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One-Stage Synthesis of Benzoacridine and Benzophenanthroline Functionalized Derivatives

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Abstract—A one-stage procedure was developed for preparing new partially hydrogenated derivatives of benzoacridine and benzophenanthroline. The procedure was a triple condensation of 6-aminoquinoline or 2-naphthylamine with formaldehyde and hydroxycyclohexylidenepropanedinitriles, functionalized analogs of cyclic β-diketones.

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Reactions of cyclic β-diketones with Schiff bases provide versatile opportunities for preparation of various fused nitrogen-containing heterocyclic systems [1–3] possessing a wide range of biological action. In the reaction of *N*-arylidene-2-naphthylamines **Ia** with dimedone (**IIb**) formed partially hydrogenated derivatives of benzo[*a*]acridine **IIIa** that were used for the synthesis of a number of compounds exhibiting a significant cytostatic action [4]. The reaction of *N*-arylidene-6-quinolylamines **Ic** with dimedone or 1,3-cyclohexanedione (**IIa**) furnished structural analogs of biologically active substances [5–7], compounds of benzophenanthroline series **IIIb**. The availability of the initial components and the simplicity of the preparation of compounds **III** combined with the possibility to use them for the synthesis of new biologically active substances prompted us to look for the ways to modify the described compounds. All the previously published syntheses based on compounds **III** involved an oxidation stage of the dihydropyridine fragment of the molecule followed by further transformations of compounds **IV** [4, 8–11] (Scheme 1). We did not find any information on prepartion of compounds **III** with the retained dihydropyridine system.

Actually, all attempts to bring into the standard reactions the carbonyl group, hydrogen atoms in the α-position relative to the carbonyl, or the amine fragment of compounds **III** were unsuccessful. This behavior of the compounds in question may be explained by the conjugation of the carbonyl and amino group through a double bond, and therefore the system as an amide vinylog possesses a reduced reactivity.

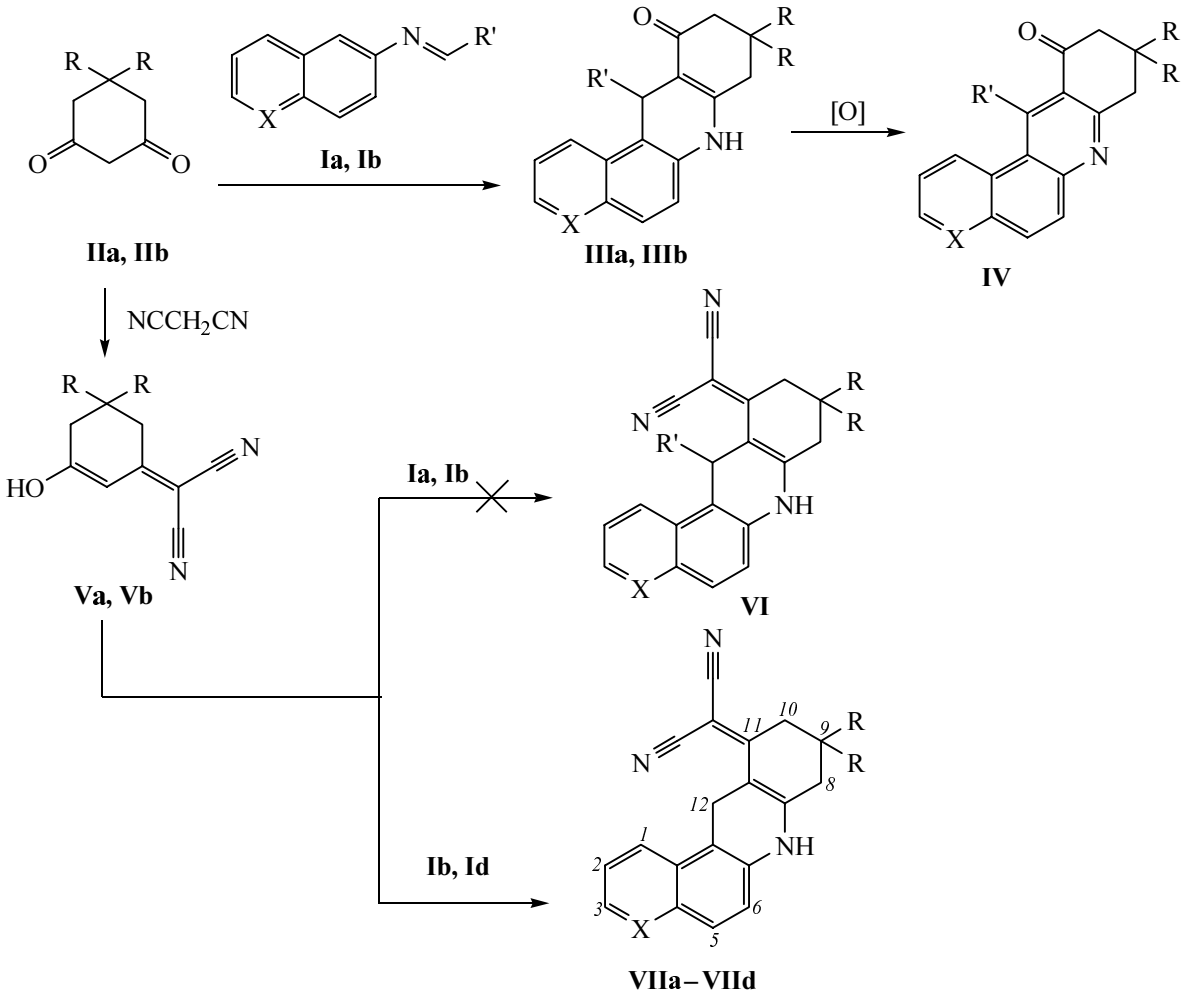
We suggested as an alternative a modific-ation of the initial diketone prior to its subsequent condens-ation with Schiff bases. To this end we chose the described in the literature [12] Knoevenagel condensation with malononitrile affording hydroxycyclohexylidenepropanedinitriles **V**. Therewith one of the electron-withdrawing oxygen atoms of the diketone is replaced by an electron-withdrawing group $C(CN)_2$ with a formal retention of the electron density distribution in the molecule.

