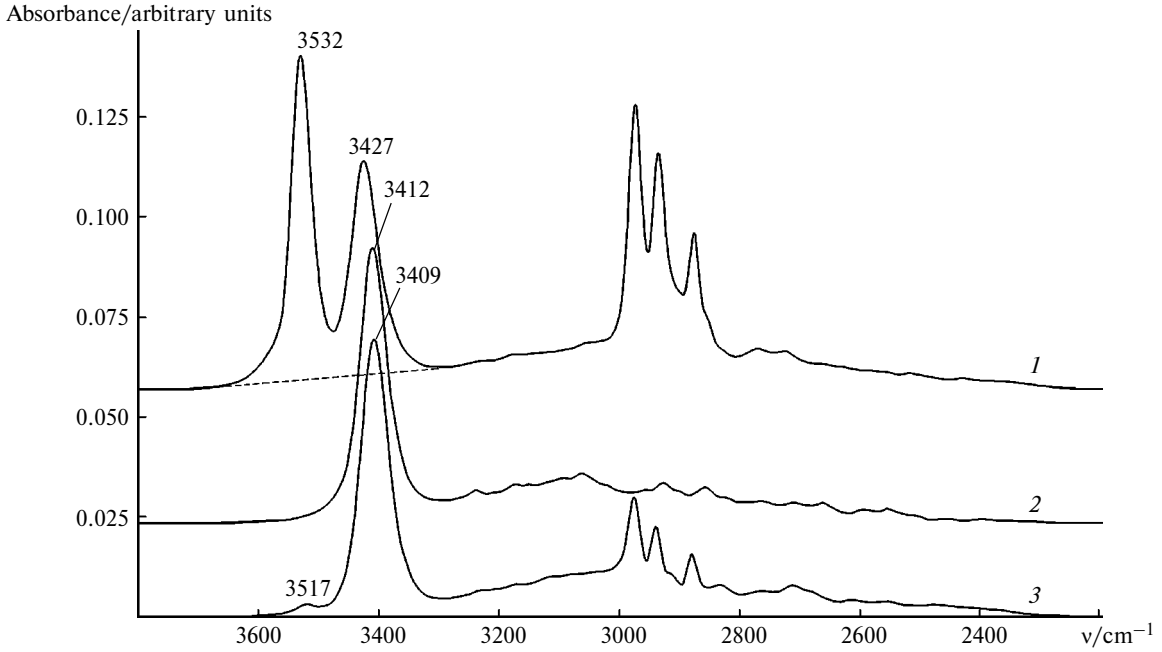


Fig. 1. IR spectra of (*1*) 3,6-diethyl-2,7-dihydroxynaphthazarin (**4c**), (*2*) naphthopurpurin (**2a**), and (*3*) 6-ethyl-2-hydroxynaphthazarin (**2d**) in $CDCl_3$ (high-frequency range).

group at C(2) of the quinonoid moiety and the carbonyl group.[13] At the same time, the β-OH group at C(7) of the benzenoid ring is characterized by higher ν(OH) values and bound to the O atom of the α-OH group at the C(8) atom by a weaker IMHB.

In this study, symmetrical dihydroxynaphthazarins such as mompain (**4a**),[19] aureoquinone (**4b**)[20] (prepared by *C*-methylation of mompain with acetyl peroxide; see Experimental), 3,6-diethyl-2,7-dihydroxynaphthazarin (**4c**), and 2,6-dihydroxynaphthazarins **5a,b**, each containing β-OH groups in both the quinonoid and benzenoid parts of the molecule, were used as basic compounds to develop a method for quantitative determination of the tautomeric ratio of (poly)hydroxynaphthazarins in solutions from the ratio between their absorbances in the maxima or from the ratio between the benzenoid and quinonoid ν(OH) band areas. In the IR spectra of these compounds, the difference between the ν(OH) in the maxima ($\Delta\nu$ = 103—113 cm^{-1}) is larger than, or equal to, the sum of their half-widths ($\Delta\nu_{1/2}$ = 84—103 cm^{-1}); for this reason, overlap of the bands may be ignored. Insofar as these absorption bands overlap the lower-frequency wing of a broad low-intensity absorption band of the α-OH stretching vibration, the spectral characteristics of ν(OH) were measured with reference to a local base line linearly extrapolated to the 3650—3300 cm^{-1} range (see Fig. 1, spectrum *1*). The ratio between the absorbances in the maxima and the ratio between the areas of the benzenoid and quinonoid ν(OH) bands, determined in such a way, were found to be 1.59±0.05 and 1.15±0.01 for basic compounds **4a—c** and **5a,b**, respectively.

It is easy to show that the composition of a tautomeric mixture of monohydroxynaphthazarin derivatives can be determined from the equations

$$[\mathbf{A}] = 100/(1 + R_a/1.59) \quad (1)$$

or

$$[\mathbf{A}] = 100/(1 + R_s/1.15), \quad (2)$$
$$[\mathbf{B}] = 100 - [\mathbf{A}], \quad (3)$$

