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SYNTHESIS OF FUROINDOLES AND BENZODIFURANS BY THE NENITZESCU REACTION

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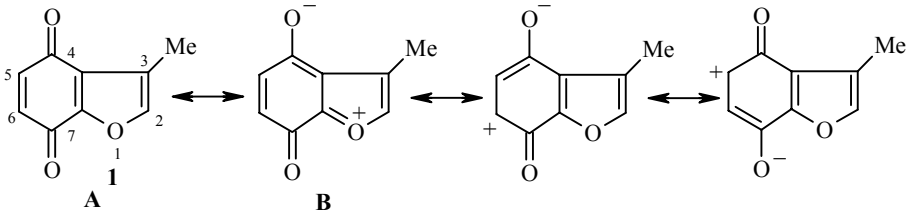
New derivatives of furoindole and benzodifuran were synthesized by the condensation of 3-methyl-4,5-dioxobenzofuran with enamines under the conditions of the Nenitzescu reaction.

Keywords: benzofuroquinone, enamine, furo[2,3-*g*]benzofuran, furoindole, Nenitzescu reaction.

The use of heterocyclic quinones in the Nenitzescu reaction is a promising trend in the synthesis of new heterocyclic compounds containing indole and benzofuran fragments and significantly extends the synthetic potentialities of the reaction [1-3].

The presence of an unsymmetrical system in certain annelated quinones, e.g., indazolequinones, creates the probability of ambiguous condensation of enamines with the quinones [1]. Moreover, frequently the cyclization of the obtained intermediate "hydroquinone adducts" also takes place in various directions [4, 5]. All this must be taken into account when conducting the Nenitzescu reaction, particularly with the use of quinones containing a heterocyclic fragment as quinone component.

In the present work the unsymmetrical benzofuran quinone 3-methyl-4,7-dioxobenzofuran (**1**) was used as starting compound [6]. If it is accepted that the mesomeric effect has the strongest influence on the comparative distribution of electron density in the quinone part of the molecule, it can be expected that the greater electron density of the oxygen in the furan ring (in comparison with the nitrogen atom) can lead to a smaller contribution from structure **B** to the resonance hybrid and, accordingly, to equalization of the electron densities at positions 5 and 6 of quinone **1**.



It seemed likely that both directions, i.e., at positions 5 and 6 with the formation of adducts of types **C** and **D**, could be realized (to a greater degree than for indazolequinones) in the reaction of the quinone **1** with enamines.

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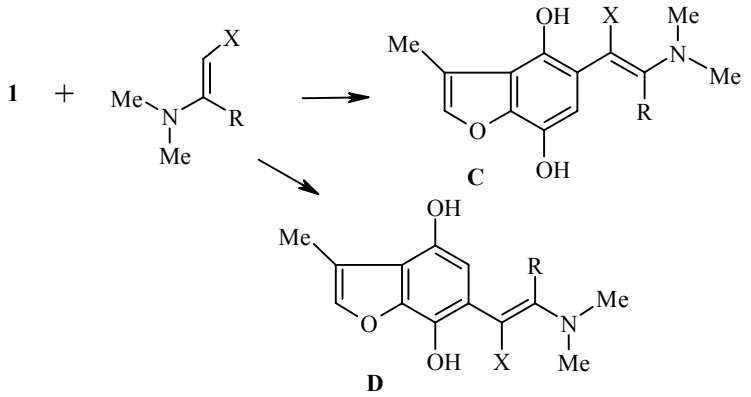


At the first stage of the investigation the condensation of the quinone **1** with the derivatives of β-aminocrotonic ester **2a-d** was studied. As a result of the reactions mixtures of products were isolated, and their composition and structure were established by ^{1}H NMR spectroscopy. Here special attention was paid to the mixtures formed in the course of the reactions before isolation and purification of the individual compounds. It was established that the preferred (and, in the case of two examples, the dominant) direction of the reaction was initial condensation at position 5 of the quinone **1** with the formation of an adduct of type **C**, as could be expected during examination of the resonance depicted above, indicating stronger electron-accepting character for the carbonyl at position 7 and, accordingly, a higher degree of depletion with electrons at position 5.

