Acetyl ketene aminals in Nenitzescu reaction

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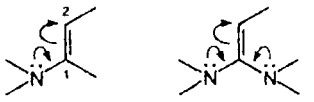
Nenitzescu reaction of acetyl ketene aminals (*N,N*-acetals) was investigated. The interaction of 2-acetyl-1-amino-1-anilinoethene with benzoquinone gave 3-acetyl-2-amino-7a-hydroxy-1-phenyl-5,7a-dihydro-1*H*-indol-5-one, which was then transformed into 3-acetyl-2-amino-6-chloro-5-hydroxy-1-phenylindole. The reaction of benzoquinone with 2-acetyl-1-amino-1-benzoylaminoethene led to the corresponding hydroquinone-adduct which was oxidized to 4-acetylamino-5-(2,5-dihydroxyphenyl)-2-phenyloxazole.

Key words: Nenitzescu reaction, enediamines, 5-hydroxyindoles, oxazole derivatives; ^{1}H and ^{13}C NMR spectra.

Enamines are known to react fairly readily with benzoquinone derivatives to give 5- and 6-hydroxyindoles and 5-hydroxybenzofurans.[1,2] Although the structures of enamines (EA) used in these transformations varied over rather wide limits, data on the employment of enediamines (EDA) are limited to only one publication devoted to the reaction of quinone with substituted ketene *N,N*-acetals.[3] Meanwhile, it appears of interest to study the Nenitzescu reaction involving acyl ketene aminals (for their use in heterocyclic synthesis, see Refs. 4—8), because the electron density in position 2 of the enamine fragment is substantially increased due to the electron-donating influence of the second amino group.



Since the electrophilic attack by an electron-deficient quinone on the C(2) atom of the enamine component, bearing a partial negative charge, is the main driving force of the Nenitzescu reaction, passing from enamines to enediamines (ketene aminals) can provide new interesting results.

In this study, we used 2-acetyl-1-amino-1-anilinoethene[9] (**1**) (an equilibrium mixture of *E,Z*-isomers) and 2-acetyl-1-amino-1-benzoylaminoethene[9] (**2**) as the initial compounds.* The reaction of enediamine **1** with benzoquinone (**3**) affords compound **4**, whose molecular weight (282, mass spectrometry data) corresponds to quinone-adduct **5**, a typical intermediate of the Nenitzescu reaction[1,2] (Scheme 1). However, data of ^{1}H and ^{13}C NMR spectroscopy (see Experimental) lead to the conclusion that the compound obtained is amino alcohol **4**. An amino alcohol with a similar structure was isolated and identified[10] in the reaction of benzoquinone with *N*-methylaminocrotonic ester. Normally these compounds are easily transformed during the Nenitzescu reaction into 5-hydroxyindoles.[1,2] However, stable amino alcohol **4** was isolated in a satisfactory yield. The structure of the compound **4** is confirmed unambiguously by the ^{13}C NMR spectrum, which exhibits two signals for the carbonyl groups (the alternative product, quinone-adduct **5**, contains three carbonyl carbon atoms) at δ 184.5 (quinone C=O) and δ 190.4 (COMe) and a signal at δ 86.7, corresponding to the C(7a)—OH fragment. The ^{1}H NMR signal of the hydroxyl proton is a broadened singlet at δ 7.34. It should be noted, however, that these data are not at variance with an alternative isomeric product (**4A**). The choice between structures **4** and **4A** was based on the ^{13}C NMR spectrum (complete spin-spin decoupling) recorded in DMSO-d_6 with an addition of an H_2O—D_2O mixture (1 : 1). Under these

* The systematic names for compounds **1** and **2** are 4-amino-4-phenylaminobut-3-en-2-one (**1**) and *N*-(1-amino-3-oxobut-1-enyl)benzamide (**2**).

