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β-(Benzofur-2-yl)- and (Indol-2-yl)enamines in the Nenitzescu Reaction

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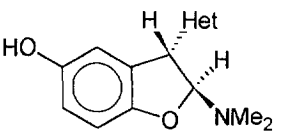
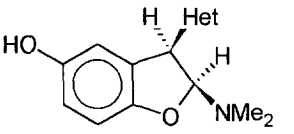
Abstract. Depending on the volume and electron-withdrawing properties of the substituents in the heterocyclic ring, reaction of β-(benzofur-2-yl)- and -(indol-2-yl)enamines with benzoquinone leads to the formation of 3-heteroarylbenzofurans, with or without a dimethylaminogroup in the position 2. If dehydrogenation is impossible, as in the case of α-methyl-β-heteroarylenamines, furo[2,3-f]benzofurans are formed.

Recently we have established[1] that β-(indol-2-yl)enamines are able to condense with benzoquinone under Nenitzescu reaction conditions. A new phenomenon - conservation of the dimethylamino group in position 2 of the newly formed benzofuran ring is not typical of this reaction [2,3] has been found. This unexpected pathway may be explained[1] by a well known stereochemical preference of S-anti-1,2-elimination for S-syn-elimination.[4]

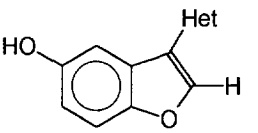


(**A**) S-sin-isomer



(**B**) S-anti-isomer

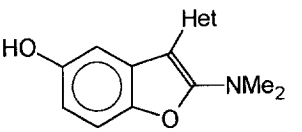
In accordance with the above considerations, it can be supposed that in the course of the Nenitzescu reaction the stereochemistry of intermediate plays an important role. In **A**-type intermediates the bulky substituents (Me_2N and Het-groups) in the positions 2 and 3 of dihydrobenzofuran ring are oriented S-anti- and these groups are at a maximum distance from each other. Therefore, their steric interaction is essentially diminished as compared with the isomer **B** where these substituents are in syn-periplanar conformation. However, 1,2-elimination (with the release of dimethylamine) in the case **A** is impeded, since the Me_2N-group in the position 2 and the proton in position 3 are oriented S-syn. On the contrary, 1,2-elimination is considerably facilitated for the intermediate **B** (S-anti-position of 2-Me_2N and 3-H groups), which results in the usual Nenitzescu reaction with the formation of benzofurans **C**.



(**C**)

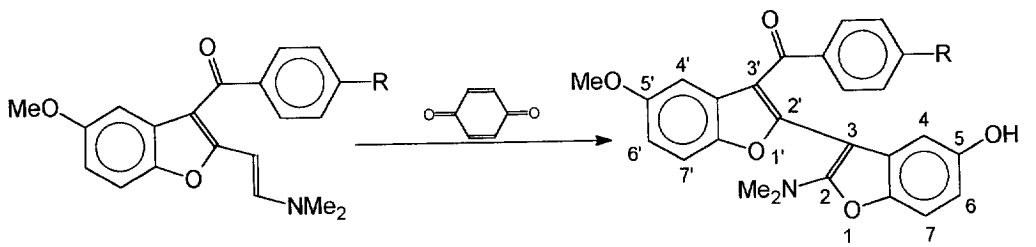
However, Me_2N and Het in **B** are drawn together which leads to unfavorable steric interactions between them, particularly if the heteroaryl group contains bulky substituents. This consideration is supported by examination of the Dreiding models. Significant steric hindrance increases the energy of **B**-type

intermediate and cause preferential **A**-type intermediate formation in these reactions. For these cases, 1,2-elimination of Me_2N is not observed and the reaction proceeds via dehydrogenation leading to 2-dimethylaminobenzofuran derivatives **D**.