As a result of the reaction of the quinone **1** with N-methyl- and N-benzylaminocrotonic esters **2a**,**b** the furo[2,3-*g*]indoles **3a**,**b** were isolated as the main reaction products. At the same time analysis of the ^{1}H NMR spectra of the unpurified products and of the mixture contained in the mother solution after the crystallization of compound **3b** makes it possible to suppose that condensation takes place not only at position 5 but also partly at position 6 (intermediates of type **D**) with the formation of furo(3,2-*g*)indoles **4a**,**b**.

In addition to the main signals (Table 1), there is a second set of signals in the ^{1}H NMR spectrum of the unpurified product **3a** (δ, ppm: 2.36 (s), 2.62 (s), 3.91 (s), 7.28 (s), 9.30 (bs)) and also in the spectrum of the unpurified product **3b** (δ, ppm: 2.33 (s), 2.61 (s), 7.48 (bs), 7.00 (m), 9.33 (bs)); the last set of signals is also present in the product isolated from the mother solution obtained after the recrystallization of compound **3b**. The presence of the indicated additional signals, close in position to the signals of the main products, including the signals belonging to the substituents at position 1 of the indole ring (δ, ppm: **3a** 3.91 (3H, s, N$\underline{CH_3}$), **3b** 7.00 (2H, m, N$\underline{CH_2}$Ph)), confirms the suggestion above about the parallel formation of the isomeric furoindoles **4a**,**b**. Here the content of the isomeric indoles **3a**-**4a** in the unpurified product amounts to ~90:10 and that of **3b**-**4b** to ~94:6, while the content of the isomeric indole **4b** in the mixture isolated from the mother solution obtained as a result of the recrystallization of **3b** increases to 33%. From the mixtures it was only possible to isolate the derivatives **3a** and **3b** in the individual form. In order to confirm the preferential formation of indoles with structure **3** the HMBC NMR spectra of compound **5** (compound **3a** transformed into the O–Ac derivative) were recorded.* While comparing the alternative structures **3** and **4** it should be noted that in structure **4** the upfield signal of C-5a should correlate with at least two protons (H-4 and H-7) while the downfield signal of C-8a should correlate with one proton H-7. In the HMBC NMR spectrum of compound **5** the reverse pattern is observed: The upfield signal of H-8a (114.3) correlates with the signal of one proton H-7 (7.43), while the downfield signal (145.6 ppm, C-5a) correlates with the signals of two protons (H-4 (7.93) and H-7 (7.43 ppm)). These data confirm the structure of compound **5** and, consequently, the structure of compound **3a**.

* Compound **5** was synthesized specially to produce a compound sufficiently soluble for recording the HMBC spectrum.

In contrast to the cases mentioned above it was not possible to detect the formation of the isomeric tricyclic indoles **4c**,**d** during the reactions of the quinone **1** with N-*p*-methoxyphenyl- and N-unsubstituted aminocrotonic esters **2c**,**d**. It was established that in these cases benzofuran cyclization takes place as well as indolization with the formation of compounds **3c**,**d**. As a result mixtures of compounds **3c**-**6** and **3d**-**6** are formed, and their ratios in the unpurified product amount to ~72:28 and 60:40 respectively. Pure furoindole **3c** was isolated from the mixture of **3c**-**6**, and it was possible to separate the mixture of **3d**-**6** and isolate the individual compounds albeit with small yields.

