Synthesis and structures of 1,1′-dialkyl-3,3′-bidiaziridines

V. Yu. Petukhova,[a]* V. V. Kuznetzov,[a] A. V. Shevtsov,[a] Yu. A. Strelenko,[a]
N. N. Makhova,[a] K. A. Lyssenko,[b] and M. Yu. Antipin[b]

[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,*
47 Leninsky prosp., 119992 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: mnn@cacr.ioc.ac.ru
[b]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,*
28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: +7 (095) 135 5085. E-mail: mishan@xray.ineos.ac.ru

First representatives of 3,3′-bidiaziridines, *viz.*, 1,1′-dialkyl-3,3′-bidiaziridines, were synthesized and isolated as mixtures of two diastereomers. In the case of Alk = Me, the diastereomers were separated. It was demonstrated by nuclear Overhauser effect experiments and X-ray diffraction analysis that the diastereomers are the racemate (*rac*-1*R**,2*R**,3*S**,1′*R**,2′*R**,3′*S**) and the *meso*-form (1*S**,2*S**,3*R**,1′*R**,2′*R**,3′*S**).

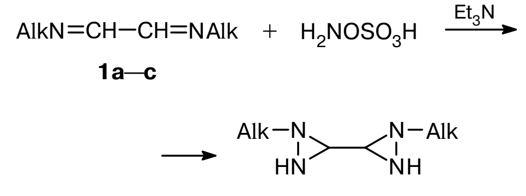
Key words: 3,3′-bidiaziridines, 1,1′-dialkyl-3,3′-bidiaziridines, pH_{opt}, diastereomers, X-ray diffraction analysis.

Only one type of compounds whose molecules contain two diaziridine rings, *viz.*, 1,1′-bis(diaziridinomethyl)amines, is known.[1] These compounds were prepared by aminomethylation of 1-*H*-diaziridines with bis(alkoxymethyl)amines. It was established that diaziridines exhibit neurotropic activity,[1,2] compounds with two diaziridine rings per molecule possessing higher activity. In this connection, it was of interest to develop simpler approaches to the preparation of this type of compounds.

In the present work, we synthesized the first representatives of 3,3′-bidiaziridines starting from the simplest dicarbonyl compound, *viz.*, from glyoxal. The following two approaches to these compounds were used: a classical procedure for the preparation of diaziridines by reactions of aldimines with aminating reagents[3,4] and a procedure developed by us.[5] The latter procedure is based on the reactions of carbonyl compounds, primary aliphatic amines, and aminating reagents in water at controlled pH of the medium.

The first approach can be used only for diimines of glyoxal prepared from amines with a branched alkyl chain, which can be isolated in the individual state.[6,7] The reactions of glyoxal with primary amines containing normal aliphatic radicals are not terminated at the stage of formation of diimines, and the latter undergo condensation or polymerization.[6] Diimines (**1a**—**c**) were synthesized according to a known procedure.[6] Their reactions with hydroxylamino-*O*-sulfonic acid (HASA) in MeOH in the presence of Et_3N afforded 1,1′-dialkyl-3,3′-bidiaziridines **2a**—**c** (Scheme 1).*

Scheme 1



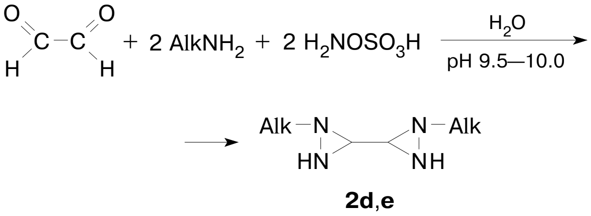
1a—**c**

2a—**c**

Alk = Pr^i (**a**); Bu^t (**b**); *cyclo*-C_6H_{11} (**c**)

1,1′-Dialkyl-3,3′-bidiaziridines containing unbranched aliphatic substituents were synthesized by the reactions of glyoxal, the corresponding amine (Alk = Me or Et), and HASA in water at controlled pH of the medium (Scheme 2). It appeared that optimum pH (pH_{opt}) in both cases varied within a narrow range (9.5—10.0) (Fig. 1), which confirms the fact established by us previously[8] that the yields of diaziridines prepared by the reactions of aldehydes, primary aliphatic amines, and aminating reagents in water depend substantially on pH of the medium.