(**D**)

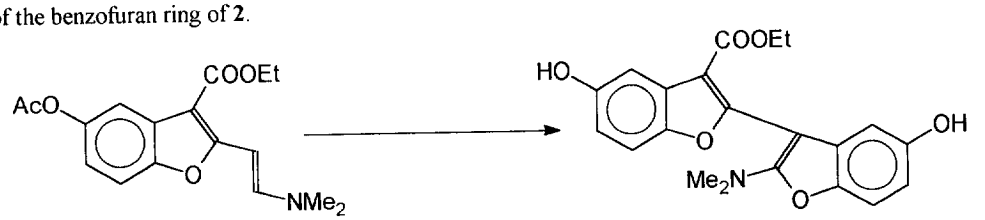
This work is devoted to the investigation of the above considerations. First of all we studied the condensation of known enamines[5] with p-benzoquinone in acetic acid at room temperature. It was established that regardless of the substituents in the benzoyl residue, the closure of the 5-hydroxybenzofuran ring with retention of the dimethylaminogroup in the position 2 takes place. A number of 2-dimethylamino-3-(3'-benzoyl-5'-methoxybenzofuryl-2'yl)-5-hydroxybenzofurans **1**a-e are synthesized by this method. The structures of the compounds obtained are proved by ^1H NMR spectroscopic data.



a R=H, b R=Me, c R=MeO, d R=Cl, e R=Br **1a-e**

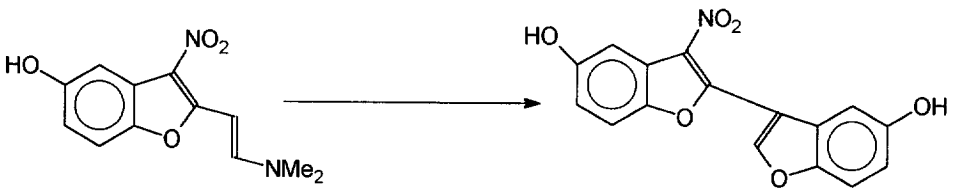
It is necessary to note that **1**b, d, e form stable molecular compounds with hydroquinone (2:1), which cannot be separated by crystallization. The ^1H NMR the signals of hydroquinone in these mixtures are at 6,55 (s, 4H, CH) and 8,62 s, 2H, OH) ppm and their intensity increases after the addition of pure hydroquinone. Though the yields of the end-products **1**a-e are moderate (which is typical of the Nenitzescu reaction), it is impossible to find even traces of products (MS) without 2-dimethylaminogroup in the reaction mixtures.

The direction of the processes is not changed for the enamines having ethoxycarbonyl group in position 3 of the benzofuran ring of **2**.



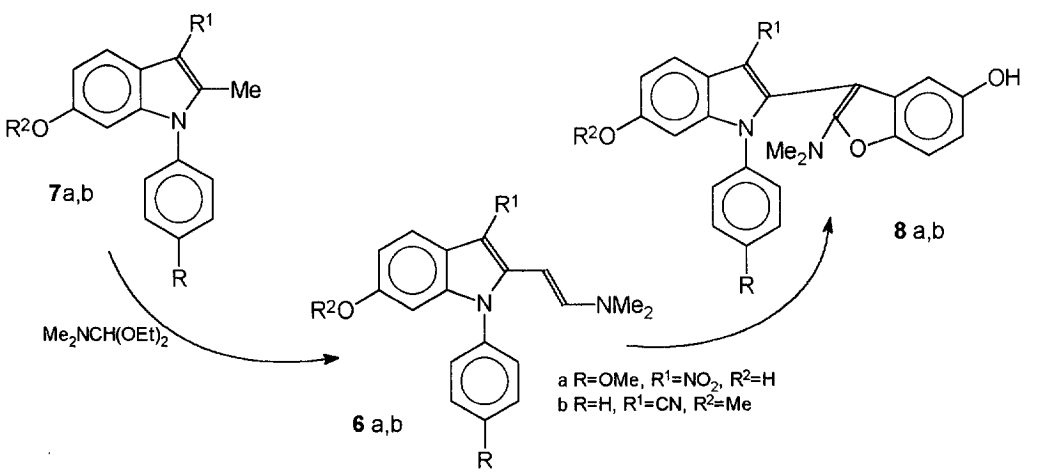
2 **3**

In other words, the presence of another carbonyl substituent in position 3 of the benzofuran system does not change the stereoselectivity of the reaction and the elimination of the dimethylamino group at the last stage of the process is not observed. On the contrary, the reaction of nitroenamine **4**[6] with quinone proceeds with the formation of 2-unsubstituted benzofuran **5**. Thus, the intermediate formed in this process is not subjected to dehydrogenation, but is stabilized by the evolution of Me_2NH.



