DIASTEREOSELECTIVE SYNTHESIS OF 1-α-PHENYLETHYL-3,3-DIMETHYLDIAZIRIDINE. CONFORMATION AND CONFIGURATION OF THREE-MEMBERED RING NITROGEN HETEROCYCLES CONTAINING AN ASYMMETRIC SUBSTITUENT ON THE NITROGEN ATOM*

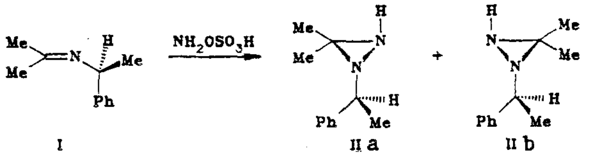
G. V. Shustov, F. D. Polyak, V. S. Nosova,
I. T. Liepinya, G. V. Nikiforovich,
and R. G. Kostyanovskii

UDC 547'717'235:
541.63:
543.422.25

The synthesis of 1-(S)-α-phenylethyl-3,3-dimethyldiaziridine from N-(S)-α-phenylacetonimine and hydroxylamine-O-sulfonic acid has been carried out with high diastereoselectivity. The absolute configuration of the diastereomers was established by comparison with oxaaziridine analogs based on their NMR and CD spectra, and atom-atomic potential calculations. A test has been proposed to establish the absolute configuration of N-α-phenylethyl-substituted three-membered ring heterocycles using NMR, and the mechanism of epimination of imines is discussed, which is similar to their oxidation mechanism.

Diaziridines are monoamine oxidase inhibitors [2, 3] and exhibit pronounced antidepressive properties [3]. For these reasons there is interest in the preparation of these compounds in optically active form via asymmetric synthesis. The reaction of O-ℓ-10 camphorsulfonyl ketoximes with amines, which has been studed previously, is characterized by low optical yields (≤ 10%) [4, 5], due to the large spatial separation between the reactive and chiral centers.

In the present paper we have shown that when these centers are proximate to one another, as in (S)-N-α-phenylethylacetonimine (I), the stereoselectivity of construction of a diaziridine ring system is significantly enhanced.



I IIa IIb

It should be noted that in contrast to acetonimine I, N-α-phenylethylbenzophenonimine and 2-phenyl-Δ^1-pyrroline [6] are not hydroxylamine-O-sulfonic acid or chloramine (from NH_3 and t-BuOCl in CH_2Cl_2 at 0-(−10)°C, apparently due to the lower electrophicity of a C=N bond conjugated with a phenyl group. The maximum yield of diaziridine II (≥90%) was obtained upon epimination under heterogeneous (two-phase) conditions (benzene—water) using a phase transfer catalyst such as triethylbenzylammonium chloride. When the reaction was carried out in the absence of a catalyst or in aqueous solution by mixing (S)-α-phenylethylamine, acetone, and hydroxylamine-O-sulfonic acid according to [7], the yield of diaziridine was reduced to 50-60%.

Diastereomers IIa and IIb are formed in an 86:14 ratio, which is significantly different from the equilibrium ratio (65.4:34.6); the same ratio is obtained in the absence of catalyst or when the reaction is carried out in aqueous solution according to [7]. The diastereomers could be separated by chromatography on silica gel. The kinetics of inversion epimerization of isomers IIb were studied polarimetrically in toluene solution at 70°C: $k = (6.1 \pm 0.1) \cdot 10^{-5}$,

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*Communication 60 in the series "Asymmetric Nitrogen"; for Communication 59, see [1].

Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Geterotsiklicheskikh Soedinenii, No. 11, pp. 1461-1465, November, 1988. Original article submitted March 30, 1987.

0009-3122/88/2411-1207$12.50

TABLE 1. Comparison of the Characteristics of Diaziridine

Compound	Kinetic ratio	$[\alpha]_{436}^{20}$, deg (c, %)	CD., $\lambda_{\max}$, nm ($\Delta\varepsilon$)	^1H, δ, ppm	
				Me_2C	MeCH (d)
IIa	86	37,6 (1)	267 (0,17), 261 (0,19), 207 (−2,67)	1,21, 1,37	1,47 (6,6)
IIб	14	−179,3 (0,7)	266 (0,05), 260 (0,05), 210 (−1,60)	1,45, 1,49	1,36 (6,6)
(2*R*,α*S*)-IIIa	82	−98,5 (1)	267 (0,08); 260 (0,03), 216 (−4,12)	1,38, 1,46	1,56 (6,4)
(2*S*,α*S*)-IIIб	18	−272 (1)	267 (0,02), 261 (−0,003), 207 (−2,45)	1,50, 1,66	1,39 (6,4)

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*Prepared by oxidation of S-(imine) I with m-chloroperbenzoic silica gel (with ether–hexene eluent).

