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Acetylation of 1-Amino-2-aryloxy-4-hydroxy-9,10-anthraquinones. Cyclization of N-Acetyl Derivatives of 1-Amino-2-aryloxy-4-hydroxy-9,10-anthraquinones into 4-Aryloxy-6-hydroxy-3*H*-naphtho[1,2,3-*d,e*]quinoline-2,7-diones

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Abstract—Acetylation of 1-amino-2-aryloxy-4-hydroxy-9,10-anthraquinone qith acetic anhydride at 70–80°C in pyridine proceeded at the hydroxy group, and in acetic acid, at the amino group. Under more stringent conditions at 80–100°C products of N,N-diacetylation and N,N,O-triacetylation were obtained. The products of N-acetylation in basic media underwent cyclization into 4-aryloxy-6-hydroxy-3*H*-naphtho[1,2,3-*d,e*] quinoline-2,7-diones.

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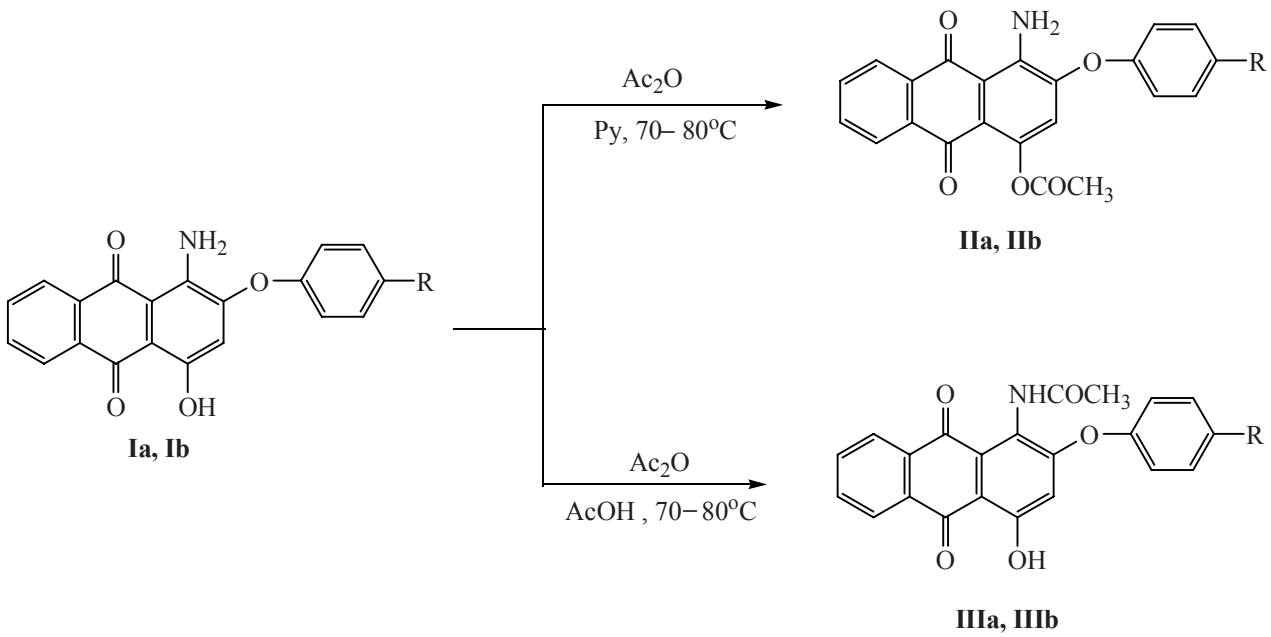
1-Acetylamino-9,10-anthraquinones are used as intermediate products in selective halogenation [1], for producing 3*H*-naphtho[1,2,3-*d,e*]quinoline-2,7-diones (anthrapyridones) [2]. 1-Acetoxy-9,10-anthraquinones are endowed with biological activity [3], suffer photolytic or base-catalyzed 1,9-acylotropic rearrangements [4, 5]. Yet no detailed publications appeared on the opportunities of a selective acetylation of 1-amino-4-hydroxy-9,10-anthraquinones containing various substituents in the position *2*. We investigated the acetylation of 1-amino-2-aryloxy-9,10-anthraquinones **Ia** and **Ib** with acetic anhydride under versatile conditions, and the findings

