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Synthesis of Isoquinoline Derivatives of Quinoxalin-2-one from Pyrrolo[2,1-*a*]isoquinoline-2,3-diones and *o*-Phenylenediamine

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Abstract—Reactions of 5,5-dialkyl-2,3,4,5-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-diones with *o*-phenylenediamine in the presence of a catalytic amount of hydrogen chloride or *p*-toluenesulfonic acid involved opening of the pyrrole ring with formation of 3-(3,3-dialkyl-1,2,3,4-tetrahydroisoquinolin-1-ylidenemethyl)quinoxalin-2(1*H*)-ones. The presence of an enamine fragment in the products was confirmed by reaction with oxalyl chloride.

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It is known [1] that the direction of reactions of fused dihydropyrrolediones with N-centered nucleophiles depends on both substrate and nucleophile nature and reaction conditions. For example, pyrrolo[2,1-*a*]isoquinoline-2,3-diones react with *o*-phenylenediamine in boiling glacial acetic acid to give fused quinoxaline derivatives [2, 3]. On the other hand, taking into account the data of [1, 4], change of the solvent and catalyst could give rise to a different reaction pathway. In particular, spiro-fused imidazoles [4] and other heterocyclic system having two nitrogen atoms may be formed. The goal of the present work was to study the structure of products formed in the reaction of pyrrolo[2,1-*a*]isoquinolin-2,3-diones **I** and **III** with *o*-phenylenediamine in the presence of hydrogen chloride and *p*-toluenesulfonic acid as catalyst.

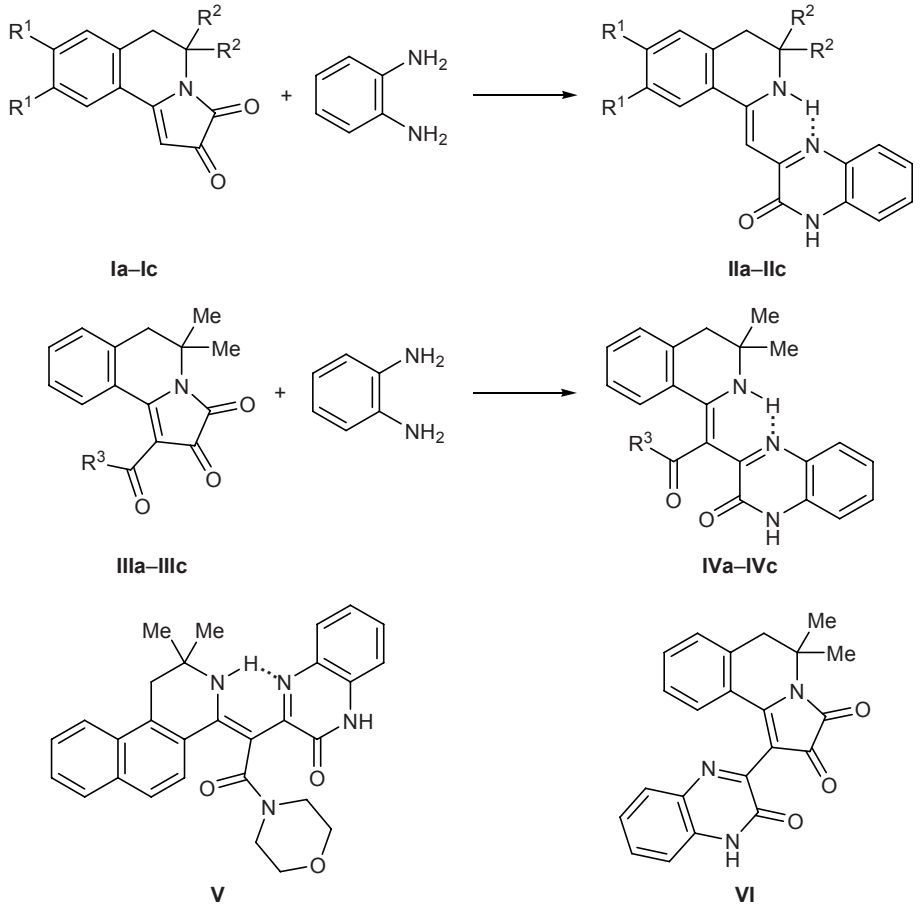
We have found that no reaction occurs between compounds **Ia**–**Ic** and *o*-phenylenediamine on heating in propan-1-ol in the absence of a catalyst (TLC). In the presence of a catalytic amount of hydrogen chloride or *p*-toluenesulfonic acid, the reaction direction was different from that observed in glacial acetic acid: in this case, quinoxalin-2-ones **IIa**–**IIc** were formed instead of fused quinoxaline derivatives (Scheme 1). Amides **IIIa**–**IIIc** reacted with *o*-phenylenediamine in a similar way to produce enamino amides **IVa**–**IVc**. The corresponding benzo[*f*]isoquinoline derivative gave rise to amide **V**.