Scheme 2



2d,**e**

Alk = Me (**d**), Et (**e**)

---

* Hereinafter, mixtures of the diastereomers of bidiaziridines, which were difficult to separate, were denoted **2a**—**e**.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 421—425, March, 2001.

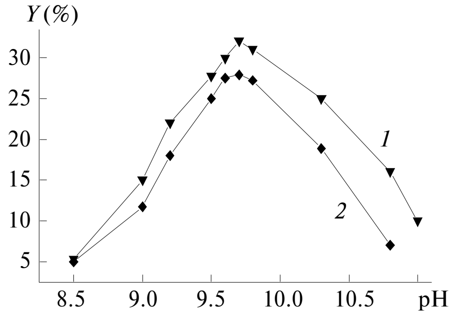


Fig. 1. Dependences of the yields (*Y*) of bidiaziridines **2d** (*1*) and **2e** (*2*) on pH of the medium (the yields were determined based on the results of iodometric titration of the reaction mixtures).

One would expect that the target compounds **2a—e** will be obtained as mixtures of diastereomers. This is associated with high configurational stability of the nitrogen atoms in diaziridines under normal conditions (the inversion barrier is 24—27 kcal mol^{-1}).[9,10] Substituents at these atoms are always in *trans* positions with respect to the plane of the ring and hence adopt the same configuration.[11,12] Therefore, both nitrogen atoms in the diaziridine ring can be considered as a single chiral center. In addition, compounds **2a—e** contain two more asymmetric centers, *viz*., the carbon atoms of the diaziridine rings. Hence it follows that four racemates (I—IV) and two *meso* forms (I and II) of compounds **2a—e** can exist (Scheme 3). A decrease in the number of stereoisomers compared to the theoretical value ($2^4 = 16$) is associated with the appearance of symmetry elements in the molecules of the *meso* forms.

Actually, using bidiaziridine **2d** as an example, it was demonstrated when the reaction mixture was chromatographed on SiO_2, the resulting product occurred (according to the ^1H NMR spectral data) as a complex mixture of diastereomers.

However, isolation of the final products by vacuum distillation or sublimation always afforded mixtures of only two diastereomers. According to the ^1H NMR spectral data, the diastereomer ratio depended on the conditions of isolation and procedures used for purification (Table 1) and varied from 2 : 1 (**2a** and **2c**) to 9 : 1 (**2e**), which is, apparently, associated with epimerization of the compounds upon heating. It should be mentioned that the signals for pairs of diastereomers in the ^1H NMR spectra do not overlap. The chemical shifts for the corresponding carbon atoms do not coincide at all only in the ^{13}C NMR spectra of the diastereomeric pairs of compounds **2d** and **2e**, whereas these shifts partially overlap in the case of the diastereomers of **2a** and **2b** and completely overlap in the case of **2c**.

The yields of the resulting bidiaziridines, the diastereomer ratios, and the selected physicochemical characteristics are given in Table 1. The spectral characteristics are listed in Table 2. In the case of the diastereomers of **2d**, we succeeded in isolating individual components by vacuum sublimation (or distillation) followed by fractional crystallization from hexane. With the aim of