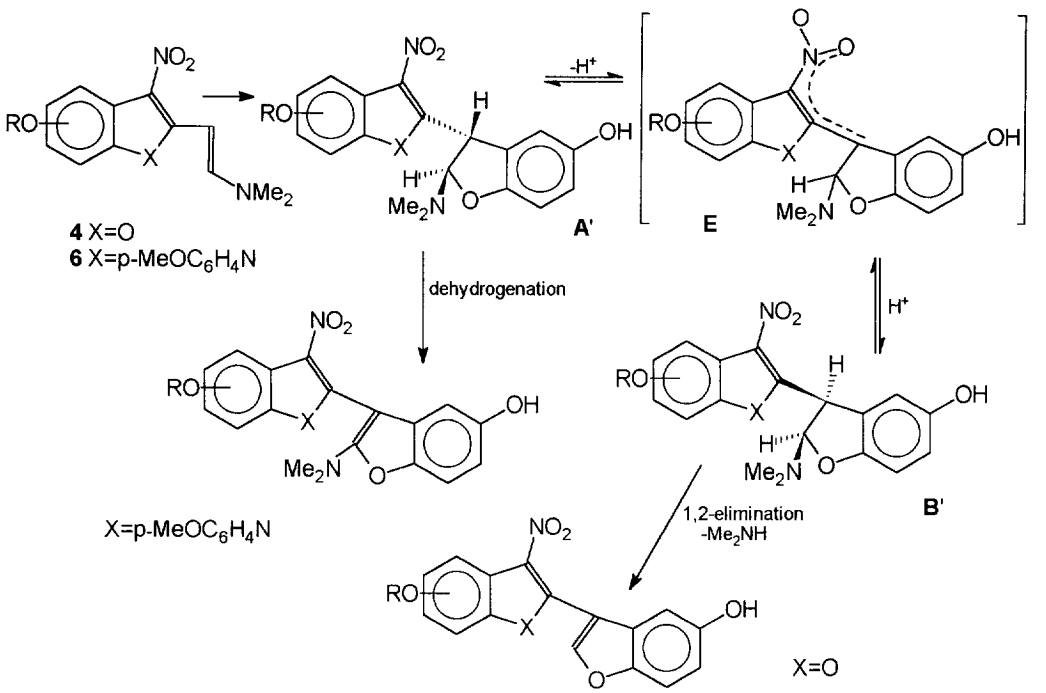
4 5

The introduction into the starting enamine of a substitutent, which is the less bulky than benzoyl and ethoxycarbonyl - NO_2-group leads to a cardinal change of the process direction. It seems to be especially interesting to introduce into the Nenitzescu reaction heteroaryl enamines with relatively small 3-substitutents (NO_2- and, particularly, cyanogroups), but with bulky groups in the position 1 of heterocycle. 3-Nitro- and 3-cyanoindolylenamines **6**a, b, having aryl substituents in position 1, meet this requirement. The compound **6**a was obtained as described previously[7] and **6**b was synthesized from 1-phenyl-2-methyl-3-cyano-6-hydroxyindole[8] by the condensation of its O-methyl derivative 7b with dimethylformamide diethylacetal. According to the above ideas, we expected the formation of the products of type **D** as a result of the condensation of **6**a, b with quinone. Indeed, the Nenitzescu reaction with the participation of **6**a, b leads to compounds with Me_2N-group in the position 2 of the benzofuran systems (**8**a, b). Compound **8**a is not obtained in the analytical pure state, but the spectral data show, that impurities are not the desdimethylamino derivatives and the structure of the main product **8**a is doubtless.