The enamine structure of the products was confirmed by annelation of pyrrole ring by the action of oxalyl chloride. Thus treatment of compound **IIa** with oxalyl chloride resulted in the formation of bright red fused heterocyclic compound **VI**.

Compounds **IIa**–**IIc**, **IVa**–**IVc**, and **V** were isolated as yellow crystalline substances. Their structure was confirmed by the IR and ^{1}H NMR data. The IR spectra of these compounds contained absorption bands due to stretching vibrations of the carbonyl (1690–1700 cm^{-1}) and NH groups (3320–3340 cm^{-1}) in the quinoxalinone fragment. In addition, amides **IVa**–**IVc** displayed amide carbonyl absorption at 1670–1680 cm^{-1}, and the band in the region 3100–3150 cm^{-1} was assigned to the isoquinoline NH group involved in intramolecular hydrogen bond. In the IR spectrum of compound **VI** absorption bands belonging to the lactam and ketone carbonyl groups were present (1750 and 1705 cm^{-1}, respectively) [5].

In the ^{1}H NMR spectra of quinoxalinones **IIa**–**IIc**, signals from protons in two methyl groups in position *3* of the isoquinoline ring appeared as a singlet, indicating magnetic equivalence of these protons. On the other hand, amides **IVa**–**IVc** and **V** displayed two

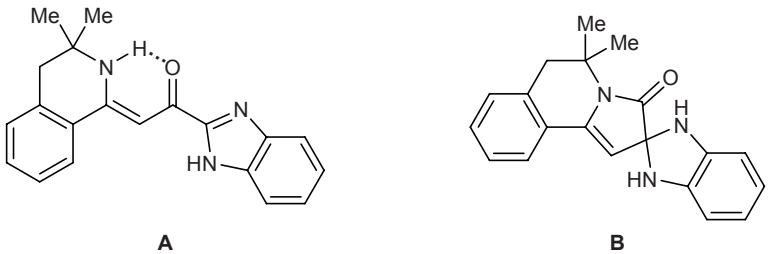
Scheme 1.



I, **II**, R^1 = H (**a**, **c**), MeO (**b**); R^2 = Me (**a**, **b**); R^2R^2 = $(CH_2)_5$ (**c**); **III**, **IV**, R^3 = morpholino (**a**), piperidino (**b**), $(CH_2)_6NH$ (**c**).

singlets from the methyl protons with a difference Δδ of about 0.5 ppm; in addition, signals from the methylene protons on C^4 were split. A probable reason is higher asymmetry of the molecule due to the presence of an amide fragment. The NH protons resonated as singlets which shifted downfield upon addition of trifluoroacetic acid. The downfield position of all NH signals suggests participation of the NH protons in intramolecular hydrogen bonding. The difference in the chemical shifts of the NH protons should be noted: the $\Delta\delta_{NH}$ value for compounds **IIa** and **IIc** is fairly small (0.2–0.3 ppm), while in the spectrum of compound **IIb** it reaches 2.23 ppm, indicating the ability of methoxy groups to be involved in direct polar conjugation. The difference $\Delta\delta_{NH}$ in the spectra of amides **IVa**–**IVc** and **V** varies from 1.67 to 2.13 ppm. Here, the electron-withdrawing amide group increases the acidity of the NH groups. However, analysis of the spectra of compounds **IIa**–**IIc**, **IVa**–**IVc**, and **V** did not allow us to rule out two more possible structures, namely benzimidazole and spirobenzimidazole derivatives like **A** and **B** (for **IIa**).

