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Synthesis of 4,7-Phenanthroline Derivatives by Condensation of Arylmethylene(6-quinolyl)amines with Hydroxy- and Nitro-substituted Acetophenone

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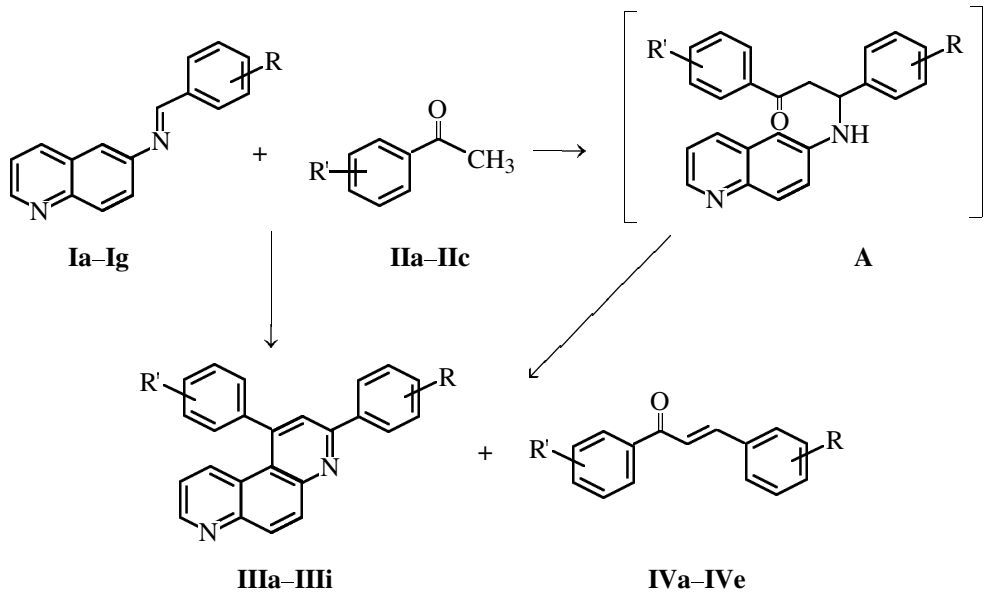
Abstract — Condensation of arylmethylene(6-quinolyl)amines with hydroxy- and nitro-substituted acetophenones was used to synthesize 1,3-diaryl-4,7-phenanthrolines containing hydroxy and nitro groups in the phenyl rings.

Functional substituents, such as hydroxy and nitro groups, in heterocyclic compounds extend the synthetic potential and diversify the physiological activity of the latter [1, 2].

Some information on the synthesis of hydroxy-substituted 4,7-phenanthrolines is available in the literature [3, 4]. These compounds are generally synthesized by Conrad–Limpach and Knorr reactions, starting from 6-quinolylamine or *p*-phenylenediamine and esters of β-oxo- and β-dicarboxylic acids. Nitro-substituted 4,7-phenanthrolines obtained by nitration of 4,7-phenanthroline are scarcely studied [5], since nitro group is hard to introduce into the azaaromatic ring by electrophilic substitution. The information concerning 4,7-phenanthrolines bearing both hydroxy and nitro substituents is lacking.

Earlier we showed that azomethines of the 6-amino-quinoline series react with acetophenone to give 1-phenyl-3-aryl-4,7-phenanthrolines [6].

Aiming at introducing two different functional substituents into the 4,7-phenanthroline molecule, in the present work we have studied for the first time the reactions of (*m*- and *p*-nitrophenylmethylene)(6-quinolyl)amines (**Ia, Ib**) with *p*-hydroxyacetophenone (**IIa**)



R = 3-NO_2 (**Ia, IIIa, IVc**), 4-NO_2 (**Ib, IIIb**), 2-OH (**Ic, IIIc, IIId**), 4-OH (**Id, IIIe, IIIf, IVd**), 2-OH,5-NO_2 (**Ie, IIIg–IIIi, IVe**), 2,4-$(OH)_2$ (**If, IVa**), 3,4-$(OH)_2$ (**Ig, IVb**); R' = 4-OH (**IIa, IIIa, IIIb, IIIg, IVc**), 3-NO_2 (**IIb, IIIc, IIIe, IIIh, IVe**), 4-NO_2 (**IIc, IIId, IIIf, IIIi, IVd**).

