Asymmetric nitrogen

78.* Sterically hindered inversion of nitrogen atoms in cyclic hydrazines: *N,N'*-dialkyl-1,3,4-oxadiazolidines; 1,3,4-thiadiazolidine; and 4,5-benzo-1,2,3,6-tetrahydropyridazine

R. G. Kostyanovsky,[a] P. Rademacher,[b] Yu. I. El'natanov,[a] G. K. Kadorkina,[a] G. A. Nikiforov,[a] I. I. Chervin,[a] S. V. Usachev,[a] and V. R. Kostyanovsky[a]*

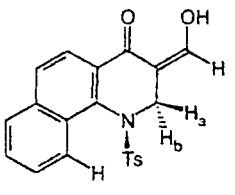
[a]N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117977 Moscow, Russian Federation. Fax: 007 (095) 938 2156

[b]Institute of Organic Chemistry, University of Essen, Germany. Fax: 49 (201) 183 3082

N,N'-Diisopropyl-substituted 1,3,4-oxadiazolidine **3c**, 1,3,4-thiadiazolidine **6**, 4,5-benzo-1,2,3,6-tetrahydropyridazine **8**, and new 3,4-dialkyl-1,3,4-oxadiazolidines **9—14** were synthesized and studied. The configurational stability of the N atoms does not change on going from compound **3c** to its *S*-analog **6** and decreases in the case of pyridazine **8**. 3,4-Di-*tert*-alkyl-1,3,4-oxadiazolidines **3d** and **11—14** were found to be promising objects for optical resolution.

Key words: *N,N'*-dialkyl-substituted 1,3,4-oxadiazolidines; 1,3,4-thiadiazolidine; 4,5-benzo-1,2,3,6-tetrahydropyridazine; nitrogen inversion; ^1H, ^{13}C NMR.

In tertiary amines,[2,3] including three-membered heterocyclic compounds with one nitrogen atom,[4] the barrier to the inversion of nitrogen decreases as the size of the *N*-substituents increases, because the pyramidal ground state is destabilized by steric interactions of the substituents. Moreover, triisopropylamine[5,6] and diisopropyl-3-pentylamine[6] are characterized by an almost planar configuration of the nitrogen atom in the ground state, which corresponds to the transition state of inversion. In the case of directed steric shielding of the transition state in dihydrobenzo[*h*]quinolones, inversion of the nitrogen atom is markedly hindered.[7] However, the activation parameters for the inversion found for compound **1** ($\Delta H^{\neq}$ = 22 kcal mol^{-1}, $\Delta S^{\neq}$ = 9.6 e.u., E_a = 23 kcal mol^{-1}, logA = 14.1) are insufficient for its optical resolution under normal conditions. It should be noted that the introduction of a substituent in position 10 and replacement of the *N*-substituent by R or by σ-electron-withdrawing groups would presumably increase the configurational stability of these compounds.



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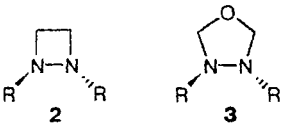
The barriers to inversion of the nitrogen atoms in cyclic hydrazines, unlike those in ordinary amines, increase with increases in the size of *N*-substituents (Table 1) due to steric destabilization of the monoplanar transition state of inversion.[11,12] If the inversion in strongly sterically hindered systems occurs *via* a biplanar transition state, this transition state should be additionally destabilized by electronic interaction between the lone electron pairs of adjacent nitrogen atoms.



2 **3**

R = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**)

According to the data of Table 1, even with the largest *N*-substituents, compounds **2d** and **3d** possess insufficient configurational stabilities to be resolved into

Table 1. Inversion barriers of the nitrogen atoms in compounds **2**[8] and **3**,[9,10] $\Delta G^{\neq}$/kcal mol^{-1} (T_c/°C)

Compound	2		3	
	$\Delta G^{\neq}$	T_c	$\Delta G^{\neq}$	T_c
a	16.3	55	10.6	−61
b	16.5	66	12.0	−31
c	16.8	66	19.4	111
d	21.8	155	>21.0	>166

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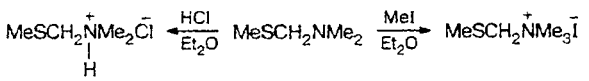
the optical isomers under normal conditions. Apparently in view of the foregoing, the problem of sterically hindered inversion of nitrogen has been neglected for almost 20 years. In addition, compound **3d**, which is the most interesting in this respect, was described in a preliminary communication without a method for its synthesis or its characteristics,[9] while in a detailed paper, this compound was not even mentioned;[10] later,[13] only its ionization potentials were reported.

Recently we synthesized compound **3d**, studied it in detail, and reestimated its inversion barrier ($\Delta G^{\neq}$ > 22.8 kcal mol^{-1} at 130 °C).[14] This made it possible to revive the idea of steric prohibition of the nitrogen inversion .

In this study, we report on the search for objects for optical resolution in the series of cyclic hydrazines, 1,3,4-oxadiazolidines,[9–18] 1,3,4-thiadiazolidines,[19–22] and 1,2,3,6-tetrahydropyridazines;[23–28] available information on these componds was limited to the above references.

1,3,4-Oxadiazolidines, which are cyclic alkoxymethylamines, are unstable with respect to acids;[17] therefore, they cannot be resolved into optical isomers *via* diastereomeric salts with chiral acids. Their stability toward acids could presumably be increased by replacing the O atom by an S atom. Using model dimethyl(methylthiomethyl)amine[29] **4** as an example, it was shown that this compound, unlike its oxygen-containing analog, forms stable salts: hydrochloride **4** · HCl and a salt **5** with methyl iodide (Scheme 1).

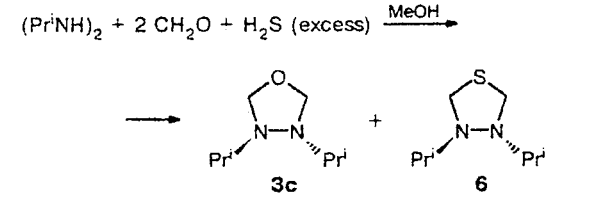
Scheme 1



4a · HCl **4** **5**

3,4-Diisopropyl-1,3,4-thiadiazolidine **6** substituted only in positions 3 and 4 and suitable for the investigation of the inversion of nitrogen atoms was prepared for the first time from 1,2-diisopropylhydrazine[30,31] (which was synthesized by the reduction of acetone azine with $NaBH_4$ by a known procedure[32]); the target compound was formed together with its oxygen analog **3c** [10,18] (Scheme 2).

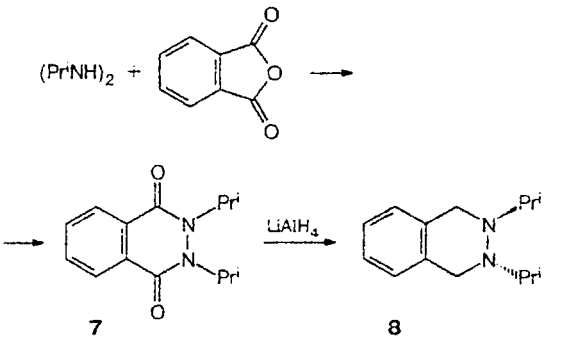
Scheme 2



Using dynamic NMR in DMSO-d_6, based on the coalescence of the signals for the protons of the diastereotopic methyl groups in the isopropyl substituents, we found the inversion barrier for the nitrogen atoms in compound **6** (T_c = 66 °C, $\Delta G^{\neq}$ = 19.1 kcal mol^{-1}), which is close to that for its oxygen analog **3c** (see Table 1). However, thiadiazolidine **6** is unstable and at 20 °C, it gradually transforms into a white powder-like polymer of an unknown structure.

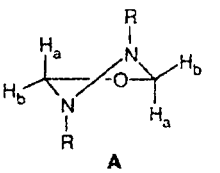
The next stage of the search involved synthesis of a six-membered cyclic hydrazine, 1,2-diisopropyl-1,2,3,6-tetrahydrobenzo[*d*]pyridazine **8**; this compound was prepared by the reduction of *N,N'*-diisopropylhydrazide of phthalic acid **7** (Scheme 3).

Scheme 3



However, according to the ^{1}H NMR spectrum, hindered inversion of the nitrogen atoms in compound **8** is observed only at low temperatures. Evaluation of the inversion barrier ($\Delta G^{\neq} \approx 13$ kcal mol^{-1} at −5 °C; this is nearly equal to the value found for the *N,N'*-dimethyl analogs[24–27]) implies that this system is also unsuitable for accomplishing the task in question. Therefore, we studied in detail 3,4-dialkyl-1,3,4-oxadiazolidines **3c,d** and new derivatives **9**—**14** synthesized according to Scheme 4.