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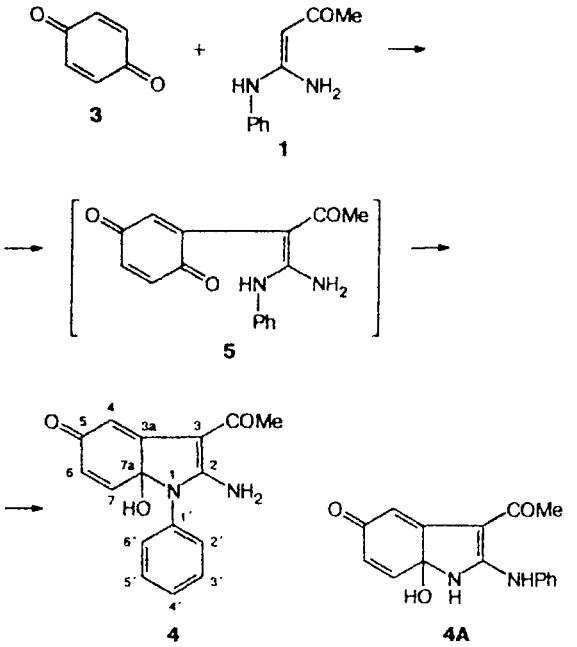
conditions, additional signals, caused by the fact that along with the initial compound **4**, the solution contained its deuterated analogs with OD, NHD, and ND_2 groups, appear in the spectrum near the signals for some carbon atoms (isotope shifts). The isotope shifts were relatively large for the carbon atoms attached directly to the above-mentioned groups (C(2): $\Delta\delta = -0.09$,* C(7a): $\Delta\delta = -0.07$) or neighboring carbon atoms (C(3): $\Delta\delta = -0.03$,* C(3a): $\Delta\delta = -0.03$, C(7): $\Delta\delta = -0.05$). An isotope shift is also observed for the C(6) atom ($\Delta\delta = +0.05$).

Scheme 1



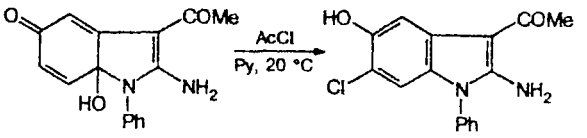
3 1 5 4 4A

The presence of only one additional signal for C(7a) and the absence of a noticeable isotope shift for C(1′) unambiguously confirm structure **4**.

Although, as mentioned above, the isolation of amino alcohol **4** is not the first example of identification of this type of intermediate during the Nenitzescu reaction, our result is nontrivial. In our opinion, the formation and stabilization of compound **4** is mainly due to the additional (to that present in ordinary enamines) electron-donating amino group present in the molecule; this accelerates cyclization of the intermediate quinone-adduct **5** but inhibits the subsequent reduction of amino alcohol **4** to give an indole derivative. The attempts to reduce compound **4** by various methods failed; in all cases, complex mixtures were formed; according to NMR spectroscopy and mass spectrometry, they did contain the target 5-hydroxyindole but we were unable to isolate it in a pure state.

* The carbon atom is responsible for two additional signals in the spectrum, arising due to mono- and dideuteration at the adjacent group.

Amino alcohol **4** was converted into 5-hydroxyindole derivative (**6**) by the reaction with acetyl chloride in pyridine.



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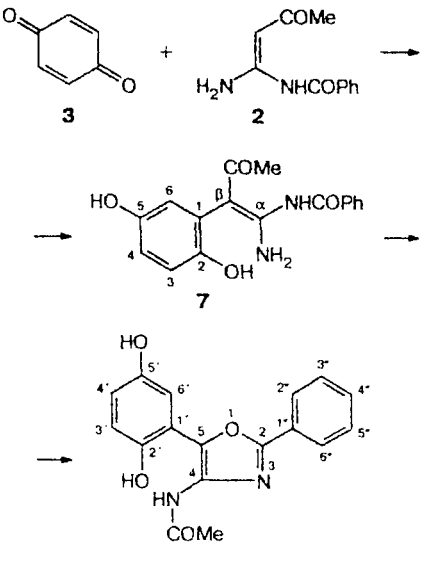
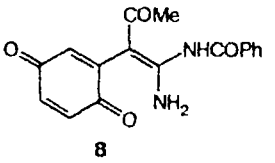
The next stage in the work was to study the reaction of quinone **3** with *N*-acylated enediamine **2**, in which the electron-donating effect of the second amine fragment is substantially decreased due to the presence of the *N*-benzoyl group. *N*-Benzoylated enediamine **2** was prepared by a known scheme;[9] according to the ^{1}H NMR spectrum in C_5D_5N, it was a mixture of *Z*- and *E*-isomers containing no more than 10% of the latter.[11] The reaction of benzoquinone (**3**) with ketene aminal **2** in various solvents smoothly gives the expected hydroquinone-adduct **7** (Scheme 2), whose structure follows unambiguously from the data of mass spectra and ^{1}H and ^{13}C NMR spectra (see Experimental). A characteristic feature of the ^{1}H NMR spectrum is the presence of two singlets for the OH groups (δ 8.50 and 8.80) and two broadened signals (δ 6.00 and 8.45), due to the amino group (one of the NH protons is involved in an N—H...O intramolecular hydrogen bond (IHB)). The NH signal for the amide group occurs in a substantially lower field (δ ~15.9), which reflects its higher acidity and participation in the IHB. All this leads to the conclusion that compound **7** has *Z*-configuration with close NHCOPh and COMe groups.

