Chemistry of Heterocyclic Compounds, Vol. 39, No. 8, 2003

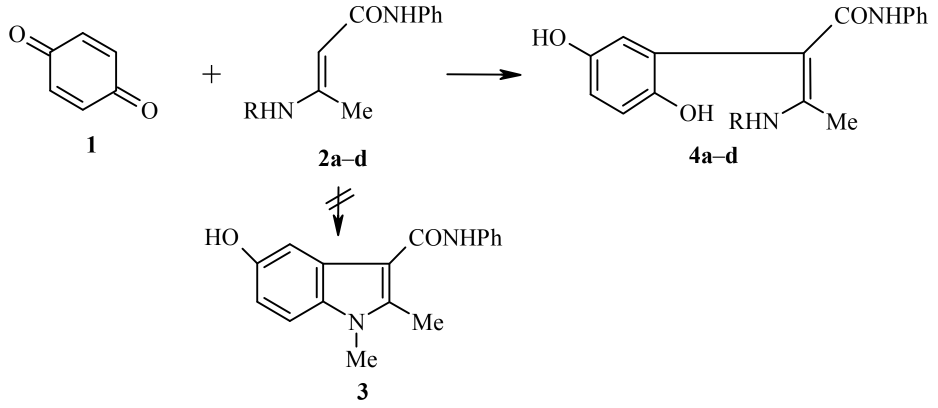
CONDENSATION OF *p*-BENZOQUINONE WITH ANILIDES OF β-AMINOCROTONIC ACID

E. K. Panisheva[1], L. M. Alekseeva[1], A. S. Shashkov[2], and V. G. Granik[1]

Benzofuranone derivatives have been synthesized by the condensation of p-benzoquinone with anilides of β-aminocrotonic acids under the conditions of the Nenitzescu reaction.

Keywords: anilides, benzofuranone, Nenitzescu reaction.

In one of the previous investigations of the Nenitzescu reaction the interaction was described of *p*-benzoquinone (**1**) with anilides of β-amino-, β-methylamino-, β-ethylamino-, and β-benzylaminocrotonic acids **2a-d**, and it was shown that in the case of enamine **2b** indolization occurs and 1,2-dimethyl-3-N-phenylcarbamoyl-5-hydroxyindole (**3**) was isolated However on using anilides **2a,c,d** the process stopped at the stage of forming the hydroquinone adducts **4a,c,d** [1]. Cyclization of these adducts leads, according to this work, to the same compound, *viz*. 3-acetyl-2,5-dihydroxy-1-phenylindole (**5**) [1]. Such differences on using the structurally similar enamines **2a-d** seems incomprehensible and in the present work the interaction of quinone **1** with anilides **2** is investigated once again. It turned out that on carrying out the reaction between the indicated compounds under the conditions of [1] referred to above, in all cases hydroquinone adducts **4a-d** were formed, i. e. the processes took place in the usual direction for the Nenitzescu reaction by condensation of the β-position of the enamines at position 2 of the benzoquinone. The structure of the compounds obtained was studied by ^{1}H NMR spectroscopy.



