Chemistry of Heterocyclic Compounds, Vol. 36, No. 4, 2000

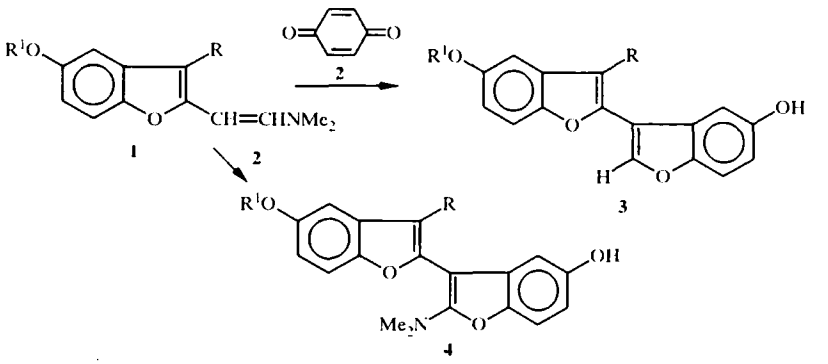
SYNTHESIS OF 2-DIMETHYLAMINO-3-HETARYL-5-HYDROXYBENZOFURANS BY THE NENITZESCU ROUTE FROM NITRO-CONTAINING ENAMINES OF THE BENZOFURAN SERIES

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

Enamines of the benzofuran series which contain nitro groups in the benzene ring of benzofuran or in 3-benzoyl substituent react with benzoquinone to form 2-dimethylamino-3-(substituted benzo-2-furyl)-5-hydroxybenzofurans.

Keywords: benzoquinone, hydroxybenzofuran, enamine, nitration, Nenitzescu reaction.

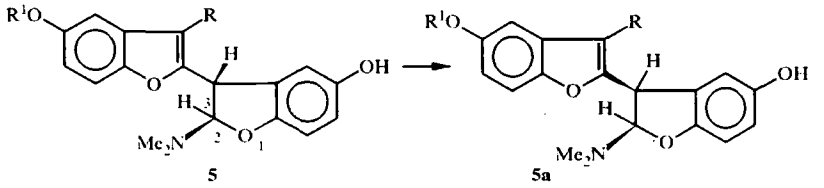
Depending upon the bulk and the extent of the electron-acceptor effect of the substituent at position 3 of the benzofuran ring, the reaction of 2-dimethylaminovinyl-3-R-5-alkoxybenzofuran enamines (**1**) with benzoquinone (**2**) can take place both with preservation and with elimination of the dimethylamino group to give 2-unsubstituted or 2-dialkylamino-3-(benzo-2-furyl)benzofurans (**3,4**) [1].



These differences in the direction of the Nenitzescu reaction [2, 3] and its dependence on the nature of the R substituent have been interpreted [1] on the basis of a consideration of the stereochemical features of the intermediate **5** and the possible "inversion" of the configuration at the $C_{(3)}$ atom during the course of the reaction to give the compound **5a**:

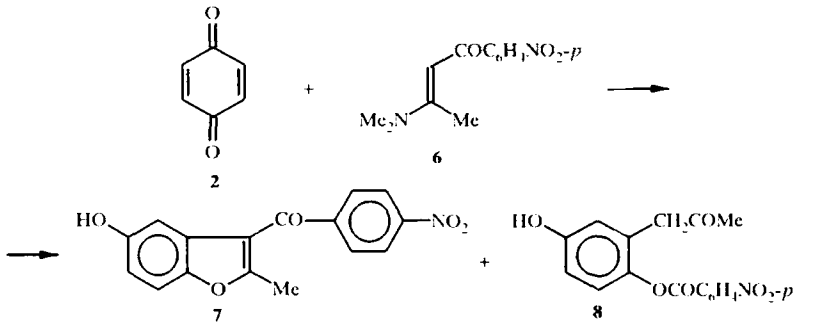
The State Science Center of the Russian Federation "NIOPIK", Moscow 103787, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 482-487, April, 2000. Original article submitted November 17, 1998.

