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REACTION OF 2-CHLORO-5-METHYLBENZOQUINONE WITH  $\beta$ -AMINOCROTONIC  
ESTER DERIVATIVES

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The reaction of 2-chloro-5-methylbenzoquinone with  $\beta$ -aminocrotonic ester derivatives was studied by PMR spectroscopy in  $CD_3COOD$ . The spectra indicate the formation of intermediate hydroquinone and quinone derivatives, which subsequently transform into the corresponding indoles. It was shown that the indolization proceeds unequivocally at the 3-position of the initial benzoquinone, and the rate of formation of the indole derivatives decreases with increase in the size of the substituent at the nitrogen atom of the  $\beta$ -aminocrotonic ester. The starting, intermediate compounds and the end products observed in the PMR spectra were identified by comparison with specially synthesized compounds.

The Nenitzescu reaction – the reaction of substituted benzoquinones with enamines – serves as the most convenient method of synthesis of 5-hydroxyindole derivatives [1]. It is known that the direction of the primary process – the addition of the enamine to quinone according to Michael is often determined by the size of the substituent at the enamine nitrogen atom [1-3]. In continuation of the study of the Nenitzescu reaction, we investigated in the present work the reaction of 2-chloro-5-methylbenzoquinone (I) with  $\beta$ -aminocrotonic ester (IIa) and its N-methyl-, N-ethyl-, and N-benzyl derivatives (IIb-d). It was unexpectedly found that when the reaction was carried out under the usual conditions ( $CH_3COOH$ , 50-55°C), compounds of two types were isolated according to the structure of the starting enamine: in the case of esters IIa,b, 2-methyl-3-ethoxycarbonyl-4-chloro-5-hydroxy-7-methylindole (IIIa) and its N-methyl derivative IIIb were isolated in low yield, while when N-ethyl- and N-benzylaminocrotonic esters (IIc, d) were used, 2-chloro-3-( $\beta$ -ethylamino- and -( $\beta$ -benzylamino- $\beta$ -methyl- $\alpha$ -ethoxycarbonyl)vinyl-5-methylhydroquinones (IVc, d) were obtained in satisfactory yields. The Michael addition takes place only at the 3-position of benzoquinone I, as unequivocally indicated by the PMR spectra: in the spectra of the isolated compounds, a splitting of the proton signals at the 6-position is observed due to the SSI [spin-spin interaction] with the methyl group of the benzene ring with  $J \approx 0.7$  Hz. On the basis of the similarity of structures of the starting compounds and since the first stage of the Nenitzescu reaction is of the same type in the reactions studied (at the 3-position of the starting quinone), we concluded that the observed difference in the

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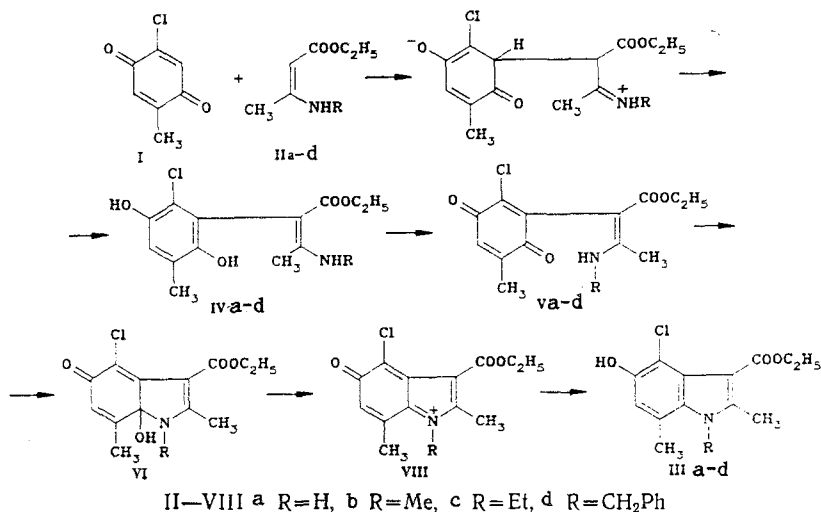
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TABLE 1. PMR Spectra of Compounds I, IIIb,c-Vb,c, VII