2, **4** **a** R = H, **b** R = Me, **c** R = Et, **d** R = PhCH$_2$

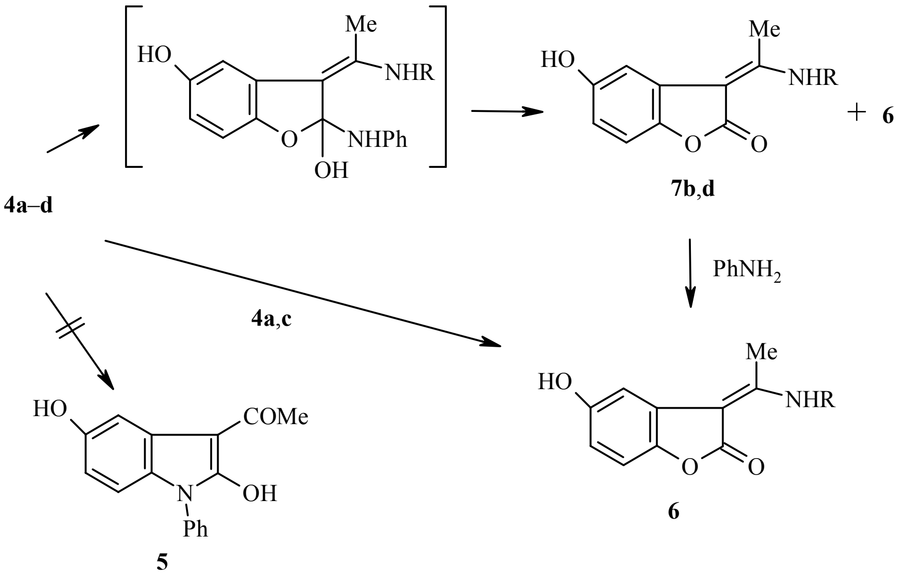
The data of the ^{1}H NMR spectra of hydroquinone adducts **4a-d** are given in Table 1.

---

[1] NIOPIK State Science Center of the Russian Federation, Moscow 103787; e-mail: makar-cl@ropnet.ru. [2] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1164-1168, August, 2003. Original article submitted February 8, 2001.

The most characteristic signals in the spectra belong to the phenolic hydroxyl at 8.37-8.72 ppm and the NH of the enamine group at 7.80 (2H, br. s, NH_2) for **4a** and at ~10 ppm for NHAlk in compounds **4b-d**. It should be noted that no signals corresponding to structure **3** were observed either in the ^1H NMR spectra of the reaction mixtures or in the mass spectra.

Cyclization of the adducts **4a-d** was carried out under the conditions of [1]. One substance **6** was successfully isolated on carrying out the cyclization of **4a,c**, but on using **4b** a mixture of **6** and **7b** (1:1) was obtained, and on using **4d** a mixture of **6** and **7d** (1:1) (the ratios were obtained from ^1H NMR spectral data). The assignments of the ^1H NMR spectra for the substances obtained are given in Table 2. It follows from these data that the compounds resulting on cyclization belong to one series, they are different from one another, and they contain the NH–R fragment. They are therefore not hydroxyindole **5**, the formation of which from all three hydroquinone adducts **4a,c,d** was postulated in [1], in which spectral data were not used for structure determination. We assume that in the present case cyclization takes place differently to that usually observed in the second stage of the Nenitzescu reaction, and includes participation of the amide fragment with fission of aniline and formation of a benzofuranone derivative. In this the enamine fragment in position 3 of the lactone portion of the molecule may be subject to a reamination reaction [2] by the aniline formed, with the formation of a mixture of enamino lactones containing different substituents at the enamine nitrogen atom. Since the physical properties of the products obtained are extremely similar, only in certain cases are pure final compounds successfully separated and isolated.



6 R = Ph, **7** **b** R = Me, **d** R = Bn

Compound **6** ($M^{+\cdot}$ = 267) was isolated in a pure state on cyclization of **4a,c** and unequivocal proof of its structure was obtained from HSQC NMR (direct correlation ^1H-^{13}C) and HMBC NMR (^1H-^{13}C correlation through 2 or 3 bonds). Chemical shifts for carbon atoms (protons with which they correlate are given in parentheses), δ, ppm: $C_{(2)}$ 170.0 (no correlation), $C_{(3)}$ 91.2 (H-4, CH_3, NH), $C_{(3a)}$ 126.2 (H-7), $C_{(4)}$ 106.1 (H-6, OH-5), $C_{(5)}$ 153.4 (H-4, 6, 7, OH-5), $C_{(6)}$ 109.8 (H-4, OH-5), $C_{(7)}$ 109.7 (no correlation), $C_{(7a)}$ 141.8 (H-4, 6, 7), $C_{(vin)}$ 160.2 (CH_3), $2C_{(2'6')}$ 125.0 (NH, H-2',3',4',5',6'), $2C_{(3'5')}$, 129.3 (H-5'6'), $C_{(1')}$ 136.7 (NH, H-2',3',5',6'), $C_{(4')}$ 126.5 (H-2',6'), CH_3 17.2 (NH). These data indicate that structure **5** does not correspond to the spectral data (for example, the absence of a correlation for the signal of the C=O is characteristic for structure **6** and definitely does not correspond to structure **5**).