 0009-3122/00/3604-0410$25.00©2000 KluwerAcademic/Plenum Publishers

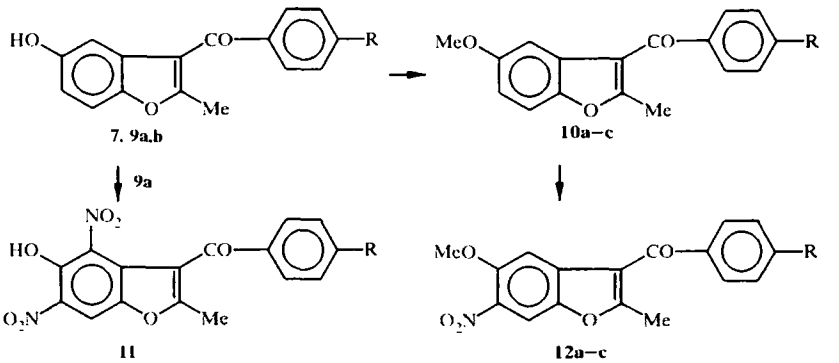


With R = NO_2, a transformation of compound **5** with an *S-syn* arrangement of the 3-H and Me_2N groups to the corresponding *trans*-related intermediate **5a** is observed and this gives rise to a possible *trans* elimination of the dimethylamino group to form a compound of type **3**.

As starting compounds for this work we selected benzofuran derivatives which contain nitro groups in the condensed benzene ring and in the benzoyl substituent, which occur to be remote from the $C_{3,3}$ reactive center after closing of the dihydrobenzofuran ring to form the compounds of type **5**. This then makes possible a study of the problem of the *S-syn* to *S-trans* configuration in such compounds. In the first step of the investigation following the usual scheme, i.e., the reaction of quinone **2** with enamino ketone 2-dimethylamino-3-*p*-nitrobenzoylprop-2-ene (**6**), we have prepared 2-methyl-3-*p*-nitrobenzoyl-5-hydroxybenzofuran (**7**). It is significant that, along with the basic process of forming the bicycle **7**, a side reaction is observed related to the formation of 3-acetonyl-4-*p*-nitrobenzoyloxyphenol (**8**). Products of type **8** were not observed when studying the reactions of benzoquinone with enamino ketones [4, 5] but similar compounds were isolated by us in the course of Nenitzescu reaction involving naphthoquinone. The scheme for formation of compound **8** is evidently similar to that proposed by us [6].



The rest of the required nitrobenzofurans were prepared from previously reported benzofurans (**9a,b, 10a,b**) [7, 8] according to the scheme:



9, 10, 11, 12 a R = H, b R = Me; **7, 10, 12** c R = NO_2

Nitration of compounds **10** occurs at both the 6 and 4 positions; in the case of benzofuran **10c** a mixture of 6- and 4-nitro derivatives was obtained in the ratio 7:3 (^{1}H NMR spectrum) but they could not be separated.

Nitrobenzofurans **10c, 11, 12a,b**, and mixture **12c** serve as the basis for further synthesis of the corresponding enamines and study of their condensation with benzoquinone. We have previously shown that the reaction of DMF diethyl acetal (**13**) occurs at 2-methyl group of benzofurans to give enamines if the components are refluxed for 4-5 h [7, 8]. The presence of nitro group in the benzoyl fragment does not prove to have a significant effect on this process and the same conditions can be used for formation of the vinyl derivative **14**. At the same time, a nitro group in position 6 markedly increases the mobility of the protons of the 2-methyl group and enamines **15a-c** are formed in mild conditions (treatment of compounds **12a-c*** with acetal **13** in DMF at 20°C).

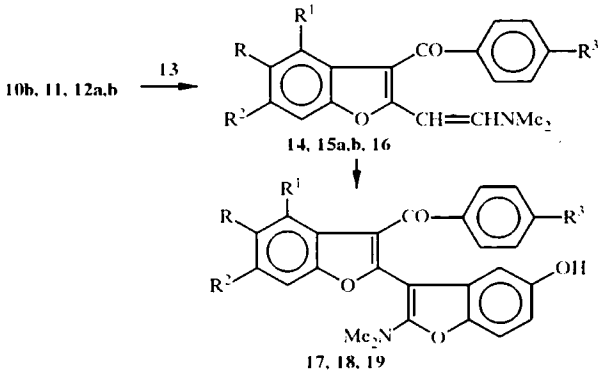
The presence of two nitro groups in compound **11** does not lead to such an effect. It is possibly connected with steric factors and the presence of the COPh, 4-NO_2, OH, and 6-NO_2 groups in close proximity leads to removal of the nitro groups from conjugation and, hence, lowers their electron-acceptor effect. It should also be considered that compounds **12a-c** have a methoxy group in position 5 but in dinitrobenzofuran **11** there is a hydroxy group which is ionized in the presence of acetal **13**. When heated, benzofuran **11** and acetal **13** form enamine **16**. Condensation of enamines **14, 15a-c, 16** with benzoquinone **2** occurs under usual Nenitzescu reaction conditions in all cases to give the 2-dimethylamino derivatives **17, 18a-c, 19**.