In a previous communication,[14] it was found that in the crystal, a molecule of compound **3d** exists in an asymmetric envelope conformation (X-ray diffraction), while in solution, it exists in a symmetrical (C_2) half-chair conformation (**A**) with the *trans*-orientation of *N*-substituents (NMR). Calculations (*ab initio* 6-31G* and 6-31+G*) of the conformation of molecule **3d** in a vacuum indicate that the symmetrical conformation **A** is preferred. The calculations reproduce the experimental geometric parameters very closely (Table 2).



A

The magnitudes of vicinal spin-spin coupling constants $^3J_{CH}$ (see Table 2) imply that the geometries of the ground states of the molecules are similar in solution.

Scheme 4

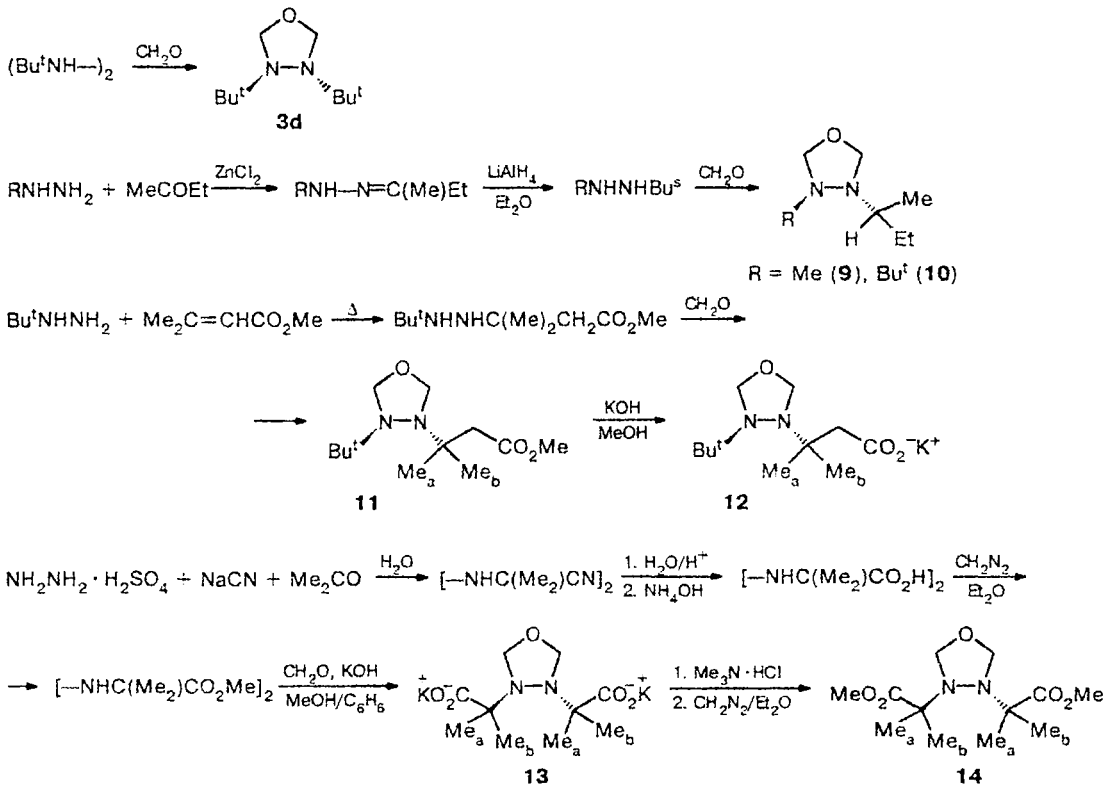


Table 2. Vicinal spin-spin coupling constants $^3J_{CH}$ (Hz), the differences $\Delta^1J_{CH_{a,b}} = {}^1J_{CH_a} - {}^1J_{CH_b}$ (Hz), and the corresponding dihedral angles (φ)

Compound	$^3J_{CH}$				$\Delta^1J_{CH_{a,b}}$
	$\underline{C}OCH_b$	$\underline{C}OCH_a$	$\underline{C}NCH_a$	$\underline{C}NCH_b$	
3c	4.4	1.5	8.0	4.0	12.2
3d	4.4	0	7.0	4.0	13.8
6	3.8	0	8.0	4.0	12.3
9[a]	—	—	5.8	5.8	0
10[b]	4.4	0	7.0 and 7.2	3.0 and 3.6	14.2 and 13.8
	(5.1)	(0)	(—)	(—)	(13.8)
11[c]	4.4	0	—	—	16.0
	(5.8)	(0)			(13.1)
13	3.7	0	6.0	3.0	13.1
14	4.0	0	7.0	4.0	13.1
	φ/deg				
3d[d]	130.8° (129±3°)	110.6° (112±3°)	138.0° (137.5±3°)	16.0° (18±3°)	—

[a] At 90 °C. [b] The spin-spin coupling constants for the $COCH_2NBu^t$ fragment in the major and minor diastereomers; the values for the $COCH_2NBu^s$ fragment are given in parentheses. [c] For the $COCH_2NBu^t$ and $COCH_2NCMe_2$ fragments (in parentheses). [d] The calculated (6-31+G*) and average experimental (X-ray diffraction; in parentheses) values for the dihedral angles in molecule **3d**.[14]

The non-equivalence of the protons in the ring methylene groups (AB spectrum) (Fig. 1) and in the geminal methyl groups at the *N*-substituent (Fig. 2), the dissimilarity of the $^1J_{CH_{a,b}}$ spin-spin coupling constants for the ring carbon atoms (Figs. 1, 2, Table 2) and the $^3J_{CNCH_{a,b}}$ constants for the carbon atoms at the *N*-substituent (Table 2), the fact that only one $^3J_{COCH_b}$ coupling constant is observed for the carbon atom of the ring (Figs. 1, 2, Table 2), the presence of a full set of signals for diastereomers (Fig. 1) in the spectra of derivatives with chiral *N*-substituents, and the presence of signals for enantiomers in the presence of a chiral shift reagent (Fig. 2, Scheme 5) indicate that these molecules are chiral.

The configurational stability of 4-*sec*-butyl-3-methyl-1,3,4-oxadiazolidine **9** is lower than that of the *N,N'*-diisopropyl derivative **2c** but is markedly higher than those of the *N,N'*-dimethyl and diethyl analogs **3a** and **3b** (Table 1 and 3). At 90 °C, when inversion of the N—Me nitrogen atom is fast on the NMR time scale, slow inversion of the second nitrogen atom still occurs (see Experimental), probably, owing to the shielding by the methyl substituent at the effectively flattened nitrogen atom. In the case of 3-*sec*-butyl-4-*tert*-butyl analog **10** (Fig. 1), inversion of the nitrogen atoms is hindered on the NMR time scale even at 120 °C. However, attempts to separate diastereomers **10** and **10'** by chromatography resulted invariably in an equilibrium mixture