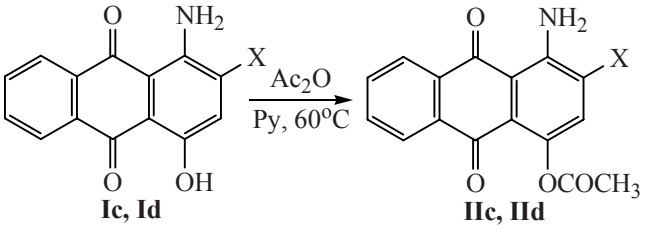


R = H (**a**), *t*-Bu (**b**).

obtained were compared with the known data on the acetylation of 1-amino-4-hydroxy-9,10-anthraquinone [6] and 1-amino-2-bromo-4-hydroxy-9,10-anthraquinone [7].

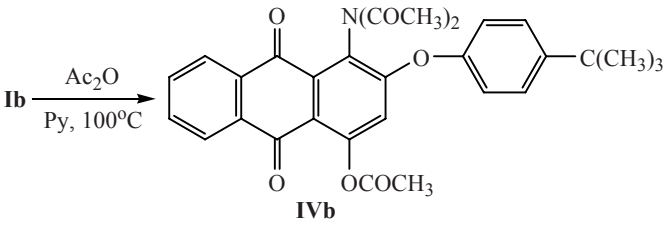
The acetylation of aminoquinones **Ia** and **Ib** with acetic anhydride in pyridine at 70–80°C involved the hydroxy groups providing 1-amino-2-aryloxy-4-acetoxy-9,10-anthraquinones **IIa** and **IIb** in high yields.

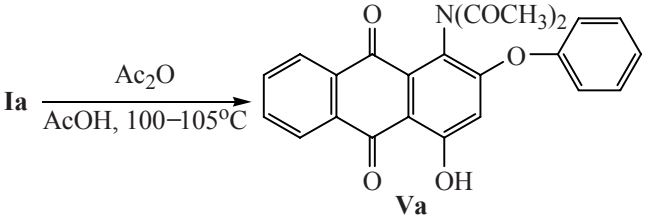
At the same time the acetylation of substrates **Ia** and **Ib** with acetic anhydride in acetic acid at 70–80°C yielded 1-acetylamino-2-aryloxy-4-hydroxy-9,10-anthraquinones **IIIa** and **IIIb**. This change in the reaction direction of compounds **Ia** and **Ib** was rather unexpected since as had been shown in [6] the acetylation of 1-amino-4-hydroxy-9,10-anthraquinone with acetic anhydride in pyridine at 50°C resulted in 1-acetylamino-4-hydroxy-9,10-anthraquinone, and at 100°C, in 1-acetylamino-4-acetoxy-9,10-anthraquinone. Apparently the aryloxy group of quinones **Ia** and **Ib** sterically deactivated the amino group in the *ortho*-position. Taking into consideration the known data that the active acylating species in the system acetic anhydride–pyridine may be *N*-acetylpyridinium [8] the hydroxy group presumably is sterically more available for this reagent than the amino group. To check the effect of the spatial factor we carried out the acetylation of 1-amino-2-bromo-4-hydroxy-9,10-anthraquinone (**Ic**) along the procedure [7] (acetic anhydride–sodium acetate), and also under our conditions (acetic anhydride–pyridine). In both cases we obtained the same product, 1-amino-2-bromo-4-acetoxy-9,10-anthraquinone (**IIc**), and not the 1-acetylamino-2-bromo-4-hydroxy-9,10-anthraquinone mentioned in [7]. 1-Amino-4-hydroxy-2-chloro-9,10-anthraquinone (**Id**) also underwent acetylation at the hydroxy group.



X = Br (**c**), Cl (**d**).