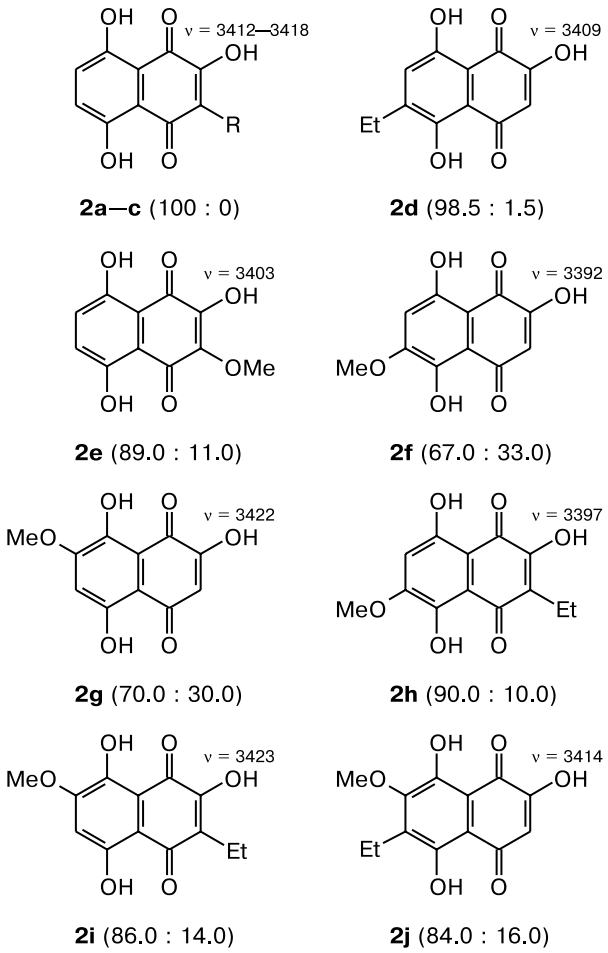
where [**A**] is the percentage of a tautomer of type **A** (*e.g.*, form **2a(A)**, see Scheme 3); [**B**] is the percentage of a tautomer of type **B** (*e.g.*, form **2a(B)**, see Scheme 3); R_a is the ratio between the absorbances in the maxima for the benzenoid and quinonoid ν(OH) bands in the IR spectrum of a compound under study; and R_s is the ratio between the areas of these bands.

The scatter of the values [**A**] calculated by Eqs. (1) or (2) did not exceed 1.5—5%. For this reason, the percentage of tautomers of types **A** and **B** were measured by a simpler and more convenient method, namely, using Eq. (1).

Monohydroxynaphthazarins

We examined compounds **2a—j**, including natural hydroxynaphthazarins **2a—d,i** and monomethyl ethers of dihydroxynaphthazarins (**2e—h,j**) (hereafter, the [**A**] : [**B**] ratio in $CDCl_3$ is given in parentheses).

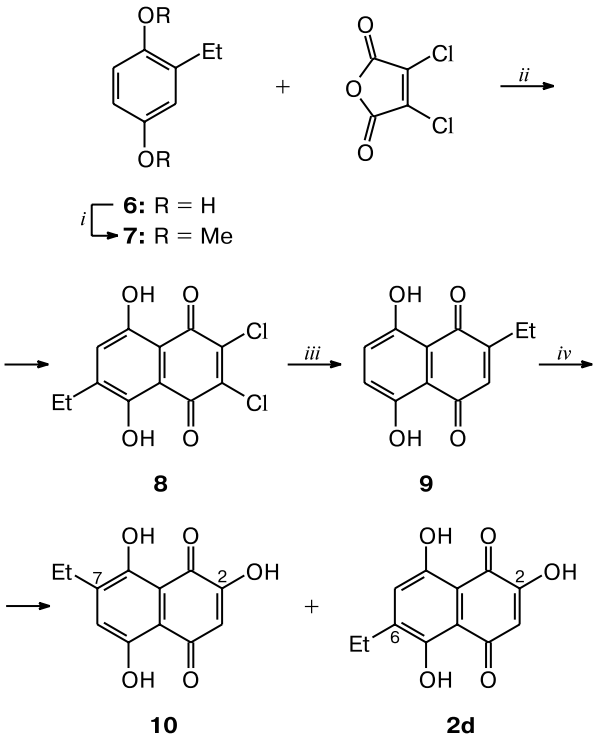
Most of the compounds studied were prepared according to the known procedures (see Experimental).



6-Ethyl-2-hydroxynaphthazarin (**2d**) was synthesized from ethylhydroquinone (**6**) in several steps (Scheme 4).[21] Cycloacylation of ether **7** (prepared by methylation of hydroquinone **6**) with dichloromaleic anhydride gave dichloronaphthazarin **8**, which was transformed into compound **9** by dehalogenation. Oxidation of naphthazarin **9** with MnO_2 in conc. H_2SO_4 afforded a mixture of 7-ethyl- (**10**) and 6-ethyl-2-hydroxynaphthazarins (**2d**), the latter being isolated by chromatography.

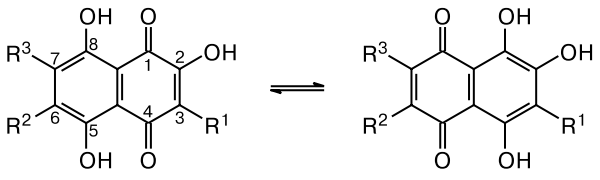
The high-frequency range of the IR spectrum of a solution of naphthopurpurin (**2a**) in $CDCl_3$ contains one narrow absorption band at 3412 cm^{-1} with a half-width of 50 cm^{-1}, which corresponds to ν(OH) (see Fig. 1, spectrum *2*). This indicates that the equilibrium **2a(A)** ⇌ **2a(B)** in the above solution is completely shifted to tautomer **2a(A)**, *i.e.*, no tautomerism of compound **2a** occurs under these conditions (Scheme 5). Thus, the IMHB between the β-OH group at the C(2) atom and the C(1) carbonyl group stabilizes compound **2a** in the tautomeric form **A**. This is in good agreement with the results of the quantum-chemical calculations[12] (see above).

Scheme 4



Reagents and conditions: *i*. Me_2SO_4, NaOH. *ii*. $AlCl_3$, NaCl, 190 °C, 5 min. *iii*. Fe, AcOH. *iv*. MnO_2, H_2SO_4, ~20 °C, 2 h.