Scheme 3

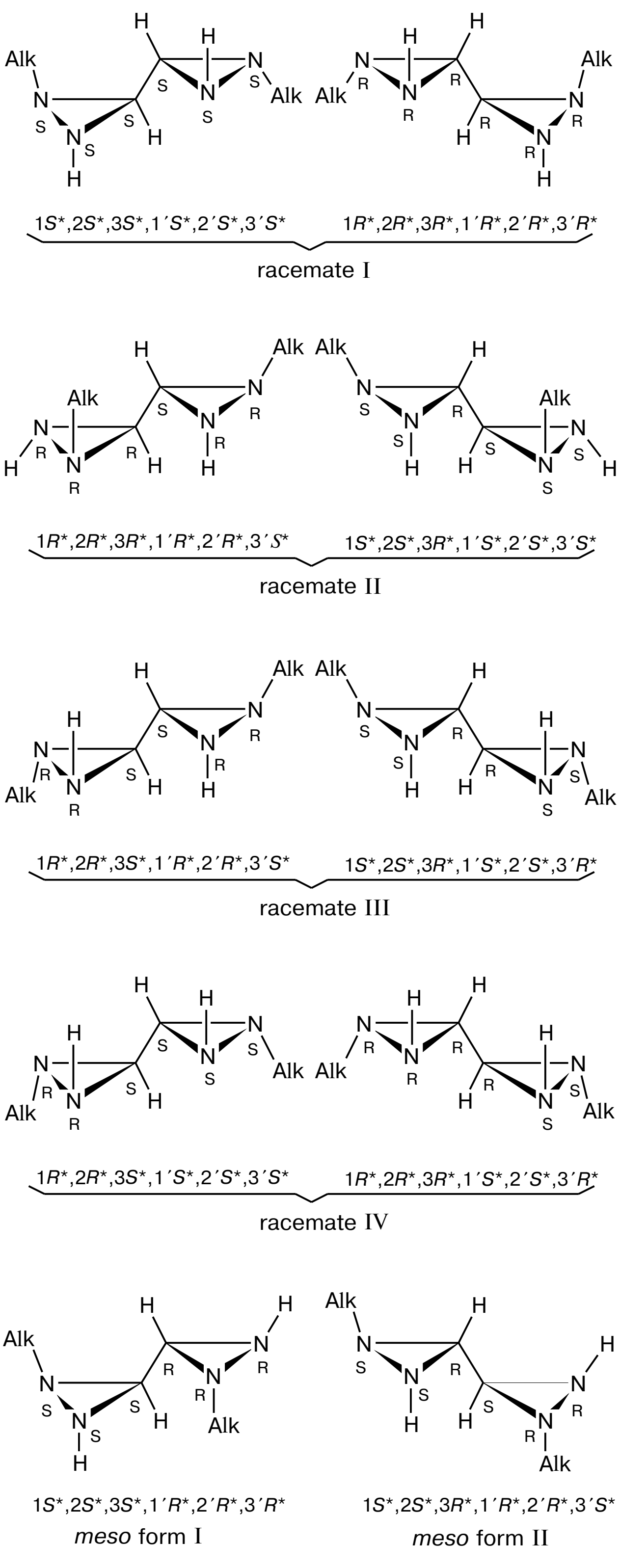


Table 1. Yields and selected physicochemical characteristics of two diastereomers of 1,1′-dialkyl-3,3′-bidiaziridines **2**

Bidiaziridines	Yield (%) (diastereomer ratio)	M.p./°C [B.p./°C (*p*/Torr)]	R_f ($CHCl_3$: MeOH = = 9 : 1)	Found / Calculated (%) C	H	N	Molecular formula
2a	78.0 (2 : 1)	70—89	0.49	$\underline{56.47}$ 56.51	$\underline{10.59}$ 10.63	$\underline{32.94}$ 32.86	$C_8H_{18}N_4$
2b	81.0 (6 : 1)	65—97	0.50	$\underline{60.61}$ 60.51	$\underline{11.11}$ 11.12	$\underline{28.28}$ 28.37	$C_{10}H_{22}N_4$
2c	76.0 (2 : 1)	157—167	0.47	$\underline{67.20}$ 67.12	$\underline{10.40}$ 10.59	$\underline{22.40}$ 22.29	$C_{14}H_{26}N_4$
2d	Mixture of diastereomers 20.0 (~3 : 1)	Mixture of crystals and a liquid	0.52	$\underline{42.17}$ 42.08	$\underline{8.88}$ 8.84	$\underline{48.95}$ 49.08	$C_4H_{10}N_4$
	meso form II: 7.0—10.0	[65—70 (1.5)] 118—119	0.52				
	racemate III: 2.1	96—97	0.52				
2e	19.0 (9:1)	Mixture of crystals and a liquid [70—75 (1.5)] 85—88	0.55	$\underline{50.64}$ 50.70	$\underline{10.08}$ 9.86	$\underline{39.28}$ 39.44	$C_6H_{14}N_4$

Table 2. Data of ^{1}H and ^{13}C NMR and IR spectroscopy for mixtures of two diastereomers of 1,1′-dialkyl-3,3′-bidiaziridines **2***

