Russian Journal of Organic Chemistry, Vol. 38, No. 1, 2002, pp. 129–133. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 1, 2002, pp. 135–139.

Synthesis of Azaphenanthrene Derivatives by Condensation of 2-Methyleneaminonaphthalene with Cyclic β-Diketones

N. G. Kozlov and A. P. Kadutskii

Institute of Physical Organic Chemistry, National Academy of Belarus Republic, ul. Surganova 13, Minsk, 220072 Belarus
e-mail: kadutskiy@tut.by

Received February 23, 2001

Abstract—2-Methyleneaminonaphthalene smoothly reacts with cyclic β-diketones to afford azaphenanthrene derivatives in high yield. The dihydropyridine ring in the products can be oxidized to pyridine ring. The oxidation products, unlike their precursors and analogs having an aryl substituent in the α-position with respect to the nitrogen atom, react with hydroxylamine at the carbonyl group to give the corresponding oximes and in some cases undergo Knoevenagel condensation with malononitrile. Hydrolysis of the condensation product yields the respective diamide.

Numerous examples of the condensation of cyclic β-diketones with Schiff bases derived from 2-naphthylamine and aromatic aldehydes have been reported [1–5] as a method of synthesis of azaphenanthrene derivatives. In some cases, the resulting fused nitrogen-containing heterocycles are structurally related to biologically active substances [6–9]. Up to now, such reactions were believed to be possible only for *N*-arylmethylene-2-naphthylamines which gave rise to products containing an aryl substituent in the α-position with respect to the nitrogen atom. We have found that 2-methyleneaminonaphthalene (**I**) also readily reacts with cyclic β-diketones, specifically with 1,3-indandione (**II**), 1,3-cyclohexanedione (**III**), and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**IV**), yielding the expected condensation products: 7-aza-7,8-dihydroindeno[2,1-*c*]phenanthren-9-one (**V**), 2,3,5,6-tetrahydro-1*H*-benzo[*a*]phenanthridin-4-one (**VI**), and 2,2-dimethyl-2,3,5,6-tetrahydro-1*H*-benzo[*a*]phenanthridin-4-one (**VII**), respectively. These compounds have no substituent in the α-position to the nitrogen atom (Scheme 1).

The reactions were carried out by heating equimolar amounts of the reactants in ethanol for a short time. As in the condensation of *N*-arylmethylene-2-aminonaphthalenes with cyclic β-diketones [10], no acid catalysis was necessary. Initial *N*-methylene-2-aminonaphthalene was usually prepared just before use from 2-aminonaphthalene and paraformaldehyde in the presence of a catalytic amount of alkali (to depolymerize paraformaldehyde).

Compounds **V**–**VII** contain a dihydropyridine ring which may be oxidized to pyridine. Compound **V** is readily oxidized in solution on boiling in air or with chromium(VI) oxide in acetic acid [11]. However, we failed to oxidize by the same procedure compounds **VI** and **VII**. We have found that azaphenanthridine derivatives **VIII**–**X** can be obtained by heating dihydro compounds **V**–**VII** with powdered sulfur in appropriate solvent at the boiling point.