Scheme 5



	a	b	c	d	e	f
R^1	H	Me	Et	H	OMe	H
R^2	H	H	H	Et	H	OMe
R^3	H	H	H	H	H	H

	g	h	i	j	k
R^1	H	Et	Et	H	Et
R^2	H	OMe	H	Et	Et
R^3	OMe	H	OMe	OMe	OMe

The introduction of electron-donating alkyl substituents at C(3) of naphthopurpurins (**2b,c**) does not shift the tautomeric equilibrium towards **B**-type tautomers. At the same time, the introduction of the ethyl substituent at position 6 of naphthopurpurin (compound **2d**) results in certain shift of the equilibrium towards tautomer **B**. Indeed, the IR spectrum of compound **2d** contains, along with the ν(OH) absorption band at 3409 cm^{-1} (form **A**),

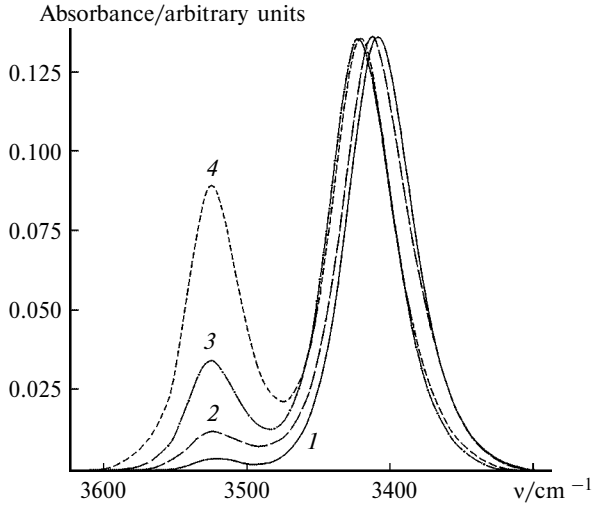


Fig. 2. Fragments of the IR spectra of (*1*) 6-ethyl-2-hydroxynaphthazarin (**2d**), (*2*) 3,6-diethyl-2-hydroxy-7-methoxynaphthazarin (**2k**), (*3*) 3-ethyl-2-hydroxy-7-methoxynaphthazarin (**2i**), and (*4*) 2-hydroxy-7-methoxynaphthazarin (**2g**) in $CDCl_3$ (ν(OH) frequency range).

a very weak band at 3517 cm^{-1} corresponding to tautomer **B** (see Fig. 1, spectrum *3* and Fig. 2, spectrum *1*). The ratio of tautomeric forms **A** and **B**, estimated for hydroxynaphthazarin **2d** from the ratios between the absorbances (R_a) in the maxima of these bands, was found to be 98.5 : 1.5 for tautomers **2d(A)** and **2d(B)** in chloroform.

The tautomeric equilibrium **2(A)** $\rightleftharpoons$ **2(B)** is significantly affected by methoxy groups. Thus 2-hydroxy-3-methoxynaphthazarin (**2e**) exists in chloroform as a mixture of **2e(A)** and **2e(B)** in the 89.0 : 11.0 ratio. Methoxy groups in position 6 or 7 (compounds **2f,g**) have nearly equal effects, shifting the equilibrium even more strongly to tautomer **B** (~30%) (see Fig. 2, spectrum *4*).

Earlier,[6] when interpreting chemical shifts of the protons at the C(3) and C(6) atoms in the ^1H NMR spectrum of compound **2g**, the latter was assumed to exist in chloroform as a ~75 : 25 mixture of two tautomers **2g(A)** and **2g(B)**, which correlates with our IR data (70 : 30). Introduction of the electron-donating ethyl substituent at position 3 of hydroxynaphthazarins **2f,g** (compounds **2h,i)**, shifts the tautomeric equilibrium, though differently, to form **A**. Interestingly, ethyl derivatives of monomethyl ether of mompain (**2i,j**) exist in chloroform as mixtures of tautomers **A** and **B** in the ~85 : 15 ratios irrespective of the position of the ethyl radical relative to the β-OH group (see Fig. 2, spectrum *3*). At the same time, the presence of two ethyl substituents in compound **2k** reduces the percentage of form **B** to 4.5% (see Fig. 2, spectrum *2*).

The half-widths of the ν(OH) absorption bands strongly depend on the solvent polarity. For instance, for the benzenoid β-OH group they change from 35—40 cm^{-1} in $CDCl_3$ to 15—17 cm^{-1} in hexane, and those for the quinonoid β-OH group, from 50—60 to 17—20 cm^{-1}, respectively, which is clearly illustrated with compound **2k** (Fig. 3).

To elucidate how the equilibrium **2(A)** $\rightleftharpoons$ **2(B)** is affected by the nature of substituents, we studied not only natural hydroxynaphthazarins **2a—d,i** and some monomethyl ethers of dihydroxynaphthazarins (**2e—h,j**), but also their analogs **2l—r**.

When a hydroxynaphthazarin molecule contains an electron-withdrawing group (*e.g.*, a Cl atom in compound **2l**) in the ring bearing the β-OH group, the tautomeric equilibrium is considerably shifted to the tautomer of type **B** as compared with compounds **2a—c**. At the same time, replacement of the electron-donating methyl substituents in compounds **2q,r** by electron-withdrawing ones (*e.g.*, Cl atoms in compounds **2m,n**) in the other ring produces no significant shift of the equilibrium. Moreover, within the homologous series of compounds **2m—p**, the tautomeric ratio in chloroform noticeably changes when passing from **2n** to **2o,p**.

