Asymmetric nitrogen
80.* Diastereomeric derivatives of 1-alkoxyaziridine-2,2-dicarboxylic acids. Synthesis, structure, and absolute configuration

*A. V. Prosyanik,[a] V. V. Rozhkov,[a] A. S. Moskalenko,[a] A. I. Mishchenko,[a†] A. Forni,[b] I. Moretti,[b] G. Torre,[b] S. Brukner,[c] L. Malpezzi,[c] and R. G. Kostyanovsky[d]**

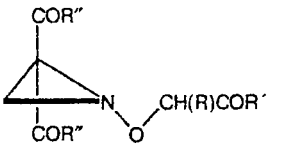
[a]*Ukrainian State University of Chemistry and Technology, 18 prosp. Gagarina, 320005 Dnepropetrovsk, Ukraine. Fax: +7 (056 2) 47 7478*
[b]*Department of Chemistry, Modena University, 183 via Campi, Modena, Italy. Fax: 39 59 373 543*
[c]*Department of Chemistry, Milan Polytechnical University, 32 pl. Leonardo da Vinci, 120133 Milan, Italy*
[d]*N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117977 Moscow, Russian Federation. Fax: +7 (095) 938 2156. E-mail: kost@center.chph.ras.ru*

Esters and amides (including ^{15}N analogs) of 1-alkoxyaziridine-2,2-dicarboxylic acids that contain *N*-alkoxy substituents (Pr^iO, RO_2CCH_2O, (*R,S*)-$RO_2CCH(Me)O$, or (*S*)-$RO_2CCH(Me)O$) were synthesized. Triamide of the last-mentioned type was isolated in the diastereomerically pure forms. The validity of the ^1H NMR criteria, which were suggested for the determination of absolute configurations of diastereomers, was confirmed by X-ray diffraction study of the (*S,S*)-form.

Key words: 1-(1-alkoxycarbonylethoxy)aziridine-2,2-dicarboxylic acids, esters, amides; diastereomers, optical activity; ^1H NMR spectra; X-ray diffraction study.

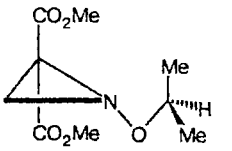
With the aim of searching for compounds with a stable chiral pyramidal nitrogen atom, esters of 1-alkoxyaziridine-2,2-dicarboxylic acids have been synthesized and studied.[2–7] Simple methods have been developed for optical activation[5,8–10] of these esters and complete resolution into antipodes[9–12] whose absolute configurations were established by X-ray structural analysis.[11,12] Their reactions were carried out with retention of the configuration of the N atom,[9–12] and the high *trans*-stereoselectivity of nucleophilic substitution at the ester group was demonstrated.[4,10–14] This opens up considerable possibilities for preparing new chiral polyfunctional synthons based on the above-mentioned esters. One approach to these compounds involves the synthesis and separation of diastereomeric derivatives of 1-alkoxyaziridine-2,2-dicarboxylic acids, which contain an asymmetrical 1-AlkO substituent with the known configuration. Previously, it has been demonstrated[7] that this approach can, in principle, be used. However, in such a case the problem of determining the configuration of the nitrogen chiral center appears. This problem has been solved by NMR spectroscopy for diastereomeric derivatives of aziridine-2-carboxylic acids, which contain chiral *N*-substituents with the known configuration,[14,15] as well as for diastereomers of 1-((1*S*)-phenylethyl)-3,3-dimethyldiaziridine and 2-((1*S*)-phenylethyl)-3,3-dimethyloxaziridine.[15,16]

In this work, we found criteria for determining configurations from the analysis of ^1H NMR spectra of racemic diastereomeric mixtures of derivatives of (*R,R/S,S*)- and (*S,R/R,S*)-1-alkoxyaziridine-2,2-dicarboxylic acids **1a—d**. These compounds were synthesized by thermolysis of triazolines, which were prepared by



1a—e, 2a,b,e

1	R	R′	R″
a	Me	OMe	OMe
b	Me	OEt	OMe
c	Me	OPr^i	OMe
d	Me	OBu^t	OMe
e	Me	NH_2	NH_2



3

2	R	R′	R″
a	H	OMe	OMe
b	H	OEt	OMe
e	H	NH_2	NH_2

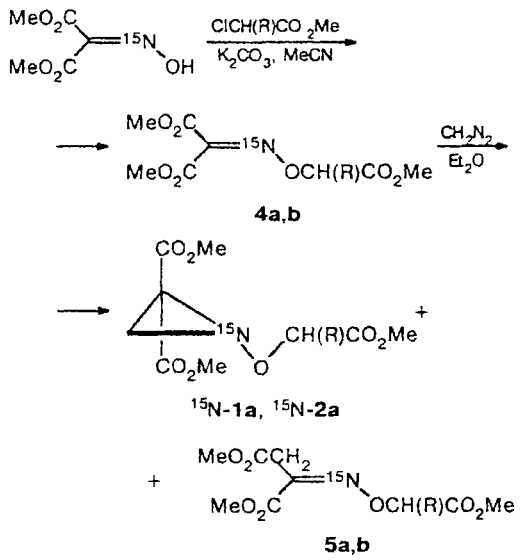
* For Part 79, see Ref. 1.
† Deceased.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 120—126, January, 1998.

reactions of the corresponding *O*-esters of isonitrosodimethyl malonates with CH_2N_2.[7] Triamide **1e** was prepared by ammonolysis of aziridine **1a** and was separated into racemic diastereomers (*R,R/S,S*)-**1e** and (*S,R/R,S*)-**1e** by crystallization.[7]

Alkoxyaziridines **2a,b** and **3** [5] and ^{15}N-alkoxyaziridines ^{15}N-**1a** and ^{15}N-**2a** were synthesized according to analogous procedures (Scheme 1). Triamide **2e** was prepared by amidation of ester **2a**.