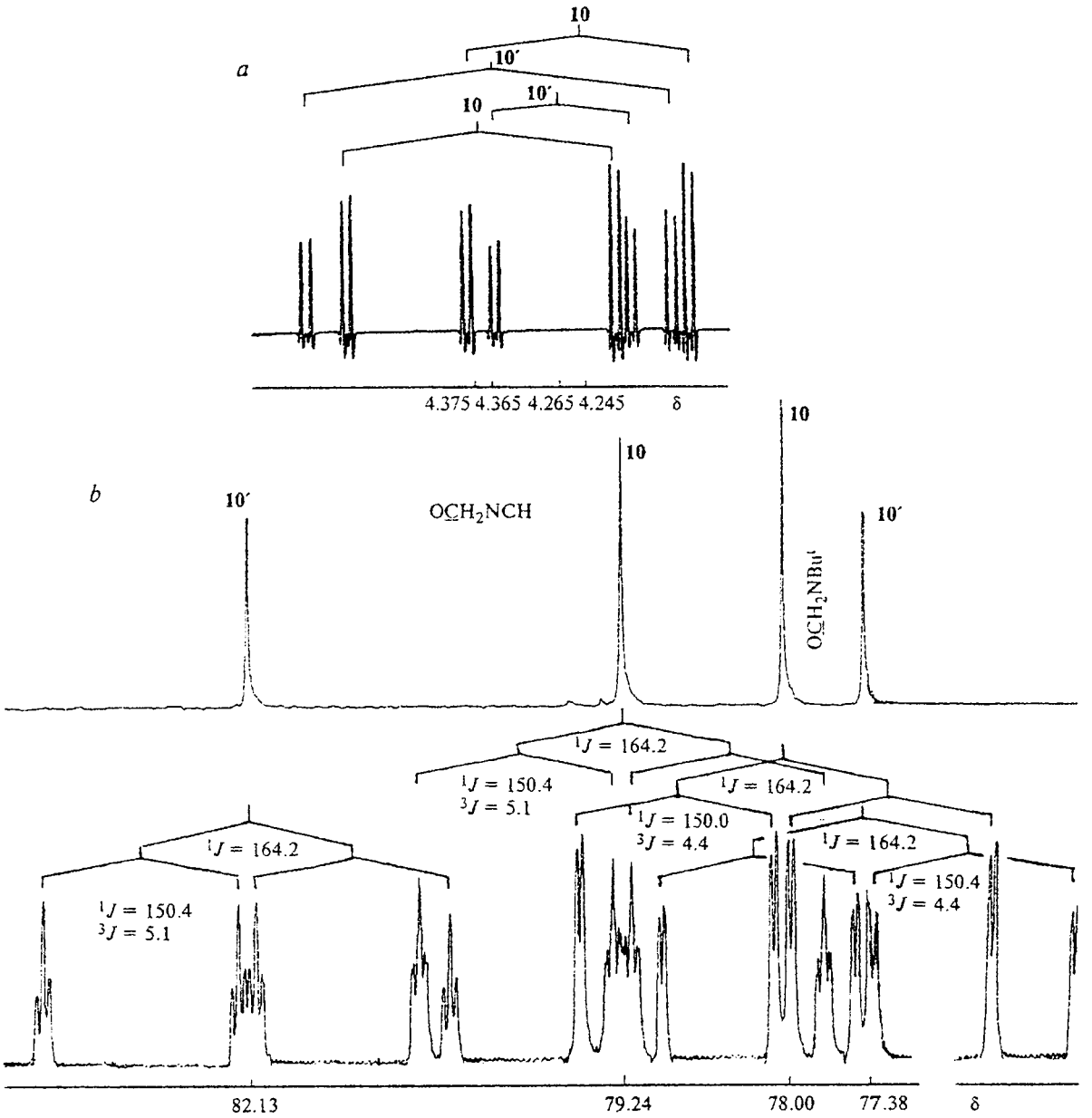


Fig. 1. NMR spectra (in $CDCl_3$) for the protons and the carbon atoms of the ring for a diastereomeric mixture of oxadiazolidine **10** and **10′** (in a ratio of 1.3 : 1.0: ^1H spectrum (*a*); $^{13}C\{H\}$ spectrum (*b*); ^{13}C spectrum (*c*) (*J*/Hz).

containing these compounds in a ratio of 1.3 : 1.0. Therefore, we have also studied *N,N′*-di-*tert*-alkyl-1,3,4-oxadiazolidines **11**—**14**. Compounds **11** and **14** are stable in alcoholic solutions and in dimethyl(α-phenylethyl)amine and do not undergo amidation with α-phenylethylamine, whereas the corresponding K salts **12** and **13** gradually decompose in alcoholic solutions (salt **13** decomposes 85% over a period of 7 days at 20 °C). Therefore, attempts to prepare diastereomerically pure ammonium salts by cationic exchange between K salts **12** and **13** and $PhCH(Me)N^+R_3X^-$, where R = H, Me; X = Cl^-, I^-, were unsuccessful. We were able to prepare a partially enriched sample of **14** by the procedure for its synthesis from the potassium salt (see Experimental) using (*S*)-(−)-$PhCH(Me)NMe_2 \cdot HCl$ instead of $Me_3N \cdot HCl$.

Thus, *N,N′*-di-*tert*-alkyl-1,3,4-oxadiazolidines are promising compounds for complete optical resolution under normal conditions, since it should be expected that replacement of the CO_2Me groups by bulkier groups would increase the inversion barrier for the nitrogen atoms.

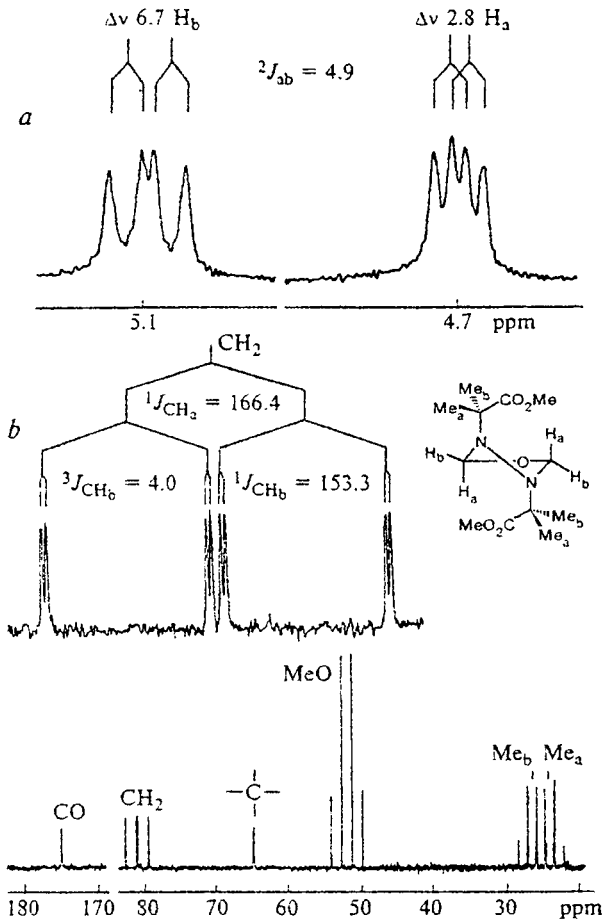


Fig. 2. NMR spectra of oxadiazolidine **14** (in C_6D_6): ^{1}H NMR: the signals for the ring protons at a **14** : Eu(tfc)$_3$ molar ratio of 12.2 (*a*); ^{13}C NMR (*J*/Hz) (*b*).

Experimental

NMR spectra were recorded on a Bruker WM-400 spectrometer (^{1}H 400.13 MHz; ^{13}C 100.62 MHz) using tetramethylsilane as the internal standard. The signals in the resulting NMR spectra were assigned based on the ^{13}C satellites in the ^{1}H spectra using double homo- and heteronuclear resonance, and also NOE and ASIS effects.[14] In the case of oxadiazolidines **10**, asymmetrically substituted at the nitrogen atoms, the signal for the carbon atom in the $OCH_2N—CH_x$ bridge is characterized by a $^3J_{CNCH_x}$ spin-spin coupling constant (Fig. 1). Melting points were determined on a Boetius RNMK-0.5 hot-stage apparatus.

Dimethyl(methylthiomethyl)amine (4) and its salts (4 · HCl, 5). Amine **4** was prepared by a known procedure,[29] yield 69%, b.p. 62—62.5 °C (95 Torr), n_D^{20} 1.4690, d_4^{20} 0.9076. Found (%): C, 45.85; H, 10.41. $C_4H_{11}NS$. Calculated (%): C, 45.67; H, 10.54. ^{1}H NMR ($CDCl_3$), δ: 1.90 (s, 6 H, Me_2N); 2.05 (s, 3 H, MeS); 3.65 (s, 2 H, CH_2). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 105 [M^+] (3.8); 58 (100); 44 (61.5).

Treatment of amine **4** with dry HCl in Et_2O afforded hydrochloride **4** · HCl, yield 89%, m.p. 142—143 °C. ^{1}H NMR (D_2O, dioxane), δ: 2.05 (s, 3 H, MeS); 2.65 (s, 6 H, Me_2N); 4.0 (s, 2 H, CH_2).

