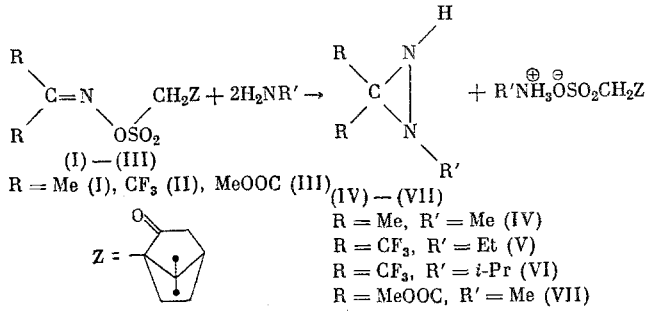
ASYMMETRIC NONBRIDGEHEAD NITROGEN

10. ASYMMETRIC SYNTHESIS OF DIAZIRIDINES*

R. G. Kostyanovskii, G. B. Shustov,
A. I. Mishchenko, and V. I. Markov

UDC 541.63:542.91:547.71

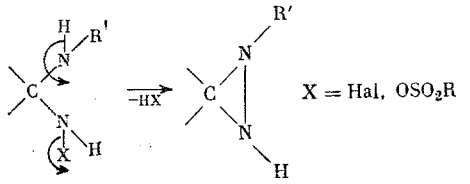
The first optically active diaziridines with only the nitrogen atoms as chiral centers were prepared by kinetic resolution of the racemate by reaction with insufficient amount of a chiral acylating agent [2]. A sufficiently general method for preparing diaziridines via the O-sulfonylketoximes [3, 4] offers possibilities for asymmetric synthesis based on the accessible *l*-10-O-camphorsulfonylketoximes (I)-(III) (Table 1)



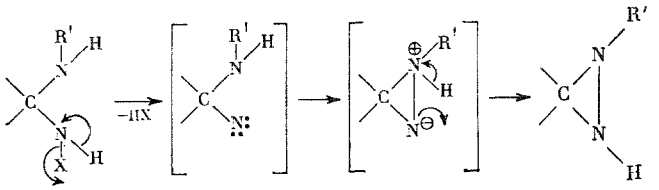
The diaziridines (IV)-(VII) possess significant optical activity (Table 2). Thus asymmetric induction can be achieved by means of the chiral leaving group, as we supposed.

Two alternative schemes have been proposed for the formation of the diaziridine ring:

a) intramolecular S_N2 substitution [5]



b) the nitrene mechanisms [6]

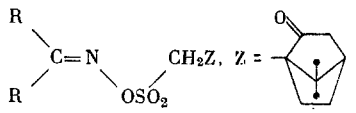


The optical activity of diaziridines (IV)-(VII) favors scheme a), in which the leaving group participates in the cyclization that determines the configuration at the ring N atom. In scheme b) the group X is lost in the step preceding cyclization, during formation of the α-aminonitrene.

* For communication 9 see [1].

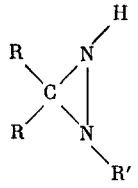
Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2026-2032, September, 1976. Original article submitted August 1, 1975.

TABLE 1. *l*-10-O-Camphorsulfonylketoximes



Compound	R	Yield, %	mp, °C	$[\alpha]_{546}^{20}$	ν, cm^{-1} (KBr)	PMR, δ, ppm; J, Hz (C_6H_6)			
						R_2C	10-CH_2	8,9-Me_2	remainder
(I)	Me	94,1	74—75 (from ether)	—19,60° (*C* 5,10, CCl_4)	1730 (C=O) 1640 w (C=N)	1,49 and 1,52	3,11 and 3,81 J_{H-H} =15,0	0,59 and 0,94	1,14—2,58
(II)	CF_3	91,2	89—90 (from MeOH)	—26,87° (*C* 5,20, MeOH)	1737 (C=O) 1640 w (C=N)	—11,04 and —14,03 (^{19}F) J_{F-F} =6,73	2,84 and 3,52 J_{H-H} =14,6	0,22 and 0,48	0,69—2,03
(III)	MeOOC	58,7	74—75 (from ether)	—39,16° (*C* 5,03, MeOH)	1730 (C=O) 1627 w (C=N)	3,00 and 3,14	3,06 and 3,78 J_{H-H} =15,0	0,33 and 0,67	0,75—2,20

