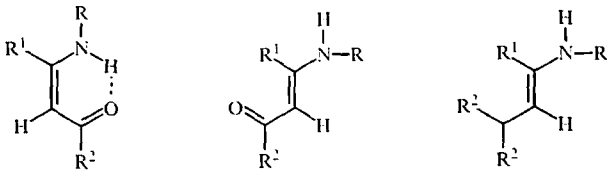
Chemistry of Heterocyclic Compounds, Vol. 35, No. 10, 1999

cis–trans ISOMERISM OF INDOLYL-ENAMINOCARBONYL COMPOUNDS

S. A. Yamashkin and M. A. Yurovskaya

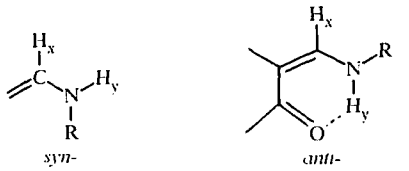
Analysis of the PMR spectra of a series of indolylenaminocarbonyl compounds: 3-(indolylamino)vinyl ketones, β-indolylaminocrotonates, N-(indolyl)aminomethylenemalonates have been performed. We have established that in the solvents used to record the spectra, the studied enamines exist in the cis-S-cis form.

Cis–trans isomerism of conjugated enamines has been widely studied [1-5]. The compounds under consideration can exist in the *S-cis* or *S-trans* form.



cis-S-*cis* *trans*-S-*cis* *trans*-S-*trans*

Usually the *cis* form is the most stable in nonpolar solvents, while the *trans* structure is the most stable in associating or polar media. But most authors agree that monosubstituted enamines tend toward preferential existence in the *cis* forms, due to the possibility of formation of a chelate ring as a result of hydrogen bonding. Interconversion of the *cis–trans* forms has been observed with a change in solvent and temperature. The most effective method of studying the structure of enamines, especially aromatic enamines, is PMR spectroscopy. For compounds containing at least one proton on the nitrogen atom, the test for the isomer structure is the chemical shift of the NH proton, which has characteristic values for the different isomers. For example, in a mixture of isomeric crotonates, the signal from the NH proton for the *cis*-chelated form is observed in the region of 7.7-8.9 ppm; for the *trans* form, in the 5.3-5.6 ppm region; in β-alkylaminovinyl ketones (aldehydes), in the region of 9.7-14 ppm (*cis*) and 5.0-6.75 ppm (*trans*). For enamines with R^1 = H, the chelate-bonded *cis-S-cis* form is responsible for the *anti* arrangement of the H_xH_y protons and the high values of the spin–spin coupling constant ($J_{xy(anti)}$ ~ 13 Hz). In *S-trans* systems, the H_x and H_y protons are situated in the *syn* position, and the magnitude of this constant is 7-8 Hz.



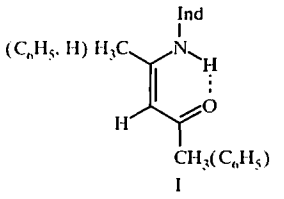
syn- *anti*-

Mordovian State Pedagogical Institute, Saransk 430007, Russia; e-mail: mgpi@si.moris.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1336-1344, October, 1999. Original article submitted November 16, 1998.

 0009-3122/99/3510-1156$22.00

The J_{xy} constant increases as the substituent R becomes more bulky.

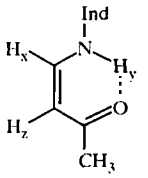
It is difficult to study *cis–trans* isomerism of the indolylenamines we have obtained because of their low solubility in nonpolar solvents. Most of the PMR spectra for enamines I, II, and III were taken in DMSO and acetone, and CCl_4 was used as the solvent only for some individual compounds. Nevertheless, the PMR data (Tables 1-3) make it possible to decide on the specific form of the enaminocarbonyl compound. Thus for 3-(indolylamino)vinyl ketones I, depending on the substituents, the chemical shifts of the NH proton fluctuate within the range of 12.07-13.50 ppm, and the chemical shift of this proton in the spectra of phenyl-substituted enamino ketones is always higher than for enamines containing alkyl groups. Occurrence of alkyl and methoxy group on the benzene ring of indole insignificantly shift the signal from the NH proton upfield. We do not observe a substantial effect of the solvent nature on the position of the signal from the NH proton. In the PMR spectra taken in CCl_4, only a weak downfield shift of the signal under discussion is observed. Comparing our results with literature data, we can conclude that according to the PMR spectral data, indolylaminovinyl ketones Ia-x (Table 1) exist in the *cis*-chelated form.



