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REACTION OF 2,3-DIOXOPYRROLO[2,1-*a*]ISOQUINOLINES WITH BINUCLEOPHILES

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The reaction of 2,3-dioxopyrrolo[2,1-a]isoquinolines with binucleophiles such as 2-amino-4-methylphenol, o-aminothiophenol, and caprolactam hydrazidine proceeds with opening of the dioxopyrroline ring and is accompanied by heterocyclization to give heteroaromatic benzoxazole, benzothiazole, and 1,2,4-triazole systems. Heterocyclization does not occur in the reaction of o-hydroxybenzylamine, o-aminobenzyl alcohol, and the hydrazide of anthranilic acid; the corresponding linear N-benzylamide, benzyl ester, and diacylhydrazide products are formed.

Keywords: *o*-aminobenzyl alcohol, 2-amino-4-methylphenol, *o*-aminothiophenol, N-benzylamide, benzyl ester, anthranilic acid hydrazide, caprolactam hydrazidine, *o*-hydroxybenzylamine, diacyl hydrazide, 5,5-dialkyl-2,3-dioxopyrrolo[2,1-*a*]isoquinolines, benzoxazole, benzothiazole, and 1,2,4-triazole derivatives.

We have already studied the reactions of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with several binucleophiles such as aliphatic diamines [1], *o*-phenylenediamine [2-4], and *o*-aminophenol [5]. These examples show that the reactions of these compounds with binucleophiles may proceed through various pathways, namely, ordinary acylation of the amino group [1], annelation of the heterocycle [2, 4], and heterocyclization with benzoxazole formation [5]. In the present work, we studied the dependence of the structure of the products on the structure of both the binucleophile and the dicarbonyl reagent.

Brief heating of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines **1a**,**c** with 2-amino-4-methylphenol in 2-propanol at reflux gives heterocyclic enamino ketones **2a**,**b**, which contain the benzoxazole residue. The use of *o*-aminothiophenol as the binucleophile in the reaction with dioxopyrrolines **1a-d** leads to benzothiazole derivatives **2c-f**. We have recently shown that dioxopyrroline ring opening occurs in the reaction of pyrroloisoquinoline **1a** with caprolactam hydrazidine to give the bicyclic 1,2,4-triazolo[4,5-*a*]azepine system [6].

When amide **1d** or ester **1e** is used as the starting reagent, the reaction proceeds analogously to give the corresponding amide **3a** and ester **3b**. In the latter case, caprolactam hydrazidine does not attack the ester group. The retention of the ester group provides the potential for further chemical transformations. When a spirocyclopentyl substituent is present in the starting dicarbonyl compound **1c**, annelation of the triazole ring is not observed. This failure may be attributed to the large bulk of the spirocyclopentyl substituent in comparison with two methyl groups. On the other hand, the bulky structure of benzo[*f*]isoquinoline is not a hindrance to annelation of the triazole ring in the formation of morpholide **4**.