Compound **19** could not be obtained in analytically pure state (the product contained a certain amount of hydroquinone) but derivative was unambigously identified using mass spectrometry and ^{1}H NMR.

TABLE 1. Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			M$^+$	mp, °C	Yield, %
		C	H	N			
7	$C_{16}H_{11}NO_5$	64.9 / 64.7	3.9 / 3.7	4.9 / 4.7	297	189-190	23.6
8	$C_{16}H_{13}NO_6$	62.2 / 62.0	4.1 / 4.2	4.3 / 4.4	315	187-188	8.3
10c	$C_{17}H_{13}NO_5$	65.2 / 65.6	4.3 / 4.2	4.5 / 4.5	311	116-117	87.6
11	$C_{16}H_{10}NO_7$	56.3 / 56.2	2.8 / 3.0	8.2 / 8.2	342	188-189	81.9
12a	$C_{17}H_{13}NO_5$	65.2 / 65.6	4.0 / 4.2	4.5 / 4.5	311	167-169	51.4
12b	$C_{18}H_{15}NO_5$	66.5 / 66.5	4.6 / 4.7	4.3 / 4.4	325	182-184	60.3
14	$C_{20}H_{18}N_2O_5$	65.4 / 65.6	4.9 / 5.0	7.4 / 7.7	366	157-158	82.4
15a	$C_{20}H_{18}N_2O_5$	65.5 / 65.6	4.9 / 5.0	7.7 / 7.7	366	204-205	70.3
15b	$C_{21}H_{20}N_2O_5$	66.1 / 66.3	5.3 / 5.3	7.2 / 7.4	380	196-197	67.2
15c	$C_{20}H_{17}N_3O_7$	58.4 / 58.4	4.2 / 4.2	10.3 / 10.2	411	278-280	31.7
16	$C_{21}H_{19}N_3O_7$	58.5 / 59.3	4.5 / 4.5	9.8 / 9.9	425	230-232	37.1
17	$C_{26}H_{20}N_2O_7$	66.6 / 66.1	4.6 / 4.3	5.6 / 5.9	472	238-240	39.0
18a	$C_{26}H_{20}N_2O_7$	66.2 / 66.1	4.2 / 4.3	5.9 / 5.9	472	245	89.8
18b	$C_{27}H_{22}N_2O_7$	64.7 / 64.3	4.4 / 4.8	5.2 / 5.6	486	216-217	45.5
18c	$C_{26}H_{19}N_3O_9$	60.6 / 60.4	3.6 / 3.7	7.5 / 8.1	517	198-200	56.3

* In the reaction of mixture **12c** with acetal **13** only 6-nitroenamine **15c** could be separated (^{1}H NMR spectrum).



14, 17 R = OMe, $R^1 = R^2 = H$, $R^3 = NO_2$;
15, 18 R = OMe, $R^1 = H$, $R^2 = NO_2$, **a** $R^3 = H$, **b** $R^3 = Me$, **c** $R^3 = NO_2$;
16, 19 R = OEt, $R^1 = R^2 = NO_2$, $R^3 = H$

Despite complications in the isolation of pure substances, according to spectroscopic data (see Experimental), it was possible to confirm with certainty that in all of the examples of the Nenitzescu reaction the compound formed contained dimethylamino group in position 2 of the newly formed, cyclized benzofuran ring. In other words, removal of the electron-acceptor substituents from the $C_{(3)}$ reaction center rules out an *S-syn* to *S-trans* type inversion of configuration and hinders elimination of dimethylamino group, the basic process being 2,3-dehydrogenation.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in DMSO-d_6, $CDCl_3$ (**8**), and acetone-d_6 (**12a,b**) on a Unity (400 MHz) spectrometer using TMS as internal standard. Mass spectra were taken on a Varian chromatographic mass spectrometer with direct introduction of the sample into the ion source. The purity of the obtained materials was proved by TLC on Silufol UV-254 plates using benzene–acetone (9:2) with visualization in UV light. Yields and parameters for the compounds prepared are given in Table 1. 3-Benzoyl-5-hydroxy(methoxy)-2-methylbenzofurans **9a,b** and **10a,b** were obtained as in method [8].