I

Polar solvents (DMSO, acetone) do not promote isomerization of the title compounds, at least at room temperature.

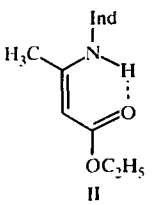
For compound Ie (Table 1), in addition to the chemical shift of the signal from the NH proton, evidence for *cis* arrangement of substituents comes from the value of J_{xy} (16 Hz), which suggests an *anti* arrangement of protons H_x and H_y.



Ie

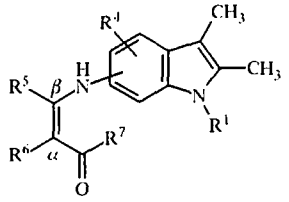
Furthermore, J_{xy} (8 Hz) supports *cis* arrangement of protons H_x and H_z relative to each other, and consequently a *trans* arrangement relative to the acetyl group.

For 3-(1H-indolylamino)vinyl ketones, in the PMR spectra a signal from the indole NH proton in the region of 10-11 ppm, i.e., upfield from the amine NH is observed. The signals from the indole NH protons are assigned based on the absence of signals in the 10-11 ppm region for enamines obtained on the basis of the corresponding N-methyleneindoles. Thus for all the indolylaminovinyl ketones, δNH(amine) is always 1-2 ppm greater than δNH(indole). In contrast, in the PMR spectra (Table 2) of indolylamino crotonates II, the signal from the NH(amine) proton is shifted downfield and, depending on the position on the benzene ring and the nature of the substituents, appears in the 8.46-10.10 ppm region, while the position of the signal from the indole NH proton is unchanged. As already noted, such chemical shifts of the enamine NH proton are typical for amino crotonates possessing the *cis* structure.



II

TABLE 1. PMR Spectral Characteristics of Enamino Ketones I



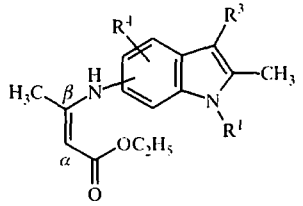
Compound	Position of NH	R^1	R^4	R^5	R^6	R^7	Chemical shifts, δ ppm*, spin–spin coupling constant, Hz										
							indole moiety							enamine moiety			
							1-H	2-H	3-H	4-H	5-H	6-H	7-H	NH	R^6	R^5	R^7
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	19
Ia	5	H	H	CH_3	H	CH_3	10.45 s	—	—	6.98 d J_{46} = 2	—	6.62 J_{76} = 8	7.06 d	12.46 s	5.00 s	—	—
Ib	5	H	H	C_6H_5	H	C_6H_5	10.59 s	—	—	6.85 d J_{46} = 2	—	6.48 q J_{76} = 8	7.00 d	13.09 s	6.07 s	7.60 m $2C_6H_5$	
Ic	5	CH_3	H	C_6H_5	H	C_6H_5	3.48 s CH_3	2.20 s CH_3	2.09 s CH_3	7.20 m				13.02 s	5.85 s	7.20 m $2C_6H_5$	
Id	5	H	H	H	H	CH_3	11.20 s	2.17 s CH_3	2.13 s CH_3	7.00 m				12.17 d $J_{NH\beta}$ = 16	5.18 d	7.40 q $J_{\alpha\beta}$ = 8	1.96 CH_3
Ie	5	H	6-OCH_3	CH_3	H	CH_3	10.41 s	2.30 CH_3	2.13 CH_3	7.13 s	—	3.79 s OCH_3	6.89 s	12.07 s	5.18 s	1.88 s CH_3	1.98 s CH_3
If	5	H	6-OCH_3	C_6H_5	H	C_6H_5	10.35 s	2.20 s CH_3	1.83 s CH_3	6.80 s	—	3.80 s OCH_3	6.50 s	12.75 s	6.07 s	7.70 m	
Ig	5	H	7-CH_3	CH_3	H	CH_3	10.50 s	2.35 s CH_3	2.12 s CH_3	6.95 s	—	2.46 s	6.60 s CH_3	12.33 s	5.14 s	1.93 s CH_3	2.00 CH_3