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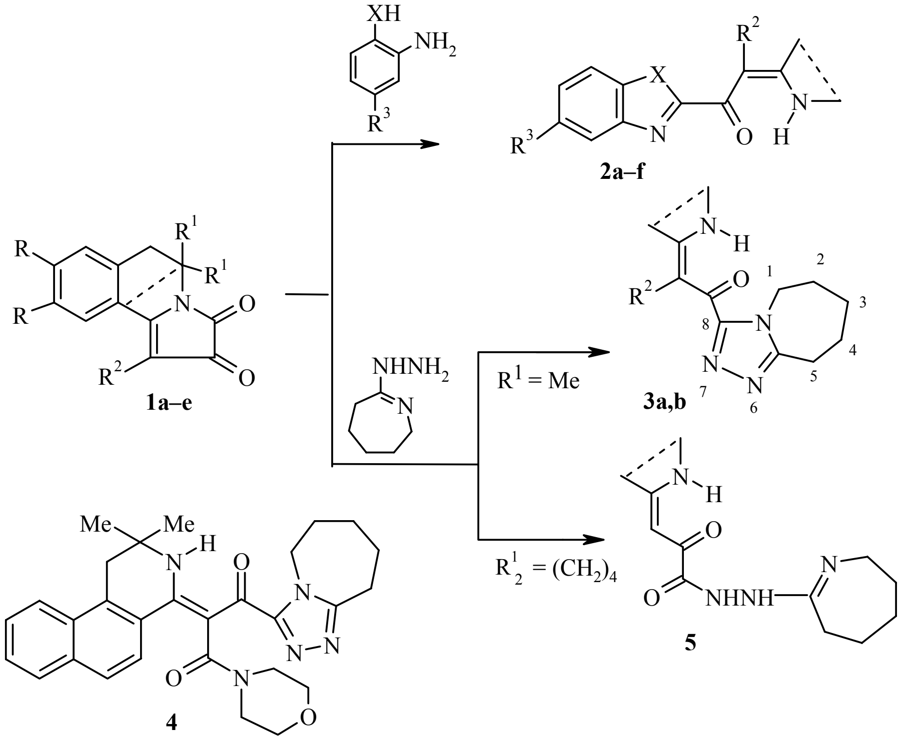
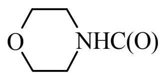
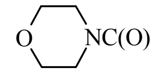
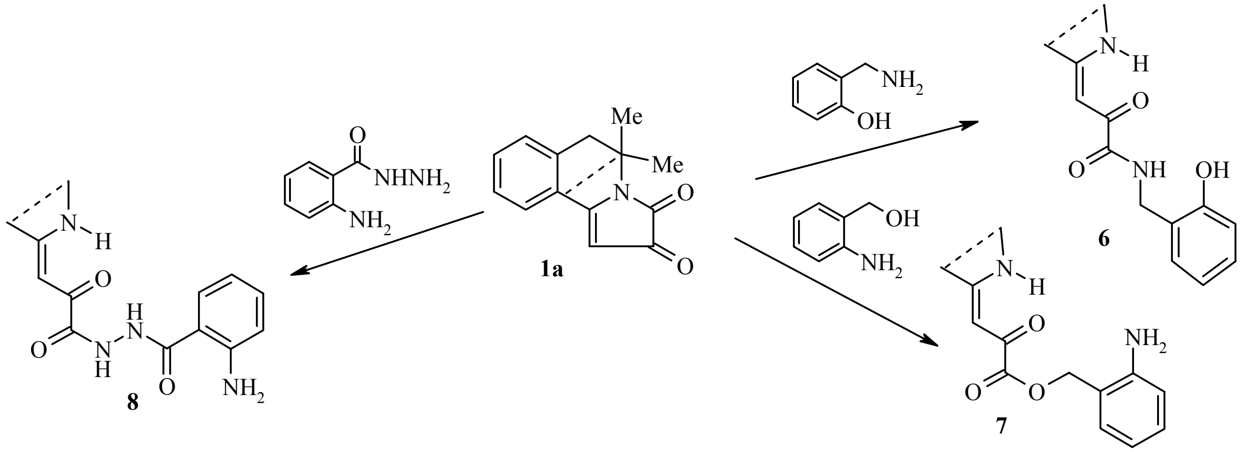
It is readily seen that heteroaromatic systems are formed in these examples of the preparation of compounds **2a-f, 3a,b,** and **4**. On the other hand, the reactions of other binucleophiles, in which the direct formation of an aromatic system is impossible, proceed differently. Thus, the reaction of dioxopyrroline **1** with *o*-hydroxybenzylamine in 2-propanol gives enamino ketoamide **6**. Thin-layer chromatography and the mixed melting point showed that only the starting reagent was recovered in an attempt to achieve heterocyclization of enamino ketoamide **6** by the action of TsOH or AcOH. New reaction products were not obtained from *o*-aminobenzyl alcohol upon simple mixing of this reagent with isoquinoline **1a** in 2-propanol or benzene. The reaction proceeds in benzene in the presence of an equimolar amount of sodium, which is in accord with previous work [7, 8], in which we showed that opening of the dioxopyrroline ring in compound **1a** proceeds readily by the action of alcoholates. Further heating of esters **7** in the presence of TsOH or AcOH does not lead