5-Hydroxy-2-methyl-3-(*p*-nitrobenzoyl)benzofuran (7) and 3-Acetonyl-4-(*p*-nitrobenzoyloxy)phenol (8). *p*-Benzoquinone (1.08 g, 10 mmol) and glacial acetic acid (10 ml) were added to 2-dimethylamino-3-(*p*-nitrobenzoyl)prop-2-ene (2.35 g, 10 mmol) and the mixture was heated to 40-50°C until the precipitate dissolved. The mixture was then stirred for 3-3.5 h at room temperature. The precipitated crystals were filtered off, washed on the filter with 50% acetic acid, and dried to give compound **7** (0.7 g). The residue of the reaction mixture was left for 2 days at room temperature. The crystals were filtered off to give 1 g of the mixture of compounds **7** and **8**. By recrystallization from acetic acid and methanol compound **8** (0.2 g) was isolated. ^1H NMR spectrum, ppm: 2.08 (3H, s, $COCH_3$); 3.55 (2H, s, CH_2); 6.80 (1H, d, J_m ~ 3.0 Hz, 2-H); 6.82 (1H, dd, J_o = 8.4 Hz, J_m = 3.0 Hz, 6-H); 7.03 (1H, d, J_o = 8.4 Hz, 5-H); 8.33 (4-H, m, arom. protons); 9.01 (1H, br. s, 1-OH). ^{13}C NMR spectrum, ppm: 28.5 ($CO\underline{C}H_3$); 45.1 (CH_2); 114.6 ($C_{(6)}$); 117.9 ($C_{(2)}$); 123.2 ($C_{(5)}$); 124.1 ($C_{(2')}$, $C_{(6')}$); 128.3 ($C_{(4)}$); 131.2 ($C_{(3')}$, $C_{(5')}$); 134.5 ($C_{(1')}$); 141.2 ($C_{(4')}$); 150.6 ($C_{(4)}$); 155.4 ($C_{(1)}$); 163.2 (OC=O); 204 ($CH_2\underline{C}OCH_3$).

3-Benzoyl-2-methyl-5-methoxy-6-nitrobenzofuran (12a). Nitric acid (*d* = 1.35, 1.5 ml) was added at room temperature to suspension of compound **10a** (2.66 g, 10 mmol) in acetic acid (20 ml). The product was stirred at room temperature for 5 h and then at 75-80°C for 5 h. The precipitated crystals formed on cooling were filtered off and washed on the filter with ether to give compound **12a** (1.6 g). ^1H NMR spectrum, ppm: 2.48 (3H, s, 2-CH_3); 3.87 (3H, s, OCH_3); 7.29 (1H, s, 4-H); 7.59-7.84 (5H, m, COC_6H_5); 8.15 (1H, s, 7-H).

2-Methyl-3-(*p*-methylbenzoyl or *p*-nitrobenzoyl)-5-methoxy-6-nitrobenzofurans (12b,c) were obtained similarly to compound **12a** from compounds **10b** and **10c** respectively. Compound **12c,c'** represents itself a mixture (~1:2) of 4- and 6-nitro isomers of 2-methyl-3-(*p*-nitrobenzoyl)-5-methoxybenzofuran **10c**.

Compound 12b. ^{1}H NMR spectrum, ppm: 2.44 (3H, s, 4'-CH_3); 2.49 (3H, s, 2-CH_3); 3.88 (3H, s, OCH_3); 7.31 (3H, s, 4-H); 7.41 (2H, m, 3'-H, 5'-H); 7.76 (2H, m, 2'-H, 6'-H); 8.16 (1H, s, 7-H).

Compound 12c. ^{1}H NMR spectrum, ppm: 2.32 (3H, s, 2-CH_3) [4-isomer]; 2.38 (2H, s, 2-CH_3) [6-isomer]; 3.80 (3H, s, OCH_3) [6-isomer]; 3.87 (3H, s, OCH_3) [4-isomer]; 7.28 (1H, s, 4-H) [6-isomer]; 7.34 (1H, d, J_o = ~ 8 Hz, 6-H) [4-isomer]; 7.92 (1H, d, J_o ~ 8 Hz, 7-H) [6-isomer]; 7.96 (2H, m, 2'-H, 6'-H) [4-isomer]; 7.98 (2H, m, 2'-H, 6'-H) [6-isomer]; 8.29 (2H, m, 3'-H, 5'-H) [4-isomer]; 8.30 (1H, s, 7-H) [6-isomer]; 8.34 (2H, m, 3'-H, 5'-H) [6-isomer].