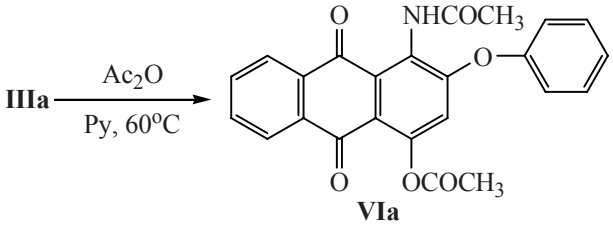
The increase in the temperature and time of the acetylation of aminohydroxyquinones **Ia** and **Ib** led to the formation of di- and triacetyl derivatives; for instance, from substance **Ib** in pyridine we obtained 1-(diacetylamino)-2-(4-*tert*-butylphenoxy)-4-acetoxyanthraquinone (**IVb**), and from compound **Ia** in acetic acid formed 1-(diacetylamino)-4-hydroxy-2-phenoxy-9,10-anthraquinone (**Va**).

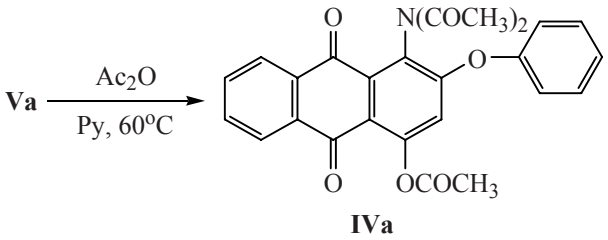




In this cases the chromatographic analysis revealed the formation also of other substances, and the purification of reaction products **IVb** and **Va** from these impurities by repeated recrystallizations decreased the yield of the target compounds. These results also differ from the known data on the acetylation of the 1-amino-4-hydroxy-9,10-anthraquinone which as mentioned before converts into 1-acetylamino-4-acetoxy-9,10-anthraquinone [6].

The products of N,O-diacetylation **VI** are best prepared by the acetylation of amides **III** in pyridine; under the same conditions *N,N*-diacetylaminoquinone **Va** underwent the acetylation into the triacetyl derivative **IVa**.





The structure of obtained products of mono-, di-, and triacetylation **I–VI** was confirmed by spectral data. The long-wave absorption maximum of products of N- or O-acetylation **II** and **III** suffered a blue shift by 130–135 nm compared with initial 1-amino-2-aryloxy-4-hydroxy-9,10-anthraquinones **I**. In the product of N,N-diacetylation **Va** in the visible region appeared only a shoulder (λ 440 nm), and compounds **IV** and **VI** in the

visible range ($\lambda > 400$ nm) had no appreciable absorption. In the IR spectra of products **IIa, IIb, IVa**, **IVb, VIa**, and **VIb** the strong absorption bands of the stretching vibrations of ester carbonyls appeared at 1765 cm^{-1}, in amides **IIIa** and **IIIb** the absorption of stretching vibrations of amide and quinoid carbonyl groups were observed at 1654–1700 cm^{-1}. The strong absorption bands of the stretching vibrations of C=O bonds of the N-acetyl groups in the spectra of compounds **IV** and **V** were present at 1700 and 1730 cm^{-1} [8].

In the ^1H NMR spectra of esters **IIa** and **IIb** the broadened signals of the protons of the primary amino group are located in the region of the aromatic protons (8.50–9.00 ppm) [8].