Scheme 2



3 2 7 9

The attempts to carry out oxidative transformation of hydroquinone-adduct **7** to a 5-hydroxyindole derivative (which is a typical route of the Nenitzescu reaction[1,2]) led to quite unexpected results. Oxidation of 2,6-dichloro-3,5-dicyanobenzoquinone in acetic acid gave the same compound as oxidation of adduct **7** with benzoquinone (**3**) in propionic acid. According to mass-spectrometry, the molecular weight of this product was 310, which coincides with that of quinone-adduct **8**. However, the fragmentation of this product (Scheme 3) did not correspond to this, quite expected, structure. Detailed analysis of the structure of the resulting compound by ^1H and ^{13}C NMR spectroscopy (full spectral data are presented in the Experimental) has shown that it contains an $NHCOCH_3$ group (whose presence causes the greatest difficulty in the interpretation of the mechanisms of these reactions). This structural fragment, NHAc, was unambiguously identified using ^{13}C NMR spectra, because the signal at δ 169.2,* appearing as a complex multiplet in the spectrum recorded without proton decoupling, turned into a quartet and a doublet in the case of selective decoupling from the protons of the NH (δNH 10) and CH_3 (δCH_3 2.03) groups, respectively. The spin-spin coupling constants, $^2J_{CCH} \approx 6$ Hz and $^2J_{CNH} \approx 3$ Hz measured in these spectra are in good agreement with the constants reported in the literature for the NHAc group.[12] In the experiments in which isotope shifts were induced (by adding an H_2O—D_2O (~1 : 1) mixture to the solvent, see above), pronounced isotope shifts were observed both for the signal at δ 169.2 (Δδ ≈ −0.11, C=O) and for the signal at δ 23.0 (Δδ = −0.04, CH_3); this also confirms the presence of the NHAc structural fragment. A significant isotope shift was also noted for the signal at δ 133.6 (Δδ = −0.11), which allowed this signal to be assigned to the carbon atom to which the NHAc group is attached.



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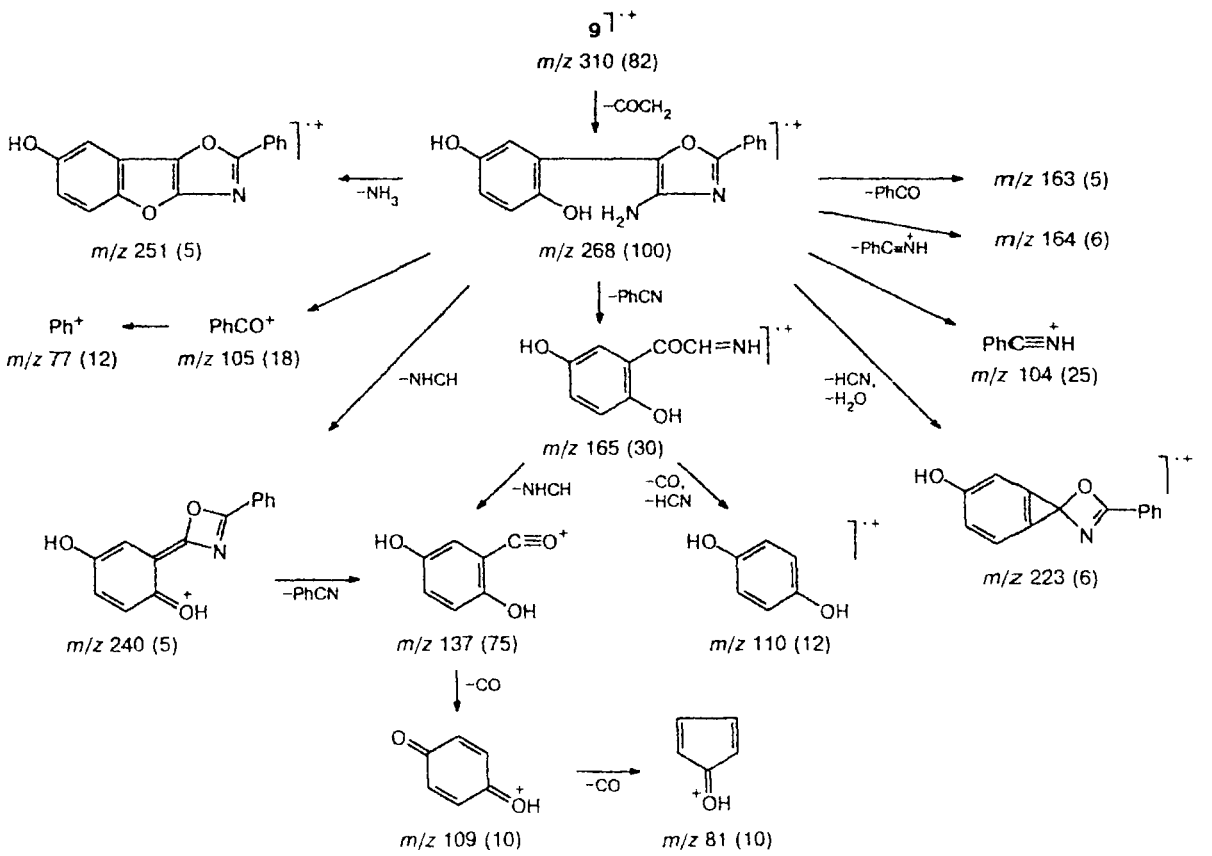
The presence of this substituent and the possibility of interconversion between two amide conformers apparently account for the peculiar feature of the ^1H NMR