Condensations of compounds **V** with Schiff bases **I** were performed by the standard procedure: The solution of equimolar reagents quantities in ethanol was heated without a catalyst. Neither *N*-arylidene-2-naphthylamines nor *N*-arylidene-6-quinolylamines reacted under these conditions, and no heterocyclic derivatives **VI** were obtained. However the condensation of dinitrile **V** with *N*-methylene-2-naphthylamine (**Ib**) gave rise to the expected benzoacridine derivatives **VIIa** and **VIIb** in plausible yields. *N*-Methylene-6-qiunolylamine (**Id**) also entered into the reaction giving benzophenanthroline derivatives **VIIc** and **VIId**.

The reaction presumably proceeds by the mechanism shown on Scheme 2.

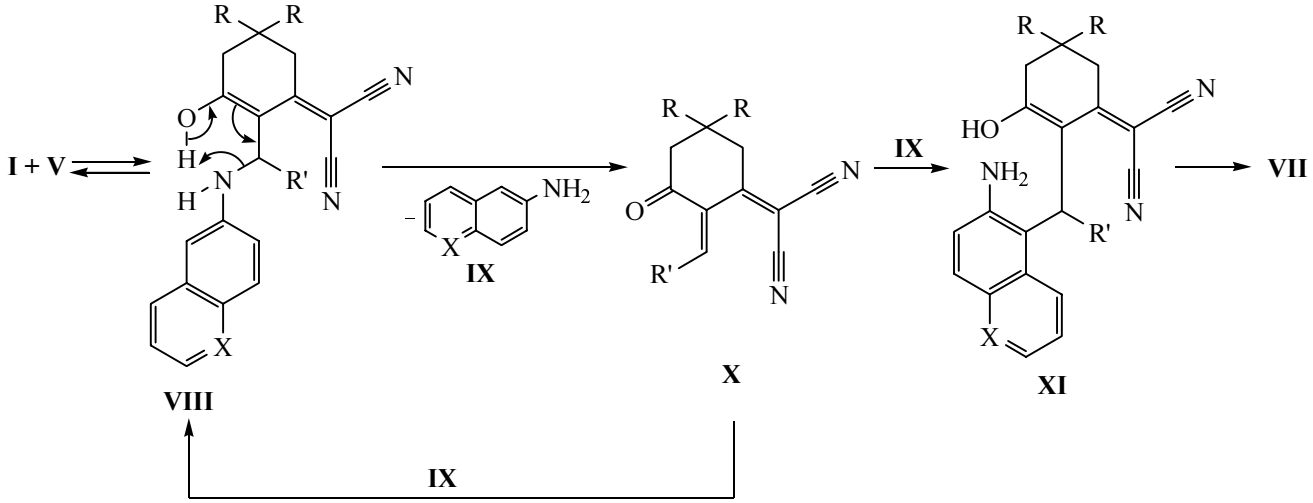
In the first stage of the reaction the nucleophilic center of the analog of β-diketone **V** attacks the electron-deficient carbon of the C=N bond in Schiff base **I** with the reversible formation of a complex aminodinitrile **VIII**. The latter eliminates aromatic amine **IX** as a result of a synchronous electrons redistribution thus converting into the key α,β-unsaturated ketone **X** where the double bond is strongly activated due to the conjugation with two