Scheme 5

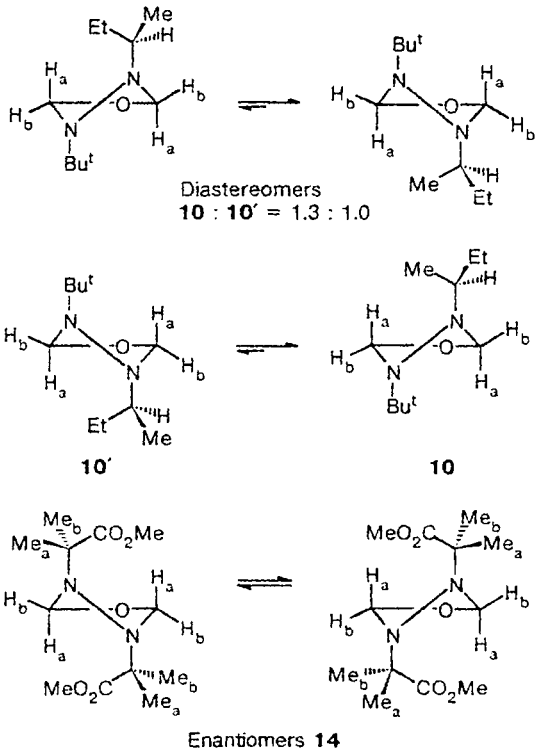


Table 3. Configurational stability of cyclic hydrazines

Compound	$\Delta G^{\#}$ /kcal mol^{-1} (T_c/°C)	Method, indicator group (Δν/Hz)
9	15±0.1 (40—49)	^{13}C{^{1}H} NMR, diastereomers $\underline{CH_2}Me$ (97), $O\underline{CH_2}NMe$ (100), $\underline{CH}$ (150)
6	19.1 (66)	^{1}H NMR, $\underline{Me_2}CH$ (3)
11	>20.6 (120)	^{1}H NMR, $\underline{Me_2}C$ (12)
10	>22.0 (120)	^{1}H NMR, diastereomers Bu^t (2.1)
3d	>23.8 (130)	^{13}C NMR, $\underline{C}Me_3$ {^{1}H, $\underline{Me_3}C$} (Δ^3J = 2.7 Hz)

The reaction of amine **4** with MeI in MeOH gave iodide **5**, yield 89%, m.p. 140—141 °C. Found (%): C, 24.13; H, 5.49; N, 6.01. $C_5H_{14}NSI$. Calculated (%): C, 24.29; H, 5.71; N, 5.67. ^{1}H NMR (D_2O, dioxane), δ: 2.1 (s, 3 H, MeS); 2.8 (s, 9 H, Me_3N^+); 4.3 (s, 2 H, CH_2).

1,2-Diisopropylhydrazine. A solution of glacial AcOH (11.5 mL, 0.2 mol) in 40 mL of dioxane was added with vigorous stirring to a cooled (5—10 °C) mixture of acetone azine (11.2 g, 0.1 mol) (b.p. 45—47 °C (22 Torr); n_D^{20} = 1.4518; ^{1}H NMR ($CDCl_3$), δ: 1.82 (s, 6 H, Me); 1.99 (s, 6 H, Me)) and $NaBH_4$ (7.6 g, 0.2 mol) in 80 mL of dioxane. The mixture was slowly heated to 65—70 °C and stirred for 4 h until gas evolution ceased. Then it was cooled to 20 °C, and 10 mL of H_2O and then 30 mL of conc. HCl were added dropwise. The precipitate was filtered off and washed with

10 mL of dioxane. The mother liquor was concentrated to dryness, the residue was dissolved in 200 mL of H_2O, and the solution was alkalized with aqueous NH_3 and extracted with ether (4×50 mL). The extract was dried with $MgSO_4$ and concentrated, and the residue was distilled to give 8.1 g (yield 70%) of the product; b.p. 120—125 °C; n_D^{20} = 1.4161 (*cf.* Refs. 30 and 31). ^{1}H NMR ($CDCl_3$), δ: 1.02 (d, 12 H, Me, ^3J = 6.1 Hz); 2.92 (hept, 2 H, CH).

3,4-Diisopropyl-1,3,4-oxadiazolidine (3c) and 3,4-diisopropyl-1,3,4-thiadiazolidine (6). A solution of 1,2-diisopropylhydrazine (3.48 g, 30 mmol) in 30 mL of MeOH was saturated with H_2S (the weight increased by 3 g (88 mmol)). After that, a solution of paraform (1.8 g, 60 mmol) in 20 mL of MeOH was gradually added with cooling (0—5 °C) and stirring, and the mixture was kept for 2 h with cooling and for 12 h at ~20 °C. Then the mixture was purged with argon, filtered, and concentrated *in vacuo*. The residue was dissolved in 100 mL of *n*-hexane, again filtered, and concentrated *in vacuo*. The residue, a thick oil with a strong smell (according to ^{1}H NMR, it was a 2 : 1 mixture of products **3c** and **6**) was chromatographed on a column with SiO_2 40/100 mm (using benzene as the eluent) to give 2.8 g (yield 59%) of 3,4-diisopropyl-1,3,4-oxadiazolidine **3c**, b.p. 54—56 °C (8 Torr) as a colorless thick oil (*cf.* Refs 10 and 18) and 1.6 g (yield 30%) of 3,4-diisopropyl-1,3,4-thiadiazolidine **6** as a colorless thick oil with a strong odor.

Product 3c. Found (%): C, 60.49; H, 11.10; N, 10.48. $C_8H_{18}N_2O$. Calculated (%): C, 60.76; H, 11.39; N, 10.13. The sample was identical to that obtained (yield 33%) by a procedure reported previously.[18] ^{1}H NMR ($CDCl_3$), δ: 1.00 and 1.08 (both d, 12 H, Me_2C, ^3J = 6.1 Hz); 2.73 (hept, 2 H, CH); 4.31 (dd, 4 H, NCH_2O, AB spectrum, Δν = 104.0, $^2J_{ab}$ = −4.9 Hz). ^{13}C NMR (C_6D_6), δ: 21.55 (qqd, Me_a, ^1J = 125.3 Hz, ^3J = 5.1 Hz, ^2J = 1.8 Hz); 21.60 (qqd, Me_b, ^1J = 125.3 Hz, ^3J = 5.1 Hz, ^2J = 1.9 Hz); 53.59 (ddd.hept, CH, ^1J = 133.3 Hz, $^3J_{CNCH_a} \approx 8.0$ Hz, $^3J_{CNCH_b} \approx {}^2J_{CCH} \approx 4.0$ Hz); 80.34 (ddddd, NCH_2O, $^1J_{CH_a}$ = 163.1 Hz, $^1J_{CH_b}$ = 151.9 Hz, $^3J_{COCH_b}$ = 4.4 Hz, $^3J_{CNCH}$ = 3.6 Hz, $^3J_{COCH_a}$ = 1.5 Hz).

Product 6. Found (%): C, 55.46; H, 10.10; N, 16.09. $C_8H_{18}N_2S$. Calculated (%): C, 55.17; H, 10.34; N, 16.09. ^{1}H NMR (DMSO-d_6), δ: 0.99 and 1.00 (both d, 12 H, Me_2C, ^3J = 6.4 Hz); 2.45 (hept, 2 H, CH); 4.06 (dd, 4 H, NCH_2S, AB spectrum, Δν = 188.0, $^2J_{ab}$ = −9.8 Hz). Based on coalescence of the signals for the Me groups: T_c = 66 °C, k = 3.33 s^{-1}, $\Delta G^{\neq}$ = 19.1 kcal mol^{-1}. ^{1}H NMR (toluene-d_8), δ: 0.83 and 0.90 (d, 12 H, Me_2C, ^3J = 6.4 Hz); 2.33 (hept, 2 H, CH); 3.84 (dd, 4 H, NCH_2S, AB spectrum, Δν = 124.0, ^2J = −9.8). ^{13}C NMR (toluene-d_8), δ: 21.88 and 22.89 (qqd, $\underline{Me}_2C$, ^1J = 125.5 Hz, ^3J = 5.1 Hz, ^2J = 2.0 Hz); 51.56 (ddd.hept, $\underline{C}H$, ^1J = 132.3 Hz, $^3J_{CNCH_a}$ = 8 Hz, $^3J_{CNCH_b}$ = $^2J_{CCH}$ = 4.0 Hz); 54.71 (ddt, NCH_2S, $^1J_{CH_a}$ = 161.0 Hz, $^1J_{CH_b}$ = 148.7 Hz, $^3J_{CNCH}$ = $^3J_{CSCH_b}$ = 3.8 Hz).