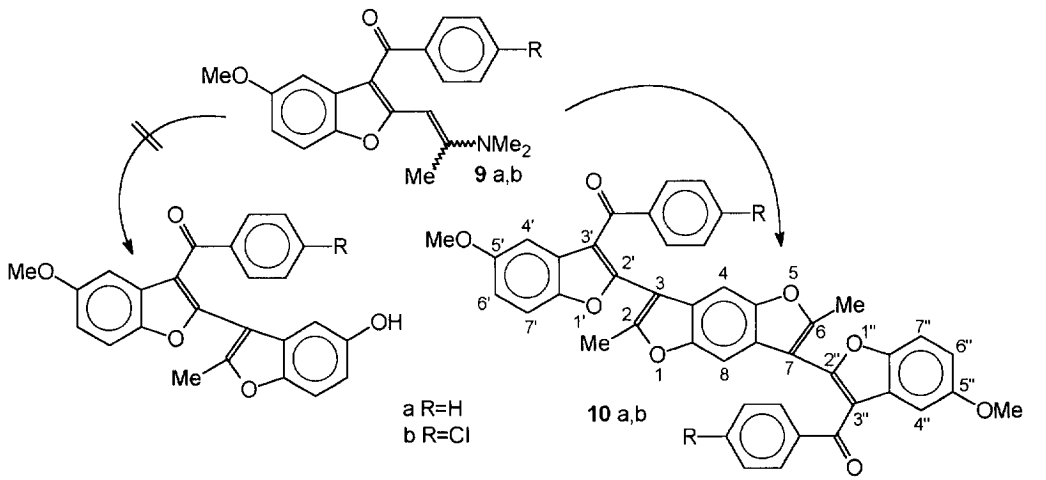


Thus, we can ascertain that steric demands in the formation of 2,3-dihydrobenzofuran intermediates in the Nenitzescu reaction have a considerable influence on the direction of the following processes leading to aromatic benzofurans. However, for the explanation of the data on reactions of 3-nitroheteroaryl enamines with quinone, an additional factor connected with the strong electron withdrawing effect of nitro group should be taken into account. This influence increases significantly the acidity of proton in the position 3 of benzofuran moiety of the intermediate **A'**, i.e. the concentration of the anion **E**, which leads to a possibility of the reversible of inversion configuration at C-3 (formation of S-anti-isomer **B'**). A similar process is described for other systems.[9] After the formation of **B'**, as a result of the recombination of **E** and H+, the inreversible step of S-anti-elimination with the formation of benzofuran derivatives without dimethylamino group in the position 2 is the main process.

The scheme below shows all the possible reactions on the examples of benzofuryl- and indolylnitroenamines:

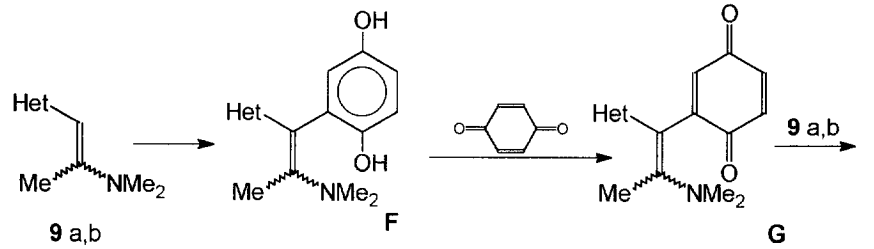


The above inversion is also theoretically possible for the carbonyl- and cyano- derivatives but, due to a lower electrononegativity of these substituents, the rate of the inversion is considerably smaller and, in the presence of bulky groups, the predominating process is dehydrogenation (probably by the action of quinone) leading to 2-dimethylamino derivatives of benzofuran. It is evident that desamination should be expected, if the starting enamine has a substituent in the α-position and the dehydrogenation is impossible, but, in this case, the reaction proceeds by unexpected way. The condensation of **9**a, b with p-benzoquinone yields furo[2,3-f]benzofurans **10**a, b instead of the expected (benzofur-2-yl)benzofurans.