Scheme 1.



I, X = CH, R' = Ar (**a**), H (**b**); X = N, R' = Ar (**c**), H (**d**); **II, V**, R = H (**a**), CH_3 (**b**); **III**, R' = Ar: X = CH, R = CH_3 (**a**), X = N, R = H (**b**); **VII,** X = CH, R = H (**a**), CH_3 (**b**); X = N, R = H (**c**), CH_3 (**d**).

Scheme 2.



electron-withdrawing groups. Aromatic amine **IX** being a binucleophile may react with α,β-unsaturated ketone **X** in either of two ways: by regenerating aminodinitrile **VIII**, or by forming aminodinitrile **XI** containing a free amino group and a fragment $(CN)_2C{=}C{-}C{=}C{-}OH$ (a vinylog of a heteroanalog of a carboxylic acid). Aminodinitrile **XI** further suffers an intramolecular cyclization providing fused structures **VII**.

The lack of reaction with *N*-arylidenearylamines may be due to steric hindrances arising in the stage of aminodinitrile **VIII** formation. The presence in the reagents molecules of bulky substituents (the conjugated cyano group in the analog of β-diketone **V** and the aromatic fragment in the *N*-arylidenearylamine) impairs the approaching of the reaction sites.

The structure of compounds synthesized was confirmed by their IR and ^{1}H NMR spectra.

IR spectra of compounds **VII** contain characteristic strong bands of cyano group vibrations in the region 2200 cm^{-1}. The absorption bands of the stretching vibrations of the aromatic CH bonds are observed in the region 3150–3050 cm^{-1}, the stretching vibrations of the CH_2 groups, in the region 3000–2830 cm^{-1}, the characteristic bands of the stretching vibrations of NH groups appear at 3325–3250 cm^{-1}.

^{1}H NMR spectra of benzoacridines **VIIa** and **VIIb** with respect to the position and the multiplicity of signals correspond to those of the partially hydrogenated benzo[*a*]acridine structure [13], the spectrum of benzophenanthroline **VIIc**, to the spectra of the partially hydrogenated benzo[*b*][4,7]phenanthroline structures [7]. The characteristic signal of the NH group appears in all the spectra as a broadened singlet of integral intensity 1H with the chemical shift 10.0–10.4 ppm, and the two methylene protons of the dihydropyridine ring (at C^{12}) give rise to a singlet of integral intensity 2H in the region 4.3–4.5 ppm. In the spectra of compounds obtained starting from dimedone the protons of two methyl groups at C^9 are observed as a singlet at 1.1ppm with the integral intensity 6H.

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrophotometer Nicolet Protege-460 from samples pelletized with KBr. ^{1}H NMR spectra were registered on spectrometers Bruker AC-500 (500 MHz) and Tesla BS-567 (100 MHz) from solutions in DMSO-d_6, internal reference TMS. The melting points were measured on the Koeffler heating block.

2-(3-Hydroxy-2-cyclohexen-1-ylidene)propanedinitrile (**Va**) and 2-(3-hydroxy-5,5-dimethyl-2- cyclohexen-1-ylidene)propanedinitrile (**Vb**) were synthesized from appropriate β-diketones by condensation with malononitrile according to the procedure [14].

***N*-Methylenearylamines Ib and Id** were obtained from the corresponding aromatic amines **IX** and paraformaldehyde without isolation from the reaction mixture.