Compound	Chemical shift, ppm (J, Hz)					
	H, arom	Ar-CH <sub>3</sub> , d	COOCH <sub>2</sub> CH <sub>3</sub>	β-CH <sub>3</sub> or 2-CH <sub>3</sub> , s	N-CH <sub>3</sub>	N-CH <sub>2</sub> CH <sub>3</sub>
I	6,78 (s, 3-H; J= =1.5); 7,03 (s 6-H)	2,03	—	—	—	—
IIIb	6,65 (q J=0,7)	2,67	4,37 (m, CH <sub>2</sub> ); 1,38 (t, CH <sub>3</sub> );	2,49	3,89 s	—
IIIc	6,65 (q J=0,7)	2,65	4,38 (q, CH <sub>2</sub> ); 1,38 (t, CH <sub>3</sub> );	2,52	—	4,33 (q, CH <sub>2</sub> ); 1,32 (t, CH <sub>3</sub> )
IVb	6,73 (q, J=0,7)	2,16	4,00 (m, CH <sub>2</sub> ); 1,07 (t, CH <sub>3</sub> );	2,04	2,99 s	—
IVc	6,74 (q, J=0,7)	2,16	3,98 (m, CH <sub>2</sub> ); 1,27 (t, CH <sub>3</sub> );	2,04	—	3,34 (q, CH <sub>2</sub> ); 1,08 (t, CH <sub>3</sub> )
Vb	6,79 (q, J=1,5)	2,06	3,99 (m, CH <sub>2</sub> ); 1,07 (t, CH <sub>3</sub> );	2,04	3,00	—
Vc	6,80 (q, J=1,5)	2,06	4,00 (m, CH <sub>2</sub> ); 1,27 (t, CH <sub>3</sub> );	2,04	—	3,36 (q, CH <sub>2</sub> ); 1,08 (t, CH <sub>3</sub> )
VII	6,72 (q 3-H; J= =0,7); 6,75 (s, 6-H)	2,12	—	—	—	—

structures of the isolated compounds is not due to basic differences in the direction of the processes, but is determined by the change in the rate of indolization with an increase in the volume of the substituent at the enamine nitrogen atom. On prolonged standing of the mother liquor from the reaction of quinone I with ester IIc, a small amount of N-ethylindole IIIc separates out, which supports the above conclusion. In order to find the dependence of the rates of the condensation process of the benzoquinone derivatives and the enamines on the steric requirements of the N-substituent of the latter, to establish the generality of the processes under consideration, and to compare the scheme of the reactions studied with known concepts on the Nenitzescu reaction [1], we studied the reaction of quinone I with N-methyl- and N-ethyl-β-aminocrotonic esters (IIb, c) by PMR spectroscopy.\*

The scheme of the Nenitzescu reaction, as accepted in the literature, can be represented (on the example of components of the reactions studied in the present work) in the form



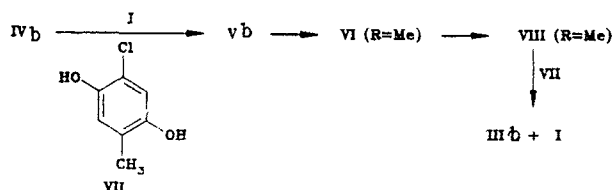
Since the reaction was carried out in acetic acid, in which the C-protonation of the intermediate β,β-disubstituted enamines of type IV, V may occur, ensuring a ready cis-trans-

\*The mother liquors were studied after filtration of indole IIIb (in the reaction of compounds I and IIb) or the hydroquinone derivative IVc (in the reaction of compounds I and IIc) after allowing the reaction mixtures to stand for 2 h (see the Experimental part).

isomerization relative to the enamine C=C bond, the influence of the mutual disposition of the quinonyl fragment and the NH group in quinones V was not dealt with in the present work.