Structures **IIa**, **A**, and **B** are isomeric; therefore, it is difficult to distinguish them by mass spectrometry,



and reliable assignment is possible only on the basis of X-ray diffraction data. X-Ray analysis of a single crystal of compound **IIa** showed (Figs. 1, 2) that the quinoxalinone fragment in its molecule is planar. The structure is stabilized by intramolecular hydrogen bond $N^3–H^3\cdots N^2$. The six-membered H-chelate ring is coplanar to the quinoxaline fragment. The double $C^3=C^4$ bond (1.383 Å) is appreciably longer, while the single $C^2–C^3$ bond (1.404 Å) is shorter, than the corresponding standard bonds, indicating essential π-conjugation in the tricyclic fragment; presumably, this conjugation is responsible for the dark yellow color of crystals of **IIa**. The N^3 and C^{12} atoms of the tetrahydropyridine fragment (Fig. 1) deviate from the plane of the benzene ring fused thereto (including the C^4 and C^{11} atoms) in the same direction by 0.383 and 0.871 Å, respectively. Orientation of the benzene ring with respect to the tricyclic fragment is characterized by the torsion angle $C^3C^4C^5C^6$ equal to 21.9°. Molecules **IIa** in crystal are linked through fairly strong intermolecular hydrogen bonds like $N–H^1\cdots O$ (2.813 Å) to form centrosymmetric dimers (Fig. 2). The symmetry-related tricyclic fragments lie in one plane, so that the crystal structure is characterized by a planar system consisting of seven rings.

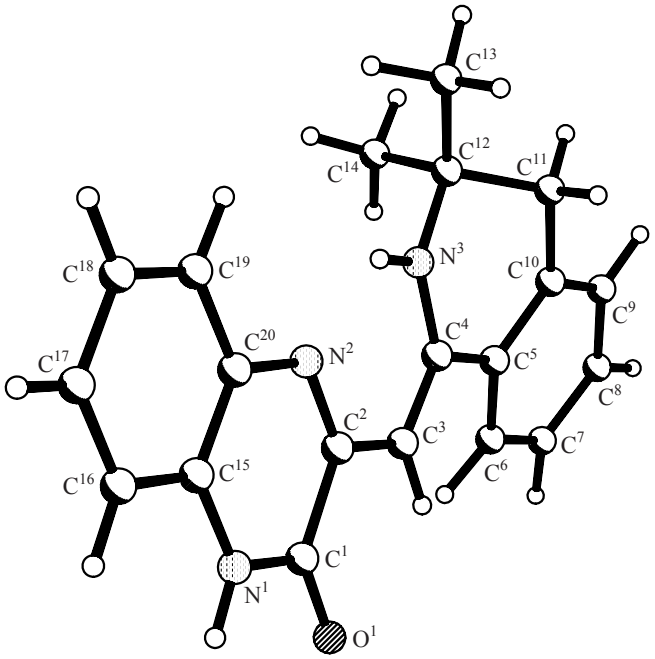


Fig. 1. Structure of the molecule of 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidenemethyl)quinoxalin-2(1*H*)-one (**IIa**) according to the X-ray diffraction data.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker 300 instrument (300 MHz) in DMSO-d_6 (compounds **IIc** and **VI**) or $CDCl_3$ (all other compounds) using hexamethyldisiloxane (δ 0.05 ppm) as internal reference.

Pyramidal crystals of compound **IIa** suitable for X-ray analysis were obtained by slow crystallization from alcohol. Monoclinic crystal system; $C_{20}H_{19}N_3O$; unit cell parameters: a = 12.531(3), b = 10.703(2), c = 12.855(3) Å; β = 106.60(3)°; V = 1652.2(6) Å^3; M 317.38; d_{calc} = 1.276 g/cm^3. A set of experimental reflection intensities was measured on a KM-4 automatic four-circle diffractometer with χ-geometry (monochromatized MoK_α irradiation, ω/2Θ scanning, 2Θ ≤ 52.1%). Total of 3021 independent reflections were measured. No correction for absorption was introduced (μ = 0.081 mm^{-1}). The structure was solved by the direct method using SIR92 program [6], followed by calculation of electron density maps. The positions of hydrogen atoms in the methyl groups and aromatic rings were set on the basis of geometry considerations, while the other hydrogen atoms were visualized from the difference syntheses of electron density. The positions of non-hydrogen atoms were refined by the full-matrix least-squares procedure in anisotropic approximation using SHELXL-97 software package [7]; the final divergence factors were R_1 = 0.0416, wR_2 = 0.1232 from 2895 reflections with $I \geq 2\sigma(I)$ and R_1 = 0.0803, wR_2 = 0.1530 from all 3021 reflections; goodness of fit 0.566.