3-Benzoyl-5-hydroxy-2-methyl-4,6-dinitrobenzofuran (11). Nitric acid (d = 1.35, 0.7 ml, 15 mmol) in acetic acid (2 ml) was added to suspension of benzofuran **9a** (1.26 g, 5 mmol) in acetic acid (10 ml) and the product was stirred for 5 h at room temperature. On the following day the precipitate was filtered off, washed on the filter with petroleum ether, and dried to give dinitro derivative **11** (1.4 g). ^{1}H NMR spectrum, ppm: 2.40 (3H, s, 2-CH_3); 7.55-7.82 (5H, m, C_6H_5); 8.34 (1H, s, 7-H).

3-Benzoyl-2-(β-dimethylaminovinyl)-5-methoxy-6-nitrobenzofuran (15a). DMF diethyl acetal (2 ml) was added to benzofuran **12a** (1.55 g, 5 mmol) in DMF (15 ml) and the product was stirred for 4 h at room temperature. The precipitated crystals were filtered, washed on the filter with ether, and dried to give nitro derivative **15a** (1.5 g).

2-(β-Dimethylaminovinyl)-3-(*p*-methylbenzoyl)-5-methoxy-6-nitrobenzofuran (15b) and 2-(β-Dimethylaminovinyl)-3-(*p*-nitrobenzoyl)-5-methoxy-6-nitrobenzofuran (15c) were obtained similarly to nitro derivative **15a** from compound **12b** and the mixture of compounds **12c,c'** respectively. ^{1}H NMR spectrum of compound **15c**, ppm: 2.68; 3.20 (6H, br. s, $N(CH_3)_2$); 3.67 (3H, s, OCH_3); 5.38 (1H, d, J = 12.4 Hz, βCH); 6.70 (1H, s, 4-H); 7.85 (2H, m, 2'-H, 6'-H); 7.90 (1H, d, J = 12.4 Hz, αCH); 7.95 (1H, s, 7-H); 8.38 (2H, m, 3'-H, 5'-H).

2-(β-Dimethylaminovinyl)-3-(*p*-nitrobenzoyl)-5-methoxybenzofuran (14) was prepared from compound **10c** as described in [8].

3-Benzoyl-5-ethoxy-2-(β-dimethylaminovinyl)-4,6-dinitrobenzofuran (16). DMF diethyl acetal (1 ml) was added to benzofuran **11** (1 g, 2 mmol) in DMF (5 ml) and refluxed for 3 h. More acetal (1 ml) was added and the reflux was continued for a further 2 h. The reaction mixture was cooled in ice and salt mixture. The precipitated crystals were filtered off, thoroughly dried on the filter, washed with ether, and dried to give dinitro compound **16** (0.46 g). ^{1}H NMR spectrum, ppm: 1.27 (3H, t, J = 7.2 Hz, $CH_2\underline{CH}_3$); 2.55-3.14 (2H, br. s, $N(CH_3)_2$); 4.10 (2H, q, J = 7.2 Hz, $\underline{CH}_2CH_3$); 4.62 (1H, d, J = 12.6 Hz, αCH); 7.52-7.70 (5H, m, C_6H_5); 7.75 (1H, d, J = 12.6 Hz, βCH); 8.25 (1H, s, 7-H).

5-Hydroxy-2-β-dimethylamino-3-(3-benzoyl-5-methoxy-6-nitrobenzofuran-2-yl)benzofuran (18a). Mixture of enamine **15a** (1.3 g, 3.5 mmol), *p*-benzoquinone (0.4 g, 3.7 mmol) and glacial acetic acid (30 ml) was heated until full dissolution of the precipitate and stirred for 3 h at room temperature. The precipitate was filtered off and washed on the filter with ether to give the bisheterocycle **18a** (1.5 g). ^{1}H NMR spectrum, ppm: 2.73 (6H, s, $N(CH_3)_2$); 3.94 (3H, s, OCH_3); 6.43 (1H, dd, J_o = 8.4 Hz, J_m = 2.4 Hz, 6-H); 6.77 (1H, d, J_m = 2.4 Hz, 4-H); 7.03 (1H, dd, J_o = 8.4 Hz, 7-H); 7.21-7.54 (5H, m, COC_6H_5); 7.60 (1H, s, 4'-H); 8.39 (1H, s, 7'-H); 9.10 (1H, s, 5-OH).