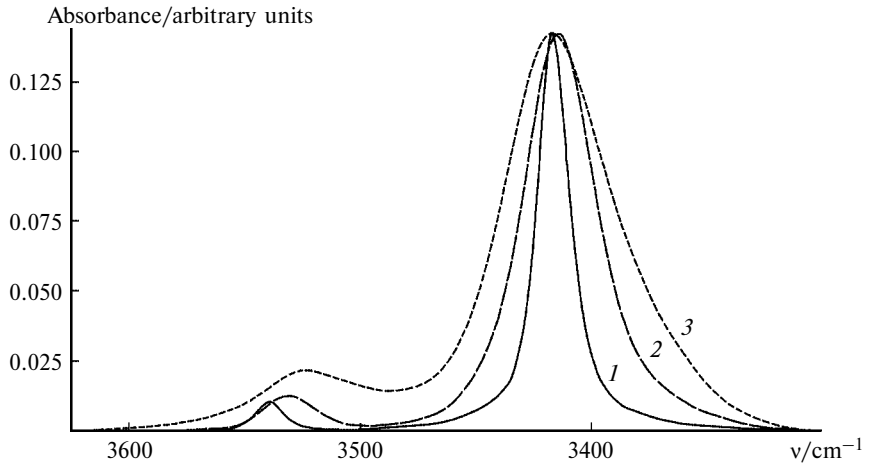
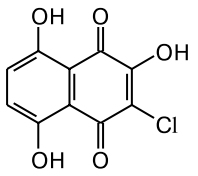
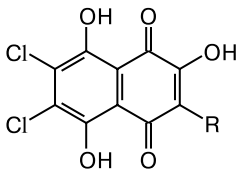


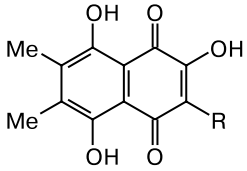
Fig. 3. Fragments of the IR spectra of 3,6-diethyl-2-hydroxy-7-methoxynaphthazarin (**2k**) in (*1*) hexane, (*2*) CCl_4, and (*3*) $CDCl_3$ (ν(OH) frequency range).



2l (91.0 : 9.0)



2m: R = H (94.0 : 6.0)
2n: R = Me (92.0 : 8.0)
2o: R = Et (97.0 : 3.0)
2p: R = Pr (98.0 : 2.0)



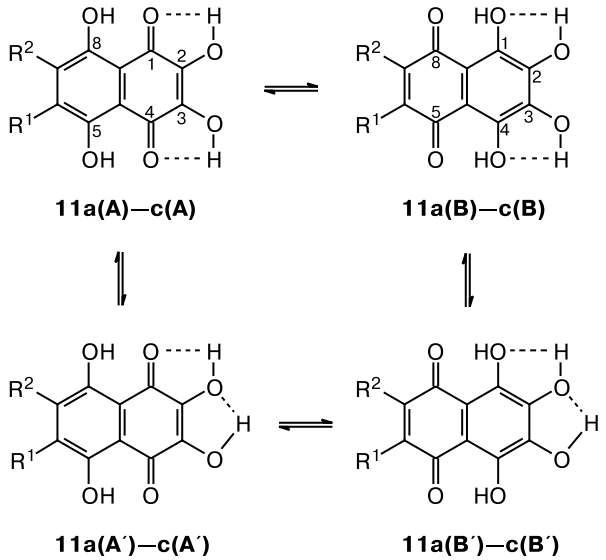
2q: R = H (95.0 : 5.0)
2r: R = Me (93.0 : 7.0)

Thus, the effect of the nature of substituents on the tautomeric equilibrium of hydroxynaphthazarins is hard to analyze since each substituent in a conjugated system interacts with both the β-OH and C=O groups, exerting opposite effects on the strength of the IMHB between them.

Dihydroxynaphthazarins

2,3-Dihydroxynaphthazarins. As already noted, the main factor stabilizing monohydroxynaphthazarins in the tautomeric form **A** (*i.e.*, 2-hydroxy-1,4-naphthoquinone form, see Scheme 5) is an IMHB between the β-OH group at the C(2) atom and the C(1) carbonyl group. However, analysis of the tautomeric equilibrium for 2,3-dihydroxynaphthazarins **11a—c** gave rather unexpected results (Scheme 6).

Scheme 6

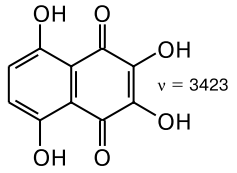


11a(A)—c(A) **11a(B)—c(B)**

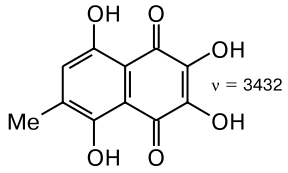
11a(A′)—c(A′) **11a(B′)—c(B′)**

$R^1 = R^2 = H$ (**a**); R^1 = Me, R^2 = H (**b**); $R^1 = R^2$ = Me (**c**)

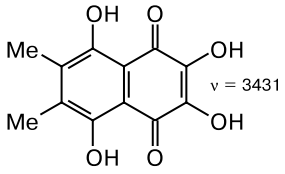
The IR spectra of spinazarins **11a—c** in $CDCl_3$ contain, along with the ν(OH) absorption band at 3431—3433 cm^{-1} of form **A**, a weak band at ~3520—3525 cm^{-1}; this indicates the presence of a second tautomer **B** in solution contrary to the expected single form **A**. In our opinion, tautomeric form **A** of compounds **11a—c** can be destabilized by the formation of other types of IMHB which involve the β-OH groups in positions 2 and 3 (see Scheme 6). This is evidenced by broadened benzenoid ν(OH) bands in the IR spectra; their half-widths ($\Delta\nu_{1/2}$ = 48—52 cm^{-1}) are comparable with $\Delta\nu_{1/2}$ of the quinonoid bands. In this case, the tautomeric [**A**] : [**B**] ratio of compounds **11a—c** in $CDCl_3$ is determined with a lower accuracy and provides no information on the effect of the Me group on the equilibrium for compounds **11a,b** in chloroform*. At the same time, this approach enables one to estimate, though less accurately, a difference in tautomeric compositions for compounds **11a,b** and naphthazarin **11c** containing two Me groups.



11a (94 : 6)



11b (94 : 6)



11c (91 : 9)

Compounds **11a,b** were obtained according to the known procedures, and dimethylspinazarin (**11c**) was synthesized by cycloacylation of 1,2,3,4-tetramethoxybenzene with dimethylmaleic anhydride in an $AlCl_3$—NaCl melt (see Experimental).