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Table 1. Yields, melting points, and elemental analyses of 1,3-diaryl-4,7-phenanthrolines **IIIa**–**IIIi**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	40	364–365	73.31	3.88	10.34	$C_{24}H_{15}N_3O_3$	73.28	3.82	10.70
IIIb	42	326–327	73.19	3.74	10.53	$C_{24}H_{15}N_3O_3$	73.28	3.82	10.70
IIIc	29	321–322	73.26	3.65	10.74	$C_{24}H_{15}N_3O_3$	73.28	3.82	10.70
IIId	24	325–326	73.09	3.74	10.93	$C_{24}H_{15}N_3O_3$	73.28	3.82	10.70
IIIe	21	319–320	73.24	3.59	10.81	$C_{24}H_{15}N_3O_3$	73.28	3.82	10.70
IIIf	31	322–323	73.39	3.96	10.57	$C_{24}H_{15}N_3O_3$	73.28	3.82	10.70
IIIg	32	349–350	70.22	3.64	10.33	$C_{24}H_{15}N_3O_4$	70.42	3.67	10.27
IIIh	30	340–341	65.49	3.01	12.64	$C_{24}H_{14}N_4O_5$	65.75	3.20	12.79
IIIi	33	337–338	65.58	3.23	12.56	$C_{24}H_{14}N_4O_5$	65.75	3.20	12.79

and the reactions of (*o*- and *p*-hydroxyphenylmethylene)(6-quinolyl)amines (**Ic, Id**) with *m*- and *p*-nitroacetophenones (**IIb, IIc**). Ketones **IIa**–**IIc** were also reacted with (2-hydroxy-5-nitrophenylmethylene)(6-quinolyl)amine (**Ie**). By varying substituents in the aldehyde moiety of Schiff base and in the phenyl nucleus of acetophenone we expected to prepare 4,7-phenanthrolines with desired groups.

The condensations were performed by refluxing equimolar amounts of azomethine and acetophenone in 1-butanol in the presence of catalytic amounts of concentrated HCl.

According to our previous findings [6], the 4,7-phenantholine nucleus is formed via intermediacy of aminoketone *A* which, in its turn, is formed by addition of the CH acid to the azomethine C=N bond, yielding a new C=C bond.

We failed to isolate intermediate aminoketones in the condensations of azomethines **Ia**–**Ie** with hydroxy- and nitro-substituted acetophenones **IIa**–**IIc**. Under the mentioned conditions, the reactions gave 1,3-diaryl-4,7-phenanthrolines **IIIa**–**IIIi** containing hydroxy and nitro groups in the phenyl rings. Under milder conditions (refluxing in ethanol) in the absence of catalysts, no reaction was observed between azomethines and acetophenones, and in the presence of HCl, hydroxynitro-substituted chalcones **IVa**–**IVe** were obtained. α,β-Unsaturated ketones **IVa**–**IVe** can be formed, on the one hand, by aldol condensation of acetophenone with the aromatic aldehyde formed by hydrolysis of the starting azomethine and, on the other, by hydramine cleavage of intermediate aminoketone **A**. In 1-butanol, apparently, both hydrolysis and cleavage of aminoketones are suppressed, and the condensation results in preferential formation of 4,7-phenanthrolines.

It should be noted that in 1-butanol, too, we could not always avoid chalcone formation. These compounds in minor amounts were isolated together with target 4,7-phenanthrolines **IIIa**, **IIIf**, **IIIh**, whereas the reactions of (dihydroxyphenylmethylene)(6-quinolyl)amines **If**, **Ig** with *p*-nitroacetophenone (**IIb**) gave compounds **IVa**, **IVb** as single products. *m*-Nitroacetophenone (**IIc**) failed to react with hydroxy-substituted azomethines **If**, **Ig**. In the reaction mixture we found nothing more than more 6-quinolylamine formed by hydrolysis of the latter.

It is known [6] that electron-donor substituents in the aldehyde moiety of azomethine molecule weaken polarization of the C=N bond and make it less active toward CH acids. When two electron-donor hydroxy groups are present in the aldehyde moiety of the azomethine molecule, it prefers hydrolysis to form enones **IVa**, **IVb**. The C=N bond in azomethines **Ic**, **Id** containing one hydroxy group is weaker deactivated toward CH acids. (Hydroxyphenylmethylene)(6-quinolyl)amines **Ic**, **Id** react with acetophenones, giving more 4,7-phenanthrolines **IIIc**–**IIIf** than enones but in lower yields than phenanthrolines **IIIa**, **IIIb** in the reactions of acetophenone **IIa** with azomethines **Ia**, **Ib** containing the electron-acceptor nitro group.

