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NEW APPROACH TO SYNTHESIS OF DERIVATIVES OF 2-(5-HYDROXYBENZOFURYL-3)NAPHTHOFURANS

T. I. Mukhanova, O. A. Lykova, L. M. Alekseeva, and V. G. Granik

Derivatives of 2-methyl-3-benzoyl-5-hydroxynaphtho[1,2-b]furans and 3-acetonyl-4-benzoylhydroxynaphthols were synthesized by the reaction of tertiary enaminoketones with p-naphthoquinone. The transformations of derivatives of 2-methyl-3-benzoyl-5-hydroxynaphtho[1,2-b]furans into naphthofurandiones with nitric acid and transformation into the corresponding enamines with DMF acetal were investigated. It was shown that when the latter react with p-benzoquinone, derivatives of 2-(5-hydroxybenzofuryl-3)naphthofurans are formed.

Since many processes of oxidative phosphorylation and electron transfer in biological systems take place with the participation of a group of substances — which are known by the general name of vitamin K and are derivatives of 1,4-naphthoquinone [1] — and the entire series of naphthofurandiones exhibit elevated and varied biological activity [2], the problem of synthesizing new compounds of this series and studying their chemical transformations is pressing. For this reason, we synthesized previously unknown derivatives of naphthofuran, including compounds containing *ortho*- and *para*-quinoid fragments, and studied their chemical and physicochemical properties.

2-Methyl-3-benzoyl-5-hydroxynaphtho[1,2-*b*]furans Ia-d, which were synthesized by condensation of tertiary enaminoketones IIa-d [3] with *p*-naphthoquinone (III) by the method described previously in [4] during a study of the Nenitzescu reaction with naphthoquinone, prepared for the first time, were used for synthesis of the naphthofurandiones. The structure of naphthofurans Ia-d obtained was demonstrated by spectral methods (see Experimental). It should be noted that the reaction of quinone III and enamines IIa-d takes place ambiguously, so that in addition to naphthofurans I, compounds were separated whose elemental analysis and molecular weight corresponded to products of hydrolysis IV of basic intermediates in synthesis of condensed furans by the Nenitzescu reaction (see review in [5]) — so-called hydroquinone adducts V. Signals of protons from a CH_2 group and one OH group are observed in the ^1H NMR spectrum of the compound separated from the reaction of quinone III and enamine II: 3.73 (2H, s, $C_{(3)}-CH_2$), 10.35 ppm (1H, s, OH). The data from the ^1H NMR spectrum indicate that the separated compound does not correspond to the structure of IVa, that is, the process does not stop in the stage of formation of hydroquinone adduct Va and the product of its hydrolysis IVa. We can hypothesize that the enol tautomer of diketone IVa is cyclized in the reaction conditions into dihydrofuran VIa, which is subsequently transformed into 3-acetonyl-4-benzoylhydroxynaphthol-1 (VIIa). A similar spectrum was obtained for compound VIIb (see Experimental).

The formation of by-products during the Nenitzescu reaction has not been described up to now. However, this transformation is probably general in character, since the formation of compounds VIIa-d was observed in all investigated reactions to obtain naphthofurans I. The probable paths of the processes during the reaction of naphthoquinone III and enaminoketones II are shown in the scheme presented below. Cyclization of compounds IV can also take place in another direction — with the formation of compounds of type VIII and subsequently isomeric acetoxy derivatives IX. However, the data from the ^{13}C NMR spectra on the example of compound VIIa unambiguously indicate that the structure of the substance obtained corresponds to benzoyloxy derivative VIIa. We have only been able to separate derivatives VIIa-d up to now; compound IX was not detected even in studying the reaction masses by PMR spectroscopy. The structure is primarily confirmed by the presence of signals of the carbonyl carbon atom, $CH_2\underline{C}OCH_3$ at 205.1 and O$\underline{C}$OPh at 165.2 ppm and signals of the