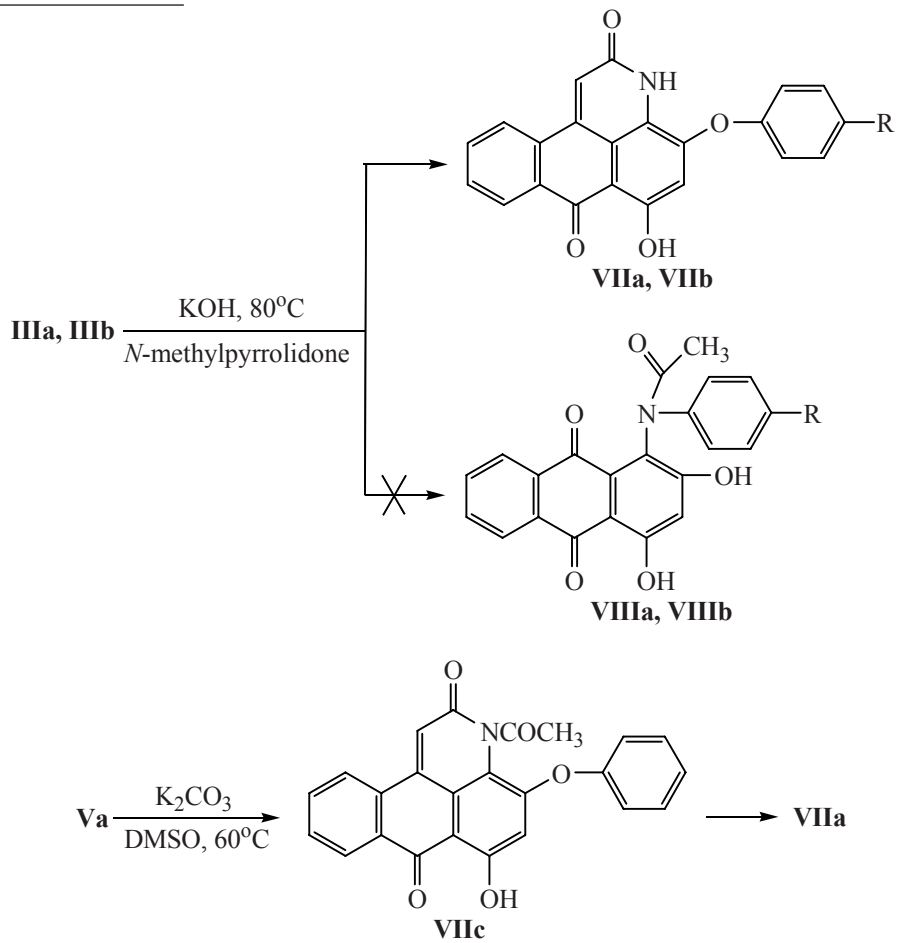
In amides **III** and **VI** the signals of NH protons appeared in the region 9.70 and 9.90 ppm respectively. In N-acetyl derivatives **III** and **V** the hydroxy group protons are present in the weak field (13.18–13.39 ppm).

The products of N-acylation **IIIa**, **IIIb**, and **Va** we used for preparation of 4-aryloxy-6-hydroxy-3*H*-naphtho-[1,2,3-*d,e*]quinoline-1,7-diones **VIIa**, and **VIIb**.

In event of compound **Va** cyclization the reaction probably involved an intermediate formation of *N*-acetylanthrapyridone **VIIc** that appartently suffered a fast transformation into the final product **VIIa**; the intermediate substance was not revealed under the conditions we used. The cyclization **III** → **VII** proceeded under the conditions where Smiles rearrangement could have occurred [9]. However the products of this rearrangement, 1-(*N*-acetylarylamino)-2,4-dihydroxy-9,10-anthraquinones **VIIIa** and **VIIIb**, did not form in our case. This fact is apparently due to the deprotonation of the substrates **IIIa** and **IIIb** at the hydroxy group causing the decrease in the NH-acidity of the acetylamino fragment and preventing its deprotonation at the N–H bond; at the same time the ionization of the O–H bond only slightly hampers the elimination of a methyl proton of the acetyl group thus leading to the 1,9-heterocyclization.

EXPERIMENTAL

Electronic spectra were recorded on a Helios Epsilon instrunebt from solutions in toluene. IR spectra were



measured on a spectrophotometer Bruker Tenzor 27 from pellets with KBr. ^{1}H NMR spectra were registered on a spectrometer Bruker DRX-500, internal reference TMS. The reaction progress was monitored and the homogeneity of the products obtained was checked by TLC on Silufol plates, eluent toluene–acetone, 10:1.