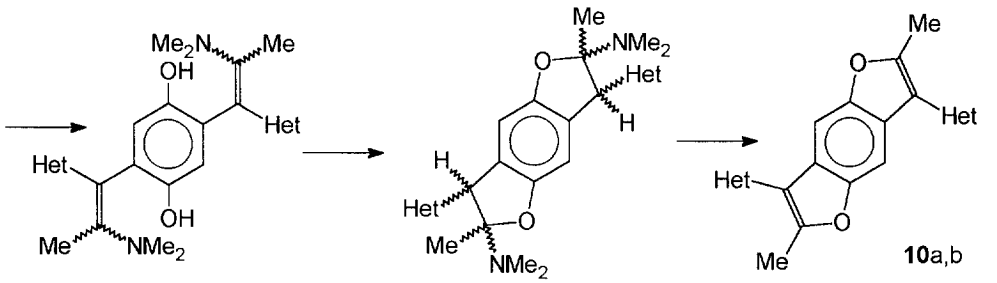


In this case, the closure of benzofuran ring is complicated by the presence of methyl group in the α-position of enamines, the closure rate is thus decreased and the oxidation of the intermediate hydroquinone

adduct **F** to quinone adduct **G** probably procedes more quickly. **G** then condenses with the starting enamine **9** to give **10**. It is also necessary to note that, due to the greater volume of the methyl group compared with proton, α-methyl substitution of enamines may equalize the chances of formation of the isomers with S-anti- and S-syn-orientation of Me_2N- and 3-H groups. At the same time, the above equilibria of type **A'⇌E⇌B'** give rise to elimination of dimethylamine with the formation of **10**. Scheme below sums up these considerations:



Het= 3-benzoyl- or p-chlorobenzoyl-5-methoxybenzofur-2-yl



The structures **10**a, b are proved by the spectral data.

Experimental

NMR-spectra were recorded using "Unity plus 400 MHz" (Varian) with TMS as internal standart in D_6-DMSO. Mass-spectra were performed using SSQ-710 Finnigan chromatomass-spectrometer under direct introduction of the samples to ion-source. TLC control: "Silufol UV-254", UV-detection.

2-Dimethylamino-3-(3'-benzoyl-5'-methoxybenzofur-2'-yl)-5-hydroxybenzofuran (1a). A solution of p-benzoquinone (1,08 g, 10 mmol) in glacial acetic acid (10 ml) was added to a solution of 2-(2'-dimethylaminovinyl)-3-benzoyl-5-methoxybenzofuran (3,21 g, 10 mmol) in glacial acetic acid (20 ml) under stirring at 20° C, the stirring was continued for 16 h. After filtration, washing with ether, drying, **1a** (1,28 g, 30%) was obtained, m.p. 215-216°C (toluene), M^+427. Found: C 73,1; H 4,9: N 3,3. $C_{26}H_{21}NO_5$ requires: C 73,1; H 5,0; N 3,3. Compounds **1b-e** are synthesized in the same manner. Yield **1b** 28,4%, m.p. 181-183°C (toluene), M^+441. Found: C 73,1; H 5,2; N 3,1. $C_{27}H_{23}NO_5$ x 1/2 $C_6H_6O_2$ requires: C 72,6; H 5,3; N 2,8. Yield **1c** 19,2%, m.p. 170-172°C (toluene), M^+457. Found: C 68,3; H 5,0; N 2,8. $C_{27}H_{23}NO_6$ requires: C 68,2; H 5,3; N 3,0. Yield **1d** 42,5%, m.p. 196-198°C (toluene), M^+461. Found: C 67,8; H 4,5; N 2,7. $C_{26}H_{20}ClNO_5$ x 1/2$C_6H_6O_2$ requires: C 67,4; H 4,5; N 2,7. $C_{26}H_{20}ClNO_5$ x 1/2$C_6H_6O_2$ requires: C 67,4; H 4,5; N 2,7. Yeild **1e** 32,9%, m.p. 179-181°C (toluene), M^+507. Found: C 61,9; H 4,1; N 2,5. $C_{26}H_{20}BrNO_5$ x 1/2 $C_6H_6O_2$ requires: C 62,0; H 4,1; N 2,5.

