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Cyclopentanone in the Synthesis of Fused 4,7-Phenanthroline Derivatives

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Abstract—Catalytic condensation of cyclopentanone with arylmethylene(6-quinolyl)amines gave previously unknown 8-aryl-10,11-dihydro-9*H*-cyclopenta[*a*]-4,7-phenanthrolines.

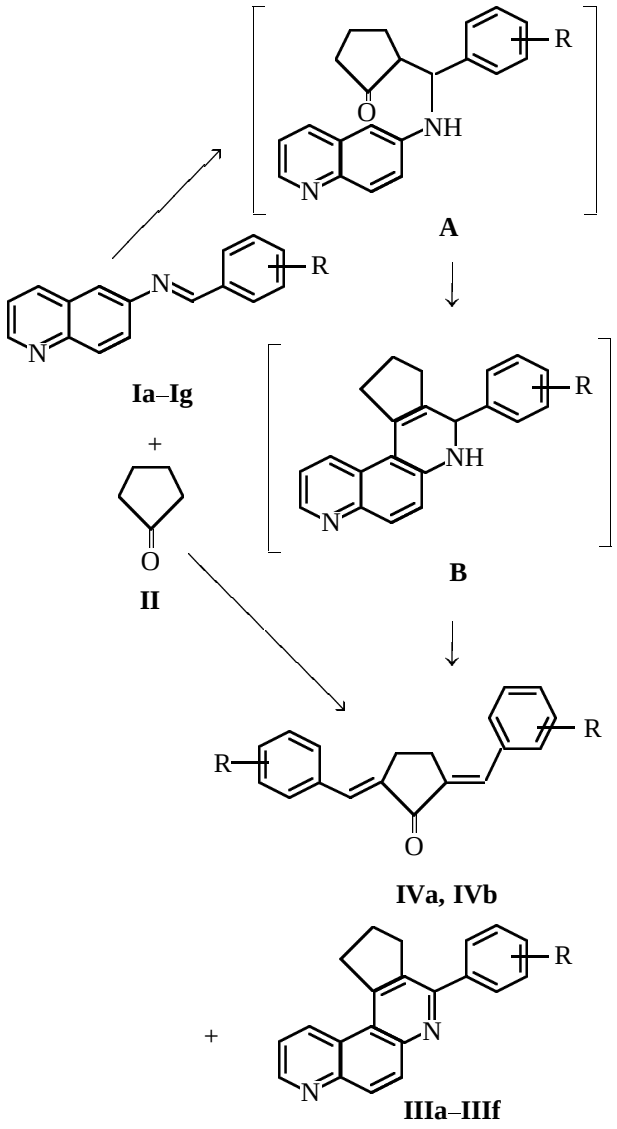
The interest in the synthesis of 4,7-phenanthroline derivatives is due to the fact that many representatives of this class of compounds have exhibited high and diverse physiological activity [1–3].

Previously we showed [4–6] that azomethines of the 6-aminoquinoline series react with cyclohexanone, 1,3-cyclohexanedione, and dimedone to give 4,7-phenanthroline derivatives with fused cyclohexane ring, which, having partially hydrogenated benzene and pyridine rings, are analogs of certain alkaloids [7]. We consider it no less interesting to introduce into the 4,7-phenanthroline molecule a cyclopentane ring. Such rings are a constituent part of polycyclic steroid structures.

In the present work we set ourselves the aim to prepare new potentially biologically active 4,7-phenanthroline derivatives containing fused cyclopentane nucleus. To this end, we reacted for the first time (arylmethylene)(6-quinolyl)amines **Ia**–**Ig** with cyclopentanone (**II**). The reaction was performed by refluxing for 3–4 h a solution of equimolar reagent amounts in an aliphatic alcohol (ethanol, butanol) in the presence of catalytic amounts of conc. HCl.

In [4–6] we showed that the synthesis of azaaromatic compounds by catalytic condensation of mono- and diketones with azomethines is a multistage procedure. First the CH acid adds to the C=N bond of the azomethine to form aminoketone **A**. The subsequent dehydrocyclization of the latter yields azaphenanthrene **B** with a partially hydrogenated pyridine nucleus. Finally, azaphenanthrene **B** undergoes dehydrogenation to give 4,7-phenanthroline with a fused carbocycle.