TABLE I (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	19
Ih	5	H	7-CH_3	C_6H_5	H	C_6H_5	10.40 s	2.26 s CH_3	—	6.63 s	—	6.90 s	2.26 s CH_3	13.00 s	6.06 s	7.65 m	
Ii	6	H	H	CH_3	H	CH_3	10.28 s	—	—	7.26 d J_{54} = 8	6.67 q	—	6.97 d J_{75} = 2	12.45 s	5.05 s	—	—
Ij	6	H	H	C_6H_5	H	C_6H_5	10.24 s	—	—	7.10 d	6.50 q	—	6.73 d	13.12 s	6.05 s	7.60	
Ik	6	H	5-CH_3	CH_3	H	CH_3	10.56 s	2.10 s CH_3	2.00 s CH_3	7.16 s	2.16 s CH_3	—	6.92 s	12.32 s	5.13 s	1.73 s CH_3	1.86 s CH_3
Il	6	H	5-CH_3	C_6H_5	H	C_6H_5	10.30 s	2.10 s CH_3	2.00 s CH_3	7.10 s	2.34 s CH_3	—	6.38 s	13.06 s	6.08 s	7.65 m $2C_6H_5$	
Im	6	CH_3	5-CH_3	CH_3	H	CH_3	3.56 s CH_3	2.16 s CH_3	2.13 s CH_3	7.23 s	2.23 s CH_3	—	7.13 s	12.26 s	5.13 s	1.76 s CH_3	1.92 s CH_3
In	6	CH_3	5-CH_3	C_6H_5	H	C_6H_5	3.30 s CH_3	2.10 s CH_3	2.00 s CH_3	7.22 s	2.34 s CH_3	—	6.55 s	12.98 s	6.08 s	7.70 m $2C_6H_5$	
Io	6	H	5-OCH_3	CH_3	H	CH_3	10.37 s	2.33 s CH_3	2.19 s CH_3	6.99 s	3.82 s OCH_3	—	7.05 s	12.17 s	5.19 s	1.94 s CH_3	2.01 s CH_3
Ip	6	H	5-OCH_3	C_6H_5	H	C_6H_5	10.15 s	2.25 s CH_3	2.15 s CH_3	6.43 s	3.90 s OCH_3	—	6.93 s	12.74 s	6.07 s	7.70 m $2C_6H_5$	
Iq	6	H	7-CH_3	CH_3	H	CH_3	9.42 s	2.29 s CH_3	2.17 s CH_3	7.28 d J_{45} = 9	6.75 d	—	2.25 s CH_3	12.55 s	5.10 s	1.75 s CH_3	2.04 s CH_3
Ir	6	H	7-CH_3	C_6H_5	H	C_6H_5	10.50 s	2.35 s CH_3	2.10 s CH_3	6.94 J_{45} = 7	6.38 d	—	2.46 s CH_3	12.94 s	6.11 s	7.65 m $2C_6H_5$	
Is	6	H	7-OCH_3	CH_3	H	CH_3	10.78 s	2.25 s CH_3	2.09 s CH_3	6.66 d	6.58 d	—	3.90 s OCH_3	12.24 s	5.17 s	1.76 s CH_3	2.01 s CH_3
It	6	H	7-OCH_3	C_6H_5	H	C_6H_5	10.73 s	2.40 s CH_3	2.31 s CH_3	6.29 d J_{45} = 11	6.14 d	—	3.80 s OCH_3	12.89 s	6.10 s	7.62 m $2C_6H_5$	
Iu	7	H	H	CH_3	H	CH_3	10.50 s	—	—	6.80 m		—	—	12.10 s	5.20 s	—	—
Iv	7	H	H	C_6H_5	H	C_6H_5	10.30 s	—	—	7.05 m			—	12.80 s	6.00 s	7.05 m $2C_6H_5$	
Iw	7	CH_3	H	CH_3	H	CH_3	—	—	—	6.90 m			—	12.10 s	5.20 s	—	—
Ix	7	CH_3	H	C_6H_5	H	C_6H_5	4.00 s CH_3	2.30 s CH_3	2.20 s CH_3	—	7.05 s	—	—	13.05 s	6.00 s	7.05 m $2C_6H_5$	

* The spectra were taken in DMSO (compounds Ia,b,i,j,u-w), in CCl_4 (compounds Iq,x), in DMSO-d_6 (compounds Ic-h,k-p,r-t).