Table 1. ^{1}H-NMR data (D_6-DMSO) for compounds 1b-e.

H	1a	1b*	1c	1d*	1e*
4-H	6,68d	6,66 d	6,64 d	6,64 d	6,64 d
6-H	6,39dd	6,40 dd	6,39 dd	6,40 dd	6,40 dd
7-H	7,0d	7,03 d	7,01 d	7,03 d	7,04 d
4'-H	7,35d	7,28 d	7,27 d	7,37 d	7,36 d
6'-H	6,98dd	6,97 dd	6,96 dd	6,99 dd	6,98 dd
7'-H	7,62d	7,61 d	7,60 d	7,62 d	7,62 dd
NMe_2	2,66s	2,73 s	2,74 s	2,75 s	2,75 s
OCH_3	3,79s	3,78 s	3,78 s	3,79 s	3,80 s
$C_6H_4(A_2B_2)$	7,41-7,52m 7,18m	7,0, 7,44	6,73, 7,52	7,51, 7,23	7,36, 7,39
(R)		(2,25 s)	(3,72 s)		
OH	9,05s	9,04 br.s	9,04s	9,06 s	9,07 s

* + hydroquinone (2:1)

2-(2'-Dimethylaminovinyl)-3-ethoxycarbonyl-5-acetoxybenzofuran (2). Dimethylformamide diethylacetal (3,0 g, 20 mmol) was added to a solution of 2-methyl-3-ethoxycarbonyl-5-acetoxybenzofuran (1,0 g, 4 mmol) in DMF (10 ml) and the mixture was refluxed for 1 h. The solution was diluted with H_2O (20 ml), the precipitate was filtrated, washed with water, dried and 2 (800 mg, 83,3%) was isolated, m.p. 233-234°C (2-propoanol), M^+317. Found: C 64,4; H 6,0; N 4,5. $C_{17}H_{19}NO_5$ requires: C 64,3; H 6,0; N 4,4.

2-Dimethylamino-3-(3'-ethoxycarbonyl-5'-hydroxybenzofur-2'-yl)-5-hydroxybenzofuran (3) was synthesized in the manner of **1a** from **2** and benzoquinone. The crude product was treated with alumina in chloroform. Yeild 88,1%, m.p. 237-238°C, M^+ 381. ^{1}H NMR (D_6-DMSO): 1,19 (t, 3H) and 4,21 (qw, 4H, OEt), 2,93 (s, 6H, Me_2N), 6,50 (d, 1H, 4-H), 6,40 (dd, 1H, 6-H), 7,13 (d, 1H, 7-H), 7,36 (d, 1H, 4'-H), 6,77 (dd, 1H, 6'-H), 7,43 (d, 1H, 7'-H), 9,00 (br.s, 1H, 5-OH), 9,40 (br.s, 1H, 5'-OH). Found: C 66,1; H 5,3; N 3,3. $C_{21}H_{19}NO_5$ require: C 66,1; H 5,0; N 3,7.