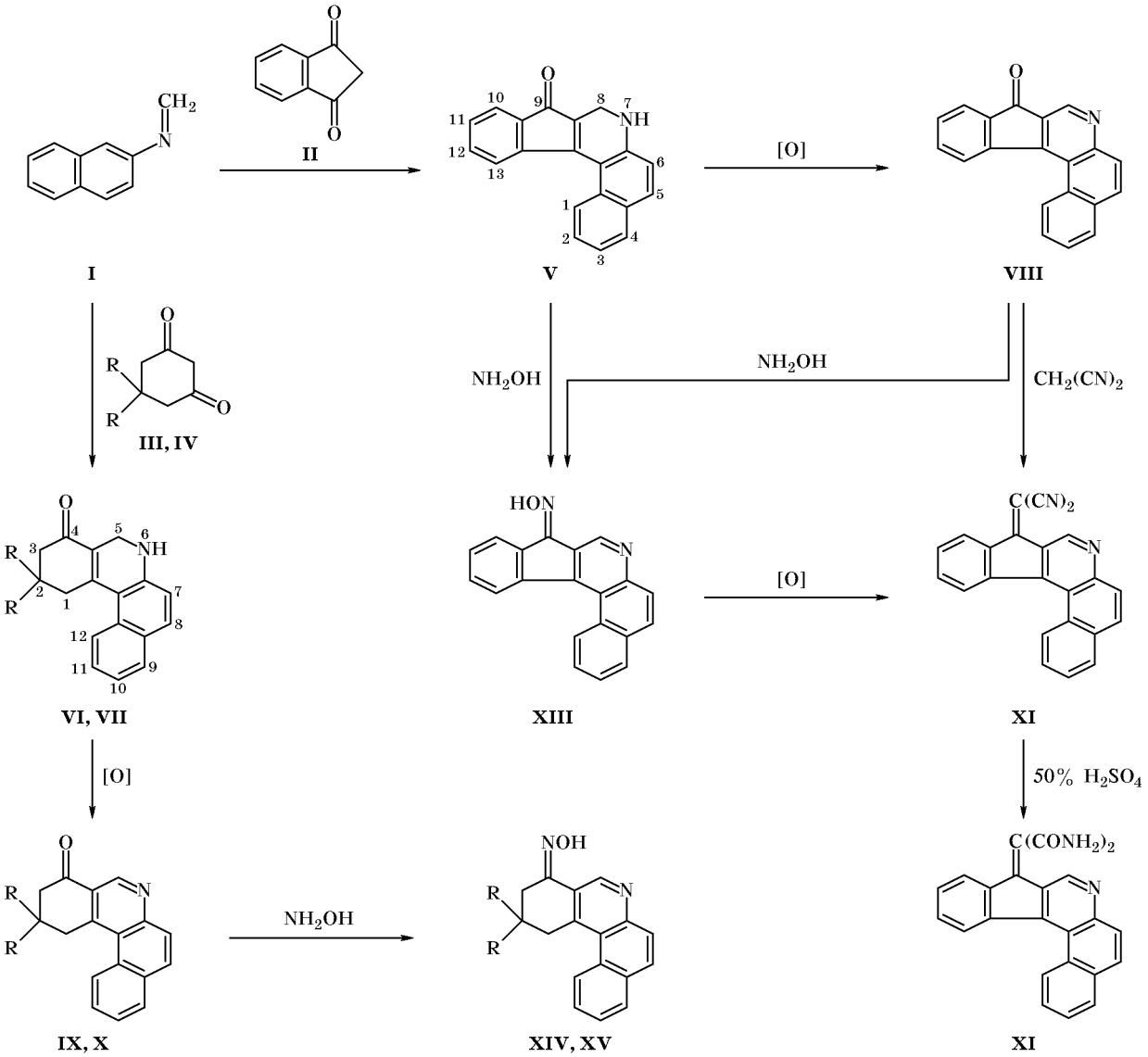
Compounds **VIII**–**X**, unlike their analogs having an aryl group in the α-position relative to the nitrogen atom and precursors **V**–**VII**, exhibit a considerably higher chemical reactivity. Treatment of **VIII**–**X** with hydroxylamine leads to formation of the corresponding oximes **XIII**–**XV** in nearly quantitative yields. Oxime **XIII** is also formed by reaction of **V** with hydroxylamine, indicating easy oxidation of the dihydropyridine ring in **V**.

According to the ^{1}H NMR data, oximes **XIV** and **XV** are formed exclusively as one of the two possible isomers (*syn* or *anti*); however, we failed to determine its configuration on the basis of the available spectral data. Oxime **XIII** obtained from compounds **V** and **VIII** was a mixture of *syn* and *anti* isomers.

Compound **VIII** was brought into the Knoevenagel condensation with malononitrile on heating in boiling

1070-4280/02/3801-0129 $27.00 © 2002 MAIK "Nauka / Interperiodica"

Scheme 1.



III, **VI**, **IX**, **XIV**, R = H; **IV**, **VII**, **X**, **XV**, R = Me.

pyridine for a short time. As a result, 2-(7-azaindeno-[2,1-*c*]phenanthren-9-ylidene)propanedinitrile (**XI**) was obtained in quantitative yield. Hydrolysis of dinitrile **XI** with sulfuric acid gave 2-(7-azaindeno-[2,1-*c*]phenanthren-9-ylidene)propanediamide (**XII**). Our attempts to effect under the same conditions Knoevenagel condensation of compounds **IX** and **X** with malononitrile were unsuccessful; also, we failed to react compound **VIII** with other classical compounds having an activated methylene group (such as diethyl malonate and ethyl cyanoacetate).