TABLE 2. Optically Active Diaziridines



Compound	R	R'	Chiral reagent	Reaction conditions			Yield, %	Optical activity		
				T, °C	τ, h	solvent		λ	$[\alpha]_\lambda^{20}$	vol.%(solvent)
(IV)	Me	Me	(I)	0	12	$MeNH_2$ (excess)	22,1	589	—4,64	7,54 (C_6H_6)
								365	—14,59	7,54 (C_6H_6)
(V)	CF_3	Et	(II)	0	48	$EtNH_2$ (excess)	57,6	589	—1,25	9,52 (CCl_4)
								365	—3,11	9,52 (CCl_4)
(VI)	CF_3	*i*-Pr	(II)	0	72	*i*-$PrNH_2$ (excess)	30,0	589	—0,13	19,41 (CCl_4)
								312	—0,22	19,41 (CCl_4)
(VII)	COOMe	Me	(III)	—35	2	CH_2Cl_2	20,5	589	0,00	12,66 ($CHCl_3$)
								365	+0,24	12,66 ($CHCl_3$)
(VII a)	COOMe	Me	(VIII b)	—4	72	CH_2Cl_2	43,6	589	—0,95	5,27 ($CHCl_3$)
(VII b)	COOMe	Me	*l*-(—)-Ephedrine	20	144	MeOH	94,7	589	+7,39	9,98 ($CHCl_3$)
								365	+24,67	9,98 ($CHCl_3$)

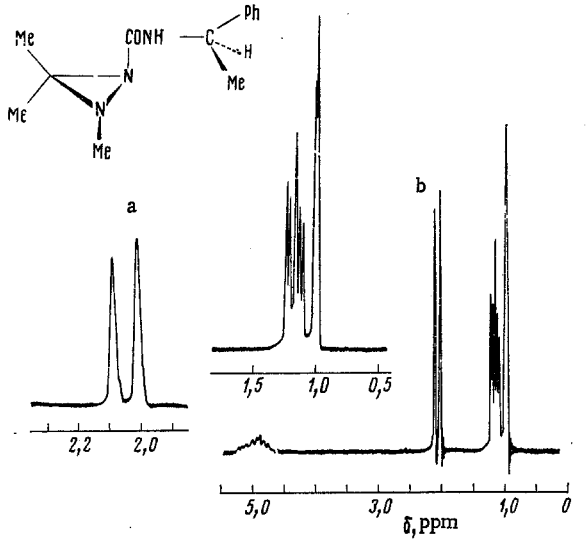


Fig. 1. PMR spectrum of 1-(R-α-phenylethyl)carbamoyl-2,3,3-trimethyldiaziridine in C_6H_6, 60 MHz.

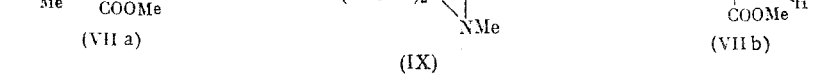
TABLE 3. Inversion Parameters of the Diaziridines

Compound	T, °C (solvent)	$\Delta G^{\neq}$ kcal/mole	$\tau_{1/2}$, h
MeNNHC(COOMe$_2$) (VII b)	70 (C_6H_6)	27,33	3,58
MeNNHC(CH$_2$)$_5$ [2]	70 (C_6H_6)	27,94	8,68
i-PrNNHC(CF$_3$)$_2$ [2] *	70 (Ph_2O)	25,10	0,28

*Converted to 70°C.

We determined the optical purity of (IV) by the method of [2]. In the PMR spectrum of the product from the reaction of (IV) with R-(−)-α-phenylethyl isocyanate, we observed two sets of signals with an intensity ratio corresponding to the diastereomeric composition of the mixture, and hence to the enantiomeric composition of (IV) (Fig. 1). The optical purity of diaziridine (IV) was 9.9%, which corresponded to the stereoselectivity of the reaction of (I) with $MeNH_2$ at 0°C. The diaziridines (V)-(VII) did not react with R-(−)-α-phenylethyl isocyanate.

Because of the presence of the functional groups (MeOOC and NH) in dimethyl 1-methyldiaziridine-3,3-dicarboxylate, we were able to use two methods for kinetic resolution



In the first, following [2] we used an insufficient amount of the chiral acylating agent. In the second we carried out a partial asymmetric amination following [7]. The increased specific rotation of (VIIb) compared with (VIIa) (Table 2) seems to be due to the greater asymmetry of the transition state as a result of the specific interaction of the polar groups of *l*-(−)-ephedrine with the diaziridine-3,3-dicarboxylic ester.

