1,2-Bis(methylamino)ethane-1,2-diol dihydrochloride as a new precursor of 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine

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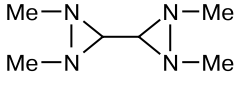
Using the synthesis of 1,2-bis(methylamino)ethane-1,2-diol dihydrochloride (**5**) as an example, it was demonstrated that aliphatic α-aminocarbinols can be stabilized as hydrochlorides. The reaction of compound **5** with *N*-chloromethylamine in $CHCl_3$ in the presence of K_2CO_3 afforded 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine as a mixture of diastereomers (a racemate and a *meso* form). The *meso* form was isolated in the individual state and its structure was established by X-ray diffraction analysis. The kinetics of inversional epimerization was studied.

Key words: 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine, 1,2-bis(methylamino)ethane-1,2-diol dihydrochloride, α-aminocarbinols, diaziridines, enantiomers, inversional epimerization, kinetics, X-ray diffraction analysis.

Diaziridines are convenient objects for studying the stereochemistry of the nitrogen atom due to their high inversion barriers (24—27 kcal mol^{-1}).[1,2] Examples of resolution of monocyclic diaziridines into enantiomers,[3—7] including spontaneous resolution,[7] were reported. It was found that certain diaziridine derivatives exhibit neurotropic activity, which increases with increasing number of diaziridine rings in the molecule.[8—10] Since the preparation of enantiomerically pure pharmaceuticals is one of the main recent problems of pharmaceutical chemistry, studies of the stereochemistry of diaziridines containing two diaziridine rings are of considerable importance.

Until recently, only bidiaziridines, in which the diaziridine rings are linked by a bridge through one of the nitrogen atoms (1,1′-bis(diaziridinomethyl)amines), were described.[9] Earlier,[11] we have synthesized 1,1′-dialkyl-3,3′-bidiaziridines **1**, which can exist as six diastereomers, *viz.*, four racemates and two *meso* forms. However, only thermodynamically most favorable diastereomers (one of the racemates and one *meso* form) were isolated. A number of physicochemical characteristics (boiling and freezing points, density, refractive index, ionization potential) of 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine (**2**), which is yet another representative of bidiaziridines, were determined in the studies.[12—14] However, neither a procedure for its synthesis nor its stereochemical features were described. It should be noted that compound **2** exists as a mixture of only two diastereomers (one racemate and one *meso* form), which allows one to rather easily separate these diastereomers and study their structures and inversional epimerization.



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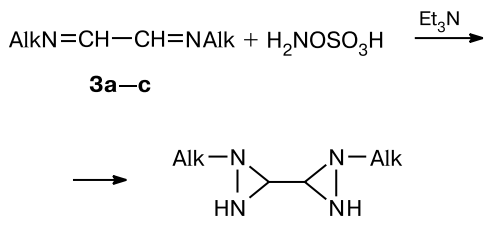
The synthesis of 1,1′-dialkyl-3,3′-bidiaziridines **1a—c** is based on the reaction of hydroxylamine-*O*-sulfonic acid with glyoxal diimines **3a—c** prepared from amines with a branched alkyl chain[15,16] (Scheme 1). These compounds can be isolated in the individual form.

Scheme 1



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

The reactions of glyoxal with primary normal aliphatic amines do not stop at the step of formation of diimines, which undergo subsequent self-condensation or polymerization.[15] Hence, 1,1′-dimethyl-3,3′-bidiaziridine (**1d**) was synthesized[11] using an approach,[17] which is based on

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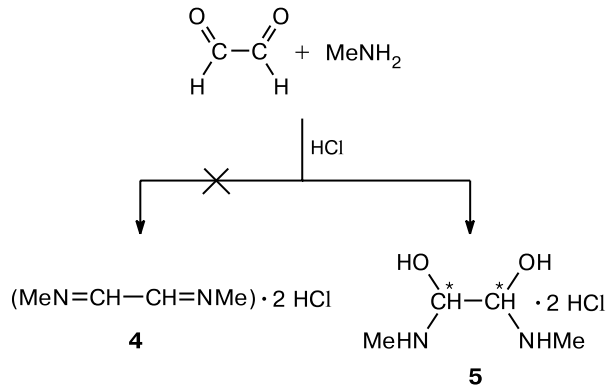
the reaction of 1 mole of glyoxal with 2 moles of methylamine and 2 moles of hydroxylamine-*O*-sulfonic acid at controlled pH of a medium. The optimum pH was found to be 9.5—10. However, the yields of the racemate and the *meso* form of **1d** were only 2.1 and 10%, respectively. Evidently, it was necessary to develop an alternative approach to the synthesis of compound **2**. The present study was aimed at searching for new procedures for the preparation of 3,3′-bidiaziridines using 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine (**2**) as an example.