The structure of the products was confirmed by the ^{1}H NMR and IR spectra. The IR spectra of **V**–**VII** contain absorption bands typical of stretching vibrations of C=O and N–H groups at 1670–1630 and 3280–3200 cm^{-1}, respectively. The low-frequency shift of these bands is explained by formation of intermolecular hydrogen bonds, in keeping with published data [12]. Stretching vibrations of the CH_2 groups give rise to absorption in the region 2950–2830 cm^{-1}, and aromatic C–H bonds are characterized by IR absorption at 3070–3040 cm^{-1}. The IR spectra of **VIII**–**X** lack NH absorption, indicating the transformation of dihydropyridine ring into pyridine moiety. The carbonyl absorption bands of compounds **VIII**–**X** are observed at 1720–1680 cm^{-1}, and

stretching vibrations of aromatic C–H bonds appear in the region 3065–3050 cm^{-1}.

The IR spectra of the products obtained by reactions at the carbonyl group contain no C=O stretching vibration band, but bands typical of the corresponding functional groups appear at 1010–1000 cm^{-1} (oximes) or 2225 cm^{-1} (dinitrile **XI**). Diamide **XII** shows in the IR spectrum two strong bands at 1670–1650 cm^{-1} (amide I) and 1630–1590 cm^{-1} (amide II), while the band at 2225 cm^{-1}, typical of the initial dinitrile, disappears.

In the ^1H NMR spectra of **V**–**VII** protons at the carbon atom neighboring to the nitrogen give a signal at δ 3.8–3.9 ppm, and the NH proton appears as a broadened singlet at δ 10.5 (**V**) or 9.2–9.3 ppm (**VI** and **VII**). No such signals are present in the spectra of dehydro derivatives **VIII**–**X**; the NCH proton gives a sharp singlet at δ 9.4 ppm. The ^1H NMR spectra of the products obtained from dimedone contain a 6H-singlet at δ 1.05 ppm, belonging to the geminal methyl groups on C^2.

The spectrum of oxime **XIII** (which is a mixture of *syn* and *anti* isomers) contains an unresolved multiplet in the region δ 7.5–9.0 ppm with its intensity corresponding to 20 protons and four one-proton singlets at δ 9.3, 9.9, 12.9, and 13.1 ppm. The singlet at 9.3 ppm belongs to 8-H, and that located at 12.9 ppm, to the NOH proton of the *syn* isomer. The signals at δ 9.9 and 13.1 ppm belong, respectively, to 8-H and NOH of the *anti* isomer. Oximes **XIV** and **XV** give rise to an unresolved multiplet (5H) in the region δ 7.5–8.2 ppm, an unresolved 1H-multiplet centered at δ 8.7 ppm, and two 1H-singlets at δ 9.5 and 11.3 ppm (11.0 ppm for compound **XIV**). The signal at 8.7 ppm was assigned to the proton on C^7, and the two downfield signals (9.5 and 11.3 or 11.0 ppm) belong to 5-H and NOH, respectively. The ^1H NMR spectrum of diamide **XII** is characterized by the presence of two two-proton multiplets at δ 7.5–7.7 and 7.7–7.9 ppm, which correspond to protons of the two NH_2 groups.

EXPERIMENTAL

The IR spectra were measured on a Protege-460 (Nikolet) Fourier spectrometer in KBr. The ^1H NMR spectra were obtained on a Tesla BS-567A instrument (100 MHz) using DMSO-d_6 as solvent and TMS as internal reference. The melting points were determined on a Koefler heating device.

2-Methyleneaminonaphthalene (**I**) can be prepared in the pure form by known procedures. However, we synthesized it just before use in an alcohol solution from 2-aminonaphthalene and paraformaldehyde in the presence of sodium hydroxide (to depolymerize paraformaldehyde) and brought into further syntheses without isolation and purification.