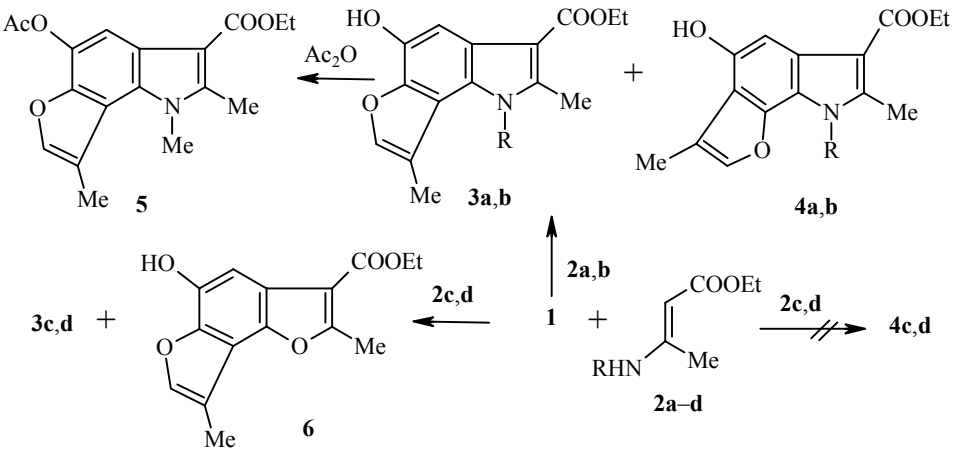
The HMBC NMR spectra were also recorded in order to determine the structure of the indole **3d** and the benzofuran **6**. In the spectrum of compound **3d**, as in the spectrum of compound **5**, the upfield signal at 114.8 ppm (C-8a) correlates with the signal of one proton H-7 (7.65 ppm). For the downfield signal of C-5a (142.2 ppm), in addition to correlation with the signals of two protons H-4 (7.40) and H-7 (7.65 ppm), correlation is observed with the signal of the proton of the hydroxyl group at position 5 (9.36 ppm), which provides further evidence for the structure of **3d**. The presence of analogous correlation peaks for the carbon atoms at positions 8a and 5a (δ, ppm: 7.26/142.7 (4-H/5a), 7.65/142.7 (7-H/5a), 9.87/142.7 (OH–H/5a), 7.65/114.9 (7-H/8a)) in the spectrum of compound **6** indicates that during the production of this compound at the stage preceding cyclization attack by the enamine takes place at position 5 of the quinone.

It should also be noted that in the ^{1}H NMR spectra of compounds **3b** and **3c**, which have aryl fragments as substituents at position 1, there is a substantial upfield shift of the signal for the protons of the methyl group at position 8 (2.16 and 1.19 ppm respectively) compared with the spectra of **3a** and **3d** (2.38-2.44 ppm). The observed shift is probably due to the effect of the anisotropy of the substituents at position 1 (CH_2Ph and *p*-$MeOC_6H_4$), which provides indirect evidence for the preferential formation of the indoles with structure **3**.

The data from the spectral investigations (see also Tables 1 and 2) indicate unambiguously that the preferred process in the investigated reaction is attack of the electron-excessive β-position of the enamines **2a**-**d** at position 5 of the quinone **1** and indole cyclization.

TABLE 1. The Characteristics of the Synthesized Compounds **3a**-**d**, **5**, **6**, **8**, and **10**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Mass spectrum, M^+	Yield, %
		C	H	N			
3a	$C_{16}H_{17}NO_4$	67.10 / 66.88	5.67 / 5.97	5.20 / 4.88	284-286 (DMF)	287	16.1
3b	$C_{22}H_{21}NO_4$	72.75 / 72.70	5.73 / 5.82	3.93 / 3.85	226-228 ($CHCl_3$)	363	12.4
3c	$C_{22}H_{21}NO_5$	69.18 / 69.64	5.74 / 5.58	3.53 / 3.69	212-215	379	8.0
3d	$C_{15}H_{15}NO_4$			4.84 / 5.13	262-264	273	2.4
5	$C_{18}H_{19}NO_5$			3.95 / 4.25	230-231 (CCl_4)	329	80.8
6	$C_{15}H_{14}O_5$	65.92 / 65.68	5.16 / 5.14		252-254	274	3.6
8	$C_{14}H_{12}O_4$	68.40 / 68.84	4.97 / 4.9		266-268	244	10.2
10	$C_{12}H_9NO_5$	57.99 / 58.30	3.53 / 3.67	5.55 / 5.67	241-243 (C_6H_6)	247	34.9



2-4 a R = Me; **b** R = CH_2Ph; **c** R = *p*-$MeOC_6H_4$; **d** R = H

The traditional route for such investigations is to study the Nenitzescu reaction using enamines containing less powerful electron acceptors than the ethoxycarbonyl group, since condensation of the quinones with such enamines often leads to a change in the direction of the reaction [1, 2].