We studied the kinetics of racemization of (VIIb) (Table 3). Our values for the inversion parameters of (VIIb) are close to the known values for 1-methyl-3,3-pentamethylenediaziridine and differ considerably from those for 1-isopropyl-3,3-bis(trifluoromethyl)diaziridine. The reduction in the inversion barrier of the last is due to the steric effect of the bulky CF_3 groups.

EXPERIMENTAL

The NMR spectra were recorded with a JEOL JNM-C-60HL spectrometer (^{1}H, 60 MHz, HMDS internal standard; ^{19}F, 56.45 MHz, CF_3COOH external standard), IR spectra were measured with a UR-10 spectrophotometer as molecular films (liquid samples) and in KBr tablets (solid samples); mass spectra were recorded with an MKh-1303 spectrometer at 30 eV. The specific rotation was measured with Polamat-A and Perkin – Elmer 141 polarimeters at 546 nm.

Dimethyl 1-Methyldiaziridine-3,3-dicarboxylate (IX). A modification of the method of [4] was used to prepare (IX) from 15.7 g (0.05 mole) of dimethyl mesoxalate O-tosyloxime and 4.20 g (1.35 mole) of CH_3NH_2 in 70 ml of CH_2Cl_2 at −35°C. The yield of (IX) was 4.11 g (47.3%), mp 67-68°C (from 1 : 5 iso-PrOH – pentane). PMR spectrum (Ph_2O, δ, ppm): 2.36 (MeN); 3.12 (NH); 3.28 and 3.42 (MeO) [4].

l-(−)- and d-(+)-Camphorsulfonyl Chloride (VIIIa) and (VIIIb). Treatment of *l*- or d-camphorsulfonic acid with excess $SOCl_2$ and a catalytic amount of DMF at 20°C (10 h) gave (VIIIa) or (VIIIb). The yield of each was 70%; (VIIIa) had mp 67-68°C (1 : 3 ether – hexane), $[\alpha]_{546}^{20}$ −38.48° (C 5.20, $CHCl_3$); (VIIIb) had mp 64-65°C (1 : 3 ether – hexane), $[\alpha]_{546}^{20}$ +36.94° (C 5.14, $CHCl_3$) [8]. PMR spectrum (CCl_4, δ, ppm): 0.9 and 1.12 (8,9-Me_2); 3.83 and 3.91 (10-CH_2), J_{H-H} = 15.0 Hz, 1.4-2.65 (remainder).

Acetone *l*-10-O-Camphorsulfonyloxime (I). After addition of 4.55 g (0.045 mole) of triethylamine to a stirred solution of 3.14 g (0.043 mole) of acetoxime and 10.78 g (0.043 mole) of (VIIIa) in 50 ml of absolute benzene at 0°C, the reaction mixture was stirred for 2.5 h at 20°C. After removal of the precipitate, this solvent was evaporated under vacuum and the residue was recrystallized from ether. We obtained 11.50 g of (I) (Table 1). Found: C 54.46; H 7.49; N 4.97%. $C_{13}H_{21}NO_4S$. Calculated: C 54.33; H 7.36; H 4.87%.

Hexafluoroacetone *l*-10-O-Camphorsulfonyloxime (II). Following the procedure used for (I), reaction of 8.15 g (0.045 mole) of hexafluoroacetone oxime, 11.02 g (0.44 mole) of (VIIIa), and 4.56 g (0.45 mole) of triethylamine in 50 ml of absolute ether gave 15.80 g of (II) (Table 1). Found: C 39.52; H 3.81; N 3.60%. $C_{13}H_{15}F_6NO_4S$. Calculated: C 39.55; H 3.82; N 3.55%.

Dimethyl Mesoxalate *l*-10-O-Camphorsulfonyloxime (III). Following the procedure used for (II), 8.06 g (0.05 mole) of dimethyl mesoxalate oxime, 12.54 g (0.05 mole) of (VIIIa), and 5.26 g (0.052 mole) of triethylamine gave 11.00 g of (III) (Table 1). Found: C 47.76; H 5.72; N 3.65%. $C_{15}H_{21}NO_8S$. Calculated: C 47.99; H 5.64; N 3.73%.