1 a R = R^2 = H, R^1 = Me; **b** R = MeO, R^1 = Me, R^2 = H, **c** R = R^2 = H, R^1_2 = $(CH_2)_4$;
d R = H, R^1 = Me, R^2 = N-morpholinocarbonyl; **e** R = H, R^1 = Me, R^2 = CO_2Et

Compound	R	R^1_2	R^2	R^3	X
2a	H	Me_2	H	Me	O
2b	H	$(CH_2)_4$	H	Me	O
2c	H	Me_2	H	H	S
2d	MeO	Me_2	H	H	S
2e	H	$(CH_2)_4$	H	H	S
2f	H	Me_2		H	S
3a	H	Me_2			
3b	H	Me_2	CO_2Et		
5	H	$(CH_2)_4$	H		

to change in the structure of this compound. Ring opening in the hydrazide of anthranilic acid also proceeds readily upon heating in 2-propanol at reflux to give N-acylated enaminoketohydrazide **8**. The course of this reaction may be monitored easily according to the color of the solution: the red color of the starting dioxopyrroline turns to yellow.



The enamino ketones obtained are yellow-orange crystalline compounds. Characteristics of the compounds synthesized for the first time are given in Table 1.

The ^{1}H NMR spectra of the products given in Table 2 contain signals for protons of substituents R^3-R^4, the 4-CH_2 group of the tetrahydroisoquinoline ring, aromatic protons of the isoquinoline ring, and protons of the substituents of the isoquinoline side chain. The spectra of ketones **2a-f**, in contrast to the spectra of starting reagents **1a-d**, show multiplets for the aromatic protons of the benzoxazole or benzothiazole rings and singlets

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, % C	H	N	S	mp, °C	Yield, %
2a	$C_{21}H_{20}N_2O_2$	75.7 75.9	6.0 6.1	8.5 8.4		202-204	70
2b	$C_{23}H_{22}N_2O_2$	76.9 77.1	6.1 6.2	7.9 7.8		208-210	61
2c	$C_{20}H_{18}N_2OS$	71.7 71.8	5.3 5.4	8.5 8.4	9.4 9.6	78-80	75
2d	$C_{22}H_{22}N_2O_3S$	66.9 67.0	5.5 5.6	7.2 7.1	8.0 8.1	198-200	85
2e	$C_{22}H_{20}N_2OS$	73.2 73.3	5.5 5.6	7.9 7.8	8.8 8.9	82-84	80
2f	$C_{25}H_{25}N_3O_3S$	67.0 67.1	5.5 5.6	9.5 9.4	7.1 7.2	118-120	43
3a	$C_{25}H_{31}N_5O_3$	66.7 66.8	6.9 7.0	15.7 15.6		118-120	62
3b	$C_{23}H_{28}N_4O_3$	67.7 67.6	7.0 6.9	13.8 13.7		102-104	65
4	$C_{29}H_{33}N_5O_3$	69.6 69.7	6.6 6.7	14.1 14.0		110-112	67
5	$C_{22}H_{28}N_4O_2$	69.3 69.4	7.3 7.4	14.8 14.7		96-98	75
6	$C_{21}H_{22}N_2O_3$	71.9 72.0	6.1 6.3	8.1 8.0		176-178	45
7	$C_{21}H_{22}N_2O_3$	71.8 72.0	6.2 6.3	8.0 8.0		102-104	32
8	$C_{21}H_{22}N_4O_3$	66.5 66.6	5.8 5.9	14.9 14.8		246-248	45