3,4-Di-*tert*-butyl-1,3,4-oxadiazolidine (3d).[14] A mixture of 1,2-di-*tert*-butylhydrazine[14] (0.75 g, 5.2 mmol) and polyoxymethylene (0.37 g, 12 mmol) in a mixture of 10 mL of benzene and 1 mL of MeOH containing a catalytic amount of KOH was kept under argon for 1.5 h at 20 °C. Then the solvents were evaporated, and the residue was recondensed *in vacuo* into a cooled trap. The crude product (0.45 g) was treated with an equivalent amount of picric acid in 5 mL of Et_2O. The precipitate of the picrate was separated, dried *in vacuo* (m.p. 120—137 °C), and dissolved in 10 mL of benzene, and the solution was washed with 10% aqueous KOH. Evaporation of the benzene followed by distillation of the residue gave 0.44 g (yield 45%) of product **3d**, b.p. 60 °C (5 Torr). Found (%): C, 64.30; H, 11.75; N, 15.30. $C_{10}H_{22}N_2O$. Calculated (%): C, 64.47; H, 11.90; N, 15.04. ^{1}H NMR (toluene-d_8), δ: 1.0 (s, 18 H, Me_3C); 4.31 (dd, 4 H, OCH_2N, AB spectrum, Δν = 164.5, ^2J = −4.9 Hz). ^{13}C NMR (benzene-d_6): 28.19 (d.hept, $\underline{Me}_3C$, ^1J = 125.7, ^3J = 4.4); 57.34 (dd.dec, $\underline{C}Me_3$, $^3J_{CNCH_a}$ = 7.0 Hz, $^3J_{CNCH_b}$ = 4.0 Hz, $^2J_{CCH}$ = 3.6 Hz); 79.87 (ddd, CH_2, $^1J_{CH_a}$ = 164.2 Hz, $^1J_{CH_e}$ = 150.4 Hz, $^3J_{COCH_e}$ = 4.4 Hz). In toluene-d_8 at 30 °C (130 °C) for the carbon atoms of the CH_2 groups, Δ^1J = 14.5 (13.7) Hz, and for the carbon atoms of the $\underline{C}Me_3$ group, Δ^3J_{CNCH} = 3.0 (2.7) Hz. From these values, the lower limits of the nitrogen inversion barriers at 130 °C were estimated: $\Delta G^{\neq}_{inv}$ > 22.7 and > 23.8 kcal mol, respectively.

Phthalic acid *N,N*-diisopropylhydrazide (7). A solution of phthalic anhydride (1.48 g, 10 mmol) and 1,2-diisopropylhydrazine (1.16 g, 10 mmol) in 10 mL of benzene was refluxed for 2 h; during this period, the solvent returned to the reaction mixture through 4 Å molecular sieves. After evaporation of the solvent, the residue was chromatographed on a column with SiO_2 40/100 mm (using $CHCl_3$ as the eluent), and the head fraction was collected. The solvent was removed, and the residue was recrystallized from *n*-hexane to give 2.2 g (yield 89%) of product **7**, m.p. 102—103 °C. Found (%): C, 68.00; H, 7.11; N, 11.69. $C_{14}H_{18}O_2N_2$. Calculated (%): C, 68.29; H, 7.32; N, 11.38. ^{1}H NMR ($CDCl_3$), δ: 1.58 (d, 12 H, Me_2C, ^3J = 6.9 Hz); 4.10 (hept, 2 H, CH); 7.74 and 8.18 (m, 4 H, C_6H_4).

1,2-Diisopropyl-1,2,3,6-tetrahydrobenzo[*d*]pyridazine (8). Hydrazide **7** (1 g, 4.06 mmol) was gradually added to a solution of $LiAlH_4$ (1.54 g, 40.6 mmol) in 50 mL of anhydrous THF, and the mixture was refluxed for 3 h and cooled. Water (5 mL) and then 20% NaOH (5 mL) were added dropwise with stirring. The precipitate was separated and washed with 20 mL of THF and 40 mL of Et_2O. The combined organic solutions were concentrated *in vacuo*, and the residue was extracted with 50 mL of benzene. The extract was washed with 20 mL of H_2O and concentrated *in vacuo* to give 0.85 g (yield 97%) of product **8** as a pale pink oil, n_D^{20} = 1.5139. Found (%): C, 77.31; H, 10.40; N, 13.16. $C_{14}H_{22}N_2$. Calculated (%): C, 77.06; H, 10.09; N, 12.84. ^{1}H NMR (toluene-d_8, −35 °C), δ: 1.17 and 1.44 (both br.d, 12 H, Me_2C, ^3J = 5.8 Hz); 2.81 (hept, 2 H, CH); 3.86 (dd, 4 H, CH_2N, AB spectrum, Δν = 140.4, $^2J_{ab}$ = −15.6 Hz); 7.03 and 7.27 (m, 4 H, C_6H_4). From coalescence of the signals for the Me groups: $T_c \approx -5$ °C, $\Delta G^{\neq} \approx 13$ kcal mol^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.05 (d, 12 H, Me_2C, ^3J = 6.2 Hz); 2.76 (hept, 2 H, CH); 3.87 (s, 4 H, CH_2N); 7.07 and 7.18 (both m, 4 H, C_6H_4). ^{1}H NMR (CD_3CO_2H + CF_3CO_2H, 1 : 1), δ: 1.32 (br.d, Me_2C, ^3J = 6.7 Hz); 3.52 (br.hept, HC); 4.41 (br.s, CH_2N); 7.33 and 7.40 (br.m, C_6H_4). ^{13}C NMR ($CDCl_3$), δ: 21.22 (qd, Me, ^1J = 125.0 Hz, ^2J = 3.6 Hz); 44.94 (tt, CH_2N, ^1J = 135.2 Hz, ^3J = 3.5 Hz); 52.0 (dt.hept, CH, ^1J = 132.2 Hz, $^2J \approx {}^3J \approx 4.4$ Hz); 125.88 (br.d, 4,5-CH_{Ar}, ^1J = 159.9 Hz); 125.93 (3,6-CH_{Ar}, ^1J = 159.1 Hz); 134.37 (br.s, 1,2-C_{Ar}).

Picrate of compound 8, m.p. 134—135 °C. Found (%): C, 53.51; H, 5.53; N, 15.52. $C_{20}H_{25}N_5O_7$. Calculated (%): C, 53.68; H, 5.63; N, 15.65. All signals in the ^{1}H NMR spectrum of the picrate of **8** were markedly broadened.

3-*sec*-Butyl-4-methyl-1,3,4-oxadiazolidine (9).

***A.* Methyl ethyl ketone *N*-methylhydrazone.** Fused $ZnCl_2$ (20 g) was added in small portions with stirring to a mixture of freshly distilled methylhydrazine (9.6 g, 0.21 mol) and methyl ethyl ketone (15 g, 0.21 mol). When the vigorous exothermal reaction was completed and the mixture was cooled to 20 °C, 20 mL of Et_2O was added, the precipitate was separated, and the solution was dried for 12 h with $MgSO_4$. After removal of

the ether, the residue was distilled (with a long dephlegmator), and the fraction with a boiling point of 120—140 °C (19.2 g) was collected. Repeated distillation gave 17.5 g (yield 83.8%) of a product, b.p. 126—130 °C, as a mixture of *syn*- and *anti*-isomers (MeNH with respect to the MeC= group) in a ratio of 5.0 : 1.0. ^{1}H NMR ($CDCl_3$), δ, *syn-isomer*: 1.04 (t, 3 H, MeCH$_2$, ^3J = 7.0 Hz); 1.68 (s, 3 H, MeC); 2.18 (q, 2 H, CH$_2$, ^3J=7.0 Hz); 2.87 (s, 3 H, MeN); *anti-isomer*: 1.06 (t, 3 H, MeCH$_2$, ^3J = 7.0 Hz); 1.90 (s, 3 H, MeC); 2.12 (q, 2 H, CH$_2$); 2.85 (s, 3 H, Me).

***B.* 1-*sec*-Butyl-2-methylhydrazine.** Methyl ethyl ketone *N*-methylhydrazone (17 g, 0.17 mol) was gradually added with stirring to a suspension of $LiAlH_4$ (8 g, 0.21 mol) in 120 mL of anhydrous Et_2O, and the mixture was refluxed for 6 h and kept for 12 h at 20 °C. At 10 °C, 25 mL of H_2O was carefully added dropwise with stirring. The precipitate was separated by decantation and washed with Et_2O (2×30 mL). The combined solutions were dried with solid KOH. After removal of the ether, the residue was distilled with a long dephlegmator to give 6.2 g (yield 36%) of the product, b.p. 124—130 °C. ^{1}H NMR (CD_3OD), δ: 0.9 (t, 3 H, MeCH$_2$, ^3J =7.0 Hz); 1.02 (d, 3 H, MeCH, ^3J =7.0 Hz); 1.24 and 1.58 (both m, 2 H, CH$_2$); 2.51 (s, 3 H, MeN); 2.75 (m, 1 H, CH).