3-(3'-Nitro-5'-hydroxybenzofur-2'-yl)-5-hydroxybenzofuran (5). p-Toluene sulfonic acid (600 mg, 4 mmol) and p-benzoquinone (400 mg, 4 mmol) was added to a solution of **4** (1,0 g, 4 mmol) in glacial acetic acid (20 ml) under stirring at 20° C. After 24 h the precipitate was filtred, washed with AcOH and water and dried. The crude product was dissolved in ether and chromatographed on SiO_2 (eluent ether). Ether was evaporated and the solid was extracted with boiling acetone, the solvent was evaporated and **5** (450 mg, 36%) is obtained, m.p. 237-238°C, M^+311. ^{1}H NMR (D_6-DMSO): 7,49 (d, 1H, 4-H), 6,94 (dd, 1H, 6-H), 7,59 (d, 1H, 7-H), 7,54 (d, 1H, 4'-H), 6,99 (dd, 1H, 6'-H), 7,69 (d, 1H, 7'-H), 9,17 (s, 1H, 2-H), 9,62 (br.s, 1H, 5-OH), 9,89 (br.s, 1H, 5'-OH). The signals at 9,62 and 9,89 ppm are exchanged upon addition of CD_3OD, the signal at 9,17 ppm is conserved. Found: C 61,8; H 3,3; N 4,3. $C_{16}H_9NO_6$ requires: C 61,7; H 2,9; 4,5.

1-p-Methoxyphenyl-2-(2'-dimethylaminovinyl)-3-nitro-6-hydroxyindole (6a). Dimethylformamide diethylacetal (3 g, 20 mmol) was added to a solution of 7a (500 mg, 2 mmol)[7] in DMF (6 ml) under stirring at 20° C. After 24 h the mixture was diluted with water, the precipitate was filtrated, washed with water, dried and **6a** (400 mg, 67,8%) was obtained, m.p. 139-141°C (dioxane), M^+353. Found: C 64,0; H 5,4; N 11,7. $C_{19}H_{19}N_3O_4$ requires: C 64,6; H 5,4; N 11,9.

1-Phenyl-2-(2'-dimethylaminovinyl)-3-cyano-6-methoxyindole (6b). The mixture of 7b (9,0 g, 34 mmol) and dimethylformamide diethylacetal (25 ml) was refluxed for 10 days. The mixture was diluted with water (200 ml) and the precipitate was collected, washed with water, dried to yield 6b (5,9 g, 54,3%), m.p. 143-145°C(2-propanol), M^+317. Found: C 75,7; H 6,0; N 13,2. $C_{20}H_{19}N_3O$ requires: C 75,4; H 6,0; N 13,0.

1-Phenyl-2-methyl-3-cyano-6-methoxyindole (7b). Anhydrous K_2CO_3 (16,8 g, 120 mmol) and MeI (42,6 g, 300 mmol) was added to a solution of 1-phenyl-2-methyl-3-cyano-6-hydroxyindole[8] (7,5 g,

30 mmol) in anhydrous DMF (80 ml) and the mixture was refluxed for 10 h. The reaction mixture was diluted with water (200 ml) and the precipitate was collected, washed with water, dried to give **7b** (6 g, 76,3%), mp.p. 137-138°C (2-propanol), M^+262. Found: C 77,8; H 5,4; N 10,7. $C_{17}H_{14}N_2O_2$ requires: C 77,7; H 5,4; N 10,6.

2-Dimethylamino-3-(1'-p-methoxyphenyl-3'-nitro-6'-hydroxyindole-2'-yl)-5-hydroxybenzofuran (8a). The p-benzoquinone (110 mg, 1 mmol) was added to a solution of **6a** (350 mg, 1 mmol) in glacial AcOH (5 ml)under stirring at 20° C and the mixture was kept for 1 h. The solution was diluted with water (30 ml) and the precipitate was collected, washed with water, dried to yield **8a** (200 mg, 31%), m.p. 206-208°C, M^+ 459. ^{1}H NMR (D_6-DMSO): 2,77,(s, 6H, Me_2N), 3,75 (s, 3H, OMe), 6,23 (d, 1H, 4- H), 6,33 (dd, 1H, 6-H), 6,60 (d, 1H, 7'-H), 6,95 (dd, 1H, 5'-H), 7,04 (d, 1H, 7-H), 8,06 (d, 1H, 4'-H), 8,87 (br.s, 1H, 5-OH), 7,3-7,5 (br.s, C_6H_4), 9,66 (br.s, 1H, 6'-OH).