TABLE 2. ^{1}H NMR Spectra of Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)					
	3-CR^{1}R^1	4(2)–CH$_2$, 2H, s	1-HC=, s	Aromatic protons, m	NH cycle, s	Other protons
2a	1.4 (6H, s, 2CH$_3$)	2.7	6.4	7.0-7.8 (7H)	11.6	2.4 (3H, s, 5-CH$_3$-benzoxazolyl)
2b	1.7–2.0 (8H, m, 4CH$_2$)	2.7	6.4	6.8-7.8 (7H)	11.8	2.5 (3H, s, 5-CH$_3$- benzoxazolyl)
2c	1.4 (6H, s, 2CH$_3$)	2.8	5.4	6.4-7.6 (8H)	11.6	—
2d	1.4 (6H, s, 2CH$_3$)	2.8	5.4	6.4-7.5 (6H)	11.6	3.7 (3H, s, CH$_3$O); 3.8 (3H, s, 2CH$_3$O)
2e	1.3–2.2 (8H, m, 4CH$_2$)	2.8	5.4	6.5-7.6 (8H)	11.6	—
2f	1.3 (6H, s, 2CH$_3$)	2.9	—	6.6-7.5 (8H)	11.5	3.2-3.9 (8H, m, 4CH$_2$ morpholine)
3a	1.2 (6H, s, 2CH$_3$)	2.8	—	7.0-7.7 (4H)	12.1	1.4-2.1 (6H, m, 3CH$_2$–C azepane); 2.4-2.6 (2H, m, CH$_2$-C=N azepane); 3.1-3.8 (2H, m, CH$_2$N azepane); 3.2-3.9 (8H, m, 4CH$_2$ morpholine)
3b	1.3 (6H, s, 2CH$_3$)	2.8	—	7.1-7.4 (4H)	8.9	1.4-2.0 (6H, m, 3CH$_2$–C azepane); 2.4-2.5 (2H, m, CH$_2$-C=N azepane); 3.1-3.8 (2H, m, CH$_2$N azepane); 1.0 (3H, t, $C\underline{H}_3CH_2O$); 4.0 (2H, q, $CH_3C\underline{H}_2O$)
4	1.2 (6H, s, 2CH$_3$)	3.1	—	7.4-8.2 (6H)	12.0	1.4-2.0 (6H, m, 3CH$_2$–C azepane); 2.4–2.5 (2H, m, CH$_2$–C=N azepane); 3.2-3.8 (2H, m, CH$_2$N azepane); 3.3-4.0 (8H, m, 4CH$_2$ morpholine)
5	1.5-1.8 (8H, m, 4CH$_2$)	2.9	6.4	7.2-7.4 (6H)	11.8	1.4-2.0 (6H, m, 3CH$_2$–C azepane); 2.4-2.7 (2H, m, CH$_2$–C=N azepane); 3.2-3.8 (2H, m, CH$_2$N azepane); 4.6 (2H, br. s, CONHNH)
6	1.3 (6H, s, 2CH$_3$)	2.9	6.4	6.4-7.8 (8H)	11.5	4.3 (2H, d, $C\underline{H}_2NH$); 8.5 (1H, t, $CH_2N\underline{H}$)
7	1.3 (6H, s, 2CH$_3$)	2.9	6.4	7.0-7.8 (8H)	11.3	3.9 (2H, s, NH$_2$)
8	1.3 (6H, s, 2CH$_3$)	3.0	6.4	6.2-8.0 (8H)	11.6	3.7 (2H, s, NH$_2$–Ar); 10.5 (2H, br. s, 2CONH)

for the NH groups of the isoquinoline ring at 11.5-11.6 ppm. The spectra of compounds **3a**,**b** also have singlets for the ring NH groups at 12.1 and 8.9 ppm, which also supports the proposed enamino ketone structure. The spectrum of morpholide **4** is similar. The spectrum of hydrazide **5** has a broad singlet for the C(O)NHNH hydrazide group at 4.6 ppm, corresponding in intensity to two NH group protons, and a singlet for the ring NH group at 11.8 ppm. The spectrum of phenol **6** has a singlet for the phenol OH group at 9.5 ppm. The spectrum of amine **7** has a singlet for the protons of the free NH_2 group at 3.9 ppm and of the ring NH group at 11.3 ppm. The spectrum of enaminoketohydrazide **8** has a broad singlet for the CONHNH hydrazide fragment at 10.5 ppm and singlet for the ring NH group at 11.6 ppm, which also supports the indicated linear structure.