2,6(7)-Dihydroxynaphthazarins. As noted above, the IR spectra of isomeric 2,7- and 2,6-dihydroxynaphthazarins containing the same substituents in positions 3 and 6(7) contain two narrow absorption bands at 3540—3390 cm^{-1} corresponding to the β-OH stretching vibrations in the quinonoid and benzenoid moieties. In the IR spectra of non-symmetrically substituted 2,6- and 2,7-dihydroxynaphthazarins, four ν(OH) absorption bands should be expected for two tautomers.

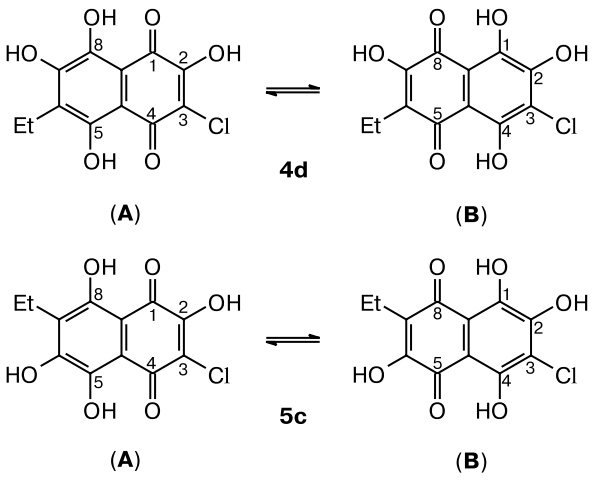
Previous[13,14] IR studies of non-symmetrically substituted 2,6(7)-dihydroxynaphthazarins in $CDCl_3$ showed that changes in frequencies of the absorption bands of the

* Compounds **11a—c** are negligibly soluble in hexane, which makes it impossible to use the aforementioned effect of narrowing ν(OH) absorption bands in their IR spectra.

benzenoid and quinonoid β-OH groups do not exceed 20 cm^{-1}, depending on the donor-acceptor effect of substituents at the C(3) and C(6(7)) atoms, while $\Delta\nu_{1/2}$ is 32—42 and 44—53 cm^{-1}, respectively. According to the Rayleigh criterion for band resolution, these bands cannot be resolved as separate spectral peaks.

As noted above, the ν(OH) band half-widths depend on the solvent polarity. This property allowed us to detect two tautomers of types **A** and **B** for 3-chloro-6-ethyl-2,7-dihydroxynaphthazarin (**4d**) and 3-chloro-7-ethyl-2,6-dihydroxynaphthazarin (**5c**) in hexane (Scheme 7).

Scheme 7



In the IR spectrum of compound **5c** in $CDCl_3$ (Fig. 4, spectrum *1*), the higher-frequency wing of the quinonoid ν(OH) band contains only an ill-resolved shoulder at ~3400 cm^{-1}. In this case, the problem of band deconvolution for the estimation of a tautomeric composition cannot be solved unambiguously. At the same time, this absorption band in hexane appears as a distinct doublet at 3400 and 3376 cm^{-1} (see Fig. 4, spectrum *2*). The first component of the doublet belongs to tautomer **5c(B)** (which follows from comparison of the ν(OH) band frequencies for 3,7-diethyl-2,6-dihydroxynaphthazarin (**5b**)), while the second component corresponds to tautomer **5c(A)**.[13] The β-OH stretching vibration in the benzenoid ring appears as a singlet at 3522 cm^{-1}, probably because of a smaller difference between their frequencies in different tautomers. Resolution of the observed doublet for the quinonoid ν(OH) band into components (see Fig. 4, curves *3*, *3′*) allows one to estimate the ratio of tautomers **A** and **B** simply by determining the ratio of the areas of the resulting components. For compounds **4d** and **5c**, the ratio was found to be 64 : 36. As expected, the dominant tautomers in solution are those of type **A** with a stronger IMHB and the Cl atom in the quinonoid ring.

Hence, we propose a simple and fairly precise method for quantitative determination of the tautomeric ratio of hydroxynaphthazarins in solutions, which is based on measuring the IR spectroscopic parameters of the β-OH groups. No simple correlations were found between the character of substituents and the tautomeric equilibrium state for such a strongly conjugated system as hydroxynaphthazarins.

Experimental

Melting points were determined on a Boetius hot stage and are given uncorrected. IR spectra were recorded on a Bruker Vector-22 FTIR spectrophotometer (resolution 2.0 cm^{-1}) in

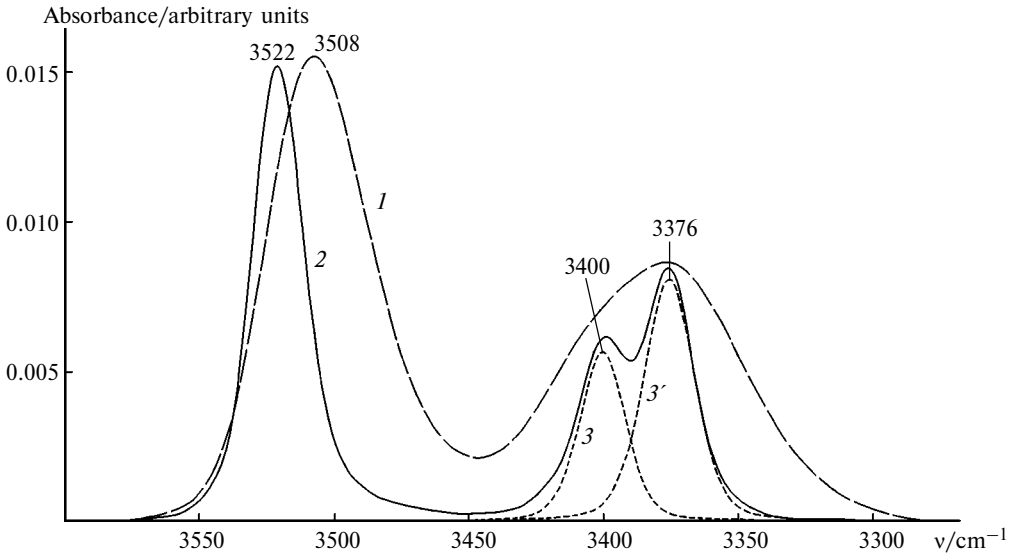


Fig. 4. Fragments of the IR spectra of 3-chloro-6-ethyl-2,6-dihydroxynaphthazarin (**5c**) in (*1*) $CDCl_3$, (*2*) hexane, and (*3*, *3′*) in hexane with band contour splitting (ν(β-OH) frequency range).

