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Reaction of 6-Aminoquinoline with Formaldehyde and Cyclic β-Diketones. Synthesis of Benzo[*b*]- and Indeno[2,1-*b*][4,7]-phenanthroline Derivatives

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Abstract—Three-component condensation of 6-aminoquinoline with formaldehyde and cyclic β-diketones (cyclohexane-1,3-dione and dimedone) gave new partially hydrogenated benzo[*b*][4,7]phenanthroline derivatives. An analogous reaction with indan-1,3-dione gave indeno[2,1-*b*][4,7]phenanthroline derivatives. The products were subjected to oxidative dehydrogenation.

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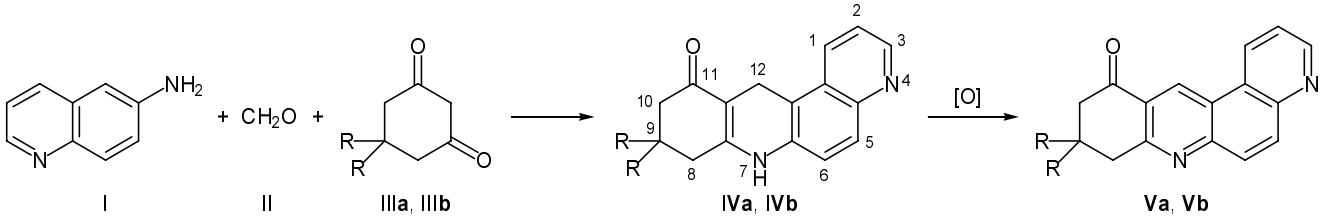
Phenanthroline derivatives are known to exhibit a broad spectrum of biological activity, which stimulates synthesis of new compounds of this series. Unsubstituted benzo[*b*][1,10]phenanthrolinones were recently reported to produce an appreciable cytostatic effect [1]. We previously described a one-step procedure for the synthesis of aryl-substituted benzo[*b*]-[4,7]phenanthrolinones via three component condensation of 6-aminoquinoline with aromatic aldehydes and cyclic β-diketones [2]. With the goal of obtaining new compounds having an unsubstituted benzo[*b*][4,7]-phenanthrolinone core, we used formaldehyde as aldehyde component in an analogous condensation.

The condensation of 6-aminoquinoline (**I**), formaldehyde (**II**), and cyclohexane-1,3-dione (**IIIa**) smoothly occurred on heating an equimolar mixture of the reactants in boiling ethanol for a short time, and the product was 7,8,9,10,11,12-hexahydrobenzo[*b*][4,7]-phenanthrolin-11-one (**IVa**, yield 67%). Under the same conditions, the reaction with dimedone (**IIIb**) instead of cyclohexane-1,3-dione gave 71% of 9,9-dimethyl-7,8,9,10,11,12-hexahydrobenzo[*b*][4,7]phenanthrolin-11-one (**IVb**) (Scheme 1).

Compounds **IVa** and **IVb** are crystalline slightly colored substances, which are poorly soluble in most organic solvents; they readily undergo partial oxidation even during recrystallization or on prolonged storage. The oxidation can be performed purposefully; for example, by treatment of compounds **IVa** and **IVb** with sodium nitrite in acetic acid we obtained the corresponding dehydro derivatives **Va** and **Vb** in more than 80% yield.