The IR spectra were taken in chloroform for solutions with $c = 0.1$ mol/liter. All the compounds obtained are enamines. The presence of broad long-wavelength bands for the stretching vibrations of the ring NH groups at 3040-3200 cm^{-1} and enamino ketone carbonyl at 1600-1620 cm^{-1}, which corresponds to an H-chelate form, is characteristic for these compounds. The carbonyl group of tertiary amines **2f, 3a,** and **4** give a band at 1640 cm^{-1}, while the ester group in the spectrum of compound **3b** gives a band at 1725 cm^{-1} and the hydrazide group carbonyl of hydrazides **5** and **8** gives a band in the vicinity of 1700 cm^{-1}. The spectra of compounds **6-8** also have bands for the stretching vibrations of the phenol OH groups at 3320 cm^{-1}, the NH amide group at 3300 cm^{-1}, the hydrazide NH group at 3340 cm^{-1}, and the free NH_2 groups at 3350-3400 cm^{-1}.

The mass spectra of compounds **2-7** contain molecular peaks, whose intensity ranges from 12% for compound **2** to 100% for ketones **2a**,**b**. The spectra of all these compounds with the exception of compounds **2a,b, 3a,b,** and **4** have peaks corresponding to the isoquinolinomethylidenocarbonyl fragment (200 for, 3,3-dimethyl-, 226 for 3-spirocyclopentyl-, and 260 for 3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline), whose intensity is 100%.

The mass spectrum of ester **7** contains a molecular ion peak (350 $[M]^+$ 33%) as well as the indicated peak at 200 (100%), corresponding to loss of the $CH_2C_6H_4NH_2$ group (65%). The spectrum of hydrazide **8** also has a the peak at 200 (6%) as well as peaks for the $C_6H_4(NH_2)CONH$ group at 135 (5%), $COC_6H_4NH_2$ group at 120 (98%), and $C_6H_4NH_2$ group at 92 (28%).

EXPERIMENTAL

The ^1H NMR spectra were taken on a Tesla BS-567A spectrometer at 100 MHz in DMSO-d_6 for compounds **6-8** and $CDCl_3$ for the other compounds with HMDS as the internal standard (0.05 ppm). The IR spectra were taken on a Specord M-80 spectrometer. The electron impact mass spectra were taken on a MAT-311 mass spectrometer at 70 eV. The purity of the compounds was checked by thin-layer chromatography on Silufol UV-254 plates using 1:3:6 acetone–ethanol–chloroform as the eluent and development by UV light and iodine vapor. Products **1a,b, 2d, 3b, 6,** and **8** were recrystallized from acetonitrile. The other compounds were recrystallized from hexane.

The preparations of starting reagents **1a-e** and benzo[*f*]isoquinoline for the synthesis of compound **4** were described in our previous work [3, 9].

1-(5-Methyl-1,5-benzoxazol-2-ylcarbonylmethylidene)-3,3-(R^1)$_2$-1,2,3,4-tetrahydroisoquinolines 2a,b. A solution of a mixture of the dioxopyrroline **1a**,**b** (10 mmol) and 2-amino-4-methylphenol (1.64 g, 15 mmol) in 2-propanol (30 mmol) was heated at reflux for 1 h with monitoring by thin-layer chromatography. The color of the solution turned from red to yellow. The solution was cooled to 20°C and 100 ml water was added. The precipitate was filtered off, dried, and recrystallized.

1-(1,3-Benzothiazol-2-ylcarbonylmethylidene)-6,7-(R^1)$_2$-3,3-(R^2)$_2$-1,2,3,4-tetrahydroisoquinolines 2c-e (General Method). A solution of a mixture of the corresponding starting reagent **1a-c** (10 mmol) and 2-aminothiophenol (1.85 g, 10 mmol) in glacial acetic acid (10 ml) was heated at reflux for 20 min with monitoring by thin-layer chromatography and cooled to 20°C. Then, water (100 ml) was added. The precipitate was filtered off, washed with ammonium hydroxide and, then, water, dried, and recrystallized.

Morpholide of 4-(1,3-Benzothiazol-2-yl)-2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-3,4-dioxobutanoic Acid (2f). A solution of a mixture of dioxopyrroline **1d** (3.4 g, 10 mmol) and 2-aminothiophenol (1.85 g, 15 mmol) in 2-propanol (30 ml) with one or two little crystals of *p*-TsOH was heated at reflux for 1 h with monitoring by thin-layer chromatography. The product was separated analogously to the procedure for **2c-e**.

