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REACTION OF NAPHTHO- AND BENZIMIDAZOLEQUINONES WITH ENAMINES. SYNTHESIS OF CONDENSED BENZOFURANS AND INDOLES

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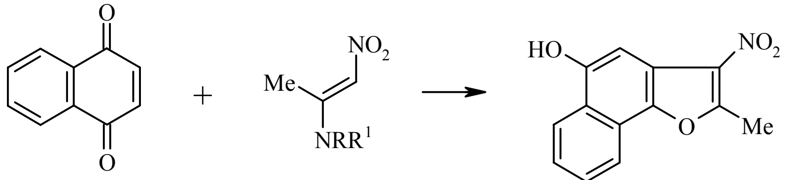
The reaction of naphthoquinone with nitroenamines and the interaction of benzimidazolequinones with derivatives of β-aminocrotonic ester have been studied. It was shown that in the first case only the synthesis of naphthofurans occurs but in the second imidazoindoles are formed.

Keywords: benzimidazolequinone, enamine, imidazoindole, naphthofuran, naphthoquinone, Nenitzescu reaction.

The synthetic potential of the Nenitzescu reaction, the condensation of quinones with enamines, has been considered in detail in the literature [1,2] and lies in the synthesis of a large number of derivatives of 5- or 6-hydroxyindoles and 5-hydroxybenzofurans unavailable practically by other methods. When studying the Nenitzescu reaction it is usual to investigate to some extent the effects of special structural features of the initial enamines or quinones on its course. Variations of enamines have been used to a significantly larger extent. The quinones chosen for this reaction were mainly substituted benzoquinones, and to a lesser extent naphthoquinone. The use of heterocyclic quinones has been limited to only two publications [3,4].

In the present work, we have used naphthoquinone **1** and benzimidazolequinone **2**, synthesized by the known procedure [5], in the Nenitzescu reaction.

The Nenitzescu reaction using naphthoquinone has been described in the literature [1], however nitroenamines, which possess reduced electrophilicity, have not been put into this reaction. We discovered that on interacting naphthoquinone with various nitroenamines **3a-d** the dominating, if not the only, direction of the process was benzofuran cyclization:



1 **3a–d** **4**

3 a-c R =H, **d** R = Me, **a** R^1 = H, **b** R^1= CH_2Ph, **c** R^1= C_6H_4OMe-*p*, **d** R^1= Me

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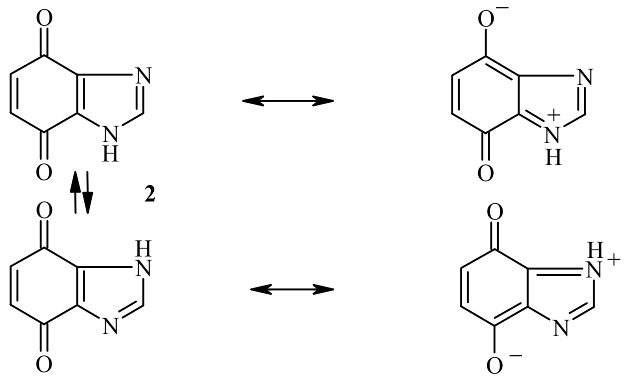
We noted in [6] that benzoquinone reacts with nitroenamines with the formation of the corresponding 6-hydroxyindoles.

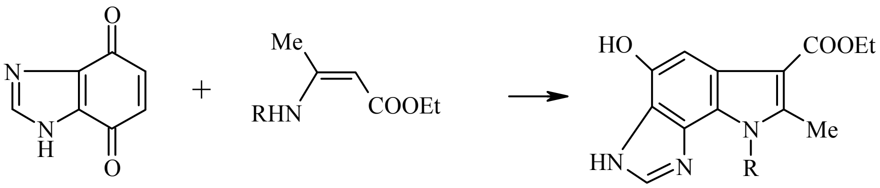
In all cases the isolated and identified product of the reaction of quinone **1** with enamines **3a-d** proved to be 5-hydroxy-2-methyl-3-nitronaphtho[1,2-*b*]furan (**4**). No other products were detected in the reaction mixture apart from compound **4** and residues of unreacted **1** and **3** (TLC, mass spectra). It seems probable that such a shift towards benzofuran compounds in the case of naphthoquinone is caused by the fact that the 5-hydroxyindole cyclization includes an oxidizing component, but the oxidation potential of naphthoquinone is significantly less than that of benzoquinone [7].

As indicated above heterocyclic quinones have been little used in the Nenitzescu reaction. In [3, 8, 9] we described the synthesis of indazolequinones and studied their interaction with various enamines leading to new pyrrolo[2,3-*e*]- and furo[2,3-*e*]indazoles.

Another heterocyclic quinone, benzimidazolequinone **2**, has been used in the Nenitzescu reaction in the present work. It turned out that like indazolequinones it did not react with nitroenamines. This becomes understandable on considering the structure of this quinone.