Substituents in the phenyl ring of acetophenone only slightly affect the condesation results. Both hydroxy- and nitro-substituted acetophenones with the same azomethine **Ie** give roughly equal yields of 4,7-phenanthrolines **IIIg**–**IIIi**.

1,3-Diaryl-4,7-phenanthrolines **IIIa**–**IIIi** are yellow high-melting crystals. Their characteristics are listed in Table 1.

The IR spectra of 4,7-phenanthrolines **IIIa**–**IIIi** contain strong characteristic stretching vibration bands

Table 2. ^{1}H NMR spectra of 1,3-diaryl-4,7-phenanthroline **IIIa, IIIb, IIId**, and **IIIf**, δ, ppm (*J*, Hz)

Comp. no.	H^2, s	H^5, d (^3J 8.8)	H^6, d (^3J 8.8)	H^8, d (^3J 4.8)	H^9, d.d (^3J 8.2, ^4J 2.8)	H^{10}, d (^3J 8.2)	Phenyl protons (^3J 8.0–8.4)	
							acetophenone	aldehyde
IIIa	8.70	9.10	9.0	9.37	8.18	9.31	7.40 d, 7.60 d	8.08 t, 8.60 d, 8.75 d, 9.13 s
IIIb	8.61	9.11	9.01	9.37	8.16	9.28	7.41 d, 7.66 d	8.43 d, 8.67 d
IIId	8.75	9.08	9.01	9.36	8.14	8.93	8.00 d, 8.70 d	7.40 m, 7.82 t, 8.24 d
IIIf	8.54	9.12	8.99	9.36	8.10	8.92	8.20 d, 8.70 d	7.36 d, 7.98 d

of the nitro groups at 1545–1530 and 1365–1355 cm^{-1}. The CH stretching vibration bands of the aromatic rings appear at 3060–3030 cm^{-1}. The bands at 720–715 and 855–850 cm^{-1} are indifferent to substituent effects and belong to out-of-plane deformation vibrations of two neighboring CH bonds [6].

A characteristic feature of the mass spectra of 4,7-phenanthrolines **IIIa**–**IIIi** is that they contain little fragment ions. The base peaks are formed by molecular ions (M^+). Low- and medium-intensity peaks are also present (5–25%) at *m/z* 271 and 300, assignable to $[M - RC_6H_4]^+$ or, for compounds **IIIg**–**IIIi** (R = 2-OH,5-NO_2), $[M - RC_6H_3]^+$ ions.

The electronic absorption spectra of phenanthrolines **IIIa**–**IIIi** show three bands in the UV range (224–263, 287–313, and 343–370 nm), which are interpreted as Clar β, *p*, and α bands [7]. Compared with the spectrim of 1,3-diphenyl-4,7-phenanthroline [8], in the spectra of compounds **IIIa**–**IIIi** we observe leveled intensities of the β and *p* bands, and, except for *o*-hydroxyphenyl-substituted phenanthrolines **IIIc**, **IIId**, smoothened vibrational structure of the α band. In the spectra of compounds **IIIc**, **IIId**, the α band is shifted bathochromically and enhanced, like in the spectra of analogous compounds of the benzo[*f*]quinoline series [9].

The ^{1}H NMR spectra of compounds **IIIa**, **IIIb**, **IIId**, **IIIf** (Table 2) were assigned based on the spectral data for 1-phenyl-3-aryl-4,7-phenanthrolines, reported in [6]. Because of the poor solubility of hydroxynitro derivatives **IIIa**, **IIIb**, **IIId**, **IIIf** in organic solvens, the spectra of these compounds were measured in CF_3COOD. In this connection, compared with the spectra of analogs measured in $CDCl_3$ [6], all signals in the spectra of hydroxynitro-substituted 4,7-phenanthrolines **IIIa**, **IIIb**, **IIIg**, **IIIf** exhibit a slight downfield shift induced by the positive charge of the phenanthroline nitrogen atoms, developed as a result of deuteration. The anisotropic effects of hydroxy and nitro groups extend to protons of the phenyl rings bearing these groups. At the same time, the spectra of compounds **IIId**, **IIIf** containing nitrophenyl substituents in the 1 position of the phenanthroline nucleus, the H^{10} signal is upfield from the respective signal of hydroxyphenyl-substituted analogs **IIIa**, **IIIb**. The H^{10} proton locating over the the phenyl ring plane, in compounds **IIId**, **IIIf** appears to fall into the shielding cone of the nitro group, which shifts this proton signal upfield. The same effect was earlier observed in the spectra of nitrobenzylidene derivatives of 4-azafluorene [10].