TABLE 2. PMR Spectral Characteristics of Amino Crotonates II



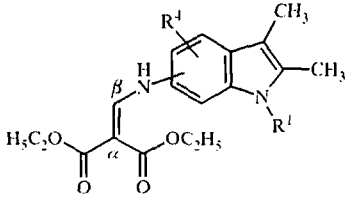
Compound	Position	R^1	R^3	R^4	Chemical shifts, δ, ppm, spin–spin coupling constants, Hz										
					indole moiety							enamine moiety			
					1-H	2-H	3-H	4-H	5-H	6-H	7-H	NH	α-H	CH_3	OC_2H_5
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
IIa	5	H	H	H	10.40 s	2.42 s CH_3	6.04 s	7.26 d J_{46} = 2	—	6.80 q J_{67} = 9	7.28 d	10.00 s	4.59 s	1.89 s	1.21 t 4.13 q J = 7
IIb	5	H	CH_3	H	10.42 s	2.37 s CH_3	2.21 s CH_3	7.24 d J_{46} = 2	—	6.84 q J_{67} = 9	7.28 d	9.82 s	4.63 s	1.92 s	1.25 t 4.13 q J = 7
IIc	5	CH_3	CH_3	H	3.62 s CH_3	2.28 s CH_3	2.15 s CH_3	7.08 s	—	6.68 q J_{67} = 9	6.93 d	10.13 s	4.48 s	1.78 s	1.17 t 4.05 q J = 7
IId	5	H	CH_3	6-CH_3	10.46 s	2.25 s CH_3	2.17 s CH_3	7.12 s	—	2.30 s CH_3	7.12 s	9.95 s	4.62 s	1.75 s	1.25 t 4.08 q J = 7
IIe	5	H	CH_3	6-OCH_3	10.27 s	2.23 s CH_3	2.10 s CH_3	7.25 s	—	3.83 s OCH_3	6.87 s	10.21 s	4.58 s	1.79 s	1.22 t 4.00 q J = 7

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
IIf	5	H	CH_3	7-CH_3	10.60 s	2.32 s CH_3	2.14 s CH_3	6.75 s	—	6.62 s	2.40 s CH_3	10.20 s	4.61 s	1.76 s	1.22 t 4.10 q $J = 7$
IIg	6	H	CH_3	H	10.40 s	2.30 s CH_3	2.14 s CH_3	7.30 d $J_{45} = 9$	6.74 q	—	7.12 d $J_{57} = 2$	9.70 s	4.55 s	1.87 s	1.20 t 4.03 q $J = 7$
IIh *cis*	6	H	CH_3	5-CH_3	10.40 s	2.30 s CH_3	2.18 s CH_3	7.21 s	2.35 s CH_3	—	7.21 s	10.02 s	4.62 s	1.75 s	1.22 t 4.10 q $J = 7$
trans					10.40 s	2.25 s CH_3	2.18 s CH_3	7.00 s	2.30 s CH_3	—	6.93 s	8.00 s	4.22 s	2.22 s	1.10 t 3.86 q $J = 7$
IIi	6	CH_3	CH_3	5-CH_3	3.51 s CH_3	2.33 s CH_3	2.20 s CH_3	7.07 s	2.33 s CH_3	—	6.78 s	9.97 s	4.46 s	1.73 s	1.27 t 4.03 q $J = 7$
IIi' *cis*	6	CH_3	CH_3	5-CH_3	3.60 s CH_3	2.31 s CH_3	2.16 s CH_3	7.19 s	2.31 s CH_3	—	7.05 s	10.05 s	4.55 s	1.73 s	1.23 t 4.06 q $J = 7$
trans					3.60 s CH_3	2.27 s CH_3	2.16 s CH_3	7.19 s	2.30 s CH_3	—	6.98 s	7.98 s	4.15 s	1.78 s	1.07 t 3.84 q $J = 7$
IIj	6	H	CH_3	5-OCH_3	9.92 s	2.18 s CH_3	2.07 s CH_3	6.58 s	3.66 s OCH_3	—	6.73 s	8.46 s	4.50 s	1.75 s	1.25 t 4.06 q $J = 7$
IIk	6	H	CH_3	7-OCH_3	10.80 s	2.26 s CH_3	2.15 s CH_3	6.63 d $J_{45} = 9$	6.54 d	—	3.91 s OCH_3	10.10 s	4.61 s	1.71 s	1.21 t 4.09 q $J = 7$
IIk' *cis*	6	H	CH_3	7-OCH_3	10.70 s	2.28 s CH_3	2.12 s CH_3	6.57 d $J_{45} = 8$	6.47 d	—	3.91 s OCH_3	10.06 s	4.53 s	1.72 s	1.21 t 4.05 q $J = 7$
trans					10.57 s	2.34 s CH_3	2.12 s CH_3	6.57 d $J_{45} = 8$	6.47 d	—	3.91 s OCH_3	7.79 s	4.13 s	2.27 s	1.07 t 3.83 q $J = 7$

* The PMR spectra were taken in CCl_4 (compounds IIc,e,i,j), in DMSO-d_6 (compounds IIa,b,d,f-h,k); compounds IIi',k', are formed after boiling of compounds IIi,k in ethyl acetate.