Bidiaziridine	IR, ν/cm^{-1}	^{1}H NMR, δ, *J*/Hz ($CDCl_3$)	^{13}C NMR, δ, *J*/Hz ($CDCl_3$)
2a	745, 772, 824, 888, 960, 976, 1088, 1144, 1184, 1220, 1340, 1384, 1460, 2936, 2952, 2976, 3064, 3184	Major diastereomer: 1.06 (d, 6 H, Me, ^3J = 6.40); 1.17 (d, 6 H, Me, ^3J = 6.40); 1.77 (m, 2 H, CH, ^3J = 6.40); 2.08 (d, 2 H, NH, ^3J = 6.30); 2.53 (d, 2 H, CH_{ring}, ^3J = 6.30) Minor diastereomer: 1.05 (d, 6 H, Me, ^3J = 6.40); 1.15 (d, 6 H, Me, ^3J = 6.40); 1.77 (m, 2 H, CH, ^3J = 6.40); 1.95 (d, 2 H, NH, ^3J = 6.30); 2.69 (d, 2 H, CH_{ring}, ^3J = 6.30)	19.77 (Me); 21.34 (Me); 57.80 ($\underline{C}Me_2$); 60.40 (C_{ring})
2b	704, 752, 832, 840, 936, 1024, 1104, 1176, 1212, 1240, 1304, 1344, 1360, 1472, 2936, 2944, 2976, 3096, 3192	Major diastereomer: 1.04 (s, 18 H, Me); 1.85 (d, 2 H, NH, ^3J = 6.40); 2.61 (d, 2 H, CH_{ring}, ^3J = 6.40) Minor diastereomer: 1.00 (s, 18 H, Me); 1.75 (d, 2 H, NH, ^3J = 6.40); 2.75 (d, 2 H, CH_{ring}, ^3J = 6.40)	25.26 and 25.72 (Me); 52.54 ($\underline{C}Me_3$); 55.37 (C_{ring})
2c**	800, 840, 872, 888, 936, 976, 1052, 1108, 1152, 1192, 1248, 1338, 1372, 1448, 2928, 2974, 3042, 3088	Major diastereomer: 1.25 (m, 12 H, $CH_2CH_2CH_2$); 1.75 (m, 10 H, CH_2CHCH_2); 2.1 (d, 2 H, NH, ^3J = 6.35); 2.72 (d, 2 H, CH_{ring}, ^3J = 6.35) Minor diastereomer: 1.25 (m, 12 H, $CH_2CH_2CH_2$); 1.75 (m, 10 H, CH_2CHCH_2); 2.28 (d, 2 H, NH, ^3J = 6.35); 2.61 (d, 2 H, CH_{ring}, ^3J = 6.35)	24.42 (CH_2); 24.68 (CH_2); 26.07 (CH_2); 30.48 (CH_2); 31.97 (CH_2); 57.55 (CH); 68.08 (C_{ring})
2d	730, 830, 1010, 1160, 1250, 1380, 1580, 2820, 2960, 3160	*Meso* form II: 2.04 (d, 2 H, NH, ^3J = 6.35); 2.43 (s, 6 H, N—Me); 2.77 (d, 2 H, CH_{ring}, ^3J = 6.35) Racemate III: 2.09 (d, 2 H, NH, ^3J = 6.34); 2.41 (s, 6 H, N—Me); 2.53 (d, 2 H, CH_{ring}, ^3J = 6.34)	47.41 (Me); 58.81 (C_{ring}); 47.31 (Me); 58.63. (C_{ring})
2e	760, 790, 830, 940, 1100, 1120, 1160, 1190, 1290, 1350, 1470, 2740, 2890, 2910, 2990, 3220	Major diastereomer: 1.05 (t, 6 H, Me, ^3J = 7.30); 2.01 (d, 2 H, NH, ^3J = 7.80); 2.25 (m, 2 H, CH, ^2J = 12.25, ^3J = 7.30); 2.48 (m, 2 H, CH, ^2J = 12.25, ^3J = 7.30); 2.72 (d, 2 H, CH_{ring}, ^3J = 7.80) Minor diastereomer:*** 1.01 (t, 6 H, Me, ^3J = 7.30); 2.05 (d, 2 H, NH, ^3J = 7.80)	12.80 and 12.91 (Me); 54.66 and 54.80 (CH_2); 57.50 and 57.67 (C_{ring})

* The absorption bands in the IR spectra are given for a mixture of diastereomers.

** DMSO-d_6.

*** It was difficult to identify the signals for the protons of the N—CH_2 and CH_{ring} groups due to an insignificant amount of this diastereomer.