For this purpose, we attempted to stabilize diimine of glyoxal and methylamine at the instant of its formation as a hydrochloride **4** (Scheme 2). We studied the reactions of concentrated solutions of glyoxal and an excess of methylamine in water followed by rapid treatment of the reaction mixture with solid NaOH and treatment of the layer that was separated out with concentrated HCl. The white crystalline precipitate that formed was studied by various physicochemical methods.

Scheme 2

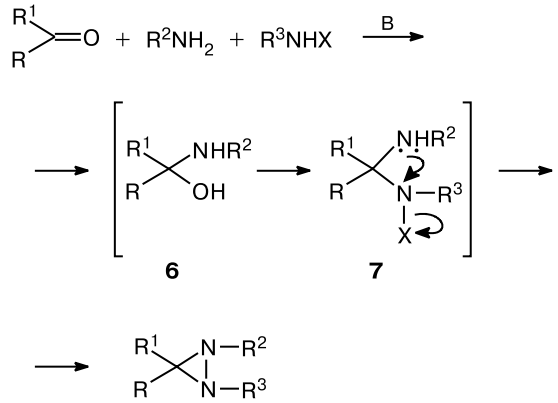


Analysis of the ^{1}H NMR spectra of a CD_3OD solution of the compound synthesized revealed no signals of the N=CH fragments of compound **4**, which would be observed at low field. Moreover, the spectroscopic data provide evidence that the reaction afforded two (rather than one) compounds. The spectrum has two groups of signals as two pairs of doublets with centers at δ 4.25 and 4.68 (^3J = 4.5 Hz) and at δ 4.28 and 4.75 (^3J = 3.6 Hz), which can be assigned to signals of the CH fragments, and two singlets at δ 2.88 and 2.90 of the N—Me fragments. The assignment of the signals was confirmed by the 2D COSY-LR spectrum, which shows cross-peaks corresponding to the spin-spin coupling constants ^3J and the long-range spin-spin coupling constants between the CH and N—Me fragments. This ^{1}H NMR spectral pattern indicates that the compound synthesized exists as a mixture of diastereomers (a racemate and a *meso*-form) of bis(α-aminocarbinol) dihydrochloride **5** (Scheme 2). In addition, the ^{1}H NMR spectrum has also signals of $MeNH_2 \cdot HCl$ (singlet at δ 2.55), which was confirmed by the addition of an authentic sample into a sample tube for NMR measurements. According to the ^{1}H NMR spectroscopic data, the percentage of bis(α-aminocarbinol) dihydrochloride **5** in the mixture was ≈45%.

Since we failed to remove $MeNH_2 \cdot HCl$ by crystallization of the mixture, it was impossible to perform elemental analysis of the reaction product. However, the results of ^{13}C NMR spectroscopy and mass spectrometry confirmed the assumed structure of compound **5**. The ^{13}C NMR spectrum shows signals of the carbon atoms of four CH fragments (at δ 91.5, 98.7, 91.8, and 98.9) and two N—Me groups (at δ 29.1 and 29.2) of a mixture of diastereomers. The assignment of the signals in the ^{13}C NMR spectrum was confirmed by the 2D ^{1}H—^{13}C HMQC technique. In the ^{13}C NMR spectrum, the signal at δ 25.0 corresponds to the carbon atom of $MeNH_2 \cdot HCl$. A molecular ion peak is absent in the mass spectrum, but the spectrum shows peaks of fragment ions corresponding to fragments of compound **5** at m/z 60 $(MeNHCHOH)^+$, 44 $(HOCHN)^+$, 42 $(MeNHC)^+$, and 36—38 (HCl). It should be noted that compound **5** appeared to be unstable in protic media. Thus, more prolonged storage of a solution of compound **5** in CD_3OD and, all the more, in D_2O led to a change in the spectral pattern.