Scheme 1

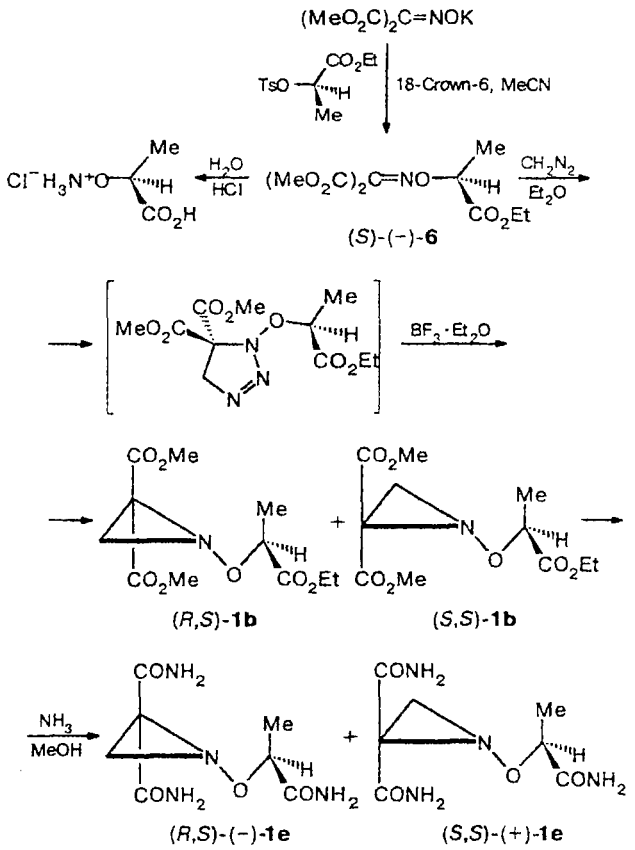


R = Me (**4a**, ^{15}N-**1a**, **5a**); H (**4b**, ^{15}N-**2a**, **5b**)

Alkoxyaziridine **1b** and triamide **1e** were synthesized in the optically active forms (Scheme 2).

Alkylation of isonitrosodimethyl malonate with (*R*)-(−)-ethyl-*O*-tosyl lactate gave *O*-ester of oxime (*S*)-(−)-**6** whose configuration was established based on the fact that the product of acid hydrolysis was identified as (*S*)-(−)-2-aminohydroxypropionic acid hydrochloride.[18] Therefore, the reaction proceeded with inversion of the configuration of the C(2) atom. A comparison of the value of optical rotation of the product with that reported previously[18] demonstrated that the optical purity of the product was no less than 92%. The reaction of *O*-ester of oxime (*S*)-(−)-**6** with an excess of CH_2N_2 followed by acid-catalyzed decomposition of intermediate triazoline yielded a mixture of (*R,S*)- and (*S,S*)-diastereomers of **1b**, which were characterized by the ^{1}H NMR spectra (Table 1). Mild amidation of aziridines **1b** afforded a mixture of diastereomeric triamides (*R,S*)-**1e** and (*S,S*)-**1e**. Crystallization of the resulting compounds gave diastereomerically pure (control by the ^{1}H NMR spectra) optically active aziridines (*S,S*)-(+)-**1e** and (*R,S*)-(−)-**1e**. The inversion barriers

Scheme 2

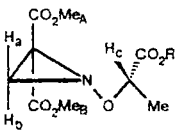


of the N atom were determined from the kinetics of their epimerization. These values and the corresponding values obtained for aziridines **1a,c,d** are of the same order of magnitude ($\Delta G^{\neq}$ = 30.4—31.3 kcal mol^{-1}):[7]

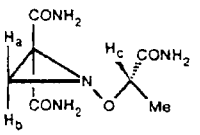
Compound	*T* /°C	$k_{inv} \cdot 10^5$ /s^{-1}	$\Delta G^{\neq}_T$ /kcal mol^{-1}	$t_{0.5}$ /h
(*S,S*)-**1e**	124	8.5±1.1	30.8±0.1	2.25
(*R,S*)-**1e**	102	1.7±1.1	30.3±0.1	11.54

In the thermodynamical equilibrium, the content of the predominant diastereomer increases slightly in the series of diastereomeric alkoxyaziridines **1** under study as the volume of the *N*-alkoxy substituent increases (see Table 1). Analysis of the parameters of the ^{1}H NMR spectrum (see Table 1) demonstrated the following facts. In most cases, the chemical shifts of the H_b and H_c protons are almost identical for each diastereomeric pair, whereas the shifts of the H_a and MeC protons differ substantially. This difference remains virtually unchanged throughout the series. In the predominant diastereomer, the protons of the MeC group are shielded to a greater extent, and the absolute values of the spin-spin coupling constant $^2J_{H_aH_b}$ are 0.3 Hz larger. The shielding of the H_a, H_c, and MeC protons increases and the absolute value of the spin-spin coupling constant $^2J_{H_aH_b}$

Table 1. Parameters of the ^1H NMR spectra of the diastereomeric derivatives of 1-alkoxyaziridine-2,2-dicarboxylic acids **1a—e** [a]



1a—d

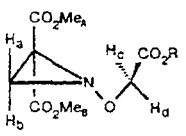


1e

Compound	R	Configuration	Equilibrium content of the diastereomer	δ (*J*/Hz) MeC [b]	H_a	H_b	Me_AO	Me_BO	R	H_c	$\Delta\delta(H_aH_b)$	$^2J_{H_aH_b}$/Hz
1a	Me	*R,R/S,S*	58	1.13	2.45	2.83	3.69	3.74	3.69	4.37	0.38	−3.1
1a	Me	*S,R/R,S*	42	1.32	2.39	2.84	3.64	3.73	3.64	4.40	0.45	−2.8
1b	Et	*S,S*	60	1.20	2.56	2.98	3.72	3.76	1.25; 4.20 (^3J = 7.5)	4.44	0.42	−3.0
1b	Et	*R,S*	40	1.38	2.49	2.96	3.63	3.69	1.26; 4.17 (^3J = 7.5)	4.47	0.47	−2.8
1c	Pr^i	*R,R/S,S*	62	1.12	2.43	2.83	3.68	3.74	1.18; 1.19; 5.01 (^3J = 6.0)	4.30	0.40	−3.0
		S,R/R,S	38	1.30	2.37	2.83	3.67	3.73	1.20; 4.96 (^3J = 6.0)	4.33	0.46	−2.7
1d	Bu^t	*R,R/S,S*	63	1.10	2.43	2.83	3.69	3.73	1.42	4.23	0.40	−2.8
		S,R/R,S	37	1.27	2.37	2.83	3.67	3.73	1.39	4.27	0.46	−2.5
1e	—	*S,S*	54	1.26	2.51	2.97	—	—	—	4.37	0.46	−3.7
		R,S	46	1.30	2.53	2.79	—	—	—	4.42	0.26	−3.5

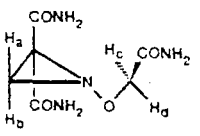
[a] Solutions (5 mol %) in CCl_4 and CD_3OD (**1e**). [b] Doublet (^3J = 7.0 Hz).