The purity of the products was checked by TLC on Silufol UV-254 plates using acetone–propan-2-ol–chloroform (1:3:6) as eluent; spots of colorless substances were detected by treatment with iodine vapor.

Compounds **IIa**, **IVa**, and **IVb** were recrystallized from acetonitrile, compound **IIb**, from cyclohexane, and the others, from propan-2-ol. The initial compounds were synthesized according to the procedures described in [2, 8].

3-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidenemethyl)quinoxalin-2(1*H*)-one (IIa). A mixture of 2.27 g (0.01 mol) of compound **Ia** and 1.62 g (0.015 mol) of *o*-phenylenediamine in 20 ml of propan-2-ol was heated to the boiling point, and either 2–3 mg of *p*-toluenesulfonic acid was added or dry hydrogen chloride was passed through the mixture until *o*-phenylenediamine hydrochloride began to separate. The mixture was heated under reflux for 15–30 min in the presence of *p*-toluenesulfonic acid or for 1–1.5 h in

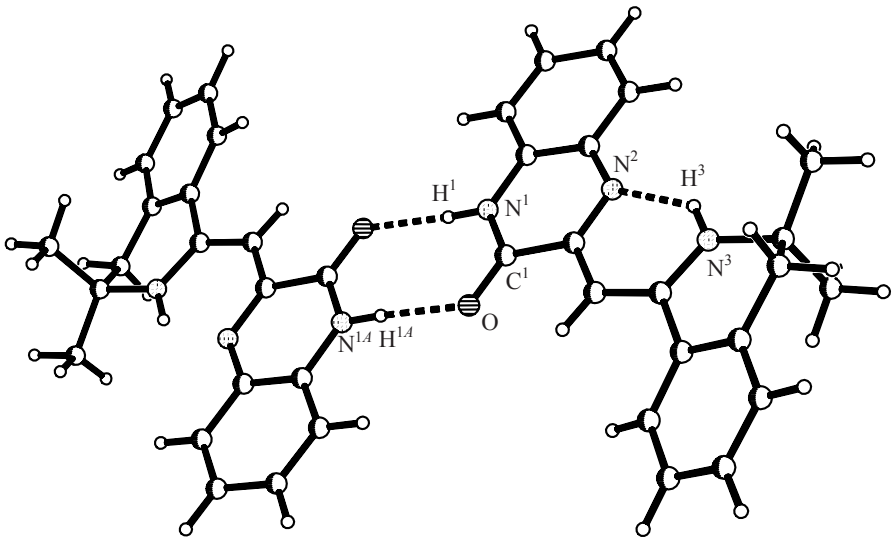


Fig. 2. Structure of centrosymmetric H-bonded dimer formed by molecules **IIa** in crystal.

the presence of hydrogen chloride (TLC), and it changed from red to yellow. The mixture was then cooled to 20°C and diluted with water, and the precipitate was filtered off, dried, and recrystallized from acetonitrile. Yield 1.2 g (85%) (TsOH), 0.85 g (61%) (HCl), dark yellow crystals, mp 162– 164°C. IR spectrum, ν, cm^{-1}: 1690 (C=O); 3100, 3320 (NH). ^{1}H NMR spectrum, δ, ppm: 1.39 s (6H, CH_3), 2.87 s (2H, 4-H), 6.55 s (1H, CH=), 7.10–7.82 m (8H, H_{arom}), 11.34 s and 11.65 s (1H each, NH). Found, %: C 75.57; H 5.87; N 13.32. $C_{20}H_{19}N_3O$. Calculated, %: C 75.68; H 6.03; N 13.24.

Compounds **IIb**, **IIc**, **IVa**–**IVc**, and **V** were synthesized in a similar way.