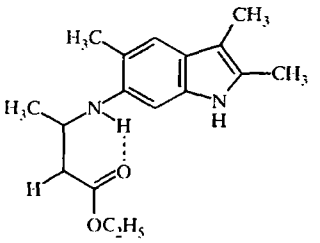
TABLE 3. PMR Spectral Characteristics of Aminomethylene Malonates



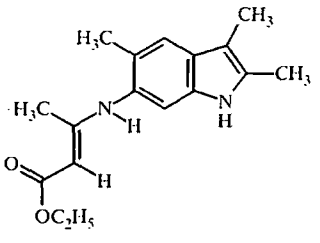
Compound	Position	R^1	R^4	Chemical shifts, δ, ppm, spin–spin coupling constants, Hz									
				indole moiety							enamine moiety		
				1-H	2-H	3-H	4-H	5-H	6-H	7-H	NH	β-H	OC_2H_5
IIIa	5	CH_3	H	3.64 s CH_3	2.36 s CH_3	2.23 s CH_3	7.35 s	—	7.35 d J_{67} = 6	7.04 d	10.84 d	8.45 d $J_{N\beta}$ = 15	1.28 m 4.20 m
IIIb	5	H	6-CH_3	10.47 s	2.30 s CH_3	2.20 s CH_3	7.28 s	—	2.40 s CH_3	7.12s	10.88s	8.44 d $J_{N\beta}$ = 15	1.30 m 4.20 m
IIIc	5	H	6-OCH_3	10.40 s	2.30 s CH_3	2.15 s CH_3	7.33 s	—	3.90 s OCH_3	6.94 s	10.95 d	8.54 d $J_{N\beta}$ = 15	1.32 m 4.20 m
IIId	5	H	7-CH_3	10.50 s	2.34 s CH_3	2.18 s CH_3	7.11 s	—	6.80 s	2.35 s CH_3	10.77 d	8.43 d $J_{N\beta}$ = 15	1.30 m 4.20 m
IIIe	6	H	5-CH_3	10.44 s	2.30 s CH_3	2.15 s CH_3	7.21 s	2.36 s CH_3	—	7.15 s	10.91 d	8.41 d $J_{N\beta}$ = 15	1.30 m 4.20 m
IIIf	6	CH_3	5-CH_3	3.60 s CH_3	2.30 s CH_3	2.15 s CH_3	7.20 s	2.36 s CH_3	—	7.13 s	—	8.55 s	1.30 m 4.20 m
IIIg	6	H	5-OCH_3	10.40 s	2.32 s CH_3	2.18 s CH_3	7.21 s	3.90 s OCH_3	—	7.05 s	11.02s	8.50 d $J_{N\beta}$ = 15	1.30 m 4.20 m
IIIh	6	H	7-CH_3	10.57 s	2.35 s CH_3	2.15 s CH_3	7.28 d J_{45} = 9	6.97 d	—	2.40 s CH_3	10.96 d	8.39 d $J_{N\beta}$ = 15	1.30 m 4.20 m
IIIi	6	H	7-OCH_3	10.90 s	2.39 s CH_3	2.35 s CH_3	6.77 d J_{45} = 9	6.60 d	—	3.92 s OCH_3	11.10 d	8.35 d $J_{N\beta}$ = 15	1.30 m 4.20 m
IIIj	7	H	H	11.00 s	—	—		7.05 m		—	10.50 d	8.50 d $J_{N\beta}$ = 15	—
IIIk	7	CH_3	H	3.80 s CH_3	2.20 s CH_3	2.10 s CH_3		7.05 m		—	11.20 d	8.20 d $J_{N\beta}$ = 14	1.30 m 4.20 m

* The PMR spectra were taken in CCl_4 (for compounds IIIf,k), in DMSO-d_6 (for compounds IIIa-d,g-j).