In the present work enamines with acetyl and nitro groups at the β-position were used. In the reaction of the quinone **1** with the enamine of acetylacetone **7a** an unpurified product containing 90% of the benzofuran **8** and 10% of the indole **9** was obtained. Compound **8** was isolated from the mixture and identified. The presence of an even stronger electron acceptor (NO_2) in the enamine **7b** leads to the exclusive formation of the benzofuran **10**, the structure of which was established on the basis of data from the ^{1}H NMR (Table 1) and HMBC NMR spectra. In the HBMC NMR spectrum of compound **10**, as also in the spectrum of compound **6**, there are the following correlation peaks, δ, ppm: 7.22/143.4 (H-4/5a), 7.78/143.4 (H-7/5a), 10.23/143.4 (OH/5a), 7.78/114.6 (H-7/8a).

TABLE 2. The ^{1}H NMR Spectra of Compounds **3a-d**, **5**, **6**, **8**, and **10***

Com-pound	Chemical shifts, δ, ppm*[2]					
	R-1	CH_3-2, s	H-4	OH-5	H-7	CH_3-8
3a	3.69, s	2.59	7.57, s	9.33, br. s	7.69, s	2.38, s
3b	5.66 (2H, s), 6.87 (2H, m), 7.27 (3H, m)	2.56	7.65, s	9.48, br. s	7.65, br. s	2.16, s
3c	3.86 (3H, s), 7.17, 7.37 (4H, AA'XX')	2.32	7.60, s	9.50, br. s	7.53, br. s	1.19, br. s
3d	11.44 (br. s)	2.68	7.40, s	9.36, br. s	7.65, br. s	2.44, s
5	3.79 (s)	2.70	7.93, s	2.43, s	7.43, br. s	2.42, br. s
6	—	2.72	7.26, s	9.86, br. s	7.65, br. s	2.39, br. s
8	—	2.74	7.37	9.80, br. s	7.74, br. s	2.38, br. s
10	—	2.79	7.22, s	10.23, br. s	7.78, br. s	2.32, br. s

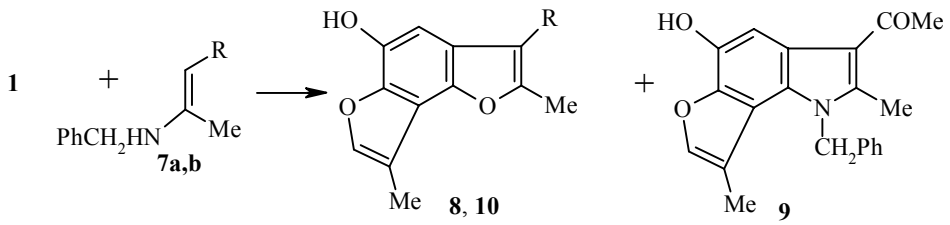
* The ^{1}H NMR spectra were recorded in deuterochloroform (compound **5**) and DMSO-d_6 (other compounds).

*[2] The signals of the protons of the methyl and methylene groups of the substituents $COOC_2H_5$ are observed in the region of: δ, 1.36-1.46 (t) and 4.27-4.40 (q) (compounds **3a-d** and **5**); the signal of the protons of the methyl group of the substituent $COCH_3$ (compound **8**) is observed at 2.54 ppm (s).

TABLE 3. The ^{13}C NMR Spectra of Compounds **3d**, **5a**, **6**, and **10***

Atom	Chemical shifts, δ, ppm*[2]			
	3d	**5**	**6**	**10**
2	142.1	143.5	161.6	159.6
3	102.9	104.9	108.5	131.1
3a	122.3	121.8	120.3	115.2
4	101.5	110.2	101.1	99.3
5	138.6	131.7	140.4	141.8
5a	142.2	145.6	142.7	143.4
7	140.5	142.2	142.0	142.8
8	114.2	113.4	113.4	113.5
8a	114.8	114.3	114.9	114.6
8б	120.5	127.9	139.7	138.2
CH_3-1	—	33.8	—	—
CH_3-2	13.7	12.0	14.1	15.0
$COOC_2H_5$-3	14.5; 58.5; 165.2	14.6; 59.5; 165.8	14.2; 59.9; 163.6	—
CH_3-8	9.5	13.7	8.9	8.8
$COCH_3$	—	20.8, 169.3	—	—

* The assignment of the signals for the C atoms was made on the basis of the HSQC and HMBC NMR spectra.
*[2] The ^1H NMR spectra were recorded in deuterochloroform (compound **5**) and DMSO-d_6 (other compounds).