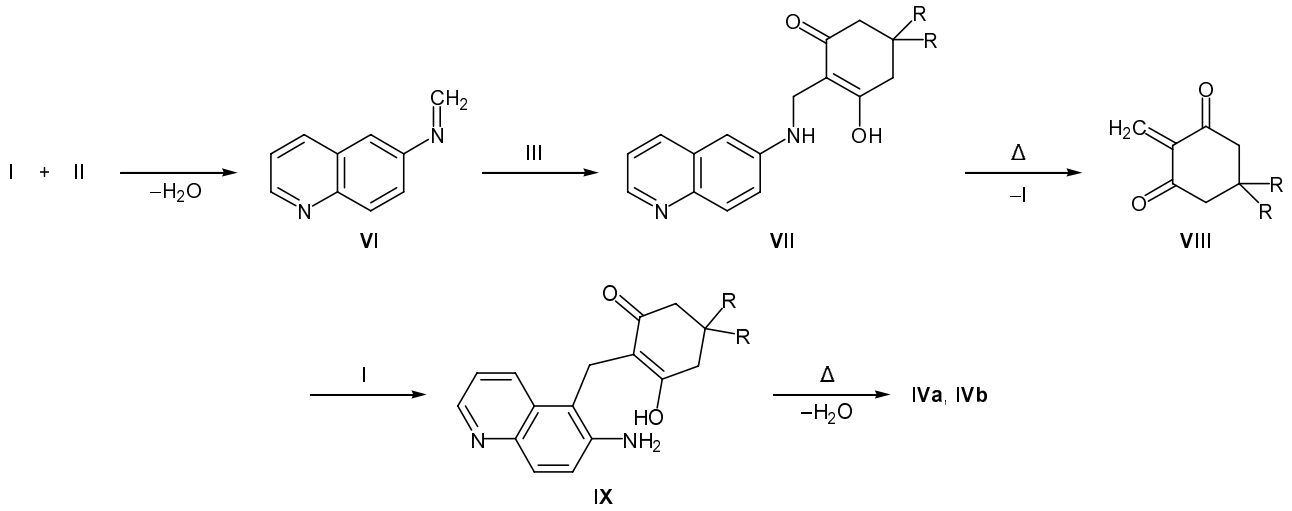
As with aromatic aldehydes, the three-component condensation with formaldehyde involves intermediate formation of Schiff base, *N*-methylidenequinolin-6-amine (**VI**). Schiff base **VI** takes up β-diketone **III** at the polarized C=N bond, yielding β-aminoketone **VII**. The latter undergoes thermal decomposition with elimination of initial amine **I** and formation of α,β-unsaturated ketone **VIII** which then reacts at the aromatic

Scheme 1.



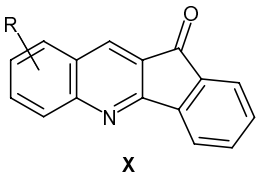
R = H (**a**), Me (**b**).

Scheme 2.



carbon atom of aminoquinoline. Aminoketone **IX** thus formed undergoes intramolecular ring closure to benzo[*b*][4,7]phenanthrolinone **IV** (Scheme 2). The presence in the molecule of aminoketone **IX** of a free amino group and vinylogous carboxylic acid fragment (O=C–C=C–OH) facilitates the cyclization which may be regarded as intramolecular aminoacylation.

In the recent years, interest in polycyclic quinoline derivatives having a fused indene fragment considerably increased [3, 4]. This interest originates primarily from the fact that these compounds were shown to exhibit antitumor activity and inhibit DNA topoisomerases. For example, pronounced cytotoxicity [5] and inhibitory effect toward DNA topoisomerase [6] were reported for a large number of indeno[1,2-*b*]quinolin-10-one derivatives **X**.



X

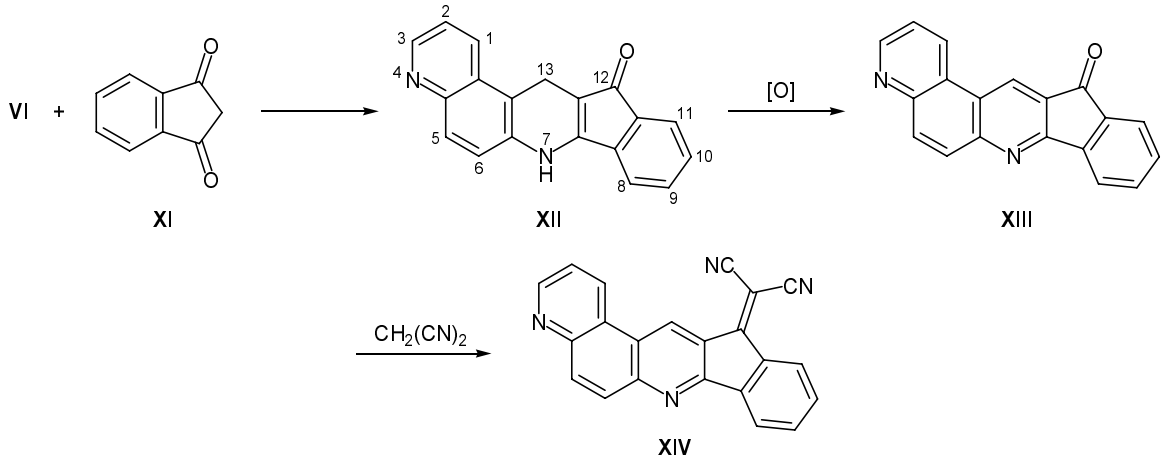
By three-component condensation of 6-aminoquinoline (**I**), formaldehyde (**II**), and indan-1,3-dione (**XI**) we synthesized analogs of indeno[1,2-*b*]quinolin-11-ones **X**, which contain an additional fused pyridine ring, 12,13-dihydro-7*H*-indeno-[2,1-*b*][4,7]phenanthrolin-12-one (**XII**) and 12*H*-indeno[1,2-*b*]][4,7]-phenanthrolin-12-one (**XIII**) (Scheme 3). The procedure for the synthesis of compounds **XII** and **XIII** and mechanism of their formation were similar to those described above.