Compounds 17 and 18b were prepared similarly from the corresponding enamines.

Compound 18b. ^{1}H NMR spectrum, ppm: 2.26 (3H, s, CH_3); 2.75 (6H, s, $N(CH_3)_2$); 3.93 (3H, s, 5-OCH_3); 6.42 (1H, dd, J_o = 8 Hz, J_m = 2.4 Hz, 6-H); 6.75 (1H, d, J_m = 2.4 Hz, 4-H); 7.05 (3H, m, 3"-H, 5"-H, 7-H); 7.47 (2H, m, 2"-H, 6"-H); 7.56 (1H, s, 4'-H); 8.38 (1H, s, 7'-H); 9.09 (1H, s, 5-OH).

Compound 17. ^{1}H NMR spectrum, ppm: 2.76 (6H, s, $N(CH_3)_2$); 3.81 (3H, s, OCH_3); 6.39 (1H, dd, J_o = 8.4 Hz, J_m = 2.4 Hz, 6-H); 6.63 (1H, d, J_m = 2.4 Hz, 4-H); 6.97 (1H, d, J_o = 8.4 Hz, 7-H); 7.01 (1H, dd, J_o = 8.4 Hz, J_m = 2.8 Hz, 6'-H); 7.42 (1H, d, J_m = 2.8 Hz, 4'-H); 7.64 (1H, d, J_o = 8.4 Hz, 7'-H); 9.08 (1H, s, 5-OH).

5-Hydroxy-2-dimethylamino-3-(3-*p*-nitrobenzoyl-5-methoxy-6-nitrobenzofuran-2-yl)benzofuran (18c). Suspension of enamine **15c** (0.21 g, 0.5 mmol), *p*-benzoquinone (0.055 g, 0.5 mmol), and glacial acetic acid (30 ml) was heated for 5 h on an ultrasonic bath. On the following day, the precipitate of insoluble starting enamine was filtered off and washed on the filter with a small amount of acetic acid. The solvent was evaporated, ether was added to the residue, and the crystalline product was filtered off, washed with ether, and dried to give bisheterocycle **18c** (0.1 g). ^{1}H NMR spectrum, ppm: 2.79 (6H, s, $N(CH_3)_2$); 3.96 (3H, s, OCH_3); 6.42 (1H, dd,

J_o = 8.4 Hz, J_m = 2.4 Hz, 6-H); 6.72 (1H, d, J_m = 2.4 Hz, 4-H); 7.01 (1H, d, J_o = 8.4 Hz, 7-H); 7.66 (1H, s, 4'-H); 7.77 (2H, m, 2"-H, 6"-H); 8.01 (2H, m, 3"-H, 5"-H); 8.43 (1H, s, 7'-H), 9.18 (1H, s, 5-OH).

5-Hydroxy-2-dimethylamino-3-(3-benzoyl-4,6-dinitro-5-ethoxybenzofuran-2-yl)benzofuran (19) was obtained similarly, as described for compound **16**. ^{1}H NMR spectrum, ppm: 1.32 (3H, t, $J \sim 6$ Hz, $OCH_2\underline{CH}_3$); 2.81 (6H, s, $N(CH_3)_2$); 4.38 (2H, q, $J \sim 6$ Hz, $OC\underline{H}_2CH_3$); 6.40 (1H, dd, J_o = 8.8 Hz, J_m = 2.4 Hz, 6-H); 6.70 (1H, d, J_m = 2.4 Hz, 4-H); 7.00 (1H, d, J_o = 8.8 Hz, 7-H); 7.23 (2H, m, 5"-H, 3"-H); 7.46 (1H, m, 4"-H); 7.62 (2H, m, 2"-H, 6"-H); 8.82 (1H, s, 7'-H); 9.14 (1H, br. s, 5-OH) as a mixture with hydroxyquinone at 6.54 (4H) and 8.61 (2-OH). Ratio 1:2.

This work was carried out with the financial support of the Russian fund for basic research (project No. 96-03-32225).

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