7-Aza-7,8-dihydroindeno[2,1-*c*]phenanthren-9-one (V). Sodium hydroxide, ~20 mg, was added to a mixture of 0.3 g (0.01 mol) of paraformaldehyde and 1.43 g (0.01 mol) of 2-aminonaphthalene in 20 ml of ethanol. The mixture was heated on a water bath (3–7 min) until paraformaldehyde completely dissolved, and a solution of 1.46 g (0.01 mol) of 1,3-indandione (**II**) in 10 ml of ethanol was added. The resulting solution was heated until a solid began to separate. It was cooled, and the precipitate was filtered off, washed with ethanol, and recrystallized from dimethylformamide. Yield 2.3 g (85%), dark crystals, mp 243–244°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 1670 (CO). ^1H NMR spectrum, δ, ppm: 3.91 s (2H, CH_2), 7.27–7.92 m (10H, H_{arom}), 10.55 br.s (1H, NH). Found, %: C 84.57; H 4.85; N 4.85. $C_{20}H_{13}NO$. Calculated, %: C 84.78; H 4.62; N 4.94.

2,3,5,6-Tetrahydro-1*H*-benzo[*a*]phenanthridin-4-one (VI) was synthesized in a similar way from 2-aminonaphthalene, paraformaldehyde, and 1,3-cyclohexanedione (**III**). Yield 85%. Fine yellow crystals with mp 264–265°C (from DMF). IR spectrum, ν, cm^{-1}: 3300 (NH), 1640 (CO). ^1H NMR spectrum, δ, ppm: 1.96 m (2H, C^2H_2), 2.30 m (2H, C^1H_2), 3.07 s (2H, C^3H_2), 3.81 s (2H, C^5H_2), 7.00–7.90 m (6H, H_{arom}), 9.20 br.s (1H, NH). Found, %: C 81.59; H 6.14; N 5.44. $C_{17}H_{15}NO$. Calculated, %: C 81.90; H 6.06; N 5.62.

2,2-Dimethyl-2,3,5,6-tetrahydro-1*H*-benzo[*a*]-phenanthridin-4-one (VII) was synthesized in a similar way from 2-aminonaphthalene, paraformaldehyde, and dimedone (**IV**). Yield 70%, colorless crystals with mp 256°C (from DMF). IR spectrum, ν, cm^{-1}: 3300 (NH), 1630 (CO). ^1H NMR spectrum, δ, ppm: 1.05 s (6H, $2CH_3$), 2.19 s (2H, C^1H_2), 2.37 s (2H, C^3H_2), 3.80 s (2H, C^5H_2), 7.06–7.90 m (6H, H_{arom}), 9.30 br.s (1H, NH). Found, %: C 82.77; H 6.68; N 5.01. $C_{19}H_{19}NO$. Calculated, %: C 82.28; H 6.9; N 5.05.

7-Azaindeno[2,1-*c*]phenanthren-9-one (VIII). Compound **V**, 0.3 g (1 mmol), was dissolved on heating in a mixture of 5 ml of DMF and 5 ml of pyridine, and 0.05 g (1.5 mmol) of powdered sulfur was added to the resulting solution. The mixture was refluxed for 30 min and cooled, and the crystals were filtered off and washed with acetone to isolate 0.28 g (94%) of almost pure compound **VIII** as yellow crystals with mp 232°C. IR spectrum, ν, cm^{-1}: 3065 (C–H_{arom}), 1720 (C=O). ^1H NMR spectrum, δ, ppm: 7.45–8.30 m (9H, H_{arom}), 8.84–9.00 m (1H, 6-H),

9.31 s (1H, 8-H). Found, %: C 85.32; H 4.06; N 4.77. $C_{20}H_{11}NO$. Calculated, %: C 85.39; H 3.94; N 4.98.

2,3-Dihydro-1*H*-benzo[*a*]phenanthridin-4-one (IX). Compound **VI**, 0.25 g (1 mmol), was dissolved on heating in 10 ml of DMF containing 10% of piperidine, and 0.05 g (1.5 mmol) of powdered sulfur was added to the resulting solution. The mixture was refluxed for 6 h, cooled, and poured into water, and the precipitate was filtered off, dried, and recrystallized from a 1:1 mixture of DMF with ethanol. Yield 70%. mp 187°C. IR spectrum, ν, cm^{-1}: 3065 (C–H_{arom}), 1680 (C=O). ^1H NMR spectrum, δ, ppm: 2.10–2.30 m (2H, C^2H_2), 2.70–2.85 m (2H, C^3H_2), 3.29 s (2H, C^1H_2), 7.65–8.25 m (5H, H_{arom}), 8.70–8.85 m (1H, 7-H), 9.42 s (1H, 5-H). Found, %: C 82.63; H 5.14; N 5.80. $C_{17}H_{13}NO$. Calculated, %: C 82.57; H 5.30; N 5.66.