Ketone **XIII** was subjected to further modification via Knoevenagel condensation with malononitrile. After heating the reactants in boiling dimethylformamide in the presence of pyridine for a short time, we isolated a bright orange substance which was identified as 2-(12*H*-indeno[2,1-*b*][4,7]phenanthrolin-12-ylidene)malononitrile (**XIV**) (Scheme 3). We failed to record its ^{1}H NMR spectrum of **XIV** because of its poor solubility in available solvents, but the proposed structure was confirmed by the IR spectrum and analytical data.

Compounds **IV** and **XII** characteristically showed in the IR spectra absorption bands in the region 3350–3150 cm^{-1} due to stretching vibrations of the NH group. Stretching vibrations of the carbonyl group conjugated with the enamine fragment gave rise to a set of absorption bands at 1590 and 1520–1470 cm^{-1}, as is typical of vinylogous amides [7]. Stretching vibration bands of aliphatic C–H bonds were observed at 3000–2800 cm^{-1} (very weak band for compound **XII**), and absorption bands in the region 3150–3000 cm^{-1} were assigned to stretching vibrations of aromatic C–H bonds. The IR spectra of dehydrogenated compounds **Va**, **Vb**, **XIII**, and **XIV** lacked NH vibration band, and stretching vibrations of the carbonyl group in **Va**, **Vb**, and **XIII** appeared at 1690–1680 cm^{-1}. Dinitrile **XIV** displayed no absorption in the carbonyl region (1700–1680 cm^{-1}), but a strong band at 2220 cm^{-1}, which is typical of nitriles, was present in its IR spectrum.

The ^{1}H NMR spectra of compounds **IVa** and **IVb** are consistent with their benzo[*b*][4,7]phenanthrolin-11-one structure [2]. The NH proton in **IV** and **XII** gave a broadened singlet at δ 9.4 ppm, and the two-

Scheme 3.



proton singlet in the region δ 3.2–3.8 ppm was assigned to methylene protons in the dihydropyridine ring ($C^{12}H_2$ in **IV** or $C^{13}H_2$ in **XII**). Neither NH nor $C^{12(13)}H_2$ signal was present in the spectra of their oxidation products, which may be used to control dehydrogenation. The ^{1}H NMR spectra of the compounds obtained from dimedone contained an additional signal from protons in the methyl groups (a 6H-singlet at δ 1.05–1.08 ppm).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protege-460 Fourier-transform spectrometer. The ^{1}H NMR spectra were measured on Bruker AC-500 (500 MHz) and Tesla BS-567 (100 MHz) spectrometers using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The melting points were determined on a Kofler melting point apparatus.

Condensation of 6-aminoquinoline (I) with formaldehyde (II) and cyclohexane-1,3-dione (IIIa), dimedone (IIIb), or indan-1,3-dione (XI) (*general procedure***).** A mixture of 1.44 g (0.01 mol) of 6-aminoquinoline (**I**) and 0.3 g (0.01 mol) of paraformaldehyde in 30 ml of ethanol was heated under reflux until it became homogeneous (~20 min). A hot solution of 0.01 mol of the corresponding β-diketone in 30 ml of ethanol was added in one portion, and the mixture was heated for 30 min under reflux and left overnight. The precipitate was filtered off, washed with ethanol and acetone, dried, and recrystallized from DMF.