* DMF-d_7 as the solvent, −40 °C (see Experimental).

Scheme 3



Note. The relative intensities of the corresponding signals (%) are given in parentheses.

and ^{13}C NMR spectra of the resulting compound, namely, broadening of the signals in the spectra recorded at room temperature. A decrease in the temperature resulted in spectral changes typical of dynamic processes of this type, and at −40 °C, the spectra contained two sets of signals in 10 : 1 ratio, which corresponded evidently to the two amide conformers.*

Based on the above results, a large number of alternative structures were analyzed, and the structure of substituted oxazole **9**, which conformed to the whole set of physicochemical data, was chosen. Specifically, it should be noted that the chemical shifts and the spin-spin coupling constants for the hydroquinone part of molecule **9** are close to those observed in the spectra of hydroquinone-adduct **7**, and the chemical shifts found experimentally for the carbon atoms of the oxazole ring in compound **9** agree well with those calculated** using the additive scheme from the chemical shifts of unsubstituted oxazole and the increments for the substituents (see Ref. 13).***

The path of the mass-spectrometric destruction of compound **9** (see Scheme 3) also agrees with the proposed structure. The mass spectrum of compound **9** exhibits an intense molecular ion peak with m/z 310. The $[M - COCH_2]^+$ peak is the most intense, which confirms the presence of an acetyl group in the molecule. The subsequent fragmentation of the $[M - COCH_2]^{\cdot +}$ ion includes elimination of PhCN and then HN=CH (see Scheme 3). In addition to the $[M - COCH_2 - PhCN]^{\cdot +}$ ion (I_{rel} = 30%), the $[PhCNH]^+$ (I_{rel} = 25%) and $[PhCO]^+$ (I_{rel} = 18%) ions are observed; the intensity of the $[M - COCH_2 - PhCO]^+$ peak does not exceed 5%. This fragmentation pattern apparently indicates that molecule **9** contains an N=C(Ph)—O fragment, and at the same time it rules out the possibility of the presence of an NHCOPh group, because the latter would certainly be manifested in the spectrum as intense $[M - COPh]^+$, $[M - COCH_2 - PhCO]^+$, and $[PhCO]^+$ peaks. It should be noted that the mass spectrum of compound **9** also contains ions with m/z 137, 110, and 109 (see Scheme 3), indicating the presence of a hydroquinone fragment.

The structure **9** is also supported by the IR spectrum, ν/cm^{-1}: 1625 (C=N); 1655 (C = O); 3170 (NH); 3240 and 3350 (OH). Acetylation of compound **9** with acetic anhydride affords a mixture of di- and triacetylated derivatives (mass spectra, ^1H and ^{13}C NMR spectra); the spectral data for this mixture correspond to the expected ones.