Table 2. Parameters of the ^1H NMR spectra of alkoxyaziridines **2a,b,e**, and **3** (**2a,b** and **3** in CCl_4 and **2e** in CD_3OD)

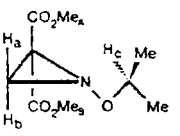


2a,b

R = Me (**a**), Et (**b**)



2e



3

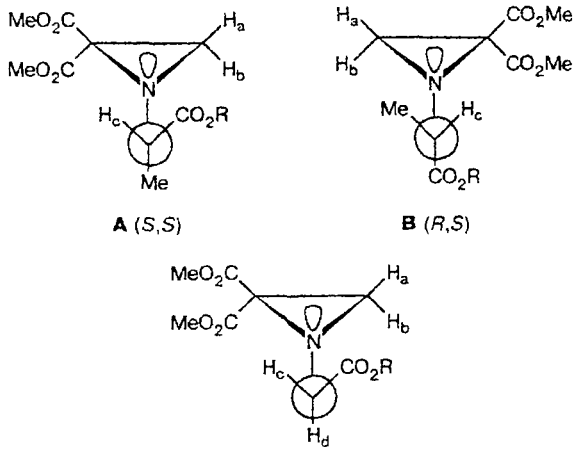
Compound	δ (*J*/Hz) $MeCH_2O$ [MeC]	H_a	H_b	Me_AO	Me_BO	CH_2O [MeO]	H_d	H_c	$\Delta\delta(H_aH_b)$	$^2J_{H_aH_b}$ Hz	$^2J_{H_cH_d}$ Hz
2a		2.57	2.97	3.78	3.83	[3.76]	4.28	4.45	0.40	−3.2	−16.1
2b	1.13 (^3J = 7.5)	2.45	2.86	3.67	3.73	4.12	4.16	4.32	0.41	−3.4	−16.0
2e		2.53	2.88	—	—	—	4.30	4.30	0.35	−3.4	
3	[0.99 and 1.15] (^3J = 6.0)	2.35	2.70	3.66	3.70	—	—	4.02	0.35	−2.3	

decreases as the volume of the alkoxy substituent increases. The difference between the chemical shifts of the protons of the ring $\Delta\delta(H_aH_b)$ remains virtually unchanged.

In model alkoxyaziridines **2**, one of the methylene protons H_c of the alkoxy substituent is similar in the parameters of the ^1H NMR spectrum (Table 2) to the H_c protons of the diastereomers of series **1** (see Table 1). This is convincingly confirmed by the results of studies of ^{15}N-alkoxyaziridines (Table 3). Previously, the calculated angular dependences[19,20] of the spin-spin coupling constants $^2J_{H15N}$ and $^3J_{H15N}$ were successfully used for assigning the protons of the aziridine ring[21] and for determining the H—C—O—N torsion angles in isoxazolidines,[22] respectively. The H_c—C—O—N dihedral angles in the molecules of the diastereomers of aziridines **1a** and **2a**, which are calculated based on the data in Table 4, are almost identical (are in the range of 15—20°), whereas the H_d—C—O—N dihedral angle in molecule **2a** differs substantially (~135°).

Based on the obtained data, it can be suggested that the effective conformations of the predominant and minor diastereomers of aziridines **1** correspond to structures **A** and **B**, respectively. The effective conformations of aziridines **2** correspond to form **C**.

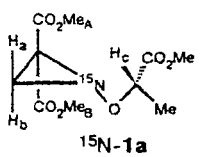
The H_c proton in all these conformers and the MeC group in structure **B** are located in the vicinity of the plane of the ring, which is the deshielding region of



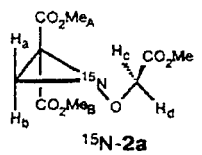
aziridine. Correspondingly, the H_d proton in the molecules of aziridines **2** is shielded to a greater extent ($\Delta\delta(H_cH_d)$ = 0.16—0.17 ppm, see Table 2), and the protons of the MeC groups in the predominant diastereomers of **1** are shielded to a greater extent than those in the minor diastereomers ($\Delta\delta$ = 0.17—0.19 ppm, see Table 1). For the Me groups of the alkoxy substituent in aziridine **3**, $\Delta\delta$ = 0.16 ppm (see Table 2). Therefore, the diastereomers of aziridines **1** that are characterized by relatively high-field and low-field signals of the MeC group adopt conformations **A** and **B**, respectively. Hence, the optically active predominant diastereomer of aziridine **1b**, which contains the carbon asymmetric center with the unambiguous *S*-configuration, has the *S*-configuration of the nitrogen chiral center because this diastereomer is characterized by the high-field signal of the MeC group (see Table 1).

The validity of the above-discussed ^{1}H NMR criteria was confirmed as follows. The assignment of the configurations of the diastereomers of triester **1b** and triamide **1e** was carried out by complete amidation of an equilibrium mixture of the diastereomers of **1b** to triamides **1e** with retention of the predominance of one

Table 3. Spin-spin coupling constants $J_{^1H^{15}N}$ of the protons of the ring and the alkoxy substituent for ^{15}N-alkoxyaziridines (in 9 : 1 CCl_4—$CDCl_3$ mixture)



^{15}N-**1a**



^{15}N-**2a**

Compound	Configuration	$^2J_{H_a{}^{15}N}$	$^2J_{H_b{}^{15}N}$	$^3J_{H_c{}^{15}N}$	$^3J_{H_d{}^{15}N}$
		Hz			
^{15}N-**1a**	*R,R/S,S*	9.5	0.5	3.4	—
^{15}N-**1a**	*S,R/R,S*	9.8	0.5	3.2	—
^{15}N-**2a**		9.5	0.3	3.9	5.9

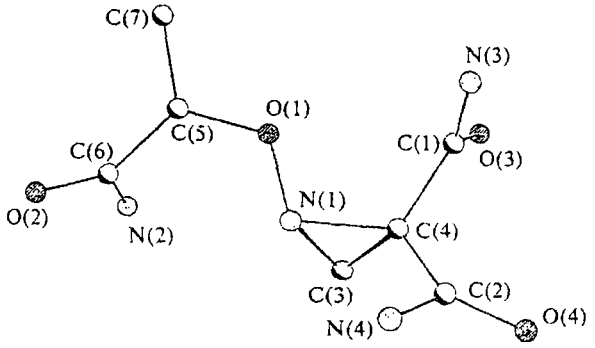


Fig. 1. Molecular structure of triamide (*S,S*)-**1e**.