3-(6,7-Dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidenemethyl)quinoxalin-2(1*H*)-one (IIb) was synthesized from 2.88 g (0.01 mol) of compound **Ib** using *p*-toluenesulfonic acid as catalyst (no reaction occurred in the presence of HCl). Yield 1.3 g (81%), light green crystals, mp 110–112°C. IR spectrum, ν, cm^{-1}: 1700 (C=O); 3100, 3330 (NH). ^{1}H NMR spectrum, δ, ppm: 1.40 s (6H, CH_3), 3.06 s (2H, 4-H), 3.88 s and 3.90 s (3H each, CH_3O), 6.57 s (1H, CH=), 6.69 s (1H, 5-H), 6.87 s (1H, 8-H), 7.17–8.01 m (4H, H_{arom}), 9.52 s and 11.85 s (1H each, NH). Found, %: C 69.97; H 6.08; N 11.24. $C_{22}H_{23}N_3O_3$. Calculated, %: C 70.0; H 6.14; N 11.13.

3-(1′,2′,3′,4′-Tetrahydrospiro[cyclohexane-1,3′-isoquinolin]-1′-ylidenemethyl]quinoxalin-2(1*H*)-one (IIc) was synthesized from 2.67 g (0.01 mol) of compound **Ic**. Yield 1.1 g (75%) (TsOH), 0.68 g (47%) (HCl), light yellow crystals, mp 210–212°C. IR spectrum, ν, cm^{-1}: 1700 (C=O); 3150, 3320 (NH). ^{1}H NMR spectrum, δ, ppm: 1.31–1.79 m (10H, CH_2), 2.89 s (2H, 4-H), 6.40 s (1H, CH=), 7.09–7.86 m (8H, H_{arom}), 11.58 s and 11.81 s (1H each, NH). Found, %: C 77.19; H 6.34; N 11.87. $C_{23}H_{23}N_3O$. Calculated, %: C 77.28; H 6.48; N 11.75.

3-[1-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-2-morpholino-2-oxoethyl]quinoxalin-2(1*H*)-one (IVa) was synthesized from 3.40 g (0.01 mol) of compound **IIIa**. Yield 1.75 (80%) (TsOH), 1.46 g (67%) (HCl), light yellow crystals, mp 195–196°C. IR spectrum, ν, cm^{-1}: 1670, 1690 (C=O); 3150, 3340 (NH). ^{1}H NMR spectrum, δ, ppm: 1.06 s and 1.54 s (3H each, CH_3), 2.70 s and 2.78 s (1H each, 4-H), 3.34–3.69 m (8H, NCH_2CH_2O), 7.14–8.0 m (8H, H_{arom}), 11.10 s and 12.85 s (1H each, NH). Found, %: C 69.64; H 5.92; N 13.07. $C_{25}H_{26}N_4O_3$. Calculated, %: C 69.74; H 6.08; N 13.01.

3-[1-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-2-oxo-2-piperidinoethyl]quinoxalin-2(1*H*)-one (IVb) was synthesized from 3.38 g (0.01 mol) of compound **IIIb**. Yield 1.68 g (70%) (TsOH), light yellow crystals, mp 205°C (decomp.). IR spectrum, ν, cm^{-1}: 1670, 1700 (C=O); 3150, 3340 (NH). ^{1}H NMR spectrum, δ, ppm: 1.07 s and 1.54 s (3H each, CH_3), 1.23–1.65 m (6H, CH_2), 2.70 s and 2.80 s (1H each, 4-H), 3.13–3.75 m (4H, CH_2N), 7.12–8.03 m (8H, H_{arom}), 10.85 s and 12.98 s (1H each, NH). Found, %: C 72.75; H 6.45; N 12.94. $C_{26}H_{28}N_4O_2$. Calculated, %: C 72.87; H 6.58; N 13.01.