EXPERIMENTAL

The IR spectra were measured on a UR-20 instrument in KBr. The mass spectra were obtained on a Varian Mat-311 spectrometer with direct inlet, ionizing energy of 70 eV, vaporization temperature 150–200°C, and ion source temperature 200°C. The UV spectra were measured in ethanol (c 10^{-4} M) on a Specord UV-Vis spectrophotometer. The ^{1}H NMR spectra were obtained on a Bruker WM-360 spectrometer (360 MHz) in CF_3COOD, internal reference TMS. The melting points were measured on a Kofler hot stage.

Arylmethylene(6-quinolyl)amines **Ia**–**Ig** were obtained by the procedure in [11].

1,3-Diaryl-4,7-phenanthrolines IIIa–IIIi. A mixture of 5 mmol of azomethine **Ia**–**Ie**, 5 mmol of hydroxy- or nitro-substituted acetophenone **IIa**–**IIc**, 20 ml of 1-butanol, and 6–8 drops of conc. HCl was heated under reflux for 2–3 h. The precipitate that formed (with compounds **IIIb**, **IIIc**, the solvent was evaporated by 1/3) was filtered off, treated with ethanolic NH_4OH (1 : 1) and water, and dried. Phenanthrolines **IIIb**, **IIIf** were recrystallized from nitrobenzene.

1,3-Diarylpropenones IVa–IVe were obtained as described for compounds **IIIa**–**IIIi**. Enones **IVc**–**IVe** were isolated by evaporation of the mother liquors after separation of the precipitates of phenanthrolines **IIIa**, **IIIf**, **IIIh**. Propenones **IVa**, **IVb** were recrystallized from ethanol–benzene, 1 : 3, and compounds

IVc–**IVe**, from nitrobenzene. Compound **IVa**: yield 42%, mp 81–82°C. IR spectrum, ν, cm^{-1}: 1700 (CO), 1535, 1355 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 285 $[M]^+$ (100), 255 (14), 249 (11), 239 (15). Found, %: C 62.89; H 3.91; N 4.77. $C_{15}H_{11}NO_5$. Calculated, %: C 63.16; H 3.86; N 4.91. Compound **IVb**: yield 49%, mp 126–127°C. IR spectrum, ν, cm^{-1}: 1690 (CO), 1530, 1360 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 285 $[M]^+$ (100), 267 (18), 255 (19), 239 (15). Found, %: C 63.21; H 3.90; N 4.66. $C_{15}H_{11}NO_5$. Calculated, %: C 63.16; H 3.86; N 4.91. Compound **IVc**: yield 8%, mp 245–246°C. IR spectrum, ν, cm^{-1}: 1670 (CO), 1540, 1360 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 269 $[M]^+$ (100), 239 (11), 223 (20). Found, %: C 66.74; H 4.01; N 5.28. $C_{15}H_{11}NO_4$. Calculated, %: C 66.91; H 4.09; N 5.20. Compound **IVd**: yield 6%, mp 204–205°C. IR spectrum, ν, cm^{-1}: 1655 (CO), 1530, 1350 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 269 $[M]^+$ (100), 251 (9), 223 (14). Found,%: C 66.71; H 3.98; N 5.11. $C_{15}H_{11}NO_4$. Calculated, %: C 66.91; H 4.09; N 5.20. Compound **IVe**: yield 9%, mp 242–243°C. IR spectrum, ν, cm^{-1}: 1680 (CO), 1535, 1360 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 314 $[M]^+$ (100), 284 (14), 268 (17). Found, %: C 57.36; H 3.11; N 8.84. $C_{15}H_{10} \cdot N_2O_6$. Calculated, %: C 57.32; H 3.18; N 8.92.

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