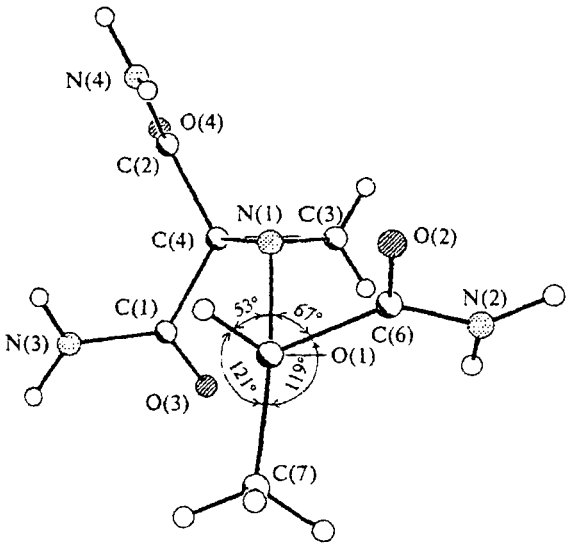


Fig. 2. Projection of the molecule of triamide (*S,S*)-**1e** along the C(5)—O(1) axis.

of the diastereomers (see Scheme 2). After their separation, it was demonstrated by ^{1}H NMR spectroscopy that the higher-melting diastereomer predominates in the initial mixture. Its absolute configuration [(*S,S*)-(+)-**1e**] was established by X-ray diffraction study with respect to the asymmetric carbon center with the known *S*-configuration (Fig. 1, Tables 4—7). The conformation of the molecule is close to the above-considered form **A** (Fig. 2). The principal geometric parameters (see Tables 5 and 6) are almost equal to the values observed in the derivatives of 1-alkoxyaziridine-2,2-dicarboxylic acids studied previously.[11,13,14] The crystal structure is characterized by a network of intra- and intermolecular H bonds as in the case of diamides of unsubstituted 2,2-dicarboxylic acid and 1-phenylaziridine-2,2-dicarboxylic acids.[23]

Taking into account the obtained structural data, the causes of the change in the spin-spin coupling constant $^2J_{H_aH_b}$ can be considered. By analogy with the known decrease in the values of $^2J_{HH}$ in the spectra of deriva-

Table 4. Coordinates of nonhydrogen atoms ($\times 10^4$) and isotropic thermal parameters (U_{eq}) in the molecule of (*S,S*)-**1e**

Atom	*x*	*y*	*z*	$U_{eq} \times 10^3$/Å^2
O(1)	−4235(8)	−3930(13)	−2149(3)	2.3(1)
O(2)	−2001(10)	846(15)	−719(4)	3.4(2)
O(3)	−5107(10)	−8483(15)	−3555(4)	3.5(1)
O(4)	−972(9)	−5277(14)	−4549(4)	2.8(1)
N(1)	−2326(10)	−3472(0)	−2541(4)	2.0(1)
N(2)	−1779(12)	−3547(17)	−608(5)	2.9(2)
N(3)	−6151(12)	−4477(18)	−4067(5)	3.8(2)
N(4)	−949(11)	−1267(19)	−3951(4)	3.2(2)
C(1)	−4737(13)	−6158(20)	−3658(5)	2.3(2)
C(2)	−1457(12)	−3815(18)	−4010(4)	1.8(2)
C(3)	−1213(12)	−6024(19)	−2587(5)	2.5(2)
C(4)	−2576(12)	−4914(17)	−3349(5)	1.6(2)
C(5)	−4471(12)	−1605(18)	−1663(5)	2.1(2)
C(6)	−2634(12)	−1364(21	−954(5)	2.2(2)
C(7)	−6638(16)	−1985(22)	−1335(6)	4.0(2)

Table 5. Bond lengths (*d*) in the molecule of (*S,S*)-**1e**

Bond	*d*/Å	Bond	*d*/Å
O(1)—N(1)	1.454(8)	N(3)—C(1)	1.332(12)
O(1)—C(5)	1.441(11)	N(4)—C(2)	1.334(13)
O(2)—C(6)	1.233(12)	C(1)—C(4)	1.506(11)
O(3)—C(1)	1.221(13)	C(2)—C(4)	1.477(11)
O(4)—C(2)	1.222(10)	C(3)—C(4)	1.502(10)
N(1)—C(3)	1.480(10)	C(5)—C(6)	1.502(10)
N(1)—C(4)	1.492(9)	C(5)—C(7)	1.541(13)
N(2)—C(6)	1.320(13)		

Table 6. Bond angles (ω) in the molecule of (*S,S*)-**1e**

Angle	ω/deg	Angle	ω/deg
N(1)—O(1)—C(5)	105.5(5)	C(1)—C(4)—C(3)	118.9(7)
O(1)—N(1)—C(4)	108.9(4)	C(1)—C(4)—C(2)	114.7(6)
O(1)—N(1)—C(3)	107.8(4)	N(1)—C(4)—C(3)	59.3(4)
C(3)—N(1)—C(4)	60.7(4)	N(1)—C(4)—C(2)	117.1(6)
O(3)—C(1)—N(3)	124.4(9)	N(1)—C(4)—C(1)	117.8(6)
N(3)—C(1)—C(4)	112.9(8)	O(1)—C(5)—C(7)	104.8(7)
O(3)—C(1)—C(4)	122.7(8)	O(1)—C(5)—C(6)	110.9(7)
O(4)—C(2)—N(4)	124.0(7)	C(6)—C(5)—C(7)	110.8(6)
N(4)—C(2)—C(4)	116.7(7)	N(2)—C(6)—C(5)	118.0(9)
O(4)—C(2)—C(4)	119.2(8)	O(2)—C(6)—C(5)	119.0(9)
N(1)—C(3)—C(4)	60.0(5)	O(2)—C(6)—N(2)	123.0(9)
C(2)—C(4)—C(3)	118.0(6)		

tives of ethylene H_2C=CHX as the electronegativity of the β-substituent X decreases,[24] a decrease in the absolute value of $J_{H_aH_b}$ in the series of aziridines **1a—d** is, apparently, caused by a decrease in the effective electronegativity of the *N*-alkoxy substituent as the +*I* effect of the R substituent in the CO_2R group increases. Apparently, the systematic decrease in the absolute value of $^2J_{H_aH_b}$ in the case of the (*S,R/R,S*)-diastereomers compared to (*R,R/S,S*)-aziridines **1a—e** is also determined by a decrease in the effective electronegativity of the *N*-alkoxy substituent.