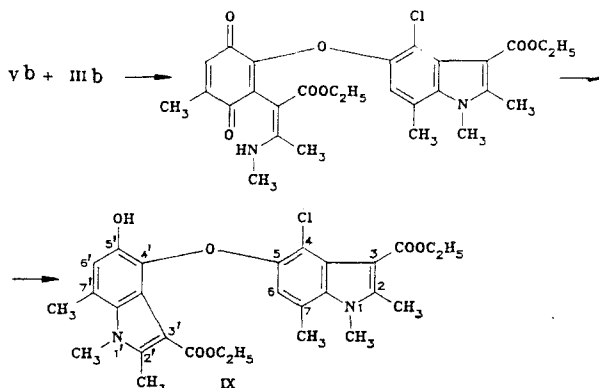
To identify the possible components of the mixtures studied, we used the hydroquinone-adduct IVb, the quinone-adducts Vb, c, and 2-chloro-5-methylhydroquinone (VII) [4]. Compound IVb was obtained by the reaction of quinone I with enamine IIb in methanol at  $-5^{\circ}\text{C}$ , while quinone-adducts Vb, c were synthesized by the oxidation of hydroquinones Ib, c. Comparison shows that the PMR spectra of the above compounds, and also of indoles IIIb, c (in  $\text{CD}_3\text{COOD}$ ) substantially differ from the spectra of the reaction mixtures, so that conclusions can be made unequivocally on the composition of compounds IVb, Vb (Table 1). Thus, the chemical shifts of the signals of the methyl and ethoxycarbonyl substituents in indoles and the corresponding quinone(hydroquinone)-adducts substantially differ (0.4-0.9 ppm). A considerable difference is also observed in the SSCC values for the 4- $\text{CH}_3$  group and 3-H proton in the spectra of the quinone I ( $J = 1.5$  Hz) and hydroquinone VII ( $J = 0.7$  Hz). A similar difference in the SSCC also holds for the quinone-(V) and hydroquinone adducts (IV). All these data indicate that in the case of reaction mixtures obtained directly after stopping of heating of compounds, the mixture contains a Michael's adduct IVb, a quinone-adduct Vb, hydroquinone VII, indole IIIb, and a small amount of the starting quinone I. The ratio of compounds IVb-Vb-VII-IIIb is  $\approx 1.5:2:3:4.5$ . After standing for 72 h at room temperature, indole IIIb becomes the main component of the mixture, which also contains small amounts of quinone I and hydroquinone VII. Decrease in the excess of the starting enamine IIb does not substantially change the pattern. Upon heating, the spectrum of the mixture of compounds I and IIc contains similar components (IVc, Vc, VII, IIIc) but in a different ratio; while the first three compounds are present in approximately equal amounts, the amount of indole IIIc in the mixture is smaller by a factor of 4 approximately. In this case, the process proceeds much more slowly (the influence of the replacement of the N-methyl group by N-ethyl), and much longer time is required to complete the process than in the preceding case - even after 8 days, an adduct of quinone Vc is still present in the mixture, and only after 14 days is the process completed - indole IIIc is prevalent in the mixture, and hydroquinone VII and quinone I are also present. Slowing down of the process when enamine IIc is used conforms well with data on the synthesis (see above), according to which the formation of indole IIIc proceeds at a lower rate than that of IIIb. In no case were signals observed which could be related to carbinolamines of type VI. Nevertheless, there are reasons to assume, that the indolization according to Nenitzescu [1] proceeds in particular via compounds of this type. The absence in the spectra of signals of compounds of this type probably indicates that they are formed more slowly than they are consumed, whereby, judging from the molecular models, the volume of the substituent at the enamine fragment nitrogen atom is particularly significant for compounds VI. This shows that in the case under consideration, the formation of carbinol-amines VI is the stage limiting the rate of the process on the whole, which in addition, is very sensitive to the steric requirements of the N-substituent.

The intermediate stages of the formation of indole IIIb were examined by PMR spectroscopy. When equimolar amounts of hydroquinone-adduct IVb and quinone I were mixed together in  $\text{CD}_3\text{COOD}$ , the reaction proceeded unequivocally (without formation of any by-products) and after 6 h, the signals of indole IIIb, hydroquinone VII, quinone-adduct Vb and quinone I were observed in the PMR spectrum of the mixture, according to which the ratio of these compounds was 1:2:3:3, and after 24 h, only the signals of indole IIIb and quinone I (1:1) were observed. In other words, quinone I oxidizes the hydroquinone-adduct IVb into quinone-adduct Vb, thus converting into hydroquinone VII. The regeneration of quinone I proceeds due to a redox reaction between hydroquinone VII and the intermediate quinoneimmonium compound VIII, as a result of which indole IIIb is also formed



When equimolar amounts of compounds Vb and VII were used, the mixture contained compounds VII, IIIb, Vb and I (1:3:3:5) after 6 h, and indole IIIb and quinone I (1:1) after 24 h.