1-Amino-4-acetoxy-2-phenoxy-9,10-anthraquinone (IIa). A mixture of 3.3 g (10 mmol) of 1-amino-4-hydroxy-2-phenoxy-9,10-anthraquinone (**Ia**) with 10 ml of pyridine and 30 ml of acetic anhydride was heated at 70°C for 3 h. On cooling the reaction mixture was poured on ice, the precipitate was filtered off and purified by recrystallization from ethanol. Yield 2.8 g (75%), mp 129–130°C. UV spectrum, λ_{max}, nm (log ε): 470 (3.8). IR spectrum, ν, cm^{-1}: 3458, 3319 (NH_2), 1765 (C=O, ester), 1653, 1636 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.26 s (3H, CH_3), 6.61 s (H^3), 7.23–7.53 m (5H, OC_6H_5), 7.84–7.89 d (2H^{6,7}, *J* 7.0 Hz), 8.08–8.24 d (2H^{5,8}, *J* 7.0 Hz). Found, %: C 70.65; H 4.02; N 3.49. $C_{22}H_{15}NO_5$. Calculated, %: C 70.77; H 4.02; N 3.75.

1-Amino-4-acetoxy-2-(4-*tert*-butylphenoxy)-9,10-anthraquinone (IIb) was analogously obtained from 4.29 g (11 mmol) of compound **Ib**. Yield 3.6 g (78%), mp 192°C. UV spectrum, λ_{max}, nm (log ε): 470 (3.9). IR spectrum, ν, cm^{-1}: 3496, 3321 (NH_2), 1760 (C=O, ester), 1661, 1639 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 s [9H, $(CH_3)_3$], 2.26 s (3H, CH_3), 6.62 s (H^3), 7.13–7.15 d, 7.50–7.51 d (4H, OC_6H_4), 7.83–7.88 m, 8.08–8.09 d (2H^{6,7}, *J* 7.0 Hz), 8.21–8.23 d (2H^{5,8}, *J* 7.0 Hz). Found, %: C 72.52; H 5.32; N 3.12. $C_{26}H_{23}NO_5$. Calculated, %: C 72.72; H 5.36; N 3.62.

1-Amino-4-acetoxy-2-bromo-9,10-anthraquinone (IIc). A mixture of 3.18 g (10 mmol) of compound **Ic** with 25 ml of pyridine and 25 ml of acetic anhydride was heated at 100–110°C for 40 min. On cooling the reaction mixture was poured on ice, the precipitate was filtered off and purified by recrystallization from acetic acid. Yield 3.2 g (88%), mp 184–185°C (in capillary). IR spectrum, ν, cm^{-1}: 3460, 3350 (NH_2), 1770 (C=O, ester), 1667, 1640 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34 s (3H, CH_3), 7.88 s (H^3), 7.89–7.91 m (2H^{6,7}), 8.05–8.07 (H^8), 8.18–8.20 (H^5). Found, %: C 52.70; H 2.71; N 4.12. $C_{16}H_{10}BrNO_4$. Calculated, %: C 53.48; H 2.78; N 3.89.

The acetylation of compound **Ic** along procedure from [7] gave an identical product **IIc** as shown by comparison of IR and ^{1}H NMR spectra; no depression of the melting point was observed at melting the mixture of samples).

1-Amino-4-acetoxy-2-chloro-9,10-anthraquinone (IId). A mixture of 2.73 g (9 mmol) of compound **Id**, 10 ml of pyridine, and 30 ml of acetic anhydride was heated at 50–60°C for 2 h. On cooling the reaction mixture was poured on ice, the precipitate was filtered off and recrystallized from ethanol. Yield 2.65 g (83%), mp 188–189°C. IR spectrum, ν, cm^{-1}: 3463, 3321 (NH_2), 1768 (C=O, ester), 1666, 1636 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34 s (3H, CH_3), 7.69 s (H^3), 7.85–7.89 m (2H^{6,7}), 8.06–8.07 (H^8), 8.17–8.18 (H^5). Found, %: C 60.15; H 3.13; N 4.21. $C_{16}H_{10}ClNO_4$. Calculated, %: C 60.85; H 3.16; N 4.43.