2-Dimethylamino-3-(1'-p-methoxyphenyl-3'-cyano-6'-methoxyindole-2'-yl)-5-hydroxybenzofuran (8b). The compound **6b** (5,9 g, 186 mmol) was added to a solution of p-benzoquinone (2,0 g, 185 mmol) in glacial AcOH (15 ml) under stirring at 20° C, the reaction mixture was kept overnight and filtrated. The mother liquid was diluted with water (100 ml) to yield **8b** (3,3 g, 42,2%), mp.p. 123-125°C (petroleum ether), M^+423. ^{1}H NMR (D_6-DMSO): 2,75 (s, 6H, Me_2N), 3,73 (s, 3H, OMe), 6,33 (d, 1H, 4-H), 6,38 (dd, 1H, 6-H), 6,76 (d, 1H, 7'-H), 7,02 (dd, 1H, 5'-H), 7,06 (d, 1H, 7-H), 7,49-7,33 (m, 5H, C_6H_5), 7,64 (d, 1H, 4'-H), 9,00 (s, 1H, 5-OH). The assignment of chemical shifts for these signals of **8a**,b is made by the comparison with above spectra of **1**a-e and **3**. Found: C 73,7; H 5,0; N 9,9. $C_{26}H_{21}N_3O_3$ requires: C 73,7; H 5,0; N 9,9.

2-(2'-Dimethylaminopropen-1'-yl)-3-benzoyl-5-methoxybenzofuran (9a). A mixture of 2-methyl-3-benzoyl-5-methoxybenzofuran (2,66 g, 10 mmol), dimethylacetamide diethylacetal (3,54 g, 22 mmol) and DMF (5 ml) was refluxed for 30 min. After cooling to 0° C, the precipitate was collected, washed with 2-propanol and ether, dried to yield **9a** (2,64 g, 78,7%), m.p. 93-94°C (2-propanol), M^+ 335. Found: C 75,1; H 6,3; N 4,0. $C_{21}H_{21}NO_3$ requires: C 75,2; H 6,3; N 4,1.

2-(2'-Dimethylaminopropen-1'-yl)-3-p-chlorobenzoyl-5-methoxybenzofuran (9b) is obtained similarly from 2-methyl-3-(4-chlorobenzoyl)-5-methoxybenzofuran and benzoquinone. Yeild 69,7%, m.p. 144-145°C (DMF), M^+ 369. Found: C 68,1; H 5,2; N 3,6. $C_{21}H_{20}ClNO_3$ requires: C 68,2; H 5,4; N 3,8.

2,6-Dimethyl-3,7-bis(3'-benzoyl-5'-methoxybenzofur-2'-yl)- furo[2,3-f]benzofurans (10a) and **2,6-dimethyl-3,7-bis(3'-p-chlorophenyl-5'-methoxybenzofur-2'-yl) furo[2,3-f]benzofurans (10b)** was synthesized in the manner of **1**a from **9**a,b and benzoquinone. For **10**a yield 32,6%, m.p. 249-251°C (DMF), M^+686. ^{1}H NMR (D_6-DMSO): 2,20 (s, 6H, 2,6-Me), 3,80 (s, 6H, 5'-, 5"-OMe), 7,63 (s, 2H, 4-,- 8-H), 7,09 (dd, 2H, 6'-,6"-H), 7,21 (d, 2H, 4'-, 4"-H), 7,48-7,72 (m, 10H, two C_6H_5), 7,73 (d, 2H, 7'-, 7"-H). Found: C 76,5; H 4,6. $C_{44}H_{30}O_8$ requires: C 77,0; H 4,4. For **10**b yield 31,5%, m.p. 318-320°C (DMF), M^+ 754. ^{1}H NMR (D_6-DMSO): 2,20 (s, 6H, 2-, 6- CH_3), 3,75 (s, 6H, 5'-,5"- OCH_3), 7.02 (dd, 2H, 6'-, 6"-H), 7,18(d, 2H, 4'-, 4"-H), 7,38-7,70 (m, A_2B_2, 8H, two COC_6H_4), 7,64 (s, 2H, 4, 8-H), 7,72 (d, 2H, 7'-H, 7"-H).

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