Morpholide (3a) and Ethyl Ester of 2-(3,3-Dimethyl-1,2,3,4-tetra-hydroisoquinolin-1-ylidene)-3-oxo-3-(1,2,4-triazolo[4,5-*a*]azepan-8-yl)propanoic Acid (3b), Morpholide of 2-(2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-ylidene)-3-oxo-3-(1,2,4-triazolo[4,5-*a*]azepan-8-yl)propanoic Acid (4), and N-(3,4,5,6-Tetrahydro-2H-azepin-2-yl)hydrazide of 2-Oxo-3-(3,3-tetramethylene-1,2,3,4-tetrahydroisoquinolin-1-ylidene)propanoic Acid (5) (General Method). 2-Hydrazino-3,4,5,6-tetrahydro-2H-azepine (caprolactam hydrazidine) (1.91 g, 15 mmol) was added to a solution of the corresponding dioxopyrroline (10 mmol) in benzene (20 ml). Upon heating to 60-70°C, the red color of the mixture disappeared over 5 min. The addition of hexane (50 ml) leads to formation of a yellow precipitate, which was filtered off, dried, and recrystallized.

2-Hydroxybenzylamide of 3-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-2-oxopropanoic Acid (6) and N-(2-Aminobenzoyl)hydrazide of 3-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene) 2-oxopropanoic Acid (8). A mixture of dioxopyrroline **1a** (2.27 g, 10 mmol) and *o*-hydroxybenzylamine (1.84 g, 15 mmol) or anthranilic acid hydrazide (2.20 g, 15 mmol) in 2-propanol (50 ml) was heated at reflux for 10 min (for compound **6**) or 90 min (for hydrazide **8**). The solution color turned from red to yellow. At the end of the reaction as indicated by thin-layer chromatographic monitoring, the solution was cooled to 20°C and diluted by adding water (100 ml). The precipitate formed was filtered off, dried, and recrystallized.

2-Aminobenzyl 2-Oxo-3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)propanoate (7). Metallic sodium (0.28 g, 12 mmol) was added to *o*-aminobenzyl alcohol (0.15 g, 12 mmol) in benzene (50 ml). Dioxopyrroline **1a** (2.27 g, 10 mmol) was added to the sodium alcoholate suspension obtained. Upon heating at reflux for 10 min, the mixture turned yellow. The solution was cooled to 20°C and hexane (100 ml) was added. The precipitate was filtered off, thoroughly washed with water, dried, and recrystallized.

REFERENCES

1. N. N. Polygalova and A. G. Mikhailovskii, *Khim. Geterotsikl. Soedin.*, 1383 (2005). [*Chem. Heterocycl. Comp.*, **41**, 1178 (2005)].
2. A. G. Mikhailovskii and V. S. Shklyaev, *Khim. Geterotsikl. Soedin.*, 946 (1994). [*Chem. Heterocycl. Comp.*, **30**, 818 (1994)].
3. A. G. Mikhailovskii, V. S. Shklyaev, and B. B. Aleksandrov, *Khim. Geterotsikl. Soedin.*, 808 (1990). [*Chem. Heterocycl. Comp.*, **26**, 674 (1990)].
4. N. N. Polygalova, A. G. Mikhailovskii, E. V. Vikhareva, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 1068 (2007). [*Chem. Heterocycl. Comp.*, **43**, 900 (2007)].
5. O. V. Surikova, A. G. Mikhailovskii, N. N. Polygalova, P. G. Neifel'd, and M. I. Vakhrin, *Zh. Org. Khim.*, **43**, 1416 (2007).
6. O. V. Surikova, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 298 (2008). [*Chem. Heterocycl. Comp.*, **44**, 231 (2008)].
7. A. G. Mikhailovskii and V. S. Shklyaev, *Khim. Geterotsikl. Soedin.*, 1697 (1995). [*Chem. Heterocycl. Comp.*, **31**, 1475 (1995)].
8. A. G. Mikhailovskii, *Khim. Geterotsikl. Soedin.*, 685 (1996). [*Chem. Heterocycl. Comp.*, **32**, 590 (1996)].
9. V. S. Shklyaev, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 963 (1987). [*Chem. Heterocycl. Comp.*, **23**, 790 (1987)].