In our opinion, the most realistic scheme of the preparation of diaziridines from carbonyl compounds, primary aliphatic amines, and aminating reagents involves the formation of α-aminocarbinol **6** and aminal product **7**, the latter being closed to form the diaziridine ring through the S_N^i mechanism in the presence of bases[17] (Scheme 3).

Scheme 3



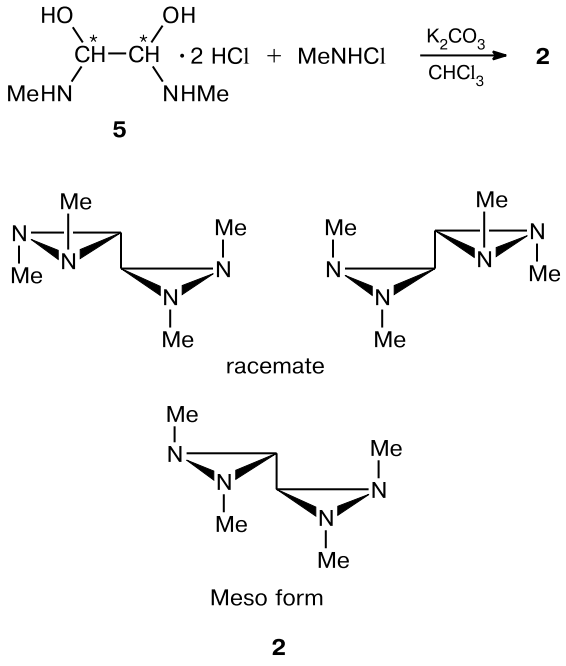
R, R^1 = Alk, CH_2—Ar; R^2, R^3 = Alk; X = Hal, OSO_3H

B is base

Since compound **5** is bis(α-aminocarbinol) dihydrochloride, 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine (**2**) can be synthesized by introducing compound **5** directly into

the reaction with *N*-chloromethylamine and a base in an organic solvent. It was unreasonable to use water or alcohols because of instability of compound **5** in these media. The reaction was carried out in chloroform or dichloromethane with the use of triethylamine, diethylamine, or potassium carbonate as a base. It was expected that after neutralization with HCl, free bis(α-aminocarbinol) **5′** would more rapidly react with *N*-chloromethylamine than undergo self-condensation. However, in the presence of organic bases, self-condensation appeared to dominate over the synthesis of diaziridine. We succeeded in synthesizing the target bidiaziridine **2** only with the use of finely ground potassium carbonate as a base under conditions[18] where the reaction was carried out in a heterogeneous medium and free bis(α-aminocarbinol) **5′** was, most likely, gradually liberated from hydrochloric salt **5** and its concentration in the solution was low at any instant of time (Scheme 4). The following conditions were found to be optimum: chloroform as the solvent, a 1.5-fold molar excess of *N*-chloromethylamine and potassium carbonate, and stirring of the reaction mixture at 20—22 °C for 6 h. The yield of bidiaziridine **2** was ≈73.6%. Its physicochemical characteristics are in complete agreement with the published data.[12]

Scheme 4



According to the ^{1}H NMR spectroscopic data, 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine (**2**) exists as a mixture of two diastereomers in a ratio of ≈3 : 2 (Fig. 1, *a*). After vacuum distillation followed by cooling to −18 °C, one of diastereomers precipitated and was obtained in the individual form (m.p. ~40 °C). The ^{1}H NMR spectrum of this diastereomer is shown in Fig. 1, *b*.