To verify this suggestion, let us consider possible stabilizing interactions, which lead to an increase in the effective electronegativity of the oxygen atom (n_p(O)—σ*(C—COX), n_σ(O)—σ*(C—Me), and n_σ(O)—σ*(C—H) for the (*R,R/S,S*)-diastereomers and n_p(O)—σ*(C—Me), n_σ(O)—σ*(C—COX), and n_σ(O)—σ*(C—H) for the (*S,R/R,S*)-diastereomers) based on the preferred conformations of the *N*-alkoxy groups. In these cases, interactions between the maximum overlapping orbitals, which have the minimum energy gap, are the governing interactions. The effective overlapping of orbitals increases as the values of the torsion angles between them approach 0° or 180°.

According to the values of $^3J_{H_c{}^{15}N}$ (see Table 3), the N—O—C—H torsion angles in the diastereomers of aziridine ^{15}N-**1a** and in molecules **1a—e** are ~20°. Assuming that the n_σ(O) orbital is in an *anti* orientation with respect to the lone electron pair of the N atom, and the n_p(O) orbital is parallel to the plane of the aziridine ring, the n_p(O)—O—C—COOR, n_σ(O)—O—C—Me, and n_σ(O)—O—C—H torsion angles in the molecules of the (*R,R/S,S*)-diastereomers and the n_p(O)—O—C—Me, n_σ(O)—O—C—COOR, and n_σ(O)—O—C—H torsion angles in the molecules of the (*S,R/R,S*)-diastereomers are ~10°, ~40°, and ~160°, respectively. In view of the equality of the torsion angles and the energy gaps, the n_σ(O)—σ*(C—H) interaction in both diastereomers is virtually identical and has no effect on the change in the effective electronegativity of the O atom. The n_σ(O) orbital is a weaker inner donor compared to the n_p(O) orbital. The conditions of overlapping are worse for the n_σ(O)—σ*(C—C) interactions than for the n_p(O)—σ*(C—C) interactions. Therefore, the n_σ(O)—σ*(C—Me) and n_σ(O)—σ*(C—COOR) interactions are substantially less efficient than the n_p(O)—σ*(C—COOR) and n_p(O)—σ*(C—Me) interactions, and they may be ignored. The σ*(C—COOR) orbital is a stronger inner

Table 7. Selected torsion angles (τ) in the molecule of (*S,S*)-**1e**

Angle	τ/deg	Angle	τ/deg	Angle	τ/deg
N(1)—O(1)—C(5)—C(6)	67.0(6)	O(1)—N(1)—C(3)—C(4)	−102.1(6)	N(4)—C(2)—C(4)—C(1)	−122.4(8)
N(1)—O(1)—C(5)—C(7)	−173.7(6)	C(3)—N(1)—C(4)—C(1)	−108.8(8)	N(4)—C(2)—C(4)—N(1)	22.0(10)
C(5)—O(1)—N(1)—C(4)	150.4(6)	O(3)—C(1)—C(4)—N(1)	97.7(10)	O(1)—C(5)—C(6)—N(2)	32.8(11)
O(1)—N(1)—C(4)—C(1)	−8.5(8)	N(3)—C(1)—C(4)—N(1)	−84.0(9)	O(1)—C(5)—C(6)—O(2)	−147.6(8)
O(1)—N(1)—C(4)—C(2)	−151.8(6)	O(3)—C(1)—C(4)—C(2)	−118.1(9)	C(7)—C(5)—C(6)—O(2)	96.5(10)
		O(4)—C(2)—C(4)—N(1)	155.0(7)		

acceptor than the σ*(C—Me) orbital. Therefore, the $n_p(O)$—σ*(C—COOR) interaction causes a more substantial increase in the effective electronegativity of the O atom compared to the $n_p(O)$—σ*(C—Me) interaction. Correspondingly, the observed absolute decrease in the value of $^2J_{H_aH_b}$ for the (*S,R/R,S*)-diastereomers compared to (*R,R/S,S*)-aziridines **1a—e** may be due to a decrease in the effective electronegativity of the *N*-alkoxy substituent.

The occurrence of the $n_p(O)$—σ*(C—COX) and $n_\sigma(O)$—σ*(C—Me) interactions is evidenced by the data of X-ray structural analysis of aziridine (*S,S*)-**1e** (see Table 7). The small values of the torsion angles between the interacting orbitals (the $n_p(O)$—O—C—$CONH_2$ and $n_\sigma(O)$—O—C—Me angles are 23.7° and 6.3°, respectively, because the N—O—C—Me angle is 173.7°) provide their efficient overlapping and cause the corresponding changes in the bond lengths (see Table 5), namely, the shortening of the O(1)—C(5) bond (1.441 Å compared to 1.459—1.489 Å for the corresponding bonds in the CO_2Et groups[14,23]), the elongation of the C(5)—C(6) bond (1.502 Å compared to 1.490 Å for the corresponding bond in diamide of adipic acid), and the elongation of the C(5)—C(7) bond (1.541 Å compared to 1.390—1.493 Å for the corresponding bonds in the CO_2Et groups).

It is known that introduction of p-acceptor substituents into the cyclopropane or aziridine ring causes an elongation of the vicinal bonds because of delocalization of the electron density from the bonding MO of the σ-donor to the antibonding MO of the p-acceptor. The efficiency of delocalization increases as the torsion angle between the interacting MOs increases. For aziridine (*S,S*)-**1e**, the C(3)—C(4) bond is 0.018 Å longer than that in unsubstituted aziridine (1.484 Å), and the C(4)—C(2) bond is 0.013 Å shorter than that in diamide of adipic acid (1.490 Å), which may be due solely to the occurrence of the σ(CC)—p*(C=O) interaction because of the favorable arrangement of the orbitals (the C(3)—C(4)—C(2)—p*(C=O) torsion angle is smaller than 8°).