The reaction of quinone I with enamines II does not proceed unequivocally and is accompanied by side-reactions. Thus, after 2 h of heating of compounds I and IIb, the filtered indole derivative IIIb contained a small amount of an impurity of a compound, traces of which were observed during the PMR examination of the mixtures. This compound was isolated by column chromatography on silica gel, and judging from the mass spectrum ( $M^+$ : 526) and PMR spectrum data ( $\text{COOCH}_2\text{CH}_3$  - 0.94 (t); 1.41 (t); 3.98 (q); 4.39 (q); 1'-, 1-, 2'-, 2-, 7'-, 7- $\text{CH}_3$  - 2.50; 2.52; 2.55; 2.74; 3.88; 3.95; 6'-, 6-H - 6.23; 6.69 ppm) is dimer IX which is possibly formed according to the following scheme:



Moreover, after the reaction of compounds I and IIc, a compound is present in the reaction mixtures, to which a signal at 6.7 ppm corresponds. Although this compound could not be identified, it is still not the carbinolamine VI, since it does not convert into indole IIIc even on prolonged standing of the solution, nor the dimer IX.

In conclusion, it should be noted that the data obtained as a result of the spectral investigation made it possible to carry out the synthesis of indole IIIc with a highly satisfactory yield from adduct IVc by prolonged standing of the solution in acetic acid in the presence of quinone I.

#### EXPERIMENTAL

The PMR spectra were recorded on a Varian XL-200 spectrometer using TMS as internal standard. The mass spectra were obtained on a Varian MAT-112 spectrometer with direct introduction of the sample into the ionic source. The temperature of the ionization chamber was 180°C, and the energy of the ionizing electrons was 70 eV. The IR spectra were run on a Perkin-Elmer 457 spectrophotometer in mineral oil.

The data of the elemental analysis for C, H, N, and Cl corresponded to the calculated values.

2,7-Dimethyl-3-ethoxycarbonyl-4-chloro-5-hydroxyindole (IIIa),  $\text{C}_{13}\text{H}_{14}\text{ClNO}_3$ . A 3.2 g portion (25 mmoles) of  $\beta$ -aminocrotonic ester (IIa) was added to a solution of 3.12 g (20 mmoles) of 2-chloro-5-methylbenzoquinone (I) [4] in 15 ml of glacial acetic acid at such a rate that the temperature of the reaction mixture did not exceed 50 to 55°C. The reaction mixture was allowed to stand at room temperature for 2 h, the precipitate that separated out was filtered off, and washed with cold acetic acid. The yield of compound IIIa was 25%, mp 167-168°C (from 2-propanol),  $M^+$ : 268. PMR spectrum ( $\text{DMSO}-d_6$ ): 1.30 (t,  $\text{CH}_2\text{CH}_3$ ); 2.37 (s, 2- $\text{CH}_3$ ), 2.49 (d, 7- $\text{CH}_3$ ), 4.21 (q,  $\text{CH}_2\text{CH}_3$ ); 6.64 (q, 6-H), 9.12 (s, NH); 11.44 ppm (s, OH). IR spectrum: 3260 (OH); 3130 (NH); 1675  $\text{cm}^{-1}$  (C=O).

1,2,7-Trimethyl-3-ethoxycarbonyl-4-chloro-5-hydroxyindole (IIIb),  $\text{C}_{14}\text{H}_{16}\text{ClNO}_3$  was obtained in a similar way as compound IIIa from quinone I and the N-methyl- $\beta$ -aminocrotonic ester (IIb),  $M^+$ : 281. IR spectrum: 3410 (OH); 1660  $\text{cm}^{-1}$  (C=O), mp 165-166°C (from 2-propanol), yield 25%.

After the separation of indole IIIb from the reaction mixture, the mother solution was allowed to stand at room temperature for 2 days. The precipitate that separated out,

comprising a mixture of compound IIIb and bisindole IX, was filtered off, and separated chromatographically on a column with silica gel L 40/100, eluting with ether. Bisindole IX ( $C_{28}H_{31}N_2ClO_6$ ) was obtained.  $M^+$ . 526. mp 217-218°C (from a hexane-acetone mixture), yield 1%.