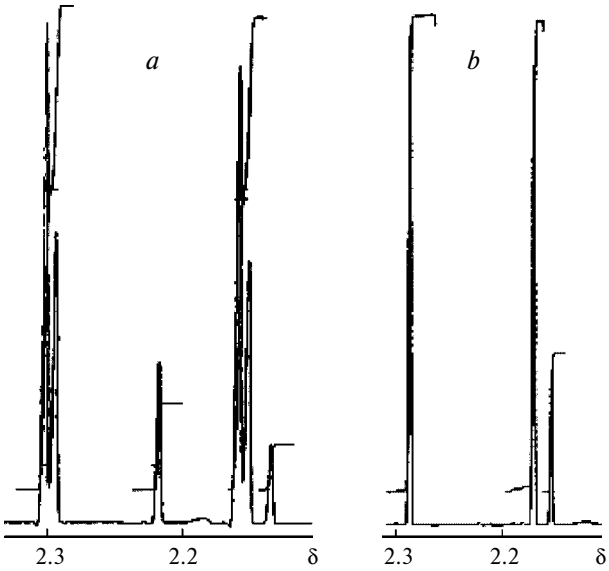


Fig. 1. ^{1}H NMR spectrum of a mixture of diastereomers **2a** (*a*) and the *meso* form **2b** (*b*) of compound **1**.

In the ^{1}H NMR spectrum of a mixture of diastereomers of **2** in an optically active solvent, *viz.*, (−)-*S*-*N*,*N*-dimethyl(1-phenyl)ethylamine, the signal of the CH protons of the liquid diastereomer splits, which indicates that the liquid diastereomer is a racemate, whereas the solid diastereomer is a *meso* form. To unambiguously establish the structures of the diastereomers of 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine (**2**), we studied the solid diastereomer by X-ray diffraction analysis. The results of this study were in complete agreement with the ^{1}H NMR spectroscopic data. Therefore, the solid diastereomer is a *meso* form, whereas the racemate was obtained as the major diastereomer.

In the crystal structure, the molecule of the *meso* form of **2** occupies a special position; the center of inversion is located at the midpoint of the C(3)—C(3A) bond. The main bond lengths (Fig. 2) are similar to the corresponding distances in 1,1′-dimethyl-3,3′-bidiaziridine (**1d**) studied earlier.[11] In particular, the N(1)—N(2) bond lengths in the *meso* forms of **2** and **1d** are 1.512(2) and 1.503(2) Å, respectively. Analysis of the crystal packing demonstrated that all intermolecular contacts correspond to usual van der Waals interactions.

After separation of the crystals of the *meso* form, the mixture contained the racemate and the *meso* form in a ratio of 4 : 1 (according to the ^{1}H NMR spectroscopic data). However, the ratio reverted to the initial value of 3 : 2 upon distillation of this mixture. Apparently, the racemate was subjected to inversional epimerization under distillation conditions. The kinetics of inversional epimerization of diastereomers of compound **2** was stud-

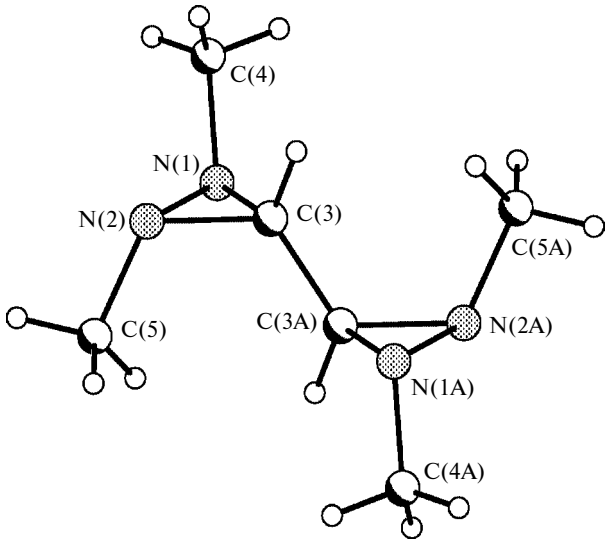


Fig. 2. Overall molecular view of the *meso*-form of **2** in the crystal.