TABLE 1. ^{1}H NMR Spectra of Hydroquinone Adducts **4a-d**

Compound	Chemical shifts (DMSO-d_6), δ, ppm (*J*, Hz)						
	OH-1,4	H-6, d	H-5, qd	H-3, d	CONHPh	β-CH_3, s	R
4a	8.63 s, 8.37 s	6.74 (*J* = 8.6)	6.61	6.47 (*J* = 2.8)	6.91 (1H, m); 7.18 (2H, m); 7.30 (2H, m); 6.93 (s, NH)	1.61	7.80 (2H, br. s, NH_2)
4b	8.40 br. s, 8.70 br. s	6.76	6.62	6.46	6.90 (1H, m); 7.18 (2H, m); 7.29 (2H, m); 6.86 (s, NH)	1.67	9.96 (1H, q, NH); 2.90 (3H, d, *J* = 6.6, CH_3)
4c	8.67 br. s, 8.45 br. s	6.75	6.63	6.48	6.91 (1H, m); 7.18 (2H, m); 7.30 (2H, m); 6.87 (1H, s, NH)	1.68	10.04 (1H, t, NH); 1.87 (t, *J* = 7.2, CH_3); 3.27 (q, CH_2)
4d	8.72 s, 8.48 s	6.78	6.65	6.50	6.88 (1H, m); 7.18 (2H, m)*; 6.96 (1H, s, NH)	1.71	10.42 (1H, t, NH); 4.50 (2H, d, *J* = 6.0, CH_2)*

---

* Multiplet at 7.27-7.45 ppm.

TABLE 2. ^{1}H NMR Spectra of Benzofuranones **6**, **7b**, and **7d**

Compound	Chemical shifts (DMSO-d_6), δ, ppm (*J*, Hz)					
	H-4, d	OH-5	H-6, qd	H-7, d	CH_3	R
6	6.86	9.04 br. s	6.52	6.95	2.45 s	7.20-7.70 (5H, m); 11.03 (br. s, NH)
Mixture (1:1)						
7b	6.80	8.87 s	6.42	6.87	2.42 s	3.10 (d, CH_3); 9.45 (q, NH, *J* = 6.0)
6	6.86	9.03 s	6.52	6.97	2.45 s	7.34-7.48 (5H, m); 11.04 (b. s, NH)
Mixture (1:1)						
7d	6.81 d	8.94 s	6.44	6.89	2.44 s	4.74 (d, CH_2); 9.85 (t, *J* = 6.0, NH)*
6	6.86 d	9.06 s	6.52	6.97	2.46 d	11.05 (br. s, NH)*

---

* 7.25-7.55 ppm ($NHCH_2$<u>Ph</u> and NH<u>Ph</u>).

TABLE 3. Characteristics of the Synthesized Compounds **4a,c,d** and **6**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Mass $[M]^+$	Yield, %
		C	H	N			
4a	$C_{16}H_{16}N_2O_3$	67.60 67.59	5.56 5.67	9.58 9.85	198.5 (*i*-PrOH)	284	51.0
4c	$C_{18}H_{20}N_2O_3$	68.89 69.21	6.41 6.45	8.72 8.97	213 (dioxane)	312	54.7
4d	$C_{23}H_{22}N_2O_3$	73.90 73.78	5.89 5.92	7.02 7.48	185.3 (C_6H_6–EtOAc)	374	56.3
6	$C_{16}H_{13}NO_3$	71.65 71.90	4.98 4.90	4.74 5.24	255.8 (MeOH)	267	20.4

The fact that enamino lactones are formed under the cyclization conditions for the hydroquinone adducts **4a-d**, which are then capable of being reaminated, was established by carrying out the reaction with a mixture of **7d** and **6** (obtained from **4d**) with an excess of aniline. In this case compound **6** is formed after boiling for 1 h and contained practically no contamination by the benzylamino derivative **7d** (TLC). Individual products were isolated from the mixture of **6** and **7b** by column and thin layer chromatography (see Table 2 and Experimental).