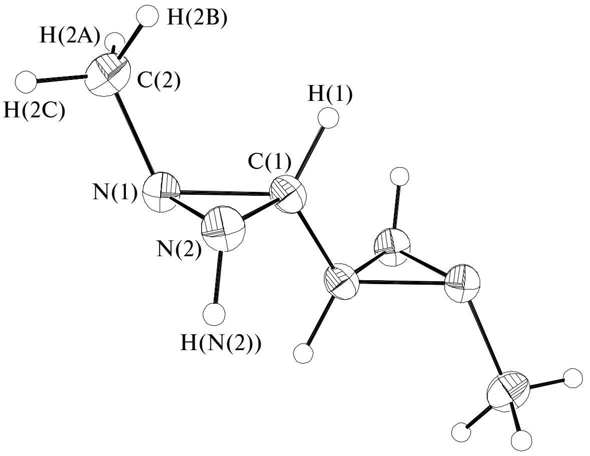


Fig. 2. Overall view of the *meso* form II of molecule **2d**; the atoms are represented by probability thermal ellipsoids (p = 50%). Main bond lengths (d) and bond angles (φ) are given below.

Bond	d/Å
N(1)—C(1)	1.445(2)
N(1)—C(2)	1.461(2)
N(1)—N(2)	1.512(1)
N(2)—C(1)	1.459(2)
C(1)—C(1A)	1.490(2)

Angle	φ/deg
C(1)—N(1)—C(2)	114.5(1)
C(1)—N(1)—N(2)	59.07(6)
C(2)—N(1)—N(2)	109.58(9)
C(1)—N(2)—N(1)	58.17(7)
N(1)—C(1)—N(2)	62.76(7)
N(1)—C(1)—C(1A)	116.0(1)
N(2)—C(1)—C(1A)	120.1(1)

establishing the configurations of the substituents in these diastereomers, the nuclear Overhauser effects (NOE) were measured. In both diastereomers under study, strong nuclear Overhauser effects were observed between the protons of the CH and N—Me groups of the diaziridine ring. This result allows the conclusion that the Me groups at the nitrogen atom and the hydrogen atoms at the carbon atom of the ring in the diastereomers under consideration are located on one side of the diaziridine ring. In addition, weak NOE between the protons of the CH and NH groups was detected for both diastereomers. Apparently, this NOE corresponds to the nuclear Overhauser effect between the protons of the CH group of one ring and the protons of the NH group of another ring. An analogous result was obtained in the nuclear Overhauser effect experiments performed for a mixture of two diastereomers of bidiaziridine **2a**. For both diastereomers, strong nuclear Overhauser effects were observed between the hydrogen atoms of the CH groups of the diaziridine ring and the protons of the isopropyl fragment. Weaker NOE were observed between the protons of the Me groups of the isopropyl substituent and of the CH groups of the diaziridine ring as well as between the protons of the CH and NH groups of the rings.* Based on these results, it can be suggested that the diastereomers isolated are the racemate III and the *meso* form II. With the aim of unambiguously establishing the stereochemistry of bidiaziridine **2d**, one of the diastereomers (characterized by a higher melting point) was studied by X-ray diffraction analysis. It was demonstrated that this diastereomer has the structure of the *meso* form II (Fig. 2). In the crystal, the molecules of this diastereomer are located on a crystallographic twofold axis passing through the midpoint of the C(1)—C(1A) bond. The bond lengths in the molecule are close to the values expected for diaziridine derivatives.[13] The C(2)N(1)N(2)H(N(2)), H(N(2))N(2)N(1)C(2), and C(2)N(1)C(1)H(1) torsion angles describing the mutual arrangement of the substituents at the nitrogen and carbon atoms are 148°, 156°, and 5°, respectively.

Analysis of the crystal packing demonstrated that the molecules are linked in layers parallel to the crystallographic plane *bc* through N—HN bonds.

Therefore, the data of X-ray diffraction analysis of one of the diastereomers of compound **2d** confirmed the results obtained in the Overhauser effect experiments. Apparently, the minor diastereomer of this compound is the racemate III. One can say with a fair degree of assurance that the mixtures of two diastereomers of 1,1′-dialkyl-3,3′-bidiaziridines **2a—c**,**e** isolated by us also consisted of the analogous *meso* forms and racemates.