The electron-donating effect of the NH group of the imidazole ring leads to a reduction in the partial positive charge on the carbon atoms of the quinone fragment, and correspondingly to decrease in their electrophilicity, and hindrance to condensation at the electron-rich β-carbon atom of enamines. Nonetheless, with enamines having a substituent less electronegative than nitro group in the β-position, *viz.* β-aminocrotonic ester derivatives **5a-c**, quinone **2** reacts in accordance with the mechanism of the Nenitzescu reaction with the formation of imidazo[4,5-*g*]indoles **6a-c**. It is important to note that in this case indole cyclization occurs exclusively (as for indazolequinone). The corresponding benzofuran was not detected either in the reaction mixture or in the purified reaction product.



5, **6** **a** R = Me, **b** R = CH_2Ph, **c** R = C_6H_4OMe-*p*

These reactions take place best in nitromethane, which as is known enables precisely the occurrence of the indole cyclization [10,11], although as was shown using the reaction of compounds **2** and **5a**, the direction of the reaction was unchanged in acetic acid. However reaction in acetic acid is accompanied by resinification and the yield of imidazoindole **6a** was not high in this case.

TABLE 1. The ^{1}H NMR Spectral Characteristics of Compounds **6a-c**

Compound	Chemical shifts, δ, ppm						
	1-NH, br. s	2-H, s	4-OH, br.s	5-H, s	6-COOEt*	7-CH$_3$, s	8-R
6a	12.5	8.05	9.40	7.35	1.38 t, 4.29 q	2.68	4.18 s
6b	12.6	8.02	9.50	7.40	1.37 t, 4.28 q	2.58	6.04 s (CH$_2$); 6.93-5.33 m (Ph)
6c	12.4	7.81	9.50	7.48	1.39 t, 4.30 q	2.48	3.91 s (OCH$_3$); 7.22 (A$_2$B$_2$)

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* *J* = 7.0 Hz.

TABLE 2. Characteristics of the Synthesized Compounds **4**, **6a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Mass, M$^+$	Yield, %
		C	H	N			
4	$C_{13}H_9NO_4$	64.3 64.19	3.4 3.73	5.80 5.76	256-260 (*i*-PrOH)	243	58*
6a	$C_{14}H_{15}N_3O_3$	62.0 61.5	5.7 5.5	15.4 15.4	270-274 (EtOH)	273	66
6b	$C_{20}H_{19}N_3O_3$	68.7 68.7	5.7 5.5	11.9 12.0	233-237 (EtOH)	349	65
6c	$C_{20}H_{19}N_3O_4$	65.7 65.7	5.1 5.2	11.8 11.5	247-249 (chloroform)	365	48

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* The yield of compound **4** obtained from quinone **1** and enamine **3a** was 30, from **1** and **3c** was 25, and from **1** and **3d** was 23%.

The results of the present investigation therefore show that heterocyclic quinones are promising starting materials for the synthesis of tricyclic indole derivatives. At the same time it was confirmed once again [3], that enamines containing a strong electron-withdrawing group in the β-position in condensation with heterocyclic or carbocyclic quinones either do not react or benzofuran cyclization predominates.

EXPERIMENTAL

The ^{1}H NMR spectra (200 MHz) were recorded on a Bruker AC-200 instrument in DMSO-d$_6$. The mass spectra were obtained on a Finnigan SSQ 710 chromato-mass spectrometer with direct insertion of samples into the ion source. Checks by TLC were performed on Silufol UV-254, visualization with UV light.

5-Hydroxy-2-methyl-3-nitronaphtho[1,2-*b*]furan (4). Suspension of naphthoquinone **1** (4.74 g, 30 mmol) and enamine **3b** (8.64 g) in glacial acetic acid (50 ml) was heated to 60-65°C with stirring and maintained at this temperature for 10 min. The heating was stopped but the stirring was continued for a further 16 h. The solid was filtered off, washed with acetic acid, with water, and dried. Compound **4** (4.21 g) was obtained. ^{1}H NMR spectrum, δ, ppm: 2.89 (3H, s, 2-CH$_3$); 7.40 (1H, s, 4-H); 7.60, 7.68, 8.08, 8.24 (4H, m, 6-, 7-, 8-, 9-H); 10.24 (1H, br. s, 5-OH).

The condensation of quinone **1** with enamines **3a,b** was carried out analogously. Yields and constants of compound **4** are given in Table 2.

6-Ethoxycarbonyl-4-hydroxy-7,8-dimethyl-1,8-dihydroimidazo[4,5-*g*]indole (6a). A. Suspension of quinone **2** (0.46 g, 31 mmol) and enamine **5a** (0.65 g, 45 mmol) in nitromethane (45 ml) was boiled with stirring for 40 min. Heating was then discontinued, and stirring of the reaction mixture continued for 16 h. The solid was filtered off, washed with petroleum ether, and dried. Compound **6a** (0.56 g) was obtained.

Compounds **6b,c** were obtained analogously.

B. Suspension of quinone **2** (0.46 g, 31 mmol) and enamine **5a** (0.65 g, 45 mmol) in glacial acetic acid (30 ml) was stirred at 20°C for 20 h. The reaction mixture was diluted with water (30 ml) and the solution neutralized to pH 7 with sodium bicarbonate. The solid was filtered off, washed with water, dried, and recrystallized twice from alcohol. Compound **6a** (0.1 g, 12%) was obtained.

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