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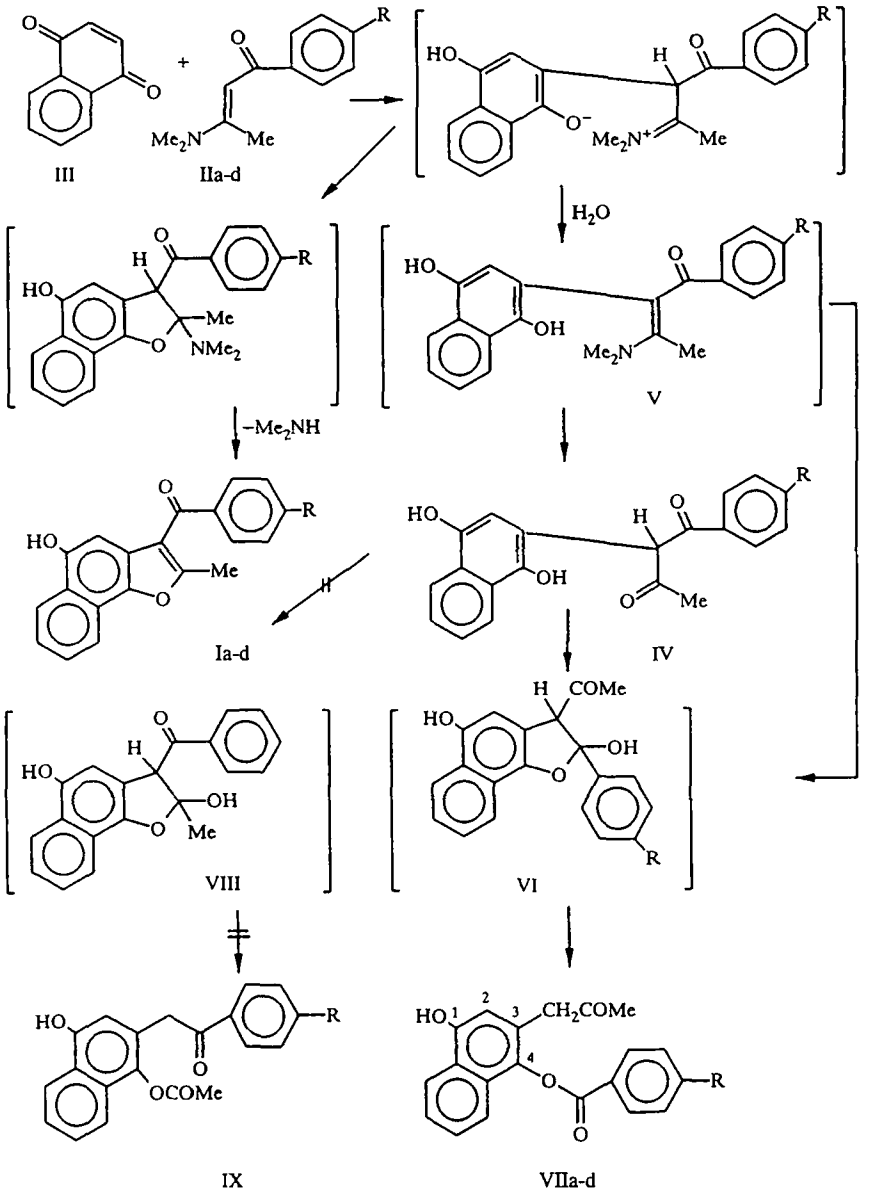
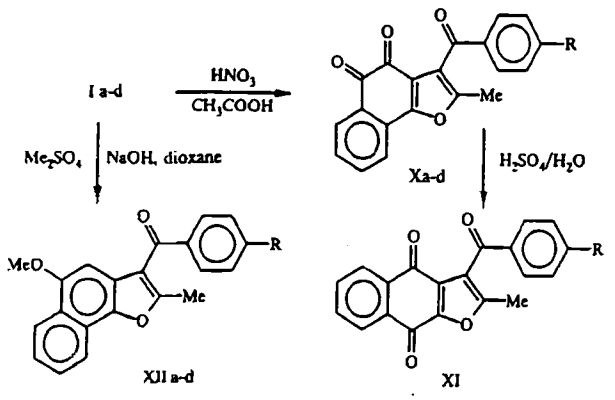
carbon atom in position 4 and 1, respectively, at 137.1 and 151.5 ppm in the ^{13}C NMR spectrum taken in the mode of suppression of proton interactions. The multiplicity of the observed signals in the mode without suppression of proton interactions is unambiguous evidence of structure VIIa (in contrast to IX): the signal of the carbonyl carbon atom in the CH_2COCH_3 substituent is in the form of a multiplet, probably caused by interaction with the protons of neighboring CH_2 and CH_3 groups, while the signal of the carbonyl carbon atom is observed in the form of a triplet for the OCOPh substituent ($J_{CO,2\text{-}H'} = J_{CO,6\text{-}H'} = 3.8$ Hz).