2,2-Dimethyl-2,3-dihydro-1*H*-benzo[*a*]phenanthridin-4-one (X) was synthesized in a similar way from compound **VII** using ethanol containing 10% of morpholine as solvent. Yield 75%, mp 148–150°C (from ethanol); published data [9]: mp 178–180°C. IR spectrum, ν, cm^{-1}: 3065 (C–H_{arom}), 1683 (C=O). ^1H NMR spectrum, δ, ppm: 1.05 s (6H, $2CH_3$), 2.63 s (2H, C^3H_2), 3.11 s (2H, C^1H_2), 7.60–8.22 m (5H, H_{arom}), 8.70–8.83 m (1H, 7-H), 9.38 s (1H, 5-H). Found, %: C 82.99; H 6.12; N 5.00. $C_{19}H_{17}NO$. Calculated, %: C 82.88; H 6.22; N 5.09.

Oximes XIII–XV (*general procedure*). *a*. A mixture of equimolar amounts of ketone **VIII–X** and hydroxylamine hydrochloride in pyridine was refluxed for 2 h and cooled to room temperature. The precipitate was filtered off, washed with acetone, dried, and recrystallized from DMF. Oximes **VIII–X** were isolated as finely crystalline colorless substances in nearly quantitative yield.

7-Azaindeno[2,1-*c*]phenanthren-9-one oxime (XIII). mp 301–304°C. IR spectrum, ν, cm^{-1}: 1010 (N–O). ^1H NMR spectrum, δ, ppm: 7.50–9.00 m (20H, H_{arom}, *syn* and *anti* isomers), 9.30 s (1H, 8-H, *syn*), 9.90 s (1H, 8-H, *anti*), 12.90 s (1H, OH, *syn*), 13.10 s (1H, OH, *anti*). Found, %: C 81.12; H 4.00; N 9.05. $C_{20}H_{12}N_2O$. Calculated, %: C 81.07; H 4.08; N 9.45.

2,3-Dihydro-1*H*-benzo[*a*]phenanthridin-4-one oxime (XIV). mp 302°C. IR spectrum, ν, cm^{-1}: 1000 (N–O). ^1H NMR spectrum, δ, ppm: 1.85–2.15 m (2H, C^2H2), 2.80 s (2H, C^3H_2), 3.08 s (2H, C^1H_2), 7.50–8.22 m (5H, H_{arom}), 8.60–8.80 m (1H, 7-H), 9.45 s (1H, 5-H), 11.05 br.s (1H, OH). Found, %: C 77.63; H 6.12; N 10.62. $C_{17}H_{16}N_2O$. Calculated, %: C 77.25; H 6.10; N 10.60.

2,2-Dimethyl-2,3-dihydro-1*H*-benzo[*a*]phenanthridin-4-one oxime (XV). mp 291°C. IR spectrum, ν, cm^{-1}: 1000 (N–O). ^1H NMR spectrum, δ, ppm: 1.05 s (6H, $2CH_3$), 2.63 s (2H, C^3H_2), 3.11 s (2H, C^1H_2), 7.50–8.22 m (5H, H_{arom}), 8.60–8.74 m (1H, 7-H), 9.50 s (1H, 5-H), 11.30 br.s (1H, OH). Found, %: C 78.29; H 6.72; N 9.50. $C_{19}H_{20}N_2O$. Calculated, %: C 78.05; H 6.89; N 9.58.

b. A mixture of equimolar amounts of ketone **V** and hydroxylamine hydrochloride was refluxed in a 1:1 DMF–pyridine mixture until the original red color disappeared (40–50 min). A solid precipitated, the mixture was cooled, and the product was filtered off and recrystallized from DMF to obtain oxime **XIII** in 95% yield.