***C.* 3-*sec*-Butyl-4-methyl-1,3,4-oxadiazolidine (9).** A solution of paraform (2 g, 66 mmol) in H_2O (3 mL) was added to a solution of 1-methyl-2-*sec*-butylhydrazine (3.4 g, 33 mmol) in 75 mL of petroleum ether (b.p. 40—70 °C). After 1 h, calcined $MgSO_4$ (10 g) was added, and the mixture was kept for 1 h. The solution was separated and concentrated, and the residue was distilled to give 2.47 g (yield 51.5%) of the product, b.p. 62—63 °C (17 Torr). Found (%): N, 19.13. $C_7H_{16}N_2O$. Calculated (%): N, 19.42. ^{1}H NMR (toluene-d_8, 30 °C), δ: 0.83 (br.s, MeCH$_2$); 0.84 and 1.00 (both br.s, MeCH); 1.41 and 1.69 (br.s, CH$_2$Me); 2.27 (br.s, MeN, CH); 3.9 (br.d, CH$_2$NMe, Δν ≈ 108 Hz); 4.2 (br.d, CH$_2$NCH, Δν ≈ 28.0 Hz). ^{1}H NMR (toluene-d_8, 90 °C), δ: 0.71 (t, 3 H, MeCH$_2$, ^3J = 7.3 Hz); 0.81 (d, 3 H, MeCH, ^3J = 6.4 Hz); 1.17 (m, 1 H, H$_a$, ^2J = −12.5 Hz, $^3J_{H_aH_x}$ = 7.3 Hz); 1.43 (m, 1 H, H$_b$, $^3J_{H_bH_x}$ = 4.9 Hz); 2.23 (s, 3 H, MeN); 2.29 (m, 1 H, H$_x$, $^3J_{H_xMe}$ = 6.4 Hz); 3.91 (s, 2 H, OCH$_2$NMe); 4.13 (dd, 2 H, OCH$_2$NCH, AB spectrum, Δν = 24.0 Hz, ^2J = −4.9 Hz). ^{13}C NMR (toluene-d_8, 90 °C), δ: 10.77 (qdt MeCH$_2$, ^1J = 125.0 Hz, ^3J = 4.4 Hz, ^2J = 4.0 Hz); 17.97 (qm, MeCH, ^1J = 126.4 Hz); 28.86 (tm, CH$_2$Me, ^1J = 125.0 Hz); 60.57 (dm, CH, ^1J = 132.2 Hz); 45.48 (qt, MeN, ^1J = 133.7 Hz, $^3J_{CNCH_2}$ = 5.8 Hz); 80.33 (tm, OCH$_2$NCH, ^1J = 156.9 Hz). In toluene-d_8 at 20 °C, the ratio of diastereomers ≈ 1.2. From coalescence of the ^{13}C signals for OCH$_2$NMe, CH, and OCH$_2$NCH in diastereomers under conditions of proton decoupling, Δν/Hz (T_c/°C) = 100 (40), 150 (46), and 164 (49), respectively; the inversion barrier was found to be $\Delta G^{\neq}$ = 15±0.1 kcal mol^{-1}.

3-*sec*-Butyl-4-*tert*-butyl-1,3,4-oxadiazolidine (10).

***A. tert*-Butylhydrazine** was obtained from the corresponding hydrochloride (m.p. 191 °C) prepared by a known procedure.[31] A solution of KOH (4.5 g, 80 mmol) in 10 mL of H_2O and then solid KOH (4 g) were added with stirring under argon to a suspension of the hydrochloride (2 g, 16 mmol) in 10 mL of Et_2O. The organic layer was separated, and the aqueous layer was extracted with 20 mL of Et_2O. The combined ethereal solutions were dried with K_2CO_3 for 12 h, concentrated, and distilled in an argon flow to give 1.4 g (yield 99%) of the hydrazine, b.p. 112—115 °C (*cf.* Ref. 31). ^{1}H NMR (C_6D_6), δ: 0.87 (s, 9 H, Me_3C); 2.32 (br.s, 3 H, HN).

***B.* Methyl ethyl ketone *N*-*tert*-butylhydrazone** was prepared from *tert*-butylhydrazine (2.77 g, 32 mmol), methyl ethyl ketone (3.67 g, 51 mmol) and fused $ZnCl_2$ (20 g) by the procedure described above for **9**. Yield 3.2 g (71.6%), b.p. 52 °C (17 Torr). The product was obtained as a mixture of *syn*- and *anti*-isomers (Bu^{t}NH with respect to the MeC group) in a ratio of 3.5 : 1.0. ***syn*-Isomer.** ^{1}H NMR ($CDCl_3$), δ: 1.05 (t, 3 H, MeCH$_2$, ^3J = 7.0 Hz); 1.18 (s, 9 H, Me_3C); 1.69 (s, 3 H, Me); 2.20 (q, 2 H, CH$_2$Me). ^{13}C NMR ($CDCl_3$), δ: 10.91 (qt, MeCH$_2$, ^1J = 126.4 Hz, ^2J = 4.4 Hz); 13.58 (q, Me, ^1J = 126.4 Hz); 28.33 (q.hept, Me_3C, ^1J = 125.0 Hz, ^3J = 4.4 Hz); 31.98 (t, CH$_2$, ^1J = 126.4 Hz); 52.84 (dec, CMe_3, ^2J = 3.6 Hz); 147.44 (br.s, C=N). ***anti*-Isomer.** ^{1}H NMR ($CDCl_3$), δ: 1.05 (t, 3 H, MeCH$_2$, ^3J = 7.0 Hz); 1.17 (s, 9 H, Me_3C); 1.89 (s, 3 H, Me); 2.12 (q, 2 H, CH$_2$Me).

***C.* 1-*sec*-Butyl-2-*tert*-butylhydrazine** was obtained from *tert*-butylhydrazone (3.2 g, 22 mmol) and $LiAlH_4$ (2.1 g, 55 mmol) in 70 mL of anhydrous Et_2O under the conditions described for reduction in the synthesis of **9** (see above). Yield 2.1 g (64.7%), b.p. 140—145 °C. ^{1}H NMR ($CDCl_3$), δ: 0.88 (t, 3 H, MeCH$_2$, ^3J = 7.0 Hz); 1.00 (d, 3 H, MeCH, ^3J = 7.0 Hz); 1.05 (s, 9 H, Me_3C); 1.25 and 1.52 (both m, 2 H, CH$_2$Me); 2.6 (m, 1 H, HC).

***D.* 3-*sec*-Butyl-4-*tert*-butyl-1,3,4-oxadiazolidines (10 and 10′)** were prepared in 50 mL of petroleum ether from 1-*sec*-butyl-2-*tert*-butylhydrazine (1.9 g, 13.2 mmol) and paraform (1.0 g, 33.3 mmol) depolymerized in 1.5 mL of distilled H_2O by the procedure described for the synthesis of the 4-methyl analog **9** (see above). Repeated distillation gave 0.8 g (yield 28.5%) of the product; b.p. 92—95 °C (18 Torr). Found (%): N, 15.27. $C_{10}H_{22}N_2O$. Calculated (%): N, 15.04. The ratio of diastereomers was 1.3 : 1.0 (according to ^{1}H NMR). **Major diastereomer (10)** (see Fig. 1 and Scheme 5). ^{1}H NMR ($CDCl_3$), δ: 0.93 (d, 3 H, MeCH, ^3J = 6.7 Hz); 0.94 (t, 3 H, MeCH$_2$, ^3J = 7.3 Hz); 1.06 (s, 9 H, Me_3C); 1.25 and 1.58 (m, 2 H, CH$_2$Me, ^2J = −13.4 Hz, ^3J = 6.7 Hz); 2.70 (m, 1 H, CH); 4.25 (dd, 2 H, OCH$_2$N, AB spectrum, Δν = 108.0 Hz, $^2J_{ae}$ = −4.6 Hz); 4.37 (dd, 2 H, OCH$_2$N, AB spectrum, Δν = 140.0 Hz, $^2J_{ae}$ = −4.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 11.21 (qtd, MeCH$_2$, ^1J = 125.0 Hz, ^2J = ^3J = 4.4 Hz); 15.91 (qm, MeCH, ^1J = 125.0 Hz); 26.60 (q.hept, Me_3C, ^1J = 125.7 Hz, ^3J = 4.4 Hz); 28.37 (tm, CH$_2$Me, ^1J = 126.0 Hz, ^2J = 4.2 Hz); 56.78 (dd.dec, CMe_3, $^3J_{CNCH_a}$ ≈ 7.0 Hz, $^3J_{CNCH_e}$ ~3.0 Hz, $^3J_{CCCH}$ = 3.6 Hz); 62.05 (dm, CH, ^1J = 134.2 Hz); 78.0 (ddd, OCH$_2$NCMe$_3$, $^1J_{CH_a}$ = 164.2 Hz, $^1J_{CH_e}$ = 150.0 Hz, $^3J_{COCH_e}$ = 4.4 Hz); 79.24 (ddt, OCH$_2$NCH, $^1J_{CH_a}$ = 164.2 Hz, $^1J_{CH_e}$ = 150.4 Hz, $^3J_{COCH_e}$ = $^3J_{CNCH}$ = 5.1 Hz) (see Fig. 1).