**Measured under conditions of selective Me_2C proton decoupling.

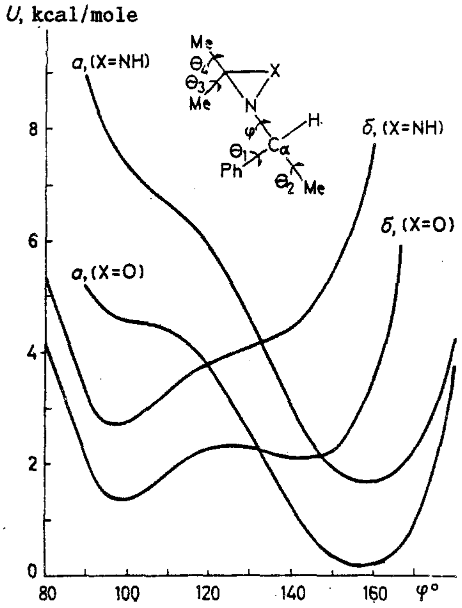


Fig. 1. Potential energy profiles for rotation about the the C_α–N bond in the diaziridines IIa,b and oxaziridines IIIa,b. Energy minima, kcal/mole (φ, deg): IIa, 1.70 (159); IIb, 2.72 (97); IIIa, 0.21 (156); IIIb 1.38 (98).

$\overleftarrow{k} = (3.26 \pm 0.07)\cdot 10^{-5}$ sec^{-1}; $\tau_{1/2} = 124$ min; $\Delta\overrightarrow{G}^{\neq} = 26.8$, $\Delta\overleftarrow{G}^{\neq} = 27.2$ kcal/mole. The high inversion barriers and correspondingly high half-conversion periods (∿ 3 months at 20°C) practically preclude the possibility.

It is known that oxidation of imide I by peracids also proceeds in high diastereoselectivity [8, 9] to give predominantly oxaziridine IIIa (2R, αS)-configuration [9] (see Table 1). There is a similarity in the NMR and CD spectra (Table 1 of the diaziridine diastereomers IIa and IIb and their corresponding oxaziridine diastereomers IIIa and IIIb. The general feature of the their CD spectra is the greater intensity of both the long-wavelength (270-240 nm, ^1L_b) and short-wavelength (240-200 nm, ^1L_a) Cotton effects in the "a" diastereomer compared to the "b" isomer. Based on the characteristic we conclude that the predominant diastereomer IIa has the (1R, 2R, αS)-configuration, and that the less favored isomer IIb has the (1S, 2S, αS)-configuration.

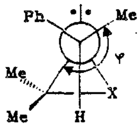
IIa, b and Oxaziridine IIIa, b Diastereomers*

(^3J, Hz)		^{13}C, δ, ppm ($^3J_{CH}$, Hz)**				
CH (κ)	Ph (м)	Me_2C	MeCH	$C_{(3)}$	CH	Ph
3,32	7,30	17,5; 28,2	24,0	57,9 (6,1)	62,1	126,4; 128,3; 144,4
3,32	7,30	17,2; 28,6	21,4	57,9 (6,1)	61,6	126,7; 128,1; 144,6
3,59	7,31	17,5; 25,9	23,1	82,0 (2,4)	62,7	126,8; 128,6; 141,5
3,59	7,31	17,1; 26,1	19,6	81,8 (2,4)	62,0	127,5; 128,3; 143,3