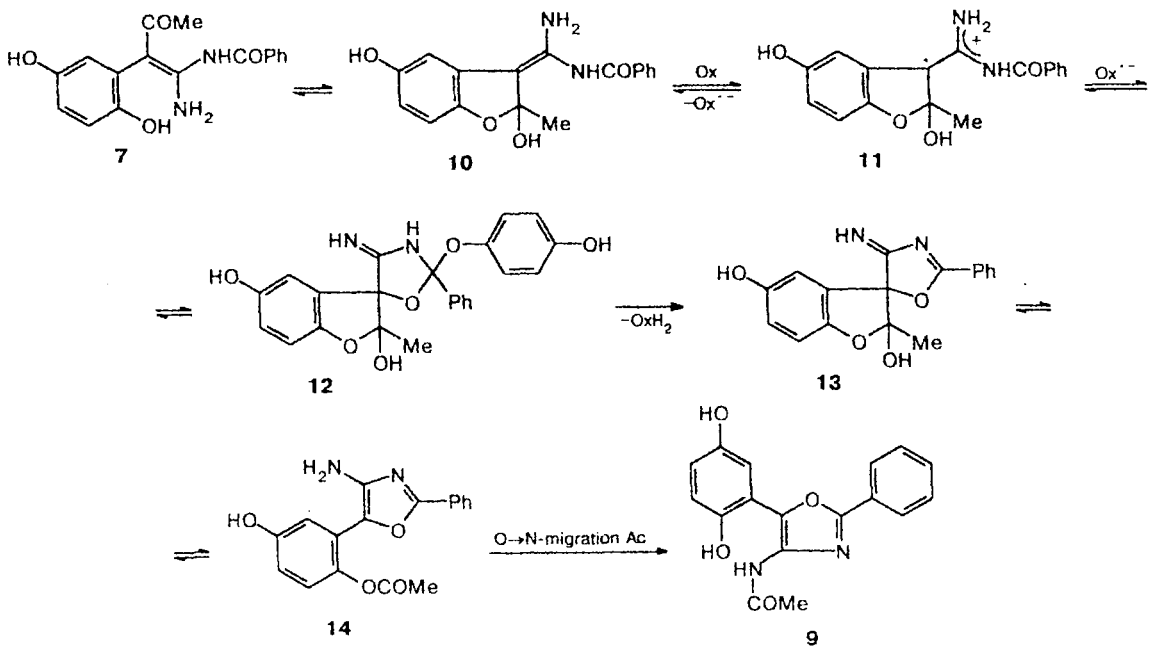
The transformation of hydroquinone-adduct **7** into oxazole **9** is rather difficult to explain. It is quite obvious that it is the presence of the enediamine fragment and the *N*-benzoyl group, able to participate in intramolecular cyclizations,[14] that is responsible for the so unusual behavior of compound **7** during its oxidation under the Nenitzescu reaction conditions. Thus, the following prob-

* The above-presented data on the selective decoupling and isotope shifts refer to the major conformer, whose signals narrow down at higher temperatures (in comparison to those of the minor conformer).

**δ: 138.7 (C(4)); 143.2 (C(5)); 162.4 (C(2)).

*** δ: 120.2 (C(4)); 122.4 (C(5)); 157.9 (C(2)).

Scheme 4



Ox is benzoquinone, OxH_2 is hydroquinone

able scheme can be proposed for the formation of oxazole **9** (Scheme 4).

According to Scheme 4, the driving force of this process is oxidation of the cyclic tautomeric form **10** of enediamine **7** at its electron-rich β-position to give radical cation **11**, whose cyclic form adds the radical anion formed from the quinone. The resulting spiro compound **12** eliminates a hydroquinone molecule (or a substituted hydroquinone molecule when substituted benzoquinones are used) to give imino oxazole **13**, which exists in equilibrium with 5-(2-acetoxy-5-hydroxyphenyl)-4-amino-2-phenyloxazole (**14**). An O→N acetyl migration (possibly involving a cyclic intermediate) affords 4-acetylamino-5-(2,5-dihydroxyphenyl)-2-phenyloxazole (**9**). Of course, alternative pathways to compound **9** also cannot be ruled out.

In conclusion it can be noted that the use of enediamines as the starting compounds in the Nenitzescu reaction gave new, unexpected results and variation of the structures of the initial quinones and eneamines remains an important line in the subsequent investigation of this reaction.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity plus spectrometer (400 MHz) using Me_4Si as the internal standard. Mass spectra were run on a Finnigan SSQ-710 GC/MS spectrometer with direct sample injection into the ion source; the energy of the ionizing electrons was 70 eV, and the temperature in the ionization chamber was 150 °C. The purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in the benzene—acetone system (9 : 2); the plates were visualized in UV light.