7,8,9,10,11,12-Hexahydrobenzo[*b*][4,7]phenanthrolin-11-one (IVa). Yield 67%, mp 307°C. IR spectrum, ν, cm^{-1}: 1400, 1510, 1590 (O=C–C=C–NH); 3025–3150 (C–H_{arom}); 3200–3300 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.85–2.01 m (2H, C^9H_2), 2.22–2.38 m (2H, C^8H_2), 2.40–2.60 m (2H, $C^{10}H_2$), 3.80 s (2H, $C^{12}H_2$), 7.33 d (1H, 6-H, J = 8.9 Hz), 7.49 d.d (1H, 2-H, J = 8.5, 4.2 Hz), 7.80 d (1H, 5-H, J = 8.9 Hz), 8.05–8.20 m (1H, 1-H), 8.70–8.80 m (1H, 3-H), 9.40 br.s (1H, NH). Found, %: C 76.65; H 5.64; N 11.20. $C_{16}H_{14}N_2O$. Calculated, %: C 76.78; H 5.64; N 11.19.

9,9-Dimethyl-7,8,9,10,11,12-hexahydrobenzo[*b*]-[4,7]phenanthrolin-11-one (IVb). Yield 71%, mp 183°C. IR spectrum, ν, cm^{-1}: 1370, 1520, 1590 (O=C–C=C–NH); 3000–3150 (C–H_{arom}); 3225–3300 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.05 s (6H, CH_3), 2.20 s (2H, C^8H_2), 2.37 s (2H, $C^{10}H_2$), 3.80 s (2H, $C^{12}H_2$), 7.35 d (1H, 6-H, J = 8.9 Hz), 7.50 d.d (1H, 2-H, J = 8.5, 4.2 Hz), 7.81 d (1H, 5-H, J = 8.9 Hz), 8.08–8.21 m (1H, 1-H), 8.70–8.80 m (1H, 3-H), 9.40 br.s (1H, NH). Found, %: C 77.63; H 6.50; N 10.10. $C_{18}H_{18}N_2O$. Calculated, %: C 77.67; H 6.52; N 10.06.

12,13-Dihydro-7*H*-indeno[2,1-*b*][4,7]phenanthrolin-12-one (XII). Yield 56%, mp > 300°C. IR spectrum, ν, cm^{-1}: 1410, 1540, 1580 (O=C–C=C–NH); 3000–3100 (C–H_{arom}); 3300–3450 (N–H). ^{1}H NMR spectrum, δ, ppm: 3.90 s (2H, $C^{13}H_2$), 7.25–8.30 m (7H, H_{arom}), 8.75–8.80 m (1H, 1-H), 8.93–9.50 m (1H, 3-H), 9.40 br.s (1H, NH). Found, %: C 80.16; H 4.20; N 9.90. $C_{19}H_{12}N_2O$. Calculated, %: C 80.27; H 4.25; N 9.85.

Oxidation of compounds IV and XII (*general procedure***).** A sample of compound **IV** or **XII** was dispersed in acetic acid, the suspension was cooled to 0°C, and a solution of an equimolar amount of sodium nitrite in a minimal volume of water was slowly added,

maintaining the temperature at 0°C. The mixture was then stirred for 1 h at room temperature and neutralized with 10% aqueous sodium hydroxide. The precipitate was filtered off, dried, and recrystallized from appropriate solvent.

8,9,10,11-Tetrahydrobenzo[*b*][4,7]phenanthrolin-11-one (Va). Yield 83%, mp 165°C (from toluene). IR spectrum, ν, cm^{-1}: 1690 (C=O), 2850–3100 (C–H_{arom}). ^1H NMR spectrum, δ, ppm: 2.05–2.32 m (2H, C^9H_2), 2.65–2.90 m (2H, $C^{10}H_2$), 3.15–3.30 m (2H, C^8H_2), 7.72 d.d (1H, 2-H, J = 8.5, 4.2 Hz), 8.06 d (1H, 6-H, J = 12 Hz), 8.21 d (1H, 5-H, J = 12 Hz), 9.00 m (1H, 1-H), 9.24 d (1H, 3-H, J = 12 Hz), 9.43 s (1H, 12-H). Found, %: C 77.40; H 4.86; N 11.29. $C_{16}H_{12}N_2O$. Calculated, %: C 77.40; H 4.87; N 11.28.