Minor diastereomer (10′) (see Fig. 1 and Scheme 5). ^{1}H NMR ($CDCl_3$), δ: 0.88 (t, 3 H, MeCH$_2$, ^3J = 7.3 Hz); 1.05 (s, 9 H, Me_3C); 1.05 (d, 3 H, MeCH, ^3J = 6.7 Hz); 1.21 and 1.53 (both m, 2 H, CH$_2$Me, ^2J = −13.4 Hz, ^3J = 3.4 Hz); 2.55 (m, 1 H, CH); 4.27 (dd, 2 H, OCH$_2$NCH, AB spectrum, Δν = 68.0 Hz, $^2J_{ae}$ = −4.6 Hz); 4.36 (dd, 2 H, OCH$_2$N—CMe$_3$, AB spectrum, Δν = 188.0 Hz, $^2J_{ae}$ = −4.6 Hz) (see Fig. 1). ^{13}C NMR ($CDCl_3$), δ: 9.91 (qtd, MeCH$_2$, ^1J = 125.0 Hz, ^2J = ^3J = 4.4 Hz); 17.06 (qm, MeCH, ^1J = 125.0 Hz); 26.59 (tm, CH$_2$Me, ^1J = 126.0 Hz, ^2J = 4.2 Hz); 26.98 (q.hept, Me_3C, ^1J = 125.7 Hz, ^3J = 4.4 Hz); 56.2 (dd.dec, CMe_3, $^3J_{CNCH_a}$ = 7.2 Hz, $^3J_{CNCH_e}$ = $^3J_{CCCH}$ = 3.6 Hz); 61.07 (dm, CH, ^1J = 134.2 Hz); 77.38 (ddd, OCH$_2$NCMe$_3$, $^1J_{CH_a}$ = 164.2 Hz, $^1J_{CH_e}$ = 150.4 Hz, $^3J_{COCH_e}$ = −4.4 Hz); 82.13 (ddt, OCH$_2$NCH, $^1J_{CH_a}$ = 164.2 Hz, $^1J_{CH_b}$ = 150.4 Hz, $^3J_{COCH_b}$ = $^3J_{CNCH}$ = 5.1 Hz) (see Fig. 1). When the sample was heated in toluene-d_8, the

value $\Delta\nu$ = 2.1 Hz for the signals of the protons of the Me_3C groups did not change in the 20—120 °C range.

3-*tert*-Butyl-4-(1-methoxycarbonylmethylisopropyl)-1,3,4-oxadiazolidine (11). ***A.*** **Methyl β-*tert*-butylhydrazinoisovalerate.** A mixture of *tert*-butylhydrazine (1 g, 1.12 mmol) and methyl β,β-dimethylacrylate (0.95 g, 0.83 mmol) was purged with argon and heated in a sealed tube for 7 days at 100 °C. The tube was opened and evacuated for 2 h at 2 Torr to give 1.7 g (yield 96%) of the product, which was used without distillation. ^{1}H NMR ($CDCl_3$), δ: 1.01 (s, 9 H, Me_3C); 1.05 (s, 6 H, Me_2C); 2.43 (s, 2 H, CH_2); 3.65 (s, 3 H, MeO). ^{13}C NMR ($CDCl_3$), δ: 27.47 (q, Me_3C, ^1J = 125.0 Hz); 42.39 (t.hept, CH_2, ^1J = 129.3 Hz, ^3J = 4.4 Hz); 52.33 and 54.38 (both s, quat. C); 173.21 (CO).

B. **3-*tert*-Butyl-4-(1-methoxycarbonylmethylisopropyl)-1,3,4-oxadiazolidine (11).** A mixture of methyl β-*tert*-butylhydrazinoisovalerate (1.6 g, 6.5 mmol) in 60 mL of petroleum ether (b.p. 40—70 °C) and paraform (0.78 g, 26 mmol) depolymerized in 1 mL of distilled H_2O was kept for 48 h at 20 °C. After addition of 2 mL of MeOH, the mixture was kept for 2 weeks at 20 °C, dried with $MgSO_4$ (12 h), filtered, and concentrated, and the residue was distilled to give 1.26 g (yield 64.6%) of the product, b.p. 132—135 °C (13 Torr). Found (%): N, 11.35. $C_{12}H_{24}N_2O_3$. Calculated (%): N, 11.47. ^{1}H NMR ($CDCl_3$), δ: 1.03 (s, 9 H, Me_3C); 1.10 and 1.24 (s, 6 H, Me_2C); 2.40 (dd, 2 H, CH_2CO, AB spectrum, $\Delta\nu$ = 112.0 Hz, $^2J_{ab}$ = −12.8 Hz); 3.63 (s, 3 H, MeO); 4.36 (dd, 2 H, $OCH_2N{-}CMe_3$, AB spectrum, $\Delta\nu$ = 188.0 Hz, $^2J_{ab}$ = −4.9 Hz); 4.38 (dd, 2 H, OCH_2NCMe_2, AB spectrum, $\Delta\nu$ = 212.0 Hz, $^2J_{ab}$ = −5.5 Hz). The value $\Delta\nu$ = 12.0 Hz for the signals of the Me_AMe_BC groups in the ^{1}H NMR spectrum in *p*-dichlorobenzene did not change on heating in the 50—120 °C range. ^{13}C NMR ($CDCl_3$), δ: 24.31 and 24.85 (both qm, $\underline{Me}_2C$, ^1J = 126.3 Hz, ^3J = 4.4 Hz); 26.91 (q.dec, $\underline{Me}_3C$, ^1J = 126.4 Hz, ^3J = 4.4 Hz); 44.32 (t.hept, $\underline{CH}_2CO$, ^1J = 129.3 Hz, ^3J = 2.9 Hz); 50.01 (q, MeO, ^1J = 145.3 Hz); 56.49 (m, $\underline{C}Me_2$); 58.66 (m, $\underline{C}Me_3$); 78.60 (ddd, $O\underline{CH}_2NCMe_3$, $^1J_{CH_a}$ = 165.7 Hz, $^1J_{CH_e}$ = 149.7 Hz, $^3J_{COCH_e}$ = 4.4 Hz); 78.82 (ddd, $O\underline{CH}_2NCMe_2$, $^1J_{CH_a}$ = 164.2 Hz, $^1J_{CH_e}$ = 151.1 Hz, $^3J_{COCH_e}$ = 5.8 Hz); 170.53 (tq, CO, ^2J = 4.4 Hz, ^3J = 3.6 Hz).

Potassium salt of 3-*tert*-butyl-4-(1-carboxymethylisopropyl)-1,3,4-oxadiazolidine (12). A mixture of oxadiazolidine **11** (1.0 g, 4.1 mmol) and KOH (0.23 g, 4.1 mmol) in 30 mL of anhydrous MeOH was refluxed for 4 h, and the solvent was evaporated to dryness. The residue was recrystallized from MeCN to give 0.85 g (yield 72.8%) of the product as white fluffy crystals, m.p. 210—212 °C. ^{1}H NMR (CD_3OD), δ: 1.07 (s, 9 H, Me_3C); 1.13 and 1.25 (both s, 6 H, Me_2C); 2.29 (dd, 2 H, CH_2CO, AB spectrum, $\Delta\nu$ = 88.0 Hz, ^2J = −11.6 Hz); 4.40 (dd, $O\underline{CH}_2NBu^t$, AB spectrum, $\Delta\nu$ = 220.0 Hz, ^2J = −4.9 Hz); 4.46 (dd, $O\underline{CH}_2NCMe_2$, AB spectrum, $\Delta\nu$ = 248.0 Hz, ^2J = −4.9 Hz).

Dipotassium salt of 3,4-bis(1-carboxyisopropyl)-1,3,4-oxadiazolidine (13) and 3,4-bis(1-methoxycarbonylisopropyl)-1,3,4-oxadiazolidine (14).

A. **2,2′-Hydrazobis(isobutyronitrile).** $H_2NNH_2 \cdot H_2SO_4$ (20 g, 154 mmol) and then acetone (17.4 g, 300 mmol) were added to a stirred solution of NaCN (15 g, 306 mmol) in 70 mL of H_2O. The mixture warmed up spontaneously to 40 °C, and an oily layer formed. This layer gradually transformed into a coarse-grained crystalline material. The mixture was stirred for 12 h at 20 °C. Then the precipitate was separated, washed with cold H_2O, and recrystallized from Et_2O to give 18 g (yield 72.3%) of the product, m.p. 89—93 °C (*cf.* Ref. 33). ^{1}H NMR (CD_3OD), δ: 1.42 (s, Me).