$CDCl_3$ in matched cells with CaF_2 windows supplied with polyethylene spacers; the layer thickness was 0.40—1.50 mm. The spectra were "smoothed" before measuring ν(OH) values. For ν(OH) with $\Delta\nu_{1/2}$ = 35—60 cm^{-1}, this procedure did not distort the measured spectroscopic parameters. Frequency measurements were performed with an accuracy of ±0.5 cm^{-1}. The concentrations of solutions of the compounds studied were (2—5)×10^{-3} mol L^{-1}. The ^1H NMR spectra were recorded on a Bruker AC-250 spectrometer (250.13 MHz) in $CDCl_3$, acetone-d_6, and DMSO-d_6 with Me_4Si as the internal standard. Mass spectra (EI) were obtained with an LKB-9000S instrument (direct inlet probe, ionizing energy 70 eV). The course of the reaction was monitored and the purity of the products was checked by TLC on Merck 60F-254 plates in hexane—acetone (2 : 1). Individual compounds were isolated from mixtures of the reaction products by preparative TLC on plates (20×20 cm) with non-fixed silica gel layer (5—40 μm, H^+ form)[18] or by column chromatography on L 40/100 silica gel (H^+ form). The yields of the compounds obtained were not optimized.

2,5,8-Trihydroxy-1,4-naphthoquinone (2a) was prepared according to the known procedure.[22] IR ($CDCl_3$), ν/cm^{-1}: 3412 m (β-OH); 1663 w, 1657 m, 1610 s (C=O); 1575 m (C=C).

2,5,8-Trihydroxy-3-methyl-1,4-naphthoquinone (2b) was prepared according to the known procedure.[16] IR ($CDCl_3$), ν/cm^{-1}: 3418 m (β-OH); 1662 w, 1638 m, 1602 s (C=O); 1571 m (C=C).

3-Ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (2c) was prepared according to the known procedure.[23] IR ($CDCl_3$), ν/cm^{-1}: 3416 m (β-OH); 1655 w, 1634 m, 1603 s (C=O); 1572 m (C=C).

Synthesis of 6-ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (2d)

Dimethyl ether of ethylhydroquinone (7) was obtained as described earlier[24] by methylation of ethylhydroquinone (**6**)[21] with dimethyl sulfate in aqueous NaOH. The yield of compound **7** was 44%, b.p. 98—100 °C (7 Torr). IR ($CDCl_3$), ν/cm^{-1}: 1590, 1501 (C=C). ^1H NMR ($CDCl_3$), δ: 1.19 (t, 3 H, Me, J = 7.8 Hz); 2.64 (q, 2 H, CH_2, J = 7.8 Hz); 3.77, 3.76 (both s, 3 H each, OMe); 6.67 (dd, 1 H, H(5), J_1 = 8.8 Hz, J_2 = 2.9 Hz); 6.75 (d, 1 H, H(3), J = 2.9 Hz); 6.76 (d, 1 H, H(6), J = 8.8 Hz). MS, m/z (I_{rel} (%)): 166 $[M]^+$ (40); 153 (10); 152 (100); 151 (17); 137 (41).

2,3-Dichloro-6-ethyl-5,8-dihydroxy-1,4-naphthoquinone (8). A mixture of dichloromaleic anhydride (23.5 g, 0.14 mol) and ether **7** (10 g, 0.06 mol) were added at 140 °C to a stirred melt of anhydrous $AlCl_3$ (195 g, 1.46 mol) and NaCl (37 g, 0.63 mol). The melt was heated to 190 °C and stirred for an additional 3 min. Then the reaction mixture was cooled and hydrolyzed with 5% HCl. The product was separated, washed with water (100 mL), dried, and purified by column chromatography in hexane—acetone (50 : 1). The yield of compound **8** was 15 g (88%), m.p. 123—125 °C. IR ($CDCl_3$), ν/cm^{-1}: 1617 s (C=O); 1575 m.sh, 1562 s (C=C). ^1H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, Me, J = 7.3 Hz); 2.73 (dq, 2 H, CH_2, J_1 = 7.3 Hz, J_2 = 1.4 Hz); 7.06 (t, 1 H, H(7), J = 1.4 Hz); 12.56, 12.90 (both s, 1 H each, α-OH). MS, m/z (I_{rel} (%)): 286, 288, 290 $[M]^+$ (100); 285, 287, 289 $[M - 1]^+$ (21); 271, 273, 275 $[M - Me]^+$ (7); 268, 270, 272 $[M - H_2O]^+$ (8); 258, 260, 262 $[M - CO]^+$ (12); 257, 259, 261 (5).