(–)-1,3,3-Trimethyldiaziridine (IV). A mixture of 7.17 g (0.0214 mole) of (I) and 40 ml of CH_3NH_2 in a sealed ampule was agitated for 1 h at 0°C and then left overnight. After removal of the excess methylamine (20°C, 40-cm column) the product was recondensed under vacuum (16 mm) and distilled at 760 mm (bath temperature 120-125°C). We obtained 0.36 g of (IV) (Table 2). IR spectrum (ν, cm^{-1}, molecular film): 3210 (NH). PMR spectrum (C_6H_6, δ, ppm): 1.26 and 1.30 (Me); 2.50 (MeN); 1.79 (NH). Mass spectrum (m/e, relative intensity, %): M^+ 86 (16), 85 (28), 71 (22), 70 (69), 57 (14), 56 (52), 55 (11), 45 (28), 44 (17), 43 (22), 42 (84), 41 (32), 39 (12), 39 (12), 31 (22), 30 (100).

(–)-1-Ethyl-3,3-bis(trifluoromethyl)diaziridine (V). A mixture of 7.92 g (0.02 mole) of (II) and 3.61 g (0.08 mole) of $EtNH_2$ in a sealed ampule was allowed to stand for 2 days with periodic agitation at 0°C and was then treated with 40 ml of cold water. The organic layer was dried over $CaCl_2$ and recondensed under vacuum (16 mm). To remove traces of amine the product was treated with dry HCl and recondensed over CaH_2. We obtained 2.38 g of (V) (Table 2), bp 82-83°C; n_D^{20} 1.3295 [6]. IR spectrum (ν, cm^{-1}, molecular film): 3220 (NH). NMR spectrum (CCl_4, δ, ppm): 1.19t (Me), J_{H-H} 7.2 Hz; 2.79m (CH_2, NH); –4.05 and –14.66 dq (CF_3), J_{F-F} = 8.1 Hz. Mass spectrum (m/e, relative intensity, %): M^+ 208 (44), 193 (28), 180 (20), 111 (13), 96 (15), 69 (18), 51 (15), 44 (14), 42 (16), 29 (100).

(–)-1-Isopropyl-3,3-bis(trifluoromethyl)diaziridine (VI). Following the preceding method, 4.3 g (0.011 mole) of (II) and 2.69 g (0.0456 mole) of iso-$PrNH_2$ (3 days, 0°C) gave 0.74 g of (VI) (Table 2), bp 68-70°C; n_D^{20} 1.3372 [2]. IR spectrum (ν, cm^{-1}, molecular film): 3220 (NH). PMR spectrum (CCl_4, δ, ppm): 1.07 and 1.12 dd (Me), J_{H-H} = 7.5 Hz; 2.73m (CH); 2.83 (NH). Mass spectrum (m/e, relative intensity, %): M^+ 222 (4.2), 207 (3), 44 (6), 43 (100), 42 (14), 41 (20).

(+)-Dimethyl 1-Methyldiaziridine-3,3-dicarboxylate (VII). A solution of 3.34 g (0.108 mole) of CH_3NH_2 in 25 ml of absolute CH_2Cl_2 was added dropwise to a stirred solution of 15.00 g (0.039 mole) of (III) in 40 ml of absolute CH_2Cl_2 at –35°C; stirring was continued for a further 2 h. After removal of the precipitate the solvent was evaporated under vacuum and the product was extracted from the residue with absolute ether. The ether was removed; the residue was recrystallized from a 1 : 5 mixture of iso-PrOH and pentane and sublimed under vacuum (0.5 mm) at 30°C. We obtained 1.36 g of (VII) (Table 2), mp 68-69°C [4]. IR spectrum (ν, cm^{-1}, KBr): 3224 (NH), 1723, 1750 (C=O). The product was identified by its PMR spectrum and by the absence of melting point depression of a mixture with (IX).

Optical Purity of (IV). A slight excess (5-10%) of R-(–)-α-phenylethyl isocyanate was added to a solution of 38 mg of (IV) in 5 ml of absolute ether; the reaction mixture was left overnight at 20°C. After removal of the ether the residue was dissolved in 1.2 ml of benzene and the PMR spectrum was recorded (δ, ppm): 0.98, 1.00, 1.15 (Me_3C); 1.15 and 1.18 dd (MeCH), J_{H-H} = 6.45 and 6.30 Hz; 2.02 and 2.11 (MeN), 4.88m (CH) (Fig. 1b); $[\alpha]_{546}^{22}$ +36.16° (C 6.36, C_6H_6). The ratio of diastereomers was determined from the integrated intensities of the signals at 2.02 and 2.11 ppm.