B. **2,2′-Hydrazobis(isobutyric acid).** A mixture of 2,2′-hydrazobis(isobutyronitrile) (10 g) and 100 mL of conc. hydrochloric aid was kept for 2 h at 0 °C and allowed to stand for 12 h at 20 °C (during this period, the dinitrile completely dissolved). Then 50 mL of H_2O was added, and the mixture was refluxed for 1 h and concentrated to dryness. The crystalline precipitate was dissolved in 50 mL of H_2O and concentrated; this operation was repeated many times until HCl was completely removed. After that, the crystalline precipitate was dissolved in 30 mL of hot H_2O, and aqueous NH_3 was added until the pH was brought to ≈ 3. The resulting precipitate was separated and dried to give 10 g (yield 81.3%) of the product, m.p. 223—226 °C (*cf.* Ref. 34). ^{1}H NMR (CD_3OD + D_2O, 20 : 1), δ: 1.47 (s, Me).

C. **Dimethyl 2,2′-hydrazobis(isobutyrate).** A suspension of the diacid (2.2 g) in 10 mL of MeOH was treated with a solution of CH_2N_2 in Et_2O until the substance completely dissolved and a persisting yellow color appeared. Evaporation *in vacuo* gave 2.2 g (yield 88%) of the product; m.p. 54 °C (from *n*-hexane) (*cf.* Ref. 34). ^{1}H NMR ($CDCl_3$), δ: 1.19 (s, MeC); 3.68 (s, MeO).

D. **Dipotassium salt of 3,4-bis(1-carboxyisopropyl)-1,3,4-oxadiazolidine (13).** A solution of paraform (2 g, 66 mmol) in 5 mL of MeOH and a solution of KOH (1.62 g, 29 mmol) in 5 mL of MeOH were added to a solution of dimethyl 2,2′-hydrazobis(isobutyrate) (3.2 g, 14 mmol) in 5 mL of benzene. After 3 h, 5 mL of *n*-hexane was added, and the mixture was kept for 5 days at 20 °C. Then the precipitate was filtered off, washed with *n*-hexane and ether, and dried *in vacuo* to give 2.6 g (yield 58.5%) of a product that did not melt when heated to 270 °C. ^{1}H NMR (CD_3OD), δ: 1.20 and 1.39 (both s, 12 H, Me_2C); 4.45 (dd, 4 H, NCH_2O, AB spectrum, $\Delta\nu$ = 56 Hz, $^2J_{ab}$ = −4.9 Hz). ^{13}C NMR (CD_3OD + D_2O, 20 : 1), δ: 23.22 and 27.91 (qq, $\underline{Me}_2C$, ^1J = 126.4 Hz; ^3J = 3.6 Hz); 68.02 (dd.hept, $\underline{C}Me_2$, $^3J_{CNCH_a} \approx 6$ Hz; $^3J_{CNCH_b} \approx {}^2J_{CCH} \approx 3$ Hz); 83.14 (ddd, NCH_2O, $^1J_{CH_a}$ = 166.4 Hz, $^1J_{CH_b}$ = 153.3 Hz, $^3J_{COCH_e}$ = 3.7 Hz); 183.96 (hept, CO, ^3J = 3.6 Hz).

E. **3,4-Bis(1-methoxycarbonylisopropyl)-1,3,4-oxadiazolidine (14).** At 0 °C, a solution of $Me_3N \cdot HCl$ (0.3 g, 3.14 mmol) in 2 mL of anhydrous MeOH was added to a solution of the dipotassium salt (0.5 g, 1.55 mmol) in 20 mL of anhydrous MeOH. Just after that, a solution of CH_2N_2 in Et_2O was added until the yellow color persisted. The mixture was kept for 12 h at 20 °C and evaporated *in vacuo*. The residue was extracted with hexane and then with benzene. Concentration of the combined extracts gave 0.2 g (yield 42.5%) of the product; m.p. 48 °C (from *n*-hexane). The product was purified by sublimation at 45 °C (1 Torr). Found (%): N, 10.15. $C_{12}H_{22}N_2O_5$. Calculated (%): N, 10.21. ^{1}H NMR ($CDCl_3$), δ: 1.34 and 1.35 (both s, 12 H, Me_2C); 3.67 (s, 6 H, MeO); 4.40 (dd, 4 H, CH_2, AB spectrum, $\Delta\nu$ = 168.0 Hz, ^2J = −4.90 Hz). The enantiomers can be detected by splitting of the signals for H_a and H_b in the presence of a chiral shift reagent (see Fig. 1). ^{1}H NMR (11 mg of compound **14** + 3 mg of Eu(tfc)$_3$ in 1 mL of C_6D_6), δ: 1.42 (s, 6 H, Me_a); 1.49 (s, 6 H, Me_b); 3.36 (s, 6 H, MeO); 4.70 (two d, 2 H, H_a, $\Delta\nu$ = 2.8 Hz, ^2J = −4.9 Hz); 5.10 (two d, 2 H, H_b, $\Delta\nu$ = 6.7 Hz, ^2J = −4.9 Hz). The $\Delta\nu$ value for the signals of methyl protons (12 Hz) did not change on heating to 120 °C in *p*-dichlorobenzene. ^{13}C NMR (C_6D_6), δ: 23.60 and 26.03 (both qq, $\underline{Me}_2C$, ^1J = 128.6 Hz, ^3J = 4.4 Hz); 51.71 (q, MeO, ^1J = 146.8 Hz); 64.54 (dd.hept, $\underline{C}N$, $^3J_{CNCH_a}$ = 7.0 Hz, $^3J_{CNCH_b} \approx {}^2J_{CCH} \approx 4.0$ Hz); 80.77 (ddd, NCH_2O, $^1J_{CH_a}$ = 166.4 Hz, $^1J_{CH_b}$ = 153.3 Hz, $^3J_{COCH_b}$ = 4.0 Hz); 174.85 (q.hept, CO, $^3J_{COCH} = {}^3J_{CCCH}$ = 3.6 Hz) (see Fig. 1).

When $Me_3N \cdot HCl$ was replaced by (*S*)-(−)-$PhCH(Me)NMe_2 \cdot HCl$, purification on a TLC plate (Kieselgel 60 (Merck), using hexane—ether, 1 : 1, as the eluent) gave 32 mg of ester **14** with $[\alpha]_{546}^{20}$ +1.1° (*c* 1.8 MeOH). Optical rotation was not observed after 5 h at 20 °C.

(*S*)-(−)-Dimethyl-α-phenylethylamine was prepared by a known procedure[35] from (*S*)-(−)-α-phenylethylamine ($[\alpha]_D^{20}$ −36°, neat), yield 50.3%; ^1H NMR ($CDCl_3$), δ: 1.37 (d, 3 H, MeCH, ^3J = 7.1 Hz); 2.19 (s, 6 H, Me_2N); 3.21 (q, 1 H, HC); 7.21 and 7.27 (m, 5 H, Ph).

(*S*)-(−)-Dimethyl-α-phenylethylamine hydrochloride, m.p. 198 °C (subl.) (from MeOH—Et_2O). ^1H NMR (CD_3OD), δ: 1.74 (d, 3 H, MeCH, ^3J = 7.0 Hz); 2.69 and 2.87 (both s, 6 H, Me_2N); 4.50 (q, CHMe), 7.52 (m, Ph).

(*S*)-(−)-Trimethyl-α-phenylethylammonium iodide was obtained by a known procedure,[35] yield 68.2%, m.p. 157 °C, $[\alpha]_D^{20}$ −19.3° (*c* 2.3 EtOH). ^1H NMR (CD_3OD), δ: 1.83 (dt, 3 H, MeCH, ^3J = 7.0 Hz, $^3J_{HN}$ = 1.8 Hz); 3.08 (s, 9 H, Me_3N^+); 4.82 (q, 1 H, HC); 7.52 and 7.6 (m, 5 H, Ph). ^{13}C NMR (^1H)(CD_3OD), δ: 15.63 (s, MeCH); 52.02 (t, Me_3N^+, $^1J_{C,N}$ = 4.2 Hz); 75.10 (s, CH); 130.20 (s); 131.70 (s); 131.75 (s); 134.3 (s, Ph).

(*S*)-(−)-Trimethyl-α-phenylethylammonium chloride was prepared by anion exchange:[36] the iodide (2 g, 7 mmol) was dissolved in 17 mL of anhydrous MeOH containing dry HCl (3 g, 80 mmol). After evaporation of the solvent, the residue was heated for 6 h at 60 °C *in vacuo*. The product was obtained in a quantitative yield as a white crystalline highly hygroscopic material. ^1H NMR (CD_3OD), δ: 1.82 (dt, 3 H, MeCH, ^3J = 6.7 Hz, $^3J_{H,N}$ = 1.8 Hz); 3.10 (s, 9 H, Me_3N); 4.87 (q, 1 H, CHMe); 7.51 and 7.64 (m, 5 H, Ph). A similar spin-spin coupling constant $^3J_{H,14N}$ was observed[37] in the case of $Et_4N^+I^-$.

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