a R = H, b R = Me, c R = Cl, d R = Br

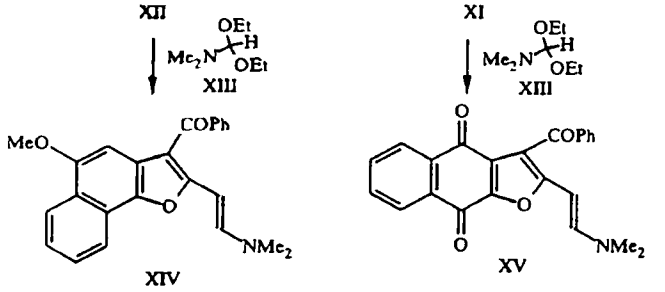
The reaction of the carbon atom in position 2 with protons of the methylene group in position 3 causes each component of the $C_{(2)}$ doublet ($J_{C(2),2\text{-}H} = 159.5$ Hz) to be additionally split into a triplet ($^3J_{C(2),C(3)H2} = 5.3$ Hz), which also supports structure VIIa.

Oxidation of 5-hydroxynaphthofurans Ia-d with nitric acid in acetic acid smoothly leads to *o*-quinones Xa-d. When tricyclic *o*-quinone Xa is treated with dilute sulfuric acid, opening of the furan ring is observed, with subsequent recyclization into *p*-quinone derivative XI — similar isomerization is known for other examples [6]. Methylation of compounds Ia-d in basic medium, conducted by the method previously developed in [7], also takes place with high yields. The corresponding 5-methoxy derivatives XIIa-d were synthesized by this method.

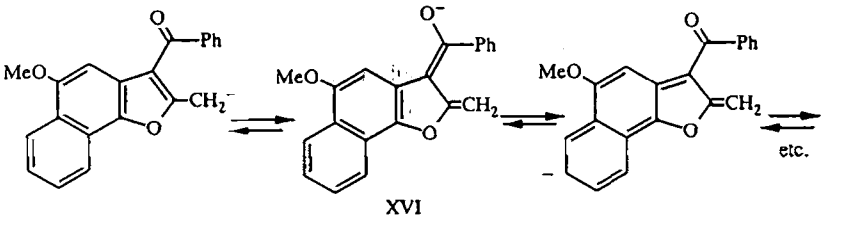


The α-methyl derivatives of naphthofurans X-XII are interesting objects for investigating the mobility of 2-methyl group protons. The possibility of introducing these compounds in condensation with dimethylformamide diethyl acetate (XIII) was investigated for this purpose. As expected, the aromatic derivative of 2-methyl-3-benzoyl-5-methoxynaphthofuran (XIIa), like 2-methyl-3-benzoyl-5-methoxybenzofuran [8] easily reacts with acetal XIII when heated, with the formation of corresponding enamine XIV. However, it was not anticipated that a striking difference would be observed between *o*- and *p*-quinoid derivatives X and XI in this respect — *p*-quinone XI is condensed with acetal XIII with the formation of dimethylaminomethylene derivative XVb, while *o*-quinone X does not enter into this reaction in either the above or more rigorous conditions.

The formation of the corresponding anions [9] is the first stage of the reaction of amide acetals with compounds having active methyl (methylene) groups, and the voluminous aromatic system of compounds of type XII well delocalize the anionic center and stabilize the anions of XVI, making it easy for the corresponding enamines to be formed:



In comparing the anions formed from *o*-quinones X and *p*-quinones XI, it is obvious that the latter are stabilized to a greater degree, since in anion XVIII, in contrast to anion XVII, an additional electron acceptor participates in charge delocalization — the cyclic carbonyl in position 9:



This participation of the carbonyl group in stabilization of the anion is probably responsible for the advantage of compounds of type XI in the reaction with amide acetals.