In the condensation of arylmethylene(6-quinolyl)-amines **Ia**–**If** with cyclopentanone **II** in the above conditions we found nor intermediate **A** nor intermediate **B**. The reaction resulted in isolation of final cyclization



R = H (**Ia, IIIa**), 2-OH (**Ib, IIIb**), 3-OH (**Ic, IIIc**), 3,4-OCH_2O (**Id, IIId**), 4-Cl (**Ie, IIIe, IVa**), 2,4-Cl_2 (**If, IIIf**), 2,3-Cl_2 (**Ig, IVb**).

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Table 1. Yields, melting points and elemental analyses of 8-aryl-10,11-dihydro-9*H*-cyclopenta[*a*]-4,7-phenanthroline **IIIa**–**IIIf**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	N	N (Hlg)		C	H	N (Hlg)
IIIa	28	212–213	85.04	5.49	9.21	$C_{21}H_{16}N_2$	85.14	5.41	9.46
IIIb	31	206–207	80.78	5.13	8.81	$C_{21}H_{16}N_2O$	81.03	5.14	9.00
IIIc	35	224–225	81.14	4.98	8.69	$C_{21}H_{16}N_2O$	81.03	5.14	9.00
IIId	27	183–184	77.59	4.63	8.37	$C_{22}H_{16}N_2O_2$	77.65	4.71	8.24
IIIe	41	227–228	76.05	4.14	8.37 (10.31)	$C_{21}H_{15}ClN_2$	76.24	4.54	8.47 (10.76)
IIIf	38	237–238	68.95	3.77	7.60 (19.17)	$C_{21}H_{14}Cl_2N_2$	69.04	3.84	7.67 (19.45)

products, 8-aryl-10,11-dihydro-9*H*-cyclopenta[*a*]-4,7-phenanthrolines **IIIa**–**IIIf** (Table 1). In milder conditions (20–50°C) in the presence and in the absence of HCl, arylmethylene(6-quinolylamines) **Ia**–**Ig** failed to react; longer reaction times (stading at 20°C for 2–3 days) resulted in tarring of the reaction mixtures.

The reactions with cyclopentanone were performed in two ways: with Schiff bases either prepared in advance from 6-quinolylamine and aromatic aldehyde and recrystallized from aliphatic alcohol [8] or generated *in situ*. In the latter case, the reactions were performed in a three-component system including 6-quinolylamine, aromatic aldehyde, and cyclopentanone. The yields of the target products per taken 6-quinolylamine were roughly equal in both cases.

The reaction with (4-chloromethylene)(6-quinolyl)-amine (**If**) gave, irrespective of whether azomethine was synthesized in advance or generated *in situ*, a by-product, 2,5-bis(4-chlorophenylmethylene) cyclopentanone (**IVa**), along with 4,7-phenanthroline. The reaction with (2,3-dichlorophenylmethylene)(6-quinolyl)amine (**Ig**) gave 2,5-bis[(2,3-dichlorophenyl)-methylene]cyclopentanone (**IVb**) as a major product. The formation of a similar compound, 2,6-dibenzylidenecyclohexanone, we observed earlier in the reaction of benzylidene(6-quinolyl)amine with cyclohexanone [4]. Previously [5, 9] we noted enhanced tendency of azomethines derived from 6-aminoquinolines for hydrolysis in acidic alcoholic media. Apparently, combined steric and electronic effects of the chlorine substituents in azomethine **Ig** result in that 2,3-dichlorobenzaldehyde formed by hydrolysis of the Schiff base prefers to condense with cyclopentanone to form diarylidene derivative **IVb**. In 4-chloro-substituted azomethine **Id**, the +*M* effect of the substituent favors formation of 4,7-phenanthroline (**IIIe**), whereas dienone **IVa** is a minor product. Unsubstituted azomethine **Ia** and 2-hydroxy-, 3-hydroxy-, 3,4-methylenedioxy-, and [(2,4-dichlorophenyl)methylene)(6-quinolyl)amines **Ib**–**Id** and if react with cyclopetanone, giving individual substituted 4,7-phenanthrolines **IIIb**–**IIId** and **IIIf**.