Experimental

The ^1H NMR spectra were recorded on Tesla BS-487C, Varian HA-100, and Bruker WM-400 spectrometers (80, 100, and 400 MHz) with Me_4Si and HMDS as internal standards.

The melting temperatures were determined on a Boetius microtable. The optical rotation was measured on a Polamat A polarimeter in a 1-dm cell. Dimethyl ethers of (^{14}N)- and (^{15}N)hydroxyiminomalonic acids were prepared according to a procedure reported previously.[6]

***O*-Potassium salt of dimethyl hydroxyiminomalonate.** A solution of KOH (3.82 g, 68 mmol) in MeOH (150 mL) was added slowly to a solution of dimethyl hydroxyiminomalonate (10 g, 62 mmol) in MeOH (50 mL). The reaction mixture was kept at 20 °C for ~24 h. The precipitate that formed was filtered off and crystallized from a 1 : 1 MeOH—Pr^iOH mixture. The salt was obtained as yellow crystals in a yield of 11 g (90%), m.p. 290 °C (with decomp.).

(*R*)-(−)-Ethyl *O*-tosyl lactate. A mixture of a cooled solution of *R*-(+)-ethyl lactate (5.0 g, 42 mmol) in anhydrous pyridine (35 mL) and a cooled solution of TsCl (16.1 g, 85 mmol) in anhydrous pyridine (35 mL) was kept at 0 °C for 12 h. Then the reaction mixture was poured onto ice (150 g) and extracted with Et_2O. The extract was stirred with an activated carbon for 0.5 h, filtered off, and concentrated. The residue was crystallized from *n*-hexane. Tosylate was obtained as white crystals in a yield of 9.5 g (83%), m.p. 34—35 °C (with decomp.), $[\alpha]_D^{33}$ −32.2° (*c* 6.36, MeOH). Found (%): C, 57.65; H, 7.72. $C_{12}H_{16}O_3$. Calculated (%): C, 57.69; H, 7.69. ^1H NMR ($CDCl_3$), δ: 1.21 (t, 3 H, MeCH$_2$, ^3J = 7.0 Hz); 1.51 (d, 3 H, MeCH, ^3J = 7.0 Hz); 2.45 (s, 3 H, MeC$_6$H$_4$); 4.11 (dq, 2 H, CH_2O, ABX_3 spectrum, Δν = 35 Hz, $^2J_{AB}$ = −10.4 Hz, $^3J_{AX}$ = $^3J_{BX}$ = 7.0 Hz); 4.92 (q, 1 H, CHMe, ^3J = 7.0 Hz); 7.34 (d, 2 H, H arom.); 7.82 (d, 2 H, H arom.).

Dimethyl (*S*)-(−)-(1-ethoxycarbonylethoxyimino)malonate ((*S*)-6). 18-Crown-6 (0.05 g) and a solution of (*R*)-(−)-ethyl *O*-tosyl lactate (7.5 g, 36 mmol) in MeCN (50 mL) were added to a suspension of *O*-potassium salt of dimethyl hydroxyiminomalnate (7 g, 35 mmol). The reaction mixture was stirred for 5 h and filtered off. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (L 40/100 silica gel, benzene as the eluent). *O*-Ester (*S*)-**6** was obtained as a colorless oil in a yield of 6.1 g (65%), n_D 1.4562, $[\alpha]_D^{32}$ −7.8° (*c* 3.6, MeOH). ^1H NMR ($CDCl_3$), δ: 1.28 (t, 3 H, MeCH$_2$O, ^3J = 7.0 Hz); 1.55 (d, 3 H, MeCH, ^3J = 7.1 Hz); 3.88 (s, 3 H, MeO); 3.92 (s, 3 H, MeO); 4.21 (dq, 2 H, CH_2O, ABX_3 spectrum, Δν = 45 Hz, $^2J_{AB}$ = −10.7 Hz, $^3J_{AX}$ = $^3J_{BX}$ = 7.0 Hz); 4.93 (q, 1 H, MeCH, ^3J = 7.1 Hz).

Determination of the optical purity of *O*-ester (*S*)-6. A solution of *O*-ester (*S*)-**6** (0.1 g, 0.38 mmol) in concentrated HCl (5 mL) was boiled for 3 h. The solvent was evaporated *in vacuo*, and the residue was crystallized from a Pr^iOH—Et_2O mixture. (*S*)-(−)-2-Aminohydroxypropionic acid hydrochloride was obtained in a yield of 38 mg (76.3%), m.p. 126—127 °C (with decomp.), $[\alpha]_D^{15}$ −105.4° (*c* 2.5, MeOH). Published data:[17] m.p. 125—127 °C (with decomp.), $[\alpha]_D^{15}$ −113.5° (*c* 2.5, MeOH).

(*S,S*)- and (*R,S*)-1-(1-Carbamoylethoxy)aziridine-2,2-dicarboxamides (1e). A solution of *O*-ester (*S*)-**6** (2.0 g, 7.7 mmol) in an excess of an ethereal solution of CH_2N_2 was kept at −5 °C for one month. Then the reaction mixture was decomposed with a catalytic amount of $Et_2O \cdot BF_3$ at this temperature (until elimination of nitrogen ceased), filtered off, and evaporated *in vacuo*. According to the ^1H NMR spectrum (see Table 1), the residue was a 60 : 40 mixture of diastereomers (*S,S/R,S*)-**1b**. The residue was dissolved in anhydrous MeOH (25 mL). Then a solution of NH_3 (2.0 g, 11.8 mmol) in anhydrous MeOH (50 mL) was added. The mixture was kept at 25 °C for 25 days and concentrated *in vacuo*. The residue was crystallized from absolute Pr^iOH. Triamide (*S,S*)-**1e** was obtained in a yield of 70 mg (4.2%), m.p. 204—206 °C, $[\alpha]_D^{20}$ +32.1° (*c* 0.5, MeOH). Triamide (*R,S*)-**1e** was obtained in a yield of 0.1 g (6.0%), m.p. 196—198 °C, $[\alpha]_D^{20}$ −19.31° (*c* 0.5, MeOH).