3-Acetyl-2-amino-7a-hydroxy-1-phenyl-5,7a-dihydro-1*H*-indol-5-one (4). A solution of benzoquinone (**3**) 1.05 g (9.5 mmol) in 10 mL of acetone was added to a solution of aminal **1** (1.5 g, 8.5 mmol) in 20 mL of acetone. The reaction mixture was heated to boiling and allowed to stand at 20 °C. The end of the reaction was detected by chromatography. The precipitate that formed was filtered off, washed with acetone, and dried to give 0.9 g (37.5%) of indolinone **4**, m.p. 200—202 °C (from MeCN). Found (%): C, 67.59; H, 5.67; N, 9.85. $C_{16}H_{14}N_2O_3$. Calculated (%): C, 68.07; H, 5.00; N, 9.92. ^{1}H NMR (DMSO-d_6), δ: 2.19 (s, 3 H, Me); 5.65 (d, 1 H, H(4), J_m = 1.6 Hz); 5.85 (dd, 1 H, H(6), J_o = 10 Hz, J_m = 1.6 Hz); 6.51 (d, 1 H, H(7), J_o = 10 Hz); 7.34 (br.s, 1 H, OH); 7.38 (m, 2 H, H(2′), H(6′)); 7.48 (m, 1 H, H(4′)); 7.55 (m, 2 H, H(3′), H(5′)); 7.94, 9.20 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 29.3 (q, Me, $^1J_{CH}$ = 125 Hz); 86.7 (t, C(7a), $^3J_{C(7a),H(6)} = {}^3J_{C(7a),H(4)}$ = 9.5 Hz); 94.1 (m, C(3)); 107.2 (dd, C(4), $^1J_{C(4),H(4)}$ = 162.5 Hz, $^3J_{C(4),H(6)}$ = 3.1 Hz); 128.9 (dt, C(4′), $^1J_{C(4'),H(4')}$ = 169.4 Hz, $^3J_{C(4'),H(2')} = {}^3J_{C(4'),H(6')}$ = 7.6 Hz); 129.2 (dt, 2 C, C(2′), C(6′), $^1J_{C(2'),H(2')} = {}^1J_{C(6'),H(6')}$ = 163 Hz, $^3J_{C(2'),H(6')} = {}^3J_{C(2'),H(4')}$ = 6.1 Hz); 129.8 (dd, C(6), $^1J_{C(6),H(6)}$ = 166.6 Hz, $^3J_{C(6),H(4)}$ = 3.8 Hz); 129.9 (dd, 2 C, C(5′), C(3′), $^1J_{C(5'),H(5')} = {}^1J_{C(3'),H(3')}$ = 162.5 Hz, $^3J_{C(5'),H(3')}$ = 9.4 Hz); 133.1 (t, C(1′), $^3J_{C(1'),H(3')} = {}^3J_{C(1'),H(5')}$ = 9 Hz); 137.4 (d, C(7), $^1J_{C(7),H(7)}$ = 167.1 Hz); 161.5 (d, C(3a), $^3J_{C(3a),H(7)}$ = 5 Hz); 164.9 (s, C(2)); 184.5 (d, C(5), $^3J_{C(5),H(7)}$ = 6 Hz); 190.4 (q, $\underline{C}OCH_3$, $^2J_{CH}$ = 5.3 Hz).

3-Acetyl-2-amino-6-chloro-5-hydroxy-1-phenylindole (6). A mixture of amino alcohol **4** (0.4 g, 1.4 mmol), AcCl (10 mL), and dry pyridine (0.2 g) was stirred for 1.5 h at 20 °C, and the precipitate was filtered off, washed with acetone, and dried to give 0.2 g (47.6%) of chloroindole **6**, m.p. 227—228 °C (from propan-2-ol). Found (%): C, 63.2; H, 4.41; N, 9.22. $C_{16}H_{13}ClN_2O_2$. Calculated (%): C, 63.90; H, 4.36; N, 9.32. ^{1}H NMR (DMSO-d_6), δ: 2.41 (s, 3 H, Me); 6.60 (s, 1 H, H(4)); 7.20 (s, 1 H, H(7)); 7.45 (m, 2 H, H(6′), H(2′)); 7.58 (m, 1 H, H(4′)); 7.65 (m, 2 H, H(5′), H(3′)). ^{13}C NMR (DMSO-d_6), δ: 29.9 (q, Me, $^1J_{CH}$ = 125 Hz); 96.2 (m, C(3)); 106.3 (d, C(4), $^1J_{C(4),H(4)}$ = 164 Hz); 109.9 (d, C(7), $^1J_{CH}$ = 164.0 Hz); 112.6 (dd, C(3a), $^3J_{C(3a),H(7)}$ = 7.6 Hz, $^2J_{C(3a),H(4)}$ = 4.6 Hz); 126.0 (d, C(6), $^3J_{C(6),H(4)}$ = 6.1 Hz); 128.2 (dt, 2 C, C(6′), C(2′), $^1J_{C(6'),H(6')} = {}^1J_{C(2'),H(2')}$ = 158.7 Hz, $^3J_{C(6'),H(2')} = {}^3J_{C(6'),H(4')}$ = 6.1 Hz); 129.5 (dd, C(7a), $^3J_{C(7a),H(4)}$ = 9.9 Hz, $^2J_{C(7a),H(7)}$ = 2.3 Hz); 129.7 (dt, C(4′), $^1J_{C(4'),H(4')}$ = 161.1 Hz, $^3J_{C(4'),H(6')} = {}^3J_{C(4'),H(2')}$ = 7.6 Hz); 131.0 (dd, 2 C, C(5′), C(3′), $^1J_{C(5'),H(5')}$ = 164 Hz, $^3J_{C(5'),H(3')}$ = 7.4 Hz); 134.0 (t, C(1′), $^3J_{C(1'),H(5')} = {}^3J_{C(1'),H(3')}$ = 9 Hz); 149.1 (dd, C(5), $^3J_{C(5),H(7)}$ = 6.1 Hz, $^2J_{C(5),H(4)}$ = 3.4 Hz); 154.6 (s, C(2)); 190.5 (q, $\underline{C}OCH_3$, $^2J_{CH}$ = 6.3 Hz).