We should note a single case when a mixture of *cis* and *trans* isomers in 1:1 ratio is detected in the PMR spectrum of compound IIh in DMSO-d_6.

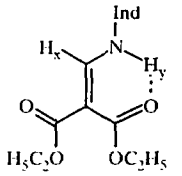


II (*cis*-)



II (*trans*-)

While the chemical shifts of the indole moieties of the isomers are practically identical, in the enamine moiety we observe considerable differences. In addition to the chemical shifts of the signals from the NH(amine) protons, which differ by 2 ppm, the *cis*-ethoxycarbonyl group affects the chemical shift of the signal from the protons of the β-CH_3 group. The signal of protons of this methyl group in the PMR spectrum of compound IIh (*trans*) is shifted 0.5 ppm downfield compared with the signal from the IIh (*cis*) isomer. The absence of interaction between the ethoxycarbonyl group and NH leads to upfield shifts of the signals from protons of the OC_2H_5 group. The signal from the vinyl proton also undergoes an upfield shift (0.4 ppm). Formation of a mixture of *cis–trans* isomers for the crotonate IIh probably should be explained by the fact that during purification, due to the low solubility, a heptane–benzene–ethyl acetate mixture heated to boiling was used, while all the rest of the amino crotonates were isolated from benzene or from a heptane–benzene mixture. In fact, after boiling amino crotonates IIi,k (isolated from heptane) in ethyl acetate followed by driving off the solvent, in the PMR spectra of these compounds in addition to the signals from protons of the *cis* form we also observe the appearance of proton signals typical for the *trans* isomer. The ratio of the characteristic signals from protons of amino crotonates of *cis* and *trans* structure is 5:1 (for compound IIi) and 6:1 (for compound IIk). The PMR spectra of indolylaminomethylene malonates III (Table 3) clearly support an *anti* arrangement of the vinyl and amine protons (J_{xy} = 14-15 Hz).



III

EXPERIMENTAL

The PMR spectra were recorded on a Bruker AS-200P and a Varian S-100X instrument, internal standard TMS. The solvent is reported in the tables.

The synthesis of the studied enamines has been described previously [6-16].

REFERENCES

1. Ya. F. Freimanis, *Chemistry of Enamino Ketones, Enamines, Enamino Thiones* [in Russian], Zinatne, Riga (1974), p. 327.
2. S. I. Yakimovich, L. A. Kayukova, and K. B. Erzhanov, *Acylation of Nitrogenous Derivatives of Carbonyl Compounds* [in Russian], Nauka, Alma-Ata (1985), p. 11.
3. S. I. Yakimovich, I. V. Zernova, K. N. Zelenin, and O. V. Solod, in: *Abstracts of the First Ural Conference on Enamines in Organic Synthesis* [in Russian], Perm' (1986), p. 33.

4. S. I. Yakimovich and I. V. Zernova, *Configurational and Conformational Isomerism of Enaminocarbonyl Compounds* [in Russian], Leningrad (1980); No. 7, p. 45.
5. S. I. Yakimovich and V. N. Nikolaev, *Topics in Physical Organic Chemistry* [in Russian], Leningrad (1984), No. 2, p. 2631.
6. P. A. Sharbatyan, S. A. Yamashkin, A. N. Kost, and L. G. Yudin, *Khim. Geterotsikl. Soedin.*, No. 1, 73 (1977).
7. S. A. Yamashkin, L. G. Yudin, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, No. 4, 493 (1983).
8. S. A. Yamashkin and N. Ya. Boriskina, *Khim. Geterotsikl. Soedin.*, No. 2, 228 (1989).
9. S. A. Yamashkin and I. A. Batanov, *Khim. Geterotsikl. Soedin.*, No. 1, 58 (1995).
10. S. A. Yamashkin, N. Ya. Kucherenko, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 11, 1499 (1995).
11. S. A. Yamashkin, N. Ya. Kucherenko, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 1, 69 (1997).
12. S. A. Yamashkin, N. Ya. Kucherenko, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 1, 75 (1997).
13. S. A. Yamashkin, N. Ya. Kucherenko, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 7, 941 (1997).
14. S. A. Yamashkin, N. Ya. Kucherenko, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 8, 1080 (1997).
15. S. A. Yamashkin and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 11, 1486 (1997).
16. S. A. Yamashkin, N. Ya. Kucherenko, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, No. 5, 673 (1998).