7a, **8** R = COMe; **7b**, **10** R = NO_2

The reasons for the substantial effect of the β-substituent in the enamines on the direction of cyclization (indole or benzofuran) and the increase in the yield of the condensed benzofurans with increase in the electronegativity of these substituents were discussed earlier [1].

Benzofuranquinone **1**, like indazolequinone [1], does not enter into the Nenitzescu reaction.

Thus, the use of heterocyclic quinones in the Nenitzescu reaction not only creates new synthetic possibilities but also embodies the whole range of their characteristics that determine the direction of the processes and depend on the nature of the heterocycle condensed with the quinone ring.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz). The HSQC and HMBC 2D spectra were recorded on a Bruker DRX-500 spectrometer, using the makers' standard procedures. The mass spectra were obtained on a Finnigan SSQ-710 chromato-mass spectrometer with direct injection of the samples into the ion source. The processes were monitored by TLC on Silufol UV-254 plates with development in UV light.

The characteristics of the obtained compounds are given in Tables 1-3.

3-Ethoxycarbonyl-5-hydroxy-1,2,8-trimethylfuro[2,3-*g*]indole (3a). To a solution of the quinone **1** (0.65 g, 4 mmol) in acetic acid (7 ml) we added with stirring the enamine **2a** (0.7 g, 5 mmol). The reaction mass was stirred at 20°C for 20 h. The precipitate was filtered off, washed with water, and dried. The unpurified product (0.37 g) was recrystallized from DMF, and 0.18 g of compound **3a** was obtained.

Compound **3b** was obtained similarly.

3-Ethoxycarbonyl-5-hydroxy-1-(4-methoxyphenyl)-2,8-dimethylfuro[2,3-*g*]indole (3c). The reaction was conducted under the conditions described for the synthesis of compound **3a** with (0.75 g, 4.6 mmol) of the quinone **1**, acetic acid (1.6 ml), and the enamine **2c** (1.63 g, 7 mmol). The obtained unpurified product (0.55 g) was boiled in carbon tetrachloride (50 ml). The hot suspension was filtered, and 0.25 g of the substance remaining on the filter was chromatographed on a column of silica gel. The product was eluted with chloroform, and 0.14 g of compound **3c** was obtained from the eluate.

5-Acetoxy-3-ethoxycarbonyl-1,2,8-trimethylfuro[2,3-*g*]indole (5). To a suspension of compound **3a** (0.35 g, 1.2 mmol) in acetic anhydride (10 ml) we added one drop of concentrated sulfuric acid, and we heated the mixture until a solution had formed. The solution was left for 30 min to cool to 20-25°C and was then diluted with water. The precipitate was filtered off, washed with water, dried, and recrystallized from carbon tetrachloride. We obtained 0.32 g of compound **5**.

3-Ethoxycarbonyl-5-hydroxy-2,8-dimethylfuro[2,3-*g*]benzofuran (6). The reaction was conducted under the conditions described for the synthesis of compounds **3a-c** with the quinone **1** (0.97 g, 6 mmol), acetic acid (6 ml), and the enamine **2d** (1.63 g, 9 mmol). The obtained unpurified product (0.25 g) was chromatographed on a column of silica gel and eluted with chloroform. From the eluate we obtained in succession 0.06 g of compound **6** and 0.04 g of compound **3d**.

3-Acetyl-5-hydroxy-2,8-dimethylfuro[2,3-*g*]benzofuran (8). The reaction was conducted under the conditions described for the synthesis of compounds **3a-c** with the quinone **1** (0.65 g, 4 mmol), acetic acid (10 ml), and the enamine **7a** (1.13 g, 6 mmol). The obtained unpurified product (0.58 g) was chromatographed on a column of silica gel with chloroform as eluant. The product isolated from the eluate was rubbed with alcohol and filtered, and 0.1 g of compound **8** was obtained.

5-Hydroxy-2,8-dimethyl-3-nitrofuro[2,3-*g*]benzofuran (10). To a solution of the quinone **1** (0.32 g, 2 mmol) in acetic acid (5 ml) while stirring we added the enamine **7b** (0.57 g, 3 mmol). The reaction mass was heated at 80°C for 10 min, and the stirring was then continued at 20°C for 20 h. The precipitate was filtered off, washed with water, and dried. We obtained 0.17 g of compound **10**.

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