2-Ethyl-5,8-dihydroxy-1,4-naphthoquinone (9). A mixture of naphthoquinone **8** (1 g, 3.6 mmol) and powdered Fe (2 g, 36 mg-at.) in 100 mL of AcOH was heated for 30 min. After cooling, the reaction mixture was filtered, and the solvent was removed under reduced pressure. The residue was alkalified with 5% NaOH to pH 8—9, and the resulting mixture was stirred without access for air until the solution turned dark blue (15—40 min). After the reaction was completed, the mixture was acidified with 10% HCl to pH 4—5. The product was extracted with ether. Compound **9** was isolated by column chromatography in hexane—acetone (50 : 1). The yield of **9** was 785 mg (73%), m.p. 125—127 °C (*cf.* Ref. 25: m.p. 123—124 °C). IR ($CDCl_3$), ν/cm^{-1}: 1656 vw, 1611 s (C=O); 1571 m (C=C). ^1H NMR ($CDCl_3$), δ: 1.24 (t, 3 H, Me, J = 7.3 Hz); 2.66 (dq, 2 H, CH_2, J_1 = 7.3 Hz, J_2 = 1.5 Hz); 6.86 (t, 1 H, H(3), J = 1.5 Hz); 7.21 (s, 2 H, H(6), H(7)); 12.47, 12.61 (both s, 1 H each, α-OH). MS, m/z (I_{rel} (%)): 219 $[M + 1]^+$ (13); 218 $[M]^+$ (100); 203 $[M - Me]^+$ (14); 200 $[M - H_2O]^+$ (13); 190 $[M - CO]^+$ (15); 189 (10); 175 (19); 172 (8).

Oxidation of ethylnaphthazarin 9. Powdered MnO_2 (570 mg, 0.8 mmol) was added in small portions at 35 °C over 1 h to a vigorously stirred solution of ethylnaphthazarin **9** (300 mg, 1.4 mmol) in 15 mL of conc. H_2SO_4. The course of the reaction was monitored by TLC. After the reaction was completed, the mixture was poured into ice, and the products were extracted with AcOEt (300 mL). The extract was washed with brine (30 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatography on SiO_2 (1500×15 mm) in CCl_4 gave compounds **2d**[19] (46 mg, 14%) and **10**[6] (98 mg, 30%).

6-Ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (2d). ^1H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, Me, J = 7.8 Hz); 2.77 (q, 2 H, CH_2, J = 7.8 Hz); 6.35, 7.07 (both s, 1 H each, H(3), H(7)); 7.42 (s, 1 H, β-OH); 11.60, 13.31 (both s, 1 H each, α-OH). IR ($CDCl_3$), ν/cm^{-1}: 3517 vw, 3409 m (β-OH); 1662 w, 1631 m, 1607 s (C=O); 1575 m (C=C).

7-Ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (10). ^1H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, Me, J = 7.8 Hz); 2.74 (q, 2 H, CH_2, J = 7.8 Hz); 6.34, 7.18 (both s, 1 H each, H(3), H(6)); 7.42 (s, 1 H, β-OH); 11.99, 12.82 (both s, 1 H each, α-OH).

2,5,8-Trihydroxy-3-methoxy-1,4-naphthoquinone (2e) was obtained according to the known procedure.[26] IR ($CDCl_3$), ν/cm^{-1}: 3492 w, 3403 m (β-OH); 1652 m, 1643 m, 1604 s (C=O); 1573 m (C=C).

2,5,8-Trihydroxy-6-methoxy-1,4-naphthoquinone (2f) was obtained according to the known procedure.[1] IR ($CDCl_3$), ν/cm^{-1}: 3512 m, 3392 m (β-OH); 1628 m, 1602 s (C=O); 1582 sh.s (C=C).

2,5,8-Trihydroxy-7-methoxy-1,4-naphthoquinone (2g) was obtained according to the known procedure.[1] IR ($CDCl_3$), ν/cm^{-1}: 3525 m, 3422 m (β-OH); 1661 w, 1629 m, 1606 s (C=O); 1585 sh.m (C=C).

3-Ethyl-2,5,8-trihydroxy-6-methoxy-1,4-naphthoquinone (2h) was obtained according to the known procedure.[1] IR ($CDCl_3$), ν/cm^{-1}: 3575 w, 3397 m (β-OH); 1629 m, 1596 s (C=O); 1580 sh.m (C=C).

3-Ethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (2i) was obtained according to the known procedure.[1] 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).

6-Ethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (2j) was obtained according to the known procedure.[14] IR ($CDCl_3$), ν/cm^{-1}: 3523 w, 3414 m (β-OH); 1662 m, 1620 s, 1614 s (C=O); 1588 s, 1575 sh.s (C=C).

3,6-Diethyl-2,5,8-trihydroxy-7-methoxy-1,4-naphthoquinone (2k) was obtained according to the known procedure.[1] IR ($CDCl_3$), ν/cm^{-1}: 3524 w, 3417 m (β-OH); 1654 w, 1623 m, 1595 s (C=O); ~1575 sh.m (C=C).

3-Chloro-2,5,8-trihydroxy-1,4-naphthoquinone (2l) was synthesized as described earlier.[27] IR ($CDCl_3$), ν/cm^{-1}: 3502 w, 3395 m (β-OH); 1652 sh.w, 1637 m, 1611 s (C=O); 1577 m, 1519 m (C=C).

6,7-Dichloro-2,5,8-trihydroxy-1,4-naphthoquinone (2m) was synthesized as described earlier.[28] IR ($CDCl_3$), ν/cm^{-1}: 3517 w, 3419 m (β-OH); 1661 w, 1630 s, 1613 s (C=O); 1558 w (C=C).

6,7-Dichloro-2,5,8-trihydroxy-3-methyl-1,4-naphthoquinone (2n) was synthesized as described earlier.[15] IR ($CDCl_3$), ν/cm^{-1}: 3510 w, 3426 m (β-OH); 1660 w, 1632 m, 1607 s (C=O); 1558 w (C=C).

6,7-Dichloro-3-ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (2o) was synthesized as described earlier.[15] IR ($CDCl_3$), ν/cm^{-1}: 3512 w, 3423 m (β-OH); 1654 w, 1630 s, 1606 s (C=O); 1554 w (C=C).

6,7-Dichloro-2,5,8-trihydroxy-3-propyl-1,4-naphthoquinone (2p) was synthesized as described earlier.[15] IR ($CDCl_3$), ν/cm^{-1}: 3514 w, 3422 m (β-OH); 1651 w, 1629 m, 1607 s (C=O); 1553 w (C=C).