2-Acetyl-1-amino-1-benzoylamino-2-(2,5-dihydroxyphenyl)ethene (7).* A mixture of ketene aminal **2** (2 g, 10 mmol), benzoquinone (**3**) (1.08 g, 10 mmol), *p*-toluenesulfonic acid (0.15 g), and $MeNO_2$ (50 mL) was heated until a homogeneous solution formed, then it was cooled to 20 °C and stirred for 5 h. The resulting precipitate was filtered off, washed with ether, and dried to give 2.8 g (91.5%) of compound **7**, m.p. 152—153 °C (from propan-2-ol). Found (%): C, 64.94; H, 5.34; N, 8.62. $C_{17}H_{16}N_2O_4$. Calculated (%): C, 65.38; H, 5.16; N, 8.97. ^{1}H NMR (DMSO-d_6), δ: 1.90 (s, 3 H, Me); 6.47 (d, H(6), J_m = 3 Hz); 6.60 (dq, H(4), J_m = 3 Hz, J_o = 8.8 Hz); 6.73 (d, H(3), J_o = 8.8 Hz); 7.69 (m, 2 H, H(3′), H(5′)); 7.70 (m, 1 H, H(4′)); 8.01 (m, 2 H, H(2′), H(6′)); 6.00, 8.45 (br.s, 2 H, NH_2); 8.50, 8.80 (br.s, 2 H, 2 OH); 15.9 (br.s, 1 H, NH). ^{13}C NMR (pyridine-d_5), δ: 26.1 (q, Me, $^1J_{CH}$ = 127 Hz); 92.4 (m, C(β)); 115.4 (dd, C(4), $^1J_{C(4),H(4)}$ = 156 Hz, $^3J_{C(4),H(6)}$ = 7.8 Hz); 116.0 (d, C(3), $^1J_{C(3),H(3)}$ = 156 Hz); 118.5 (dd, C(6), $^1J_{C(6),H(6)}$ = 156 Hz, $^3J_{C(6),H(4)}$ = 5.2 Hz); 121.6 (d, C(1), $^3J_{C(1),H(3)}$ = 6.1 Hz); 126.2 (dt, C(2′), C(6′), $^1J_{C(2'),H(2')} = {}^1J_{C(6'),H(6')}$ = 161 Hz, $^3J_{C(2'),H(4')} = {}^3J_{C(2'),H(6')}$ = 7.0 Hz); 127.0 (dd, C(3′), C(5′), $^1J_{C(3'),H(3')} = {}^1J_{C(5'),H(5')}$ = 162.5 Hz, $^3J_{C(3'),H(5')}$ = 7.6 Hz); 131.0 (dt, C(4′), $^1J_{C(4'),H(4')}$ = 161 Hz, $^3J_{C(4'),H(6')} = {}^3J_{C(4'),H(2')}$ = 7.1 Hz); 131.6 (t, C(1′), $^3J_{C(1'),H(5')} = {}^3J_{C(1'),H(3')}$ = 7.6 Hz); 148.5 (dt, C(2), $^3J_{C(2),H(4)} = {}^3J_{C(2),H(6)}$ = 10 Hz, $^2J_{C(2),H(3)}$ = 3 Hz); 150.0 (dt, C(5), $^3J_{C(5),H(3)}$ = 10 Hz, $^2J_{C(5),H(4)} = {}^2J_{C(5),H(6)}$ = 3.0 Hz); 155.8 (s, C(α)); 166.7 (m, $NH\underline{C}OCH_3$); 192.6 (q, $\underline{C}OCH_3$, $^2J_{CH}$ = 5.3 Hz).