(^{15}N)Dimethyl (1-methoxycarbonylethoxyimino)malonate (4a). Finely dispersed K_2CO_3 (1.66 g, 12 mmol) was added with cooling to a solution of (^{15}N)dimethyl hydroxyiminomalonate (1.61 g, 10 mmol) in MeCN (25 mL). The reaction mixture was stirred for 30 min until the solution turned yellow. Then a solution of methyl 2-chloropropionate (1.5 g, 12 mmol) in MeCN (10 mL) was added, and the reaction mixture was stirred for 15 h. The mixture was poured

into ice water (100 mL) and extracted with Et_2O. The extract was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was distilled. Ester **4a** was obtained in a yield of 1.61 g (65%), b.p. 140 °C (2 Torr), n_D^{20} 1.4540. ^1H NMR (9 : 1 CCl_4—$CDCl_3$ mixture), δ: 1.45 (d, 3 H, MeCH, ^3J = 7.1 Hz); 3.76 (s, 6 H, 2 MeO); 3.79 (s, 3 H, MeO); 4.76 (dq, 1 H, CHO, $^3J_{H15N}$ = 2.3 Hz).

(^{15}N)Dimethyl (methoxycarbonylmethoxyimino)malonate (4b). *O*-Ester **4b** was prepared as described above in 80% yield. ^1H NMR (9 : 1 CCl_4—$CDCl_3$ mixture), δ: 3.80 (s, 3 H, MeO); 3.88 (s, 3 H, MeO); 3.90 (s, 3 H, MeO); 4.78 (d, 2 H, CH_2O, $^3J_{H15N}$ = 4.2 Hz).

Dimethyl (ethoxycarbonylmethoxyimino)malonate was prepared as described above, the yield was 80%, b.p. 143 °C (2 Torr), m.p. 37.5 °C. Found (%): C, 43.67; H, 5.34; N, 5.53. $C_9H_{13}NO_7$. Calculated (%): C, 43.73; H, 5.31; N, 5.67. ^1H NMR (CCl_4), δ: 1.22 (t, 3 H, $MeCH_2$); 3.82 (s, 3 H, MeO); 3.84 (s, 3 H, MeO); 4.18 (q, 2 H, $MeCH_2O$, ^3J = 7.0 Hz); 4.69 (s, 2 H, CH_2O).

(^{15}N)Dimethyl 1-(methoxycarbonylethoxy)aziridine-2,2-dicarboxylate (^{15}N-1a) and (^{15}N)dimethyl (1-methoxycarbonylethoxyimino)succinate (5a). A solution of ester **4a** (1.17 g, 4.5 mmol) in an excess of an ethereal solution of CH_2N_2 was kept at 20 °C for 2 weeks. Then the solution was filtered and concentrated *in vacuo*. A mixture of aziridine ^{15}N-**1a** and *O*-ester **5a** was obtained in a ratio of 3 : 1 (according to the integral intensity of the signals of the ester groups in the ^1H NMR spectrum) as an yellowish oil in a yield of 1.1 g. The mixture was chromatographed on a column (L 100/160 silica gel, benzene as the eluent). Aziridine ^{15}N-**1a** was obtained in a yield of 0.68 g (56.4%), n_D^{20} 1.4592. Compound **5a** was identified from the ^1H NMR spectrum (9 : 1 CCl_4—$CDCl_3$ mixture), δ: 1.55 (d, 3 H, MeCH, ^3J = 7.1 Hz); 3.64 (ddd, 2 H, CH_AH_B, ABX spectrum, Δν = 44 Hz, $^2J_{AB}$ = −16.0 Hz, $^3J_{H_A15N}$ = $^3J_{H_B15N}$ = 1.5 Hz); 3.71 (s, 3 H, MeO); 3.76 (s, 3 H, MeO); 3.89 (s, 3 H, MeO); 4.89 (dq, 1 H, CHO, $^3J_{H15N}$ = 2.4 Hz).

(^{15}N)Dimethyl 1-(methoxycarbonylmethoxy)aziridine-2,2-dicarboxylate (^{15}N-2a) and (^{15}N)dimethyl (methoxycarbonylmethoxyimino)succinate (5b). Aziridine ^{15}N-**2a** and *O*-ester **5b** were obtained from *O*-ester **4b** in a ratio of 3 : 1 according to an analogous procedure. The yield of ^{15}N-**2a** was 0.68 g (58%), n_D^{20} 1.4952. Compound **5b** was identified from the ^1H NMR spectrum (9 : 1 CCl_4—$CDCl_3$ mixture), δ: 3.61 (d, 2 H, CCH_2, $^3J_{H15N}$ = 1.1 Hz); 3.71 (s, 3 H, MeO); 3.78 (s, 3 H, MeO); 3.87 (s, 3 H, MeO); 4.79 (d, 2 H, CH_2O, $^3J_{H15N}$ = 4.1 Hz).

Dimethyl 1-(ethoxycarbonylmethoxy)aziridine-2,2-dicarboxylate (2b) and dimethyl (ethoxycarbonylmethoxyimino)succinate. Aziridine **2b** and dimethyl (ethoxycarbonylmethoxyimino)succinate were obtained from dimethyl (ethoxycarbonylmethoxyimino)malonate in a ratio of 3 : 1 by a procedure analogous to that described above. The yield of aziridine **2b** was 66.7%, n_D^{20} 1.4960. Found (%): C, 45.86; H, 5.91; N, 5.44. $C_{10}H_{15}NO_7$. Calculated (%): C, 45.97; H, 5.78; N, 5.36. Succinate was identified from the ^1H NMR spectrum (CCl_4), δ: 1.23 (t, 3 H, $MeCH_2$, ^3J = 7.0 Hz); 3.55 (s, 2 H, CCH_2); 3.60 (s, 3 H, MeO); 3.76 (s, 3 H, MeO); 4.13 (q, 2 H, $MeCH_2$); 4.66 (s, 2 H, CH_2O).

1-(Carbamoylmethoxy)aziridine-2,2-dicarboxamide (2e). Liquid NH_3 (0.5 g, 29 mmol) was added to a solution of aziridine **2a** (1 g, 3.8 mmol) in anhydrous MeOH (20 mL) containing a catalytic amount of MeONa. The reaction mixture was kept at 20 °C for 3 days and concentrated *in vacuo*. The residue was crystallized from Pr^iOH. Amide **2e** was obtained as colorless crystals in a yield of 0.6 g (78.2%), m.p. 94—96 °C. Found (%): C, 35.64; H, 4.94; N, 27.74. $C_6H_{10}N_4O_4$. Calculated (%): C, 35.64; H, 4.95; N, 27.72.