1-(Acetylamino)-4-hydroxy-2-phenoxy-9,10-anthraquinone (IIIa). A mixture of 3.31 g (10 mmol) of compound **Ia**, 5 ml of acetic anhydride, and 35 ml of acetic acid was heated at 80°C for 10 h. On cooling the reaction mixture was poured on ice, the precipitate was filtered off and recrystallized from ethanol. Yield 2.70 g (75%), mp 198°C. UV spectrum, λ_{max}, nm (log ε): 465 (4.0). IR spectrum, δ, cm^{-1}: 3275 (NH), 1630, 1658 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.07 s (3H, CH_3), 6.48 s (H^3), 7.17–7.18 d, 7.29–7.32 t, 7.31–7.52 t (5H, OC_6H_5, *J* 8.0 Hz), 7.92–7.94 m (2H^{6,7}), 8.13–8.22 m (2H^{5,8}), 9.70 s (1H, NH), 13.18 c (1H, OH). Found, %: C 70.80; H 4.04; N 3.66. $C_{22}H_{15}NO_5$. Calculated, %: C 70.77; H 4.02; N 3.75.

1-(Acetylamino)-2-(4-*tert*-butylphenoxy)-4-hydroxy-9,10-anthraquinone (IIIb) was analogously obtained from 3.87 g (10 mmol) of compound **Ib**. Yield 3.00 g (70%), mp 204–205°C. UV spectrum, λ_{max}, nm (log ε): 470 (3.8). IR spectrum, ν, cm^{-1}: 3349 (NH), 1672, 1658 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 s [9H, $(CH_3)_3$], 2.07 s (3H, CH_3), 6.60 s (H^3), 7.13–7.15 d, 7.50–7.51 d (4H, OC_6H_4, *J* 8.0 Hz), 7.92–7.94 m (2H^{6,7}), 8.13–8.22 m (2H^{5,8}), 9.72 s (1H, NH), 13.20 s (1H, OH). Found, %: C 72.13; H 5.26; N 3.06. $C_{26}H_{23}NO_5$. Calculated, %: C 72.72; H 5.36; N 3.62.

1-(Diacetylamino)-4-acetoxy-2-phenoxy-9,10-anthraquinone (IVa). A mixture of 1.60 g (4 mmol) of compound **Va**, 4 ml of pyridine, and 15 ml of acetic anhydride was heated at 50–60°C for 2 h. The precipitate settled after cooling was filtered off and purified by recrystallization from butanol. Yield 1.70 g (94%), mp 195–196°C. UV spectrum, λ_{max}, nm (log ε): 340 (3.6). IR spectrum, ν, cm^{-1}: 3328 (OH), 1771 (C=O, NHCO), 1729, 1707, 1671 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.38 s (9H, $3CH_3$), 7.05 s (H^3), 7.15–7.55 m (5H, OC_6H_5), 7.90–8.00 (2H^{6,7}), 8.10–8.15 m (2H^{5,8}), 13.39 s (1H, OH). Found, %: C 68.80; H 3.66; N 3.03. $C_{26}H_{19}NO_7$. Calculated, %: C 68.27; H 4.15; N 3.06.

1-(Diacetylamino)-4-acetoxy-2-(4-*tert*-butylphenoxy)-9,10-anthraquinone (IVb). A mixture of 3.7 g (7 mmol) of compound **Ib**, 80 ml of pyridine, and 10 ml of acetic anhydride was heated at 80°C for 3 h. Then 10 ml more of the anhydride was added, and the stirring at 80°C was continued for 2 h, the reaction mixture was cooled, poured on ice, the separated precipitate was filtered off and purified by a double recrystallization from ethanol. Yield 1.5 g (31%), mp 191–192°C. IR spectrum, ν, cm^{-1}: 1767 (C=O, ester), 1731, 1701 (C=O, amides), 1672 (C=O, anthraquinonea). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 s [9H, $C(CH_3)_3$], 2.31 s [6H, $CO(CH_3)_2$], 2.35 s (3H, $OCOCH_3$), 7.06–7.07, 7.51–7.50 m (4H, OC_6H_4), 7.89–7.91, 8.08–8.10 m (4H). Found, %: C 70.67; H 5.20; N 3.44. $C_{30}H_{27}NO_7$. Calculated, %: C 70.17; H 5.26; N 2.72.