2,5,8-Trihydroxy-6,7-dimethyl-1,4-naphthoquinone (2q) was synthesized as described earlier.[29] IR ($CDCl_3$), ν/cm^{-1}: 3520 w, 3406 m (β-OH); 1660 w, 1621 m, 1603 s (C=O); 1578 sh.m (C=C).

2,5,8-Trihydroxy-3,6,7-trimethyl-1,4-naphthoquinone (2r) was synthesized as described earlier.[30] IR ($CDCl_3$), ν/cm^{-1}: 3524 w, 3414 m (β-OH); 1662 w, 1624 m, 1583 s (C=O); 1575 sh.m (C=C).

2,5,7,8-Tetrahydroxy-1,4-naphthoquinone (mompain, 4a) was synthesized as described earlier.[18] IR ($CDCl_3$), ν/cm^{-1}: 3530 m, 3428 m (β-OH); 1602 s (C=O, C=C). IR (dioxane), ν/cm^{-1}: 3198 (β-OH); 1651 w, 1630 m, 1607 s (C=O); ~1585 sh.m (C=C).

2,5,7,8-Tetrahydroxy-3,6-dimethyl-1,4-naphthoquinone (aureoquinone, 4b) (see Ref. 20). Acetyl peroxide[31] was added in small portions to a boiling solution of mompain **4a** [18] (110 mg, 0.5 mmol) in 30 mL of Bu^{t}OH. The reaction was terminated when the conversion was ~60% (TLC). The solvent was removed; preparative TLC of the residue gave 2,5,7,8-tetrahydroxy-3-methyl-1,4-naphthoquinone[1] (R_f 0.32) and product **4b** (35%), R_f 0.43, m.p. 256—260 °C. IR ($CDCl_3$), ν/cm^{-1}: 3532 m, 3428 m (β-OH); 1662 w, 1633 m, 1609 s, 1589 s (C=O); ~1575 sh.s (C=C). ^{1}H NMR (DMSO-d_6), δ: 2.00 (s, 6 H, 2 Me); 11.23, 13.82 (both s, 1 H each, α-OH). ^{1}H NMR (acetone-d_6), δ: 2.12 (s, 6 H, 2 Me); 9.48 (br.s, 2 H, 2 OH); 12.10, 13.72 (both s, 1 H each, α-OH). MS, *m/z* (I_{rel} (%)): 251 $[M + 1]^+$ (23); 250 $[M]^+$ (100); 234 (16); 223 (32); 222 (19).

3,6-Diethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (4c) was obtained according to the known procedure.[13] IR ($CDCl_3$), ν/cm^{-1}: 3532 m, 3427 m (β-OH); 1654 vw, 1630 sh.m, 1602 s (C=O); 1587 s, ~1560 sh.s (C=C).

3-Chloro-6-ethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (4d) was obtained according to the known procedure.[13] IR ($CDCl_3$), ν/cm^{-1}: 3525 m, 3418 m (β-OH); 1653 vw, 1630 m, 1604 s (C=O); 1586 sh.m (C=C).

2,5,6,8-Tetrahydroxy-1,4-naphthoquinone (5a) was obtained according to the known procedure.[18] IR ($CDCl_3$), ν/cm^{-1}: 3509 m, 3392 m (β-OH); 1602 s (C=O, C=C).

3,7-Diethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone (5b) was obtained according to the known procedure.[13] IR ($CDCl_3$), ν/cm^{-1}: 3512 m, 3394 m (β-OH); 1653 w, 1630 sh.m, 1599 s (C=O); 1580 sh.m (C=C).

3-Chloro-7-ethyl-2,5,6,8-tetrahydroxy-1,4-naphthoquinone (5c) was obtained according to the known procedure.[13] IR ($CDCl_3$), ν/cm^{-1}: 3508 m, 3377 m (β-OH); 1631 sh.m, 1606 s (C=O); 1597 s, 1587 sh.s (C=C).

2,3,5,8-Tetrahydroxy-1,4-naphthoquinone (11a) was obtained according to the known procedure.[22] IR ($CDCl_3$), ν/cm^{-1}: ~3520 vw, 3433 m (β-OH); 1692 m, 1663 w, 1602 s (C=O); 1571 m (C=C).

2,3,5,8-Tetrahydroxy-6-methyl-1,4-naphthoquinone (11b) was obtained according to the known procedure.[32] IR ($CDCl_3$), ν/cm^{-1}: ~3525 vw, 3432 m (β-OH); 1694 m, 1641 w, 1599 s (C=O); 1576 m (C=C).

2,3,5,8-Tetrahydroxy-6,7-dimethyl-1,4-naphthoquinone (11c). A mixture of 1,2,3,4-tetramethoxybenzene (7.5 g, 0.04 mol) and dimethylmaleic anhydride (10.3 g, 0.08 mol) was added at 140 °C to a stirred melt of anhydrous $AlCl_3$ (81.0 g, 0.60 mol) and NaCl (16.2 g, 0.28 mol). The melt was heated to 180 °C and stirred for an additional 8 min. The reaction mixture was cooled and hydrolyzed with 5% HCl (1 L). Crude product **11c** precipitated within 12 h was separated, washed with hot water (200 mL), dried, and purified by column chromatography in hexane—acetone with a gradient from 10 : 1 to 4 : 1. The yield of compound **11c** was 6.2 g (62%), R_f 0.37, m.p. 283—285 °C (from dioxane). IR ($CDCl_3$), ν/cm^{-1}: 3525 w, 3431 m (β-OH); 1693 m, 1642 w, 1598 s (C=O), 1576 m (C=C). ^{1}H NMR (acetone-d_6), δ: 2.26 (s, 6 H, 2 Me); 8.96 (s, 2 H, 2 β-OH); 12.71 (s, 2 H, 2 α-OH). MS, *m/z* (I_{rel} (%)): 251 $[M + 1]^+$ (16); 250 $[M]^+$ (100); 249 (34); 222 (31); 221 (16).

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