2-(7-Azaindeno[2,1-*c*]phenanthren-9-ylidene)-propanedinitrile (XI). Compound **VIII**, 0.2 g (0.7 mmol), was dissolved on heating in 10 ml of a 1:1 DMF–pyridine mixture, 0.05 g (0.75 mmol) of malononitrile was added, and the mixture was refluxed for 20–25 min and cooled. The precipitate was filtered off, washed with acetone, dried, and recrystallized from DMF–pyridine (1:1). Yield 0.23 g (~100%). Orange fibrous crystals, mp 293–294°C. IR spectrum, ν, cm^{-1}: 2225 (CN). ^1H NMR spectrum, δ, ppm: 7.45–8.30 m (9H, H_{arom}), 8.84–9.00 m (1H, 6-H), 9.20 s (1H, 8-H). Found, %: C 83.98; H 3.06; N 13.1. $C_{23}H_{11}N_3$. Calculated, %: C 83.88; H 3.37; N 12.76.

2-(7-Azaindeno[2,1-*c*]phenanthren-9-ylidene)-propanediamide (XII). Compound **XI**, 0.4 g (1.2 mmol), was dissolved in 5 ml of 50% sulfuric acid, and the solution was heated for 25–30 min on a boiling water bath, cooled, and poured onto ice. The bright yellow precipitate was filtered off, washed with water and aqueous ammonia and dried. Yield 0.43 g (~98%); mp >320°C (from DMF). IR spectrum, ν, cm^{-1}: 1670–1650 (amide I), 1630–1590 (amide II). ^1H NMR spectrum, δ, ppm: 7.50–7.70 m (2H, NH_2), 7.70–7.90 m (2H, NH_2), 7.95–8.30 m (9H, H_{arom}), 8.55–8.70 m (1H, 6-H), 9.51 s (1H, 8-H). Found, %: C 75.72; H 4.26; N 11.00. $C_{23}H_{15}N_3O_2$. Calculated, %: C 75.60; H 4.14; N 11.50.

REFERENCES

1. Lielbriedis, I.E. and Gudrinietse, E.Yu., *Izv. Akad. Nauk Latv. SSR, Ser. Khim. Nauk*, 1969, no. 2, pp. 193–196.
2. Lielbriedis, I.E. and Veretennikova, N.I., *Izv. Akad. Nauk Latv. SSR, Ser. Khim. Nauk*, 1971, no. 4, pp. 453–455.

3. Starkov, A.Ya., Gudrinietse, E.Yu., and Zitsane, D.R., *Khim. Geterotsikl. Soedin.*, 1974, no. 8, pp. 1011–1030.
4. Lielbriedis, I.E., Chirkova, V.V., and Gudrinietse, E.Yu., *Izv. Akad. Nauk Latv. SSR, Ser. Khim. Nauk*, 1968, no. 2, pp. 251–254.
5. Kozlov, N.S. and Nugumanov, Z.Z., *Izv. Akad. Nauk BSSR*, 1968, no. 1, pp. 67–69.
6. Rodionov, V.M., Suvorov, I.N., and Shagalov, L.V., *Dokl. Akad. Nauk SSSR*, 1952, vol. 82, no. 5, pp. 731–737.
7. Smidrkal, J., *Collect. Czech. Chem. Commun.*, 1988, vol. 53, pp. 3186–3187.
8. Watts, W.J., Lawler, C.P., and Knoerzer, T., *Eur. J. Pharmacol.*, 1993, vol. 239, pp. 271–276.
9. Martinez, R., Toscano, R.A., Lingaza, J.E., and Sanchez, N., *J. Heterocycl. Chem.*, 1992, vol. 29, pp. 1385–1389.
10. Kozlov, N.S., *5,6-Benzokhinoliny* (5,6-Benzoquinolines), Minsk: Nauka i Tekhnika, 1979, pp. 70–71.
11. Lielbriedis, I.E., Chirkova, V.V., and Gudrinietse, E.Yu., *Izv. Akad. Nauk Latv. SSR, Ser. Khim. Nauk*, 1969, no. 2, pp. 197–199.
12. Kozlov, N.G. and Gusak, K.N., *Russ. J. Org. Chem.*, 1999, vol. 35, no. 3, pp. 402–414.