Condensation of *N*-methylenearylamines Ib and Id with hydroxycyclohexylidenepropanedinitriles V. A mixture of 0.01 mol of amine **IX** and 0.3 g (0.01 mol) of paraformaldehyde in 30 ml of ethanol was heated to complete dissolution of both reagents (~20 min). To the clear solution obtained was added in one portion a hot solution of 0.01 mol of an appropriate hydroxycyclohexylidenepropanedinitrile **V** in 30 ml of ethanol. The mixture was boiled for 2 h and left overnight. The precipitated crystals of compound **VII** were separated, washed with ethanol and acetone, and dried. The sample for analysis was crystallized from aqueous DMF.

2-{8,9,10,12-Tetrahydrobenzo[*a*]acridine-11(7*H*)-ylidene}propanedinitrile (VIIa). Yield 67%, mp 253°C. IR spectrum, ν, cm^{-1}: 2200 (CN), 3260 (NH). ^{1}H NMR spectrum, δ, ppm: 1.65–1.97 m (2H, C^{9}H$_2$), 2.55–2.70 m (2H, C^{8}H$_2$), 3.00–3.11 m (2H, C^{10}H$_2$), 4.33 s (2H, C^{12}H$_2$), 7.13 d (1H, C^{6}H, *J* 9 Hz), 7.35–8.00 m (5H$_{arom}$), 10.07 br.s (1H, NH). Found, %: C 80.80; H 5.01; N 14.00. $C_{20}H_{15}N_3$. Calculated, %: C 80.78; H 5.08; N 14.13.

2-{9,9-Dimethyl-8,9,10,12-tetrahydrobenzo[*a*]-acridine-11(7*H*)-ylidene}propanedinitrile (VIIb). Yield 72%, mp >310°C. IR spectrum, ν, cm^{-1}: 2200 (CN), 3275 (NH). ^{1}H NMR spectrum, δ, ppm: 1.10 s (6H, 2CH$_3$), 2.42 s (2H, C^{8}H$_2$), 2.57 s (2H, C^{10}H$_2$), 4.50 s (2H, C^{12}H$_2$), 7.17 d (1H, C^{6}H, *J* 9 Hz), 7.45 t (1H$_{arom}$), 7.61 t (1H$_{arom}$), 7.67 d (1H$_{arom}$), 7.78 d (1H$_{arom}$), 7.86 d (1H$_{arom}$), 10.32 br.s (1H, NH). Found, %: C 81.31; H 5.84; N 12.77. $C_{22}H_{19}N_3$. Calculated, %: C 81.20; H 5.89; N 12.91.

2-{8,9,10,12-Tetrahydrobenzo[*b*]-4,7-phenanthroline-11(7*H*)-ylidene}propanedinitrile (VIIc). Yield 58%, mp 221°C. IR spectrum, ν, cm^{-1}: 2200 (CN), 3260 (NH). ^{1}H NMR spectrum, δ, ppm: 1.85–1.99 m (2H, C^{9}H$_2$), 2.55–2.72 m (2H, C^{8}H$_2$), 3.00–3.21 m (2H, C^{10}H$_2$), 4.40 s (2H, C^{12}H$_2$), 7.40 d (1H, C^{6}H, *J* 9 Hz), 7.50–9.00 m (4H$_{arom}$), 10.20 br.s (1H, NH). Found, %: C 76.38; H 4.70; N 18.80. $C_{19}H_{14}N_4$. Calculated, %: C 76.49; H 4.73; N 18.78.

2-{9,9-Dimethyl-8,9,10,12-tetrahydrobenzo[*b*]-4,7-phenanthroline-11(7*H*)-ylidene}propanedinitrile (VII d). Yield 70%, mp 290°C. IR spectrum, ν, cm^{-1}: 2200 (CN), 3280 (NH). ^1H NMR spectrum, δ, ppm: 1.10 s (6H, $2CH_3$), 2.40 s (2H, C^8H_2), 2.55 s (2H, $C^{10}H_2$), 4.45 s (2H, $C^{12}H_2$), 7.39 d (1H, C^6H, *J* 9 Hz), 7.57 s ($1H_{arom}$), 7.80 s ($1H_{arom}$), 7.95 s ($1H_{arom}$), 8.80 s ($1H_{arom}$), 10.35 br.s (1H, NH). FOUND, %: C 77.19; H 5.64; N 17.20. $C_{21}H_{18}N_4$. Calculated, %: C 77.28; H 5.56; N 17.17.

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