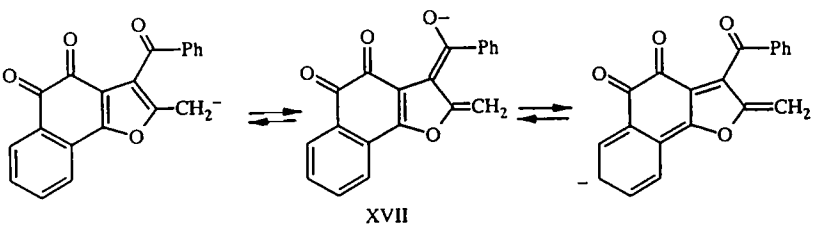
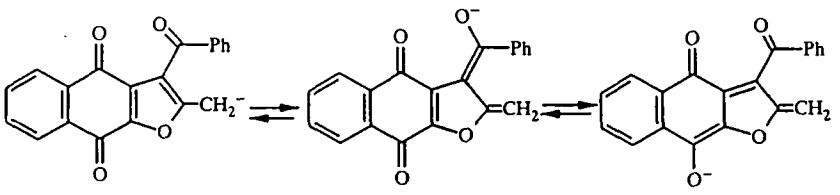


TABLE 1. Characteristics of Synthesized Compounds Ia-d, VIIa-d, Xa-d, XI, XIIa-d, XIV, XV, XXII, XXIII

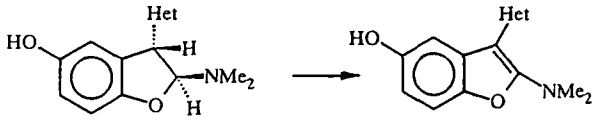
Compound	Found, %				Empirical formula	Calculated, %				M^+	mp, °C*	Yield, %
	C	H	N	Cl(Br)		C	H	N	Cl(Br)			
Ia	78,87	4,72	—	—	$C_{20}H_{14}O_3$	79,46	4,67	—	—	302	243...244	25
Ib	79,63	5,05	—	—	$C_{21}H_{16}O_3$	79,73	5,10	—	—	316	271...273	26
Ic	70,99	3,65	—	10,37	$C_{20}H_{13}ClO_3$	71,33	3,89	—	10,53	—	266...267	24
Id	62,85	3,38	—	(21,78)	$C_{20}H_{13}BrO_3$	63,01	3,44	—	(21,96)	—	263...265	22
VIIa	74,60	4,99	—	—	$C_{20}H_{16}O_4$	74,99	5,03	—	—	320	202...204	12
VIIb	75,28	5,37	—	—	$C_{21}H_{18}O_4$	75,43	5,43	—	—	334	219...220	10
VIIc	67,54	4,22	—	10,62	$C_{20}H_{15}ClO_4$	67,71	4,26	—	9,9	—	234...235	13
VIId	60,17	3,78	—	(20,73)	$C_{20}H_{15}BrO_4$	60,17	3,79	—	(20,22)	—	245...247	8
Xa	75,73	3,68	—	—	$C_{20}H_{12}O_4$	75,94	3,82	—	—	316	206...208	56
Xb	76,43	4,45	—	—	$C_{21}H_{14}O_4$	76,35	4,27	—	—	330	198...199	63
Xc	68,39	3,36	—	10,23	$C_{20}H_{11}ClO_4$	68,48	3,16	—	10,11	—	232...233	60
Xd	60,80	3,02	—	(19,82)	$C_{20}H_{11}BrO_4$	60,78	2,81	—	(20,22)	—	255...257	52
XI	75,89	4,03	—	—	$C_{20}H_{12}O_4$	75,94	3,82	—	—	316	239...240	Quant.
XIIa	79,79	5,02	—	—	$C_{21}H_{16}O_3$	79,73	5,10	—	—	316	129...130	96
XIIb	79,68	5,36	—	—	$C_{22}H_{18}O_3$	79,98	5,49	—	—	—	138...139	95
XIIc	71,82	4,22	—	10,29	$C_{21}H_{15}ClO_3$	71,90	4,31	—	10,11	—	152...153	95
XIId	63,77	3,81	—	(20,30)	$C_{21}H_{15}BrO_3$	63,81	3,83	—	(20,20)	—	154...155	92
XIV	77,60	5,77	3,61	—	$C_{24}H_{11}NO_3$	77,61	5,70	3,77	—	371	181...182	84
XV	74,13	4,52	3,63	—	$C_{23}H_{17}NO_4$	74,38	4,61	3,77	—	371	251...252	65
XXII	75,39	5,03	2,95	—	$C_{30}H_{23}NO_5$	75,46	4,86	2,93	—	477	255...257	46
XXIII	74,56	3,25	—	—	$C_{27}H_{14}O_6$	74,65	3,25	—	—	434	259...260	32