Experimental

The IR spectra were recorded on a UR-20 spectrometer in KBr pellets. The NMR spectra were measured on a Bruker WM-250 (^{1}H, 250 MHz) and Bruker AM-300 (^{13}C, 75.5 MHz) spectrometers. The nuclear Overhauser effects were measured on a Bruker DRX-500 spectrometer; the chemical shifts are given in the δ scale relative to Me_4Si. TLC was carried out on Silufol UV-254 plates; spots were visualized with I_2 vapor and independently by spraying the TLC plates with a solution of diphenylamine in acetone followed by heating of the plates. The value of pH of the medium was monitored using an EV-74 ionometer. The decomposition temperatures of the resulting compounds were determined on a Boetius PHMK 05 instrument. X-ray diffraction study was performed on a Smart 1000 CCD diffractometer.

1,1′-Dialkyl-3,3′-bidiaziridines 2a—c (general procedure). Triethylamine (12.12 g, 0.12 mol) and a 95% HASA solution (7.12 g, 0.06 mol) were successively added to a solution of the corresponding 1,2-bis(alkyliminoethane) (0.03 mol) in MeOH (60 mL) at −5—0 °C. The reaction mixture was kept at −3—0 °C for 1 h and then at 18—20 °C for 12 h. The solvent was evaporated *in vacuo* and the residue was sublimed. Mixtures of diastereomeric 1,1′-diisopropyl-3,3′-bidiaziridines (**2a**) (4.0 g, 78%), sublim.t. 40—42 °C (15 Torr), 1,1′-di-*tert*-butyl-3,3′-bidiaziridines (**2b**) (4.81 g, 81%), sublim.t. 70—72 °C (15 Torr), and 1,1′-dicyclohexyl-3,3′-bidiaziridines (**2c**) (5.70 g, 76%), sublim.t. 100—101 °C (15 Torr), were obtained.

1,1′-Dialkyl-3,3′-bidiaziridines 2d,e (general procedure). A 36% aqueous solution of glyoxal (6.4 mL, 0.05 mol) was added to a solution of the corresponding primary amine (0.1 mol) in water (50 mL) at 0—5 °C and then pH was adjusted to the required value by adding a 50% aqueous solution of H_2SO_4 at 0—5 °C. At the same temperature, a 95% HASA solution (11.9 g, 0.1 mol) was added portionwise, pH being maintained

---

* Measurements of the nuclear Overhauser effects for compounds **2a**,**c**,**e** present difficulties due to complex multiplicities of the signals for the corresponding protons.

by the simultaneous addition of a 30% aqueous solution of KOH. The reaction mixture was kept at 5—10 °C for 1 h and then at 18—20 °C for 4—5 h, pH being maintained in the above-mentioned range. The yields of the resulting diaziridines were determined by iodometric titration[14] (see Fig. 1) (the maximum yield was achieved in the pH range of 9.5—10.0). The reaction mixture was saturated with NaCl and extracted with $CHCl_3$ (3×60 mL). The extract was dried over K_2CO_3 and the solvent was evaporated *in vacuo* (the temperature of the bath was ≤25 °C). 1,1′-Dimethyl-3,3′-bidiaziridine (**2d**) was isolated according to two procedures (***A*** and ***B***).

A. Isolation was carried out on a column with silica gel μ 40/100 using a 8.5 : 1.5 $CHCl_3$—MeOH mixture as the eluent. At pH_{opt} = 9.5—10, compound **2d** (the ratio between the *meso* form II and the racemate III was 3 : 1) was obtained in a yield of 1.14 g (20%). After sublimation (sublim.t. was 40—45 °C (1.5 Torr)) and fractional crystallization of the mixture of the diastereomers of bidiaziridine **2d** from hexane, the *meso* form II, m.p. 118—119 °C, and the racemate III, m.p. 96—97 °C, were obtained in yields of 0.40 g (7%) and 0.12 g (2.1%), respectively.

B. Isolation was carried out by vacuum distillation followed by sublimation and additional recrystallization from hexane. The *meso* form II, b.p. 65—68 °C (1.5 Torr), m.p. 118—119 °C, was obtained in a yield of 0.57 g (10%).