The structure of the products was proved by UV, ^{1}H NMR (Table 2), and IR spectroscopy and mass spectrometry.

The IR spectra of substituted 4,7-phenanthrolines **IIIa**–**IIIf**, unlike those of azomethines **Ia**–**If**, lack a strong band at ~1635–1630 cm^{-1}, characteristic of stretching vibrations of exocyclic C=N bonds. The lack in the IR of compounds **IIIa**–**IIIf** of characteristic CO and NH absorption bands expected in the spectra of intermediates **A** and **B** suggests that latter have converted into the target 4,7-phenanthrolines. The spectra contain bands at 3060–3030 cm^{-1} due to stretching vibrations of C–H bonds in aromatic rings. Stretching vibrations of cycloalkane CH_2 groups give rise to two bands at 2950–2940 and 2890–2870 cm^{-1}.

The base peaks in the mass spectra of substituted 4,7-phenanthrolines **IIIa**–**IIIf** belong to molecular ions (M^+, 100%). The spectra also contain fairly intense $[M - RPh]^+$ ion peaks at *m*/*z* 230 (25–40%) and low-intensity (5–10%) peaks formed by successive expulsion from the molecular ion of cyclopentane CH_2 groups.

The electronic absorption spectra of compounds **IIIa**–**IIIf** (Table 2) lie in the UV region and are similar to the spectrum of their carbocyclic analog, phenanthrene [10]. The bands at 220–254, 280–286, and 334–363 nm in the spectra of compounds **IIIa**–**IIIf** are interpreted as Clar β-, ρ-, and α-bands, respectively [11]. Compared with the spectrum of phenanthrene, the fine structure of the α-band in the spectra of 4,7-phenanthrolines is smoothened because

Table 2. UV [λ_{max}, nm (log ε)] and ^{1}H NMR [δ, ppm (*J*, Hz)] spectra of 8-aryl-10,11-dihydro-9*H*-cyclopenta[*a*]-4,7-phenanthrolines **IIIa**–**IIIf**

Comp. no.	UV spectrum	^{1}H NMR spectrum							
		H^1, d (^3J 4.2)	H^2, d.d (^3J 8.4, ^4J 4.2)	H^3, d (^3J 8.4)	H^5, H^6, d.d (^3J 9.2)	H^9, t (^3J 8.0)	H^{10}, quintet (^3J 8.0)	H^{11}, t (^3J 8.0)	Ar–H
IIIa	221 (4.49), 243 (4.65), 281 (4.74), 334 (3.66), 349 (3.51)	9.00	7.58	8.88	8.25	3.70	2.29	3.30	7.46 m, 7.83 m
IIIb	220 (4.52), 235 (4.62), 254 (4.62), 285 (4.68), 348 (4.06), 363 (4.03)	8.94	7.61	9.02	8.20	3.65	2.25	3.40	6.80–7.40 m, 9.40 s (OH)
IIIc	225 (4.50), 246 (4.67), 283 (4.75), 335 (3.68), 347 (3.57)	9.06	7.75	8.95	8.20	3.75	2.22	3.25	6.90 m, 7.32 m, 9.62 s (OH)
IIId	224 (4.46), 244 (4.70), 281 (4.76), 337 (3.63), 349 (3.58)	9.01	7.76	8.90	8.22	3.72	2.25	3.24	6.63 s, 6.80 s, 5.88 m (OCH_2O)
IIIe	223 (4.50), 244 (4.63), 280 (4.72), 338 (3.79), 350 (3.66)	8.99	7.50	8.89	8.19	3.69	2.28	3.22	7.35 d, 7.70 d (^3J 7.8)
IIIf	224 (4.48), 243 (4.65), 286 (4.73), 337 (3.74), 346 (3.61)	9.15	7.78	9.02	8.20	3.80	2.27	3.25	7.60 m, 7.70 m

of the accumulation in the system of nitrogen atoms. Substituents in the phenyl ring have almost no effect of the positions and intensities of absorption bands, except for the *o*-OH group: The α-band in compound **IIIb** is more intense and strongly shifted bathochromically.