*Compounds Ia-d, VIIa-d, Xa-d, and XXIII were recrystallized from acetic acid; XIIb, XIId, and XIV were recrystallized from isopropanol; XIIa and XIIc were recrystallized from heptane, XI from methanol, and XXII from toluene.



XVIII

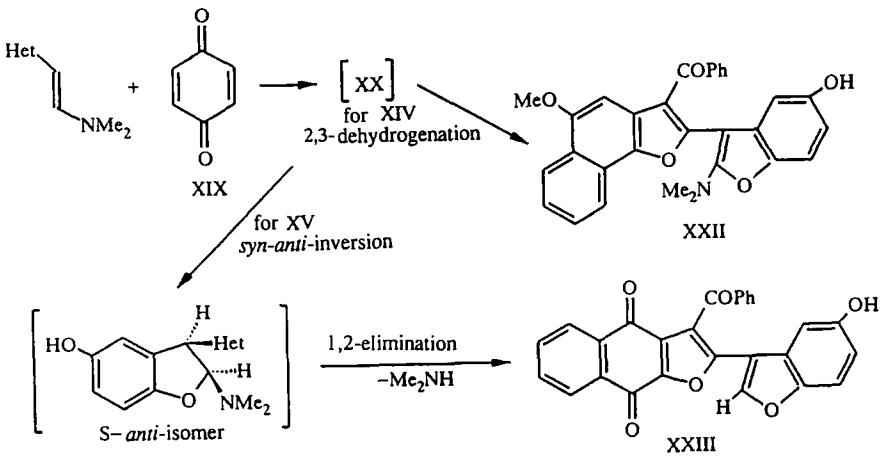
Addition of enamines XIV and XV to the reaction with *p*-benzoquinone XIX could give additional information on the stereochemical characteristics of the Nenitzescu reaction — this aspect of the reaction has been very inadequately studied [5]. We showed in [10] that unexpected preservation of the dimethylamino group in position 2 of the newly formed benzofuran ring is observed in the reaction of 2-dimethylaminovinyl-3-aroylbenzofurans with *p*-benzoquinone XIX. The causes of this event, uncharacteristic of the Nenitzescu reaction, are discussed in detail in [10]. The interpretation of these data is based on the fact that basic intermediate XX formed during the Nenitzescu reaction contains 3-H and a 2-dimethylamino group in *S-syn*-orientation for steric reasons, and this prevents elimination of dimethylamine and promotes 2,3-dehydrogenation with the formation of 2-dimethylamino derivatives XXI.



XX XXI

Based on this examination, the hypothesis, subsequently experimentally confirmed in [10], was advanced that the presence of strong electron-acceptor substituents (NO_2, for example) in the starting Het−CH=CH−NMe_2 enamine could cause relatively fast *S-syn*−*S-anti*-isomerization and thus elimination of dimethylamine and formation of benzofuran derivatives containing no 2-Me_2N substituent. It is understood that if the proposed interpretation is valid, when the Nenitzescu reaction of enamines XIV and XV is conducted, obtaining a benzofuran derivative with preservation of the 2-dimethylamino group should be expected for the first case, and in the second case, the presence of such a strong electron-acceptor as the annelated benzoquinone ring could lead to *syn-anti*-inversion and thus the formation of a new benzofuran ring with no substituent in position 2. The experimental data totally confirm these considerations. 2-(2-Dimethylamino-5-hydroxybenzofuryl-3)-3-benzoyl-5-methoxynaphtho[1,2-*b*]furan (XXII) was synthesized in the reaction of enamine XIV with *p*-benzoquinone, and in similar condensation of quinone XIX with enamine XV, 2-(5-hydroxybenzofuryl-3)-3-benzoyl-4,9-dihydronaphtho[2,3-*b*]-furandione-4,9 (XXIII) was obtained. In the first case, the dimethylamino group in position 2 of the newly formed benzofuran ring is preserved, while in the second case, it is eliminated (the schemes explaining these events are shown below).