acid according to [8] and separated chromatographically on

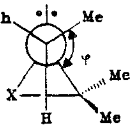
The assignment of configuration was verified by calculating the potential energy as a function of the angle of rotation φ (C_{Me}–C_α–N–C_{ring}) around the C_α-N bond in the diastereomeric diaziridines IIa,b and oxaziridines IIIa, b using the atom-atomic potential method (see Fig. 1). The residual torsional angles θ_1, θ_2, θ_3, and θ_4 were optimized for each calculated point in the function versus φ ; the energy minimum with respect to the angle θ_1 features an almost perpendicular orientation of the phenyl ring relative to the C_{Me}–C_α–C_{Ph} plane. These calculations correctly predict the greater thermodynamic stability of the "a" diastereomer compared to the "b" isomer (Fig. 1), although the value of the energy difference is comparable to the accuracy error of the method. There is also a similarity in the torsional functions of the diastereomeric diaziridines IIa and IIb and the oxaziridines IIIa and IIIb of known absolute configuration; the "b" diastereomer in each case is conformationally more flexible (mobile) than the "a" isomer. The minimum potential energy for both diastereomers "a" and "b" relative to the angle φ corresponds to a conformation in which the three-membered ring is shielded by the smallest substituent attached to C_α, namely the H atom. This is consistent with the NMR spectral data for compounds IIa,b and IIIa,b (Table 1). The fact that the orientation of the α-proton in the substituent attached to the N atom is identical in both the "a" and "b" diastereomers is indicated as well by the observation that the chemical shifts of this proton are superimposable for all of these compounds and that the SSCC $^3J_{CH}$ between the H atom and the carbon atom in the diaziridine ring are also identical.

Analysis of the literature data for aziridine IV, diaziridine V, and oxaziridine VI reveals that this type of conformation is the most stable one both in solution and in the crystalline state for all three-membered ring nitrogen heterocycles containing an asymmetric substituent attached to the nitrogen atom.

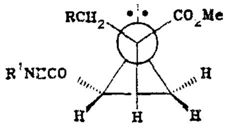


a

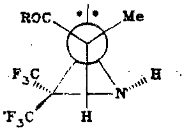
X=NH, O



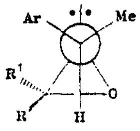
b



IV



V

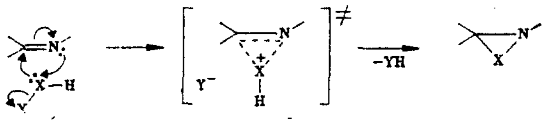


VI

IV R=R^1=H; R=Ph, R^1=CH(CH_2Ph)CO_2Me [10]; V R=OH, OMe, OEt [11]; VI Ar=Ph, R=H, R^1=C_6H_4Br-*p* [12]; Ar=R=R^1=Ph [13]; Ar=Ph, R—R^1=$(CH_2)_2$CH(*t*-Bu)$(CH_2)_2$ [14]; Ar=$C_6H_2Me_3$-2,4,6, R=R^1=Ph [15]

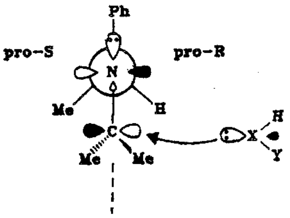
It is also apparent that in this experimentally determined most favorable conformation the methyl groups attached to the carbon atom in the three-membered ring in the "a" diastereomer are located nearer to the magnetically anisotropic phenyl group and are thus more shielded than in the "b" diastereomer (Table 1). If follows, therefore, that the relative chemical shift of the substituent protons attached to the carbon atom in the ring can serve as a criterion to determine the configuration of three-membered ring nitrogen heterocycles containing an N-α-phenylethyl substituent.

The fact that the stereochemical result of epimination and oxidation of imine I is identical suggests that the mechanisms of these two reactions should also be similar. In both cases the slowest step, and hence the stereo-determining step, in the reaction involves addition of the epiminating (hydroxylamine-O-sulfonic acid) or epoxidizing agent (peracid) to the C=N bond [9; 16, p. 118]. However, the predominance of the "a" diastereomer in both the kinetic and equilibrium mixtures, as well as the fact that the "a"/"b" ratio is independent of the reaction conditions, indicate that the transition state for the stereocontrolling or stereodetermining step is affected by the same factors as the ground state of the products. We assume, therefore, that the second step in these reactions, namely, closure of the three-membered ring, occurs almost simultaneously with addition of the reagent.



X=O, Y=OCOR; X=NH, Y=OSO_3H