4-Acetylamino-5-(2,5-dihydroxyphenyl)-2-phenyloxazole (9). *A.* A mixture of adduct **7** (0.62 g, 2 mmol) and benzoquinone (**3**) (0.215 g, 2 mmol) in 10 mL of $EtCO_2H$ was stirred for 5 h at 20 °C and for 2 h at 70 °C. The next day the precipitate was filtered off, washed with ether, and dried to give 0.41 g (66.5%) of oxazole **9**, m.p. 251—253 °C (from propan-2-ol). Found (%): C, 65.42; H, 4.55; N, 9.10. $C_{17}H_{14}N_2O_4$. Calculated (%): C, 65.80; H, 4.55; N, 9.03.

B. A suspension of adduct **7** (0.16 g, 0.5 mmol) and 2,6-dichloro-3,5-dicyanobenzoquinone (0.06 g, 0.5 mmol) in 5 mL of glacial AcOH was stirred for 2 h at 20 °C. The next day the precipitate was filtered off, washed with ether, and dried to give 0.09 g (56.6%) of compound **9**. ^{1}H NMR (DMF-d_7, −40 °C), δ, the major conformer (90%): 2.03 (s, 3 H, Me); 6.73

* The systematic name for compound **7** is *N*-[1-amino-2-(2,5-dihydroxyphenyl)-3-oxobut-1-enyl]benzamide.

(dq, 1 H, H (4′), J_o = 8.8 Hz, J_m = 3.2 Hz); 6.82 (d, 1 H, H (3′), J_o = 8.8 Hz); 7.01 (d, 1 H, H(6′), J_m = 3.2 Hz); 7.52 (m, 3 H, H(3″), H(4″), H(5″)); 7.98 (m, 2 H, H(2″), H(6″)); 9.57, 9.96, 10.00 (br.s, 3 H, NH, 2 OH); the minor conformer: 2.16 (s, 3 H, Me); 6.82 (dq, 1 H, H(4′), J_o = 8.8 Hz, J_m = 3.2 Hz); 6.93 (d, 1 H, H(3′), J_o = 8.8 Hz); 7.07 (d, 1 H, H(6′), J_m = 3.2 Hz); 7.52 (m, 3 H, H(3″), H(4″), H(5″)); 8.05 (m, 2 H, H(2″), H(6″)); 9.20, 9.75, 10.80 (br.s, 3 H, NH, 2 OH). ^{13}C NMR (DMF-d_7, −40 °C), δ, the major conformer: 23.0 (q, Me, $^1J_{CH}$ = 125); 114.9 (d, C(4′), $^1J_{C(4'),H(4')}$ = 157.6 Hz);* 164 (m, C(1′)); 117.4 (d, C(3′), $^1J_{C(3'),H(3')}$ = 157.6 Hz);* 117.6 (d, C(6′), $^1J_{C(6'),H(6')}$ = 157.6);* 126.2 (d, 2 C, C(6″), C(2″), $J_{C(6''),H(6'')}$ = 161.8 Hz); 127.7 (t, C(1″), $^3J_{C(1''),H(5'')}$ = $^3J_{C(1''),H(3'')}$ = 7.6 Hz); 129.8 (d, 2 C, C(3″), C(5″), $J_{C(3''),H(3'')}$ = 161.8 Hz); 131.1 (d, C(4″), $^1J_{C(4''),H(4'')}$ = 161.8 Hz); 133.6 (s, C(4)); 140.4 (br.s, C(5)); 148.4 (t, C(2′), $^3J_{C(2'),H(4')}$ = $^3J_{C(2'),H(6')}$ = 7.5 Hz);** 150.8 (d, C(5′), $^3J_{C(5'),H(3')}$ = 8.3 Hz);** 158.4 (t, C(2), $^3J_{C(2),H(2'')}$ = $^3J_{C(2),H(6'')}$ = 4 Hz); 169.2 (dq, $\underline{C}OCH_3$, $^2J_{CO,CH_3}$ = 6.1 Hz, $^2J_{CO,NH}$ = 3.1 Hz).

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* Indirect CH spin-spin coupling constants are not given because the doublet components are broadened due to the exchange process between the amide conformers.

** The $^2J_{CH}$ values are not presented, because the doublet and triplet components are broadened.

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