The structure of the 2-(benzofuryl-3)naphthofurans XII and XXIII obtained follows from the ^1H NMR data.



S-*anti*-isomer XIX XXII XXIII

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded in DMSO-D_6 on a Unity Plus 400 MHz spectrometer (Varian) with TMS as internal standard. The mass spectra were obtained on a Varian chromatograph–mass spectrometer with direct introduction of the sample into the ion source. The purity of the synthesized compounds was verified on Silufol UV-254 plates in the benzene–acetone system, 9:1, with development in UV light.

The characteristics of the synthesized compounds are reported in Table 1.

2-Methyl-3-benzoyl-5-hydroxynaphtho[1,2-*b*]furans Ia-d and 3-Acetonyl-4-benzoylhydroxynaphthol-1 VIIa-d. While stirring, 10 mmole of *p*-naphthoquinone III in 10 ml of glacial acetic acid at room temperature was added to 10 mmole of enamines IIa-d in 5 ml of glacial acetic acid. After 4-5 h, the precipitated crystals were filtered off, washed on the filter with 50% acetic acid, and dried. ^1H NMR spectrum of compound Ia: 2.49 (3H, s, $C_{(2)}-CH_3$), 6.93 (1H, s, 4-H), 7.56-8.19 (4H, m, arom. H), 7.58-7.80 (5H, m, Ph), 10.01 ppm (1H, s, OH).

The mother liquor was left overnight. The precipitated crystals were filtered off, washed on the filter with 50% acetic acid, and dried. ^1H NMR spectrum of compound VIIa: 2.07 (3H, s, $COCH_3$), 3.73 (2H, s, $C_{(3)}-CH_2$), 6.82 (1H, s, 2-H), 7.48-8.17 (4H, m, arom. H), 7.65-8.21 (5H, m, Ph), 10.35 ppm (1H, s, OH). ^1H NMR spectrum of compound VIIb: 2.06 (3H, s, $COCH_3$), 2.45 (3H, s, CH_3), 3.71 (2H, s, $C_{(3)}-CH_2$), 6.80 (1H, s, 2-H), 7.47-8.15 (8H, m, arom. H + H_{Ph}), 10.31 ppm (1H, s, OH). ^{13}C NMR spectrum of compound IIa: 29.5 (CH_3), 45.4 (CH_2), 110.2 ($C_{(2)}$), 121.1, 122.8, 125.3, 127.4, 129.4, 130.2, 134.4 ($C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$, $C_{(6')}$ and $C_{(2')}$, $C_{(5')}$ and $C_{(3')}$, $C_{(4')}$), 124.8, 124.9, 127.8, 128.9 ($C_{(4a)}$, $C_{(8a)}$, $C_{(1')}$, $C_{(3)}$), 137.1 ($C_{(4)}$), 151.5 ($C_{(1)}$), 165.2 (OC=O), 205.1 ppm (C=O).

2-Methyl-3-benzoyl-4,5-dihydronaphtho[1,2-*b*]furan-4,5-diones Xa-d. While stirring, 1.2 ml of nitric acid (d = 1.37) in 2 ml of glacial acetic acid was added by drops to a suspension of 10 mmole of naphthofurans Ia-d in 15 ml of glacial acetic acid at room temperature, heated until the sediment dissolved, and boiled for 15 min. The crystals separated after cooling to room temperature were filtered off and dried. ^1H NMR spectrum of compound Xa: 2.41 (3H, s, $C_{(2)}-CH_3$), 7.45-7.89 (5H, m, Ph), 7.58-7.94 ppm (4H, m, arom. H).

2-Methyl-3-benzoyl-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione (XI). Here 0.5 g (16 mmole) of compound Xa was dissolved in a mixture of 75 ml of conc. H_2SO_4 and 15 ml of water, heated in a boiling water bath for 1.5 h, cooled, and diluted with 450 ml of water. The precipitated crystals were filtered off, washed on the filter with water, and dried, yielding 0.5 g of compound XI (quantitative). ^1H NMR spectrum: 2.47 (3H, s, $C_{(2)}-CH_3$), 7.51-7.94 ppm (9H, m, H_{Ph} + arom. H).