Kinetic Resolution of the Racemate (IX). Reaction with (VIIIb). A solution of 1.33 g (0.005 mole) of (VIIIb) in 20 ml of absolute CH_2Cl_2 was added to a solution of 1.74 g (0.01 mole) of (IX) and 0.51 g (0.005 mole) of triethylamine in 20 ml of absolute CH_2Cl_2 at –78°C and the reaction mixture was left for three days at –4°C. After removal of the precipitate, the solvent was evaporated under vacuum and the product was extracted from the residue with benzene. The benzene was removed, and the residue was recrystallized from iso-PrOH and sublimed under vacuum (0.5 mm) at 30°C. We obtained 0.36 g of (VIIa) (Table 2), mp 67-68°C [4]. The product was identified by its PMR spectrum and by the absence of melting point depression of a mixture with (IX).

Reaction with *l*-(–)-Ephedrine. A solution of 2.96 g (0.017 mole) of (IX) and 1.40 g (0.0085 mole) of *l*-(–)-ephedrine ($[\alpha]_{546}^{20}$ –21.06° (C 7, 12, $CHCl_3$)) in 30 ml of absolute methanol with traces of MeONa was held for six days at 20°C. After removal of the solvent the residue was chromatographed on a column (L 40/100 silica gel, 50 : 50 chloroform – ether). We obtained 1.40 g of (VIIb) (Table 2), bp 67-68°C [4]. The product was identified by its PMR spectrum and by the absence of melting point depression of a mixture with (IX).

Kinetics of Racemization of (VIIb). Sealed ampules each of 1.1 ml containing a solution of (VIIb) in C_6H_6 (C 4.0) were simultaneously placed in a thermostat (70 ± 0.1°C, water heat transfer medium). At fixed intervals (1.5-2.0 h) one of the ampules was removed and rapidly cooled to −7°C. At the end of the experiment the ampules were opened and the specific rotation at 404 nm was measured. The absence of decomposition of the sample during the experiment was verified from the PMR spectrum. The value of k_{rac} was calculated by least squares in the parameters $\ln [\alpha]_{404}^{20} - \tau$ (h) with an error of ≤0.2%. We calculated the value of the inversion barrier from k_{rac} by the modified Eyring equation, $\Delta G_T^{\neq} = 4.57\,T\,(10.32 + \log 2T/k_{rac})$ kcal/mole, and the racemization half-life from the equation $\tau_{1/2} = \ln 2/k_{rac}$ (Table 3).

CONCLUSIONS

1. We have carried out the asymmetric synthesis of diaziridines by reaction of *l*-(−)-10-O-camphorsulfonylketoximes with primary amines, thus completely excluding the possibility of cyclization by the nitrene mechanism.

2. Dimethyl 1-methyldiaziridine-3,3-dicarboxylate was enriched with the (+)- and (−)-enantiomers by reaction with insufficient amount of *l*-(−)-ephedrine and d-(+)-10-camphorsulfonyl chloride, respectively. We determined the inversion parameters of the nitrogen atoms from the kinetics of racemization of the (+)-enantiomer.

LITERATURE CITED

1. R. G. Kostyanovskii, A. V. Prosyanik, V. I. Markov, I. A. Zon, and A. E. Polyakov, Izv. Akad. Nauk SSSR, Ser. Khim., 1559 (1976).
2. R. G. Kostyanovskii and A. E. Polyakov, Dokl. Akad. Nauk SSSR, 219, 873 (1974); Izv. Akad. Nauk SSSR, Ser. Khim., 1671 (1974); 198 (1975).
3. Yu. V. Zeifman, E. G. Abduganiev, E. M. Rokhlin, and I. L. Knunyants, Izv. Akad. Nauk SSSR, Ser. Khim., 2737 (1972).
4. R. G. Kostyanovskii, G. B. Shustov, and V. I. Markov, Izv. Akad. Nauk SSSR, Ser. Khim., 2823 (1974).
5. E. Schmitz, Three-Membered Rings with Two Heteroatoms [Russian translation], Mir (1970), p. 118.
6. B. L. Dyatkin, K. N. Makarov, and I. L. Knunyants, Tetrahedron, 27, 51 (1971).
7. R. G. Kostyanovskii, V. F. Rudchenko, and V. I. Markov, Izv. Akad. Nauk SSSR, Ser. Khim., 1685 (1975).
8. J. Read, J. Chem. Soc., 2761 (1930).