In the ^{1}H NMR spectra of 4,7-phenanthrolines **IIIa**–**IIIf** (Table 2), cycloaliphatic protons appear as two triplets and a quintet at 2.22–3.80 ppm. The signals of phenanthroline protons we assigned using spectral data for 1,3-diaryl-4,7-phenanthrolines [12]. Compared with the spectra of the latter compounds, the H^1 and H^2 signals of the cyclopentane 4,7-phenanthroline derivatives are strongly shifted downfield, on account of the anisotropic deshielding of these protons as a result of substitution of the 1-phenyl ring by a fused aliphatic cycle.

EXPERIMENTAL

The IR spectra were measured on a Specord IR-75 instrument. The mass spectra were obtained on an MKh-1320 instrument at 50 eV with direct inlet and an ion source temperature of 250°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 Tesla BS-567 spectrometer (100 MHz) in $CDCl_3$ for **IIIa**, **IIIb**, **IIIe**, **IVa**, and **IVb** and in DMSO-d_6 for **IIIc**, **IIId**, and **IIIf**; internal reference TMS. The melting points were determined on a Kofler hot stage.

8-Aryl-10,11-dihydro-9*H*-cyclopenta[*a*]-4,7-phenanthrolines IIIa–IIIf. *a*. A mixture of 0.1 mol of azomethine **Ia**–**IIIf**, 0.1 mol of cyclopentanone **II**, 8 drops of conc. HCl, and 30 ml of 1-butanol (**Ia**, **Ic**, **Ie**, and **If**) or ethanol (**Ib** and **Id**) was refluxed for 3 h. After cooling, a precipitate formed and was filtered off, washed with 25% ammonia, and recrystallized from ethanol–benzene, 3 : 1.

b. Cyclopentanone (**II**), 0.1 mol, and 7–8 drops of conc. HCl were added to a heated (50°C) solution of 0.1 mol of 6-quinolylamine and 0.1 mol of aldehyde in 30 ml of 1-butanol (benzaldehyde, 3-hydroxy-, 4-chloro-, and 2,4-dichlorobenzaldehyde) or ethanol (salicylaldehyde and 3,4-methylenedioxybenzaldehyde), and the mixture was refluxed for 3 h. Products **IIIa**–**IIIf** were isolated as in method *a*. Yield 30–42%.

2,5-Bis(4-chlorophenylmethylene)cyclopentanone (IVa) was synthesized as described for compounds **IIIa**–**IIIe**. Dienone **IVa** was isolated by

evaporation of the mother liquor after separation of 4,7-phenanthroline **IIId**, and recrystallized from ethanol. Yield 6% (method *a*) and 8% (method *b*), mp 186–187°C. IR spectrum, ν, cm^{-1}: 3060 (CH_{arom}), 2920, 2830 (CH_{aliph}), 1680 (CO), 1595 (C=C). ^1H NMR spectrum, δ, ppm: 2.92 s (4H, CH_2), 7.25 d, 7.52 d (8H, H_{arom}), 7.79 s (2H, CH). Found, %: C 69.21; H 4.11; Cl 21.36. $C_{19}H_{14}Cl_2O$. Calculated, %: C 69.30; H 4.26; Cl 21.58.

2,5-Bis(2,3-dichlorophenylmethylene)cyclopentanone (IVb) was prepared in a similar way from cyclopentanone and 2,3-dichlorophenylmethylene-6-quinolylamine (**Ig**) (method *a*) or ketone **II**, 6-quinolylamine, and 2,3-dichlorobenzaldehyde (method *b*). The product was recrystallized from ethanol–benzene, 2 : 1. Yield 26% (method *a*) and 31% (method *b*), mp 215–216°C. IR spectrum, ν, cm^{-1}: 3065 (CH_{arom}), 2930, 2840 (CH_{aliph}), 1675 (CO), 1590 (C=C). ^1H NMR spectrum, δ, ppm: 2.95 s (4H, CH_2), 7.10–7.50 m (6H, H_{arom}), 7.85 s (2CH). Found, %: C 57.08; H 3.22; Cl 35.53. $C_{19}H_2Cl_4O$. Calculated, %: C 57.29; H 3.02; Cl 35.68.

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