2-Methyl-3-benzoyl-5-methoxynaphtho[1,2-*b*]furans XIIa-d. Here 15 mmole of 5-hydroxynaphthofuran derivative Ia was dissolved in 10 ml of dioxane. Then 25 ml of a 2N solution of caustic soda and 5 ml of dimethyl sulfate were added to the suspension obtained. The reaction mixture was stirred for 3 h at room temperature. The precipitated crystals were filtered off, washed with water, and dried.

2-(β-Dimethylaminovinyl)-3-benzoyl-5-methoxynaphtho[1,2-*b*]furans (XIV). A mixture of 3.16 g (10 mmole) of naphthofuran XIIa and 20 ml of dimethylformamide diethylacetal was boiled for 6 h. The reaction mixture was cooled with ice and salt. The precipitated crystals were filtered off and washed on the filter with isopropyl alcohol, yielding 3.14 g (84%) of compound XIV. ^1H NMR spectrum: 2.90 (6H, br. s, $N(CH_3)_2$), 3.75 (3H, s, OCH_3), 5.27 (1H, d, J = 13.2 Hz, H-α), 6.70 (1H, s, 4-H), 7.80 (1H, d, J = 13.2 Hz, H-β), 7.40-8.20 ppm (9H, m, H_{Ph} + arom. H).

2-(β-Dimethylaminovinyl)-3-benzoyl-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione (XV). A mixture of 3.16 g (10 mmole) of naphthofurandione XI, 5 ml of dimethylformamide diethylacetal, and 15 ml of dimethylformamide was boiled for 30 min. The reaction mixture was cooled with ice and salt. The precipitated crystals were filtered off, washed on the filter with isopropyl alcohol, and dried, yielding 2.41 g (65%) of compound XV. ^1H NMR spectrum: 3.00 (6H, br. s, $N(CH_3)_2$), 5.29 (1H, d, J = 12.4 Hz, H-α), 7.67 (1H, d, J = 12.4 Hz, H-β), 7.44-7.58 (5H, m, Ph), 7.70-7.84 ppm (4H, m, arom. H).

2-Dimethylamino-3-(3-benzoyl-5-methoxynaphtho[1,2-*b*]furan-2-yl)-5-hydroxybenzofuran (XXII). While stirring, 0.54 g (5 mmole) of *p*-benzoquinone in 5 ml of glacial acetic acid was added to a solution of 1.85 g (5 mmole) of enamine XIV in 10 ml of glacial acetic acid. The reaction mixture was left overnight. The precipitated crystals were filtered off, washed on the filter with 50% acetic acid and ether, and dried, yielding 1.13 g (46%) of XXII. ^1H NMR spectrum: 2.75 (6H, s, $N(CH_3)_2$), 4.00 (3H, s, OCH_3), 6.41 (1H, q. d, J_1 = 2.4, J_2 = 8.4 Hz, 6-H), 6.78 (1H, d, J = 2.4 Hz, 4-H), 7.03 (1H, d, J = 8.4 Hz, 7-H), 7.35 (1H, s, 4'-H), 7.20-7.56 (5H, m, Ph), 7.70-8.28 ppm (4H, m, arom. H').

3-(3-Benzoyl-4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]furan-2-yl)-5-hydroxybenzofuran (XXIII) was obtained similar to compound XXII from 3.71 g (10 mmole) of enamine XV and 1.08 g (10 mmole) of *p*-benzoquinone in 25 ml of glacial acetic acid. Yield of 1.42 g (32%). ^1H NMR spectrum: 6.88 (1H, q. d, J_1 = 8.4, J_2 = 2.8 Hz, 6-H), 7.41 (1H, d, J = 8.4 Hz,

7-H), 7.46 (1H, d, J = 2.8 Hz, 4-H), 7.49-7.97 (5H, m, Ph), 7.81-8.19 (4H, m, arom H'), 8.20 (1H, s, 2-H), 9.60 ppm (1H, s, OH).

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