1,1′-Diethyl-3,3′-bidiaziridines (**2e**) were isolated by sublimation (sublim.t. was 40—45 °C (1.5 Torr)) followed by crystallization from hexane. A mixture of the diastereomers of bidiaziridine **2e** (according ^{1}H NMR spectral data, the ratio of the diastereomers was ~9 : 1) was obtained in a yield of 1.35 g (19%), m.p. 75—88 °C.

X-ray diffraction study of the *meso* form II (1*S,2*S**,3*R**,1′*R**,2′*R**,3′*S**) of bidiaziridine 2d.** Single crystals were prepared by vacuum sublimation followed by crystallization from hexane. The crystals of $C_4H_{10}N_4$ are monoclinic, space group $C2/c$, a = 17.894(3) Å, b = 4.6303(8) Å, c = 8.190(1) Å, β = 113.686(4)°, V = 621.4(2) Å^3, Z = 4, M = 114.16, d_{calc} = 1.220 g cm^{-3}, μ(Mo-Kα) = 0.84 cm^{-1}, $F(000)$ = 248. The intensities of 1146 reflections were measured at 110 K (λ(Mo-Kα) = 0.71072 Å, ω scanning technique, the scan step was 0.3°, frames were exposed for 10 s, $2\theta < 59°$). The structure was solved and refined with the use of 681 independent reflections. The structure was solved by the direct method and refined by the full-matrix least-squares method in the isotropic-anisotropic approximation based on F^2. The positions of the hydrogen atoms were located from difference Fourier syntheses and refined isotropically. The final values of the R factors were as follows: wR_2 = 0.1669 and GOF 1.062 using all independent reflections (R_1 = 0.0594 based on F using 574 reflections with $I > 2\sigma(I)$). All calculations were performed with the use of the SHELXTL PLUS 5.0 program package. The complete tables of the atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 9703-33021a) and by the INTAS European Foundation (Grant 99-0157).

References

1. R. G. Kostyanovskii, G. V. Shustov, and O. L. Nabiev, *Khim.-farm. Zh.*, 1986, **20**, 671 [*Pharm. Chem. J.*, 1986, **20** (Engl. Transl.)].
2. L. I. Khmel′nitskii, N. N. Makhova, O. V. Lebedev, L. V. Epishina, and L. I. Suvorova, *Tez. dokl. II s"ezda farmatsevtov Latv. SSR* [*Abstrs. of Papers, II Meeting of Pharmacists of Latv. SSR*], Riga, 1984, (in Russian).
3. E. Schmitz and D. Habisch, *Chem. Ber.*, 1962, **95**, 680.
4. E. Schmitz and K. Schinkowski, *Chem. Ber.*, 1964, **97**, 49.
5. V. V. Kuznetsov, N. N. Makhova, Yu. A. Strelenko, and L. I. Khmel′nitskii, *Izv. Akad. Nauk, Ser. Khim.*, 1991, 2861 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 2496 (Engl. Transl.)].
6. J. Carson, *J. Am. Chem. Soc.*, 1953, **75**, 4337.
7. M. D. Hurwitz, US Pat. 2, 582, 128, Jan. 8, 1952; *Chem. Abstr.*, 1952, **46**, 8146f.
8. V. V. Kuznetsov, N. N. Makhova, and L. I. Khmel′nitskii, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1410 [*Russ. Chem. Bull.*, 1997, **46**, 1534 (Engl. Transl.)].
9. A. Mannschreck and W. Seitz, *Angew. Chem.*, 1969, **81**, 224.
10. R. G. Kostyanovskii and G. V. Shustov, *Dokl. Akad. Nauk SSSR*, 1977, **232**, 1081 [*Dokl. Chem.*, 1977 (Engl. Transl.)].
11. A. Mannschreck, R. Radeglia, E. Grundemann, and R. Ohme, *Chem. Ber.*, 1967, **100**, 1778.
12. G. V. Shustov, A. B. Zolotoi, N. L. Zaichenko, O. A. Dyachenko, L. O. Atovmyan, and R. G. Kostyanovsky, *Tetrahedron*, 1984, **40**, 2151.
13. *Structure Correlations*, Eds. H.-B. Burgi and Y. D. Dunitz, VCH: Weinheim, 1994, **1**, 767—780.
14. H. J. Abendroth, *Angew. Chem.*, 1961, **73**, 67.

Received December 21, 1999;
in revised form October 9, 2000