9,9-Dimethyl-8,9,10,11-tetrahydrobenzo[*b*][4,7]-phenanthrolin-11-one (Vb). Yield 81%, mp 182°C (from ethanol). IR spectrum, ν, cm^{-1}: 1680 (C=O), 2850–3100 (C–H_{arom}). ^1H NMR spectrum, δ, ppm: 1.08 s (6H, CH_3), 2.69 s (2H, $C^{10}H_2$), 3.18 s (2H, C^8H_2), 7.75 m (1H, 2-H), 8.12 d (1H, 6-H, J = 9 Hz), 8.24 d (1H, 5-H, J = 9 Hz), 9.01 m (1H, 1-H), 9.29 d (1H, 3-H, J = 8 Hz), 9.48 s (1H, 12-H). Found, %: C 78.23; H 6.01; N 10.10. $C_{18}H_{16}N_2O$. Calculated, %: C 78.24; H 5.84; N 10.14

12*H*-Indeno[2,1-*b*][4,7]phenanthrolin-12-one (XIII). Yield 92%, mp 286°C (from DMF). IR spectrum, ν, cm^{-1}: 1720 (C=O), 2900–3100 (C–H_{arom}). ^1H NMR spectrum, δ, ppm: 7.63 t (1H, 10-H, J = 8 Hz), 7.75 m (1H, 2-H), 7.81 m (2H, 8-H, 9-H), 8.07 d (1H, 1-H, J = 8 Hz), 8.26 d (1H, 5-H, J = 10 Hz), 8.29 d (1H, 6-H, J = 10 Hz), 9.01 s (1H, 11-H), 9.37 d (1H, 3-H, J = 8 Hz), 9.42 s (1H, 13-H). Found, %: C 80.85; H 3.55; N 9.90. $C_{19}H_{10}N_2O$. Calculated, %: C 80.84; H 3.57; N 9.92.

2-(12*H*-Indeno[2,1-*b*][4,7]phenanthrolin-12-ylidene)malononitrile (XIV). A mixture of 0.28 g (0.001 mol) of ketone **XIII**, 0.1 g (0.0015 mol) of malononitrile, and 1 ml of pyridine in 5 ml of DMF was heated to the boiling point. An orange fibrous material separated. The mixture was cooled, and the precipitate was filtered off, washed with acetone, dried, and recrystallized from DMF (a 0.2-g portion of the crude product dissolved completely in 50 ml of boiling DMF and precipitated almost quantitatively on cooling). Yield 0.2 g (60%), mp 341°C. IR spectrum, cm^{-1}: 745 s, 850 s, 1250 w, 1310 w, 1350 m, 1420 s, 1500 m, 1510 s, 1605 m, 2220 s, 3300–3500 w.br. Found, %: C 80.00; H 3.04; N 16.96. $C_{22}H_{10}N_4$. Calculated, %: C 79.99; H 3.05; N 16.96.

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REFERENCES

1. Bongui, J.B., Elomri, A., Seguin, E., Tillequin, F., Pfeiffer, B., Renard, P., Pierre, A., and Atassi, G., *Chem. Pharm. Bull*., 2001, vol. 49, p. 1077.
2. Kozlov, N.G., Gusak, K.N., Tereshko, A.B., Firgang, S.I., and Shashkov, A.S., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1181.
3. Deady, L.W., Desneves, J., Kaye, A.J., Thompson, M., Finlay, G.J., Baguley, B.C., and Denny, W.A., *Bioorg. Med. Chem*., 1999, vol. 7, p. 2801.
4. Brana, M.F., Cacho, M., Gradillas, A., de Pascual-Teresa, B., and Ramos, A., *Curr. Pharm. Des*., 2001, vol. 7, p. 1745.
5. Deady, L.W., Kaye, A.J., Finlay, G.J., Baguley, B.C., and Denny, W.A., *J. Med. Chem*., 1997, vol. 40, p. 2040.
6. Deady, L.W., Desneves, J., Kaye, A.J., Finlay, G.J., Baguley, B.C., and Denny, W.A., *Bioorg. Med. Chem*., 2000, vol. 8, p. 977.
7. Cortes, E., Martinez, R., Avila, G.J., and Toscano, R.A., *J. Heterocycl. Chem*., 1988, vol. 25, p. 895.