Selected bond lengths (d/Å)		Bond angles (ω/deg)	
N(1)—N(2)	1.503(2)	C(3)—N(1)—N(2)	59.4(1)
N(1)—C(3)	1.454(2)	N(1)—C(3)—N(2)	62.0(1)
N(2)—C(3)	1.466(3)	C(3)—N(2)—N(1)	58.6(1)
C(3)—C(3A)	1.481(4)		

Table 1. Epimerization of diastereomers of **2** at 80 °C (x_∞ = 63.3%)

τ /min	a	x	$x_\infty - x$	$\ln(x_\infty/(x_\infty - x))$	$(\vec{k} + \overleftarrow{k}) \cdot 10^3$ /min
		(%)			
5	97.0	3.0	60.3	0.048	8.04
10	94.8	5.2	58.1	0.086	8.01
20	90.8	9.2	54.1	0.157	7.53
40	83.9	16.1	47.2	0.295	7.44
80	71.5	28.5	34.8	0.596	7.42
160	56.4	43.6	19.7	1.165	7.31
320	43.2	56.8	6.5	2.315	7.20
440	39.3	60.7	2.6	3.198	7.33
560	36.8	63.2	—	—	—
680	36.6	63.4	—	—	—
800	36.7	63.3	—	—	—

Note. Here and in Tables 2—4, the following notations are used: a is the concentration of the starting *meso* form at the moment τ; x is the concentration of the racemate at the moment τ; x_∞ is the concentration of the racemate corresponding to the equilibrium (in all cases, x_∞ was calculated as the arithmetic mean of the three last in time values of x; τ is the time; $\vec{k}$ is the rate constant of the direct reaction (isomerization of the *meso* form to the racemate); $\overleftarrow{k}$ is the rate constant of the reverse reaction (isomerization of the racemate to the *meso* form). The rate constants of the direct and reverse reactions and the kinetic parameters of the process were calculated by equations reported in the study.[19] The activation energy was calculated by the modified Eyring equation.[20]

Table 2. Epimerization of diastereomers of **2** at 90 °C (x_∞ = 61.9%)

τ/min	a	x	$x_\infty - x$	$\ln(x_\infty/(x_\infty - x))$	$(\vec{k} + \overleftarrow{k}) \cdot 10^3$ /min
		(%)			
5	93.3	6.7	55.2	0.114	2.29
10	87.1	12.9	49.0	0.234	2.34
15	82.2	17.8	44.1	0.339	2.26
20	77.1	22.9	39.0	0.462	2.31
30	69.2	30.8	31.1	0.684	2.28
40	62.5	37.5	24.4	0.932	2.33
80	48.2	51.8	10.1	1.816	2.27
160	38.3	61.7	—	—	—
320	37.2	62.1	—	—	—
440	38.0	61.9	—	—	—

Table 3. Epimerization of diastereomers of **2** at 100 °C (x_∞ = 61.6%)

τ/min	a	x	$x_\infty - x$	$\ln(x_\infty/(x_\infty - x))$	$(\vec{k} + \overleftarrow{k}) \cdot 10^3$ /min
		(%)			
5	79.2	20.8	40.8	0.410	8.20
10	65.8	34.2	27.4	0.810	8.01
15	56.8	43.2	18.4	1.208	8.06
20	50.7	49.3	12.3	1.611	8.06
30	43.8	56.2	5.4	2.434	8.11
40	40.7	59.3	2.3	3.288	8.30
80	38.4	61.6	—	—	—
160	38.6	61.4	—	—	—
320	38.2	61.8	—	—	—

Table 4. Epimerization of diastereomers of **2** at 110 °C (x_∞ = 61.6%)

τ/min	a	x	$x_\infty - x$	$\ln(x_\infty/(x_\infty - x))$	$(\vec{k} + \overleftarrow{k}) \cdot 10^3$ /min
		(%)			
2.5	75.1	24.9	36.7	0.520	20.8
5	61.5	38.5	23.1	0.981	19.6
10	47.2	52.8	8.8	1.951	19.5
15	41.9	58.1	3.5	2.870	19.1
20	39.6	60.4	1.2	3.938	19.7
25	38.9	61.1	0.5	4.810	19.3
40	38.5	61.5	—	—	—
80	38.3	61.7	—	—	—
160	38.4	61.6	—	—	—

ied by ^{1}H NMR spectroscopy. The study was carried out for one of diastereomers (the solid *meso* form). Equal amounts of the *meso* form were placed in sample tubes for ^{1}H NMR measurements and the tubes were heated at 80, 90, 100, and 110 °C. At certain intervals, the samples were rapidly cooled, dissolved in $CDCl_3$, and kept in a refrigerator. Each subsequent sample was subjected to