4-Chloro-3-( $\beta$ -methylamino- $\beta$ -methyl- $\alpha$ -ethoxycarbonyl)vinyl-5-methylhydroquinone (IVb,  $C_{14}H_{18}ClNO_4$ ). A suspension of quinone I in 20 ml of methanol was added slowly at  $-5^\circ C$  to a solution of 1.56 g (10 mmoles) of  $\beta$ -aminocrotonic ester IIb in 10 ml of methanol. The precipitate of compound IVb that separated out was filtered off, washed with methanol, and dried, mp 189-190°C [from a hexane-acetone (1:1) mixture], yield 26%.  $M^+$ . 299. IR spectrum: 3450 (OH), 3270 (NH), 1630  $cm^{-1}$  (C=O).

2-Chloro-3-( $\beta$ -ethylamino- $\beta$ -methyl- $\alpha$ -ethoxycarbonyl)vinyl-5-methylhydroquinone (IVc,  $C_{15}H_{20}ClNO_4$ ) was obtained in a similar manner as compound IIIa from quinone I and  $\beta$ -aminocrotonic ester IIc,  $M^+$ . 313. mp 177-178°C [from a hexane-acetone (1:1) mixture], yield 50%. IR spectrum 3460, 3360-3240 (OH, NH), 1630  $cm^{-1}$  (C=O).

The mother solution remaining after the separation of compound IVc from the reaction mixture was allowed to stand at room temperature for 7 days. The precipitate that separated out was filtered off and recrystallized from ethanol to yield 1-ethyl-2,7-dimethyl-3-ethoxycarbonyl-4-chloro-5-hydroxyindole (IIIc,  $C_{15}H_{18}ClNO_3$ ). Yield 7%.  $M^+$ . 295. IR spectrum: 3310 (OH), 1670  $cm^{-1}$  (C=O).

2-Chloro-3-( $\beta$ -benzylamino- $\beta$ -methyl- $\alpha$ -ethoxycarbonyl)vinyl-5-methylhydroquinone (IVd,  $C_{20}H_{21}ClNO_4$ ) was obtained in a similar manner as compound IIIa from quinone I and  $\beta$ -aminocrotonic ester IID,  $M^+$ . 275. mp 171-172°C (from methanol), yield 60%. IR spectrum: 3440, 3390, 3270 (OH, NH), 1626  $cm^{-1}$  (C=O).

1-Ethyl-2,7-dimethyl-3-ethoxycarbonyl-4-chloro-5-hydroxyindole (IIIc) (from adduct IVc). A solution of 0.35 g (1.1 mmole) of compound IVc and 0.172 g (1.1 mmole) of quinone I in 15 ml of glacial acetic acid was allowed to stand at room temperature for 60 h. The acetic acid was evaporated, and the residue was ground with isopropanol. The precipitate of indole IIIc was filtered off, mp 167-167.5°C (from methanol), yield 65%.

2-Chloro-3-( $\beta$ -methylamino- $\beta$ -methyl- $\alpha$ -ethoxycarbonyl)vinyl-5-methylbenzoquinone (Vb,  $C_{14}H_{18}ClNO_4$ ). A solution of 0.25 g (0.84 mmole) of compound IVb in 200 ml of absolute ether was shaken for 30 min with 0.5 g of silver oxide. The solution was filtered, and the filtrate was evaporated. The residue was ground with hexane, and the precipitate of compound Vb was filtered off, mp 89-91°C (from hexane), yield 90%. IR spectrum: 3250 (NH), 1640, 1580  $cm^{-1}$  (C=O).

2-Chloro-3-( $\beta$ -ethylamino- $\beta$ -methyl- $\alpha$ -ethoxycarbonyl)vinyl-5-methylbenzoquinone (Vc,  $C_{15}H_{18}ClNO_4$ ) was obtained in a similar way as compound Vb, mp 123-125°C (from hexane), yield 90%. IR spectrum: 3250 (NH), 1640, 1585  $cm^{-1}$  (C=O).

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