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer in DMSO-d_6, the two-dimensional spectra on a Bruker DRX 500 (500 MHz) using the company's standard procedures. The mass spectra were obtained on a Finnigan SSQ 710 chromato-mass spectrometer with direct insertion of samples into the ion source. A check on the purity of products was effected by TLC on Silufol UV 254 plates, visualizing in UV light. The characteristics of the obtained compounds are given in Tables 1-3.

α-(2,5-Dihydroxyphenyl)-β-methylaminocrotonic Acid Anilide (4b). Anilide **2b** (5.4 g, 3 mmol) and dichloroethane (86 ml) were added at one time to a solution of quinone **1** (2 g, 2 mmol) in dichloroethane (20 ml). The reaction mixture was heated to boiling and the solvent (~75 ml) distilled off. The precipitated residue was cooled, filtered off, and washed with cooled dichloroethane. Yield 2.5 g (30%); mp 186.4°C (aqueous *i*-PrOH, 1:1). Found, %: C 68.18; H 6.03; N 9.40. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44; H 6.08; N 9.40. $M^{+\cdot}$ 298.

Compounds 4a,c,d were obtained analogously to compound **4b**.

5-Hydroxy-3-(1-phenylaminoethylidene)-2,3-dihydrobenzofuran-2-one (6). Reaction was carried out under the conditions described in [1]. Compounds **4a** or **4c** were taken in an experiment, boiling for 1-2 h in AcOH with conc. H_2SO_4 (1-2 drops). Compound **6** was isolated in 26-31% yield.

Benzofuranone derivatives 6 and 7b were obtained under the conditions described in [1]. In an experiment **4b** (4.5 g), AcOH (60 ml), and conc. H_2SO_4 (3 drops) were taken. A mixture of **6** and **7b** (3.2 g, 45%) was obtained. The mixture was suspended in the minimum amount of chloroform–ethyl acetate 1:1 mixture and chromatographed on a column of silica gel, eluting with chloroform–ethyl acetate 1:1. In sequence compound **6** [yield 14%; mp 255.8°C (MeOH–Me$_2$CO, 2:1), $[M]^{+\cdot}$ 267] and a mixture (0.5 g) of **6** and **7b** were isolated. The mixture was chromatographed by the ascending method on Silufol UV 254 plates in the system benzene–ethanol–triethylamine, 10:2:1.5. The chamber was previously saturated for 1 h, plates were air-dried for 5 min, and scanned in UV light. Compound **7b** (0.05 g) was isolated, $[M]^{+\cdot}$ 205 (see Table 2 for ^1H NMR spectra).

Compound 7d was obtained analogously.

Reamination of a Mixture of 6 and 7b. Aniline (7 g) was added to a solution of a mixture of **6** and **7b** in AcOH (15 ml), and the mixture boiled for 2-3 h. The end of the reaction was determined chromatographically. The reaction solution was diluted with water and left at room temperature overnight. The precipitated solid was filtered off, washed with water, and dried. Yield of compound **6** 0.4 g (65%); mp 255.8°C (AcOH), $[M]^{+\cdot}$ 267.

The work was carried out thanks to Grant No. 99-03-32973 from the Russian Fund for Fundamental Investigations (RFFI).

REFERENCES

1. A. N. Grinev, V. N. Ermakova, I. A. Mel'nikova, and A. P. Terentiev, *Zh. Obshch. Khim.*, **31**, 2303 (1961).
2. V. G. Granik, *Usp. Khim.*, **53**, 651 (1984).