Table 5. Kinetic parameters of epimerization of diastereomers of compound **2**

T/°C	$\vec{k}\cdot10^{-5}$	$\overleftarrow{k}\cdot10^{-5}$	$\ln\vec{A}$ ($\ln\overleftarrow{A}$)	$\Delta\vec{G}$ ($\Delta\overleftarrow{G}$)	$\vec{E}_A$ ($\overleftarrow{E}_A$)
	s^{-1}			kcal mol^{-1}	
80	7.92±0.43	4.59±0.43	−8.25±0.53	27.35±0.24	30.59±0.56
90	23.73±0.43	14.61±0.43	(−7.85±0.53)	(27.70±0.24)	(30.78±0.56)
100	83.82±1.81	52.25±1.81			
110	202.61±8.75	126.57±8.75			

more prolonged heating followed by analogous workup. After completion of epimerization, the ^{1}H NMR spectra of all samples were recorded. At the moment τ, the diastereomer ratio was determined from the integral intensity ratio (%) of the signals of both the N—CH_3 and CH groups by calculating the average values (Tables 1—4).

The kinetic parameters of the epimerization process are given in Table 5.

To summarize, the synthesis of 1,2-bis(methylamino)ethane-1,2-diol dihydrochloride (**5**) demonstrated that aliphatic α-aminocarbinols can be stabilized as hydrochlorides. Hydrochloride can generate free unstable 1,2-bis(methylamino)ethane-1,2-diol in the reactions in aprotic solvents with the use of K_2CO_3 as a base. Compound **5** proved to be an efficient precursor for the preparation of 1,2,1′,2′-tetramethyl-3,3′-bidiaziridine (**2**) in good yield as a mixture of diastereomers (a racemate and a *meso* form). The *meso* form was isolated and its structure was confirmed by X-ray diffraction analysis. The kinetics of inversional epimerization was studied.

Experimental

The IR spectra were recorded on a UR-20 spectrometer in KBr pellets. The ^{1}H NMR spectra were measured on Bruker WM-250 (250 MHz) and Bruker DRX-500 (500 MHz) spectrometers. The ^{13}C NMR spectra were recorded on Bruker AM-300 (75.5 MHz) and Bruker DRX-500 (125 MHz) spectrometers. The chemical shifts are given in the δ scale relative to the signal of Me_4Si. The TLC analysis was carried out on Silufol-UV-254 plates; visualization was carried out with iodine vapor and independently by spraying with a solution of diphenylamine in acetone followed by heating of the plates. The melting point was determined on a Boetius RNMK 05 hot-stage apparatus. X-ray diffraction study was carried out on a Syntex $P2_1$ diffractometer. The mass spectra were obtained on a Varian MAT CH-6 instrument.

1,2-Bis(methylamino)ethane-1,2-diol dihydrochloride (5). A 40% aqueous solution of glyoxal (32 mL, 0.29 mol) was added dropwise to a 30% aqueous solution of methylamine (100 mL) at −5—0 °C. The reaction mixture was stirred at 60 °C for 2 h, cooled to 0 °C, and saturated with solid NaOH. The organic layer was separated and dissolved in $CHCl_3$ (30 mL). Concentrated HCl (90 mL) was added dropwise at a temperature from −5 to −10 °C. The reaction mixture was kept at 18—20 °C for 2 h. The precipitate that formed was filtered off, washed with cold concentrated HCl and acetone, and dried in air. 1,2-Bis(methylamino)ethane-1,2-diol dihydrochloride (**5**) was obtained in a yield of 30 g as a mixture with methylamine hydrochloride (according to the ^{1}H NMR spectroscopic data, the mixture contained 45% of compound **5**; 24% of the theoretical value), m.p. 136—137 °C (decomp.). IR, ν/cm^{-1}: 840, 920, 1030, 1090, 1140, 1180, 1250, 1330, 1370, 1430, 1470, 1570, 2395, 2730, 2750, 2790, 2820, 2970, 3060. ^{1}H NMR of a mixture of diastereomers (CD_3OD), δ: 2.55 (s, 3 H, $MeNH_2\cdot HCl$); 2.88 and 2.90 (both s, 3 H each, Me); 4.25, 4.68 (dd, 2 H, CH, ^3J = 4.5 Hz); 4.28, 4.75 (dd, 2 H, CH, ^3J = 3.6 Hz). ^{13}C NMR of a mixture of diastereomers (CD_3OD), δ: 25.0 ($MeNH_2\cdot HCl$); 29.1, 29.2 (Me); 91.5, 91.8, 98.7, and 98.9 (CH). MS, m/z (I_{rel} (%)): 60 $[M - MeNHCHOH]^+$ (22), 44 $[M - HOCHN]^+$ (12), 42 $[M - MeNHC]^+$ (71), 36 $[M - HCl]^+$ (100), 38 $[M - HCl]^+$ (35).