1-(Diacetylamino)-4-hydroxy-2-phenoxy-9,10-anthraquinone (Va). A mixture of 3.3 g (9 mmol) of compound **Ia** and 20 ml of acetic anhydride was heated at 100°C for 25 h. The precipitate settled after cooling was filtered off and purified by double recrystallization from acetic acid. Yield 2.8 g (68%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 3328 (OH), 1771 (C=O, NHCO), 1729, 1707, 1671 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.38 s [6H, $(CH_3)_2$], 6.59 s (H^3), 7.05–7.44 m (5H, OC_6H_5), 7.77–7.79 ($2H^{6,7}$), 8.20–8.35 m ($2H^{5,8}$), 13.39 s (1H, OH). Found, %: C 70.12; H 3.66; N 3.03. $C_{24}H_{17}NO_6$. Calculated, %: C 69.39; H 4.09; N 3.37.

1-(Acetylamino)-4-acetoxy-2-phenoxy-9,10-anthraquinone (VIa). A mixture of 2.5 g (6 mmol) of compound **IIIa**, 4 ml of pyridine, and 20 ml of acetic anhydride was heated at 50–60°C for 2 h. The reaction mixture was cooled, poured on ice, the separated precipitate was filtered off and purified by a recrystallization from ethanol. Yield 2.2 g (81%), mp 189–190°C. UV spectrum, λ_{max}, nm (log ε): 340 (3.5). IR spectrum, ν, cm^{-1}: 3436 (NH), 1770 (C=O, ester), 1732 (C=O, NHCO), 1703, 1674 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.31–2.34 m (6H, $2CH_3$), 7.04 s (H^3), 7.14–7.51 m (5H, OC_6H_5), 7.88–7.90 m ($2H^{6,7}$), 8.08–8.10 m ($2H^{5,8}$), 9.95 s (1H, NH). Found, %: C 68.74; H 4.13; N 3.08. $C_{24}H_{17}NO_6$. Calculated, %: C 69.39; H 4.09; N 3.37.

6-Hydroxy-4-phenoxy-3*H*-naphtho[1,2,3-*d,e*]-quinoline-2,7-dione (VIIa). A mixture of 0.5 g (1.4 mmol) of compound **Va** and 10 ml of DMSO in the presence of 0.4 g of K_2CO_3 was heated at 60°C for 12 h. On cooling the reaction mixture was poured on ice and acidified with HCl. The yellow precipitate was filtered off and purified by recrystallization from aqueous DMF, 1:2. Yield 0.32 g (76%), mp 210–211°C. IR spectrum, ν, cm^{-1}: 3105 (NH), 1661, 1623 (C=O). ^1H NMR spectrum, δ, ppm: 6.40 s (H^5), 7.30–7.60 m (5H, OC_6H_5), 7.88 s (H^1), 8.37 d ($2H^{8,9}$), 8.63 d ($2H^{7,10}$), 11.70 br.s (1H, NH), 13.80 s (1H, OH). Found, %: C 74.32; H 3.64; N 3.69. $C_{22}H_{13}NO_4$. Calculated, %: C 74.36; H 3.66; N 3.94.

4-(4-*tert*-Butylphenoxy)-6-hydroxy-3*H*-naphtho[1,2,3-*d,e*]quinoline-2,7-dione (VIIb). A mixture of 0.70 g (1.6 mmol) of compound **IIIb** and 10 ml of *N*-methylpyrrolidone in the presence of 0.4 g of KOH was heated at 80°C for 12 h. On cooling the reaction mixture was poured on ice and acidified with HCl. The separated precipitate was filtered off and purified by recrystallization from acetic acid. Yield 0.5 g (75%), mp 215–216°C. IR spectrum, ν, cm^{-1}: 3228 (NH), 1696, 1651 (C=O). ^1H NMR spectrum, δ, ppm: 1.70 s [9H, $(CH_3)_3$], 6.45 s (H^5), 7.30–7.60 m (4H, OC_6H_4), 7.88 s (H^1), 8.37 d ($2H^{8,9}$), 8.63 d ($2H^{7,10}$), 11.85 br.s (1H, NH), 13.85 s (1H, OH). Found, %: C 76.02; H 4.90; N 3.55. $C_{26}H_{21}NO_4$. Calculated, %: C 75.91; H 5.10; N 3.40.

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