3-[2-(Azepan-1-yl)-1-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-2-oxoethyl]quinoxalin-

2(1*H*)-one (IVc) was synthesized from 3.52 g (0.01 mol) of compound **IIIc**. Yield 1.72 g (82%) (TsOH), dark yellow crystals, mp 197–198°C. IR spectrum, ν, cm^{-1}: 1670, 1690 (C=O); 3150, 3340 (NH). ^1H NMR spectrum, δ, ppm: 1.06 s and 1.55 s (3H each, CH_3), 1.23–1.75 m (8H, CH_2), 2.72 s and 2.80 s (1H each, 4-H), 3.15–3.75 m (4H, CH_2N), 7.0–8.01 m (8H, H_{arom}), 11.0 s and 13.12 s (1H each, NH). Found, %: C 73.19; H 6.68; N 12.72. $C_{27}H_{30}N_4O_2$. Calculated, %: C 73.27; H 6.83; N 12.60.

3-[1-(2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]-isoquinolin-4-ylidene)-2-morpholino-2-oxoethyl]-quinoxalin-2(1*H*)-one (V) was synthesized from 3.90 g (0.01 mol) of 5,5-dimethyl-2,3,5,6-tetrahydrobenzo[*f*]pyrrolo[2,1-*a*]isoquinoline-2,3-dione. Yield 1.94 g (76%) (TsOH), dark yellow crystals, mp 160°C (decomp.). IR spectrum, ν, cm^{-1}: 1680, 1690 (C=O); 3120, 3380 (NH). ^1H NMR spectrum, δ, ppm: 1.06 s and 1.64 s (3H each, CH_3), 3.18 s and 3.33 s (1H each, 4-H), 3.39–3.78 m (8H, OCH_2CH_2N), 7.17–7.70 m (10H, H_{arom}), 11.0 s and 13.12 s (1H each, NH). Found, %: C 72.31; H 5.72; N 11.77. $C_{29}H_{28}N_4O_3$. Calculated, %: C 72.47; H 5.87; N 11.65.

5,5-Dimethyl-1-(3-oxo-3,4-dihydroquinoxalin-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2,3-dione (VI). Triethylamine, 1.4 ml (0.01 mol), and oxalyl chloride, 0.43 ml (0.005 mol), were added in succession at 20°C to a mixture of 1.58 g (0.005 mol) of compound **IIa** in 150 ml of anhydrous diethyl ether. After 1 h, the precipitate was filtered off, thoroughly washed with water to remove triethylamine hydrochloride, dried, and recrystallized from propan-2-ol. Yield 0.72 g (60%), dark yellow crystals, mp 255–256°C. IR spectrum, ν, cm^{-1}: 1690, 1705, 1750 (C=O); 3330 (NH). ^1H NMR spectrum, δ, ppm: 1.51 s (6H, CH_3), 3.08 s (2H, 4-H), 7.18–7.71 m (8H, H_{arom}), 12.40 s (1H, NH). Found, %: C 71.62; H 3.70; N 11.52. $C_{22}H_{17}N_3O_3$. Calculated, %: C 71.72; H 3.83; N 11.40.

REFERENCES

1. Mashevskaya, I.V. and Maslivets, A.N., *Khim. Geterotsikl. Soedin*., 2006, p. 3.
2. Mikhailovskii, A.G., Shklyaev, V.S., and Aleksandrov, B.B., *Khim. Geterotsikl. Soedin*., 1990, p. 808.
3. Polygalova, N.N., Mikhailovskii, A.G., and Vakhrin, M.I., *The Chemistry and Biological Activity of Synthetic and Natural Compounds: Nitrogen-Containing Heterocycles*, Kartsev, V.G., Ed., Moscow: ICSPF, 2006, vol. 1, p. 402.
4. Ivashchenko, A.V., Drushlyak, A.G., and Titov, V.V., *Khim. Geterotsikl. Soedin*., 1984, p. 667.
5. Maslivets, A.N. and Mashevskaya, I.V., *2,3-Digidro-2,3-pirroldiony* (2,3-Dihydropyrrole-2,3-diones), Perm: Perm. Gos. Univ., 2005, p. 21.
6. Altomare, A., Cascarano, G., Giacovazzo, C., and Gualardi, A.G., *J. Appl. Crystallogr*., 1993, vol. 26, p. 343.
7. Sheldrick, G.M., *SHELX97. Programs for Crystal Structure Analysis*, Göttingen, Germany: Univ. of Göttingen, 1998.
8. Mikhailovskii, A.G. and Shklyaev, V.S., *Khim. Geterotsikl. Soedin*., 1994, p. 946.