1,2,1′,2′-Tetramethyl-3,3′-bidiaziridine (2). ***A.*** Diethylamine or triethylamine (0.4 mol) and a mixture of dihydrochloride **5** and methylamine hydrochloride (28.4 g, the amount of **5** in the mixture was 12.8 g = 0.066 mol) were added to a solution of *N*-chloromethylamine (0.46 mol) in $CHCl_3$ (360 mL) at a temperature from −5 to −10 °C. The reaction mixture was stirred at 20—22 °C for 6 h. The precipitate that formed was filtered off and washed with $CHCl_3$ (3×50 mL). The solvent was removed on a rotary evaporator at a temperature of ≤40 °C. The test for the presence of diaziridine in the residue with the use of an acidified solution of KI was negative.

B. The synthesis was carried out as described in the method ***A*** but with the use of finely ground potassium carbonate (180 g) as a base. After removal of the solvent, the residue was distilled off *in vacuo* using a water-aspirator pump and the fraction with b.p. 67—70 °C (20 Torr) was collected. A mixture of diastereomers of bidiaziridine **2** was obtained in a yield of 6.9 g (73.6%). The precipitate, which was obtained after cooling of the reaction mixture to −18 °C for 3 h, was filtered off, washed with a small amount of cold hexane, dried in air for 2—3 h, and placed in a closed vessel (the product is highly volatile). The *meso* form of compound **2** was obtained in a yield of 1.1 g (15%) m.p. ~40 °C. IR, ν/cm^{-1}: 880, 910, 960, 1080, 1110, 1150, 1160, 1190, 1280, 1310, 1380, 1410, 1440, 1460, 1650, 1670, 2790, 2880, 2940, 2980. ^{1}H NMR ($CDCl_3$), δ: *meso* form, 2.15 (s, 1 H, CH); 2.17 and 2.29 (both s, 3 H each, CH_3); racemate, 2.18 (s, 3 H, CH_3); 2.22 (s, 1 H, CH); 2.31 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$), δ: *meso* form: 40.6, 47.1 (CH_3); 60.2 (CH); racemate: 40.4 and 46.8 (CH_3); 61.8 (CH).

X-ray diffraction analysis of single crystals of the *meso* form of compound **2** was carried out on an automated Syntex $P2_1$ diffractometer (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, θ/2θ scanning technique, θ_{max} = 26°). Colorless

crystals ($C_5H_{14}N_4$, M = 130.20 g mol^{-1}) are monoclinic, space group $P2_1/c$, at T = 163 K, a = 5.781(3), b = 7.306(3), c = 9.674(5) Å, β = 96.80(4)°, V = 405.7(3) Å^3, Z = 2 (Z' = 0.5), d_{calc} = 1.066 g cm^{-3}. The structure was solved by direct methods and refined by the full-matrix least-squares method against F^2_{hkl} with anisotropic thermal parameters for all nonhydrogen atoms. The hydrogen atoms were revealed from the difference electron density map and refined isotropically. The final reliability factors were as follows: wR_2 = 0.1 006, GOOF = 1.040 based on all reflections (R_1 = 0.0493 based on 462 reflections with $I > 2\sigma(I)$), 75 parameters were refined. Calculations were carried out using the SHELXTL PLUS 5.10 program package.

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