X-ray diffraction study of aziridine (*S*,*S*)-1e was carried out on an automated NONIUS CAD-4 diffractometer (Mo-Kα radiation, graphite monochromator, θ/2θ scanning technique, θ_{max} = 26°). A total of 1125 independent reflections were measured of which 661 reflections with $I > 2\sigma(I)$ were used in the solution of the structure. Colorless crystals of (*S*,*S*)-**1e** ($C_7H_{12}N_4O_4$, M = 216.1) are monoclinic, at 20 °C, a = 6.250(1) Å, b = 5.085(1) Å, c = 16.245(2) Å, β = 98.77(1)°, V = 510.2 Å^3, d_{calc} = 1.406 g cm^{-3}, Z = 2, $F(000)$ = 228, space group $P2_1$.

The structure was solved by the direct method using the MULTAN-80 program and refined isotropically by the full-matrix least-squares method using the SHELX-76 program. The positions of the H atoms were calculated geometrically and refined using the riding model. The refinement converged to R = 6.4%, GOF = 1.25. The molecular geometry and crystal packing were calculated using the PARST program.

This work was financially supported by the INTAS (Grant 94-2839) and the Russian Foundation for Basic Research (Project No. 97-03-33021).

References

1. V. V. Rozhkov, V. N. Voznesensky, and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 116 [*Russ. Chem. Bull.*, 1998, 115 (Engl. Transl.)].
2. R. G. Kostyanovsky, A. V. Prosyanik, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1974, 482 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1974, **23** (Engl. Transl.)].
3. R. G. Kostyanovsky, V. I. Markov, A. I. Mishchenko, and A. V. Prosyanik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 250 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1977, **26** (Engl. Transl.)].
4. R. G. Kostyanovsky, V. F. Rudchenko, A. V. Prosyanik, M. D. Isobaev, I. I. Chervin, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 628 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1977, **26** (Engl. Transl.)].
5. R. G. Kostyanovsky, A. V. Prosyanik, A. I. Mishchenko, G. V. Shustov, I. I. Chervin, N. L. Zaichenko, A. P. Pleshkova, P. N. Belov, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 1780 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28** (Engl. Transl.)].
6. R. G. Kostyanovsky, A. I. Mishchenko, A. V. Prosyanik, and N. L. Zaichenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 1572 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 1421 (Engl. Transl.)].
7. A. V. Prosyanik, A. I. Mishchenko, N. L. Zaichenko, G. V. Shustov, P. N. Belov, and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 596 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 546 (Engl. Transl.)].
8. R. G. Kostyanovsky, V. F. Rudchenko, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1975, 1685, 2621 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1975, **24** (Engl. Transl.)].
9. R. G. Kostyanovsky and V. F. Rudchenko, *Dokl. Akad. Nauk SSSR*, 1976, **231**, 878 [*Dokl. Chem.*, 1976 (Engl. Transl.)].
10. R. G. Kostyanovsky, V. F. Rudchenko, and G. V. Shustov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 1687 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1977, **26** (Engl. Transl.)].

11. V. F. Rudchenko, O. A. D'yachenko, A. B. Zolotoi, L. O. Atovmyan, and R. G. Kostyanovsky, *Dokl. Akad. Nauk SSSR*, 1979, **246**, 1150 [*Dokl. Chem.*, 1979 (Engl. Transl.)].
12. V. F. Rudchenko, O. A. D'yachenko, A. B. Zolotoi, L. O. Atovmyan, I. I. Chervin, and R. G. Kostyanovsky, *Tetrahedron*, 1982, **38**, 961.
13. A. B. Zolotoi, O. A. D'yachenko, L. O. Atovmyan, V. F. Rudchenko, and R. G. Kostyanovsky, *Zh. Strukt. Khim.*, 1984, **25**, 159 [*J. Struct. Chem. (USSR)*, 1984, **25** (Engl. Transl.)].
14. A. B. Zolotoi, O. A. D'yachenko, L. O. Atovmyan, V. F. Rudchenko, I. I. Chervin, and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin.*, 1984, 48 [*Chem. Heterocycl. Compd.*, 1984 (Engl. Transl.)].
15. A. V. Eremeev, F. D. Polyak, A. F. Mishnev, Ya. Ya. Bleidelis, E. E. Liepin'sh, Sh. S. Nasibov, I. I. Chervin, and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin.*, 1982, 1495 [*Chem. Heterocycl. Compd.*, 1982 (Engl. Transl.)].
16. I. V. Solodin, F. D. Polyak, A. V. Eremeev, I. A. Vosekalna, E. E. Liepin'sh, I. I. Chervin, and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin.*, 1985, 1355 [*Chem. Heterocycl. Compd.*, 1985 (Engl. Transl.)].
17. G. V. Shustov, F. D. Polyak, V. S. Nosova, I. T. Liepinya, G. V. Nikiforovich, and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin.*, 1988, 1461 [*Chem. Heterocycl. Compd.*, 1988 (Engl. Transl.)].
18. E. L. Schumann, L. A. Paquette, B. V. Heinselman, D. P. Wallach, J. P. Da Vanso, and M. E. Oreig, *J. Med. Pharm. Chem.*, 1962, **5**, 464.
19. A. Bax and R. Freeman, *J. Magn. Reson.*, 1981, **44**, 542.
20. R. Wasylishen and T. Shaefer, *Can. J. Chem.*, 1972, **50**, 2989.
21. I. I. Chervin, A. A. Fomichev, A. S. Moskalenko, N. L. Zaichenko, A. E. Aliev, A. V. Prosyanik, V. N. Voznesensky, and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 1110 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 972 (Engl. Transl.)].
22. A. V. Prosyanik, A. I. Mishchenko, A. B. Zolotoi, N. L. Zaichenko, O. A. D'yachenko, L. O. Atovmyan, V. I. Markov, and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 2050 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
23. S. Brukner, L. Malpezzi, A. V. Prosyanik, and S. V. Bondarenko, *Acta Crystallogr., C*, 1985, **41**, 215, 219.
24. V. F. Bystrov, *Usp. Khim.*, 1972, **41**, 513 [*Russ. Chem. Rev.*, 1972, **41** (Engl. Transl.)].

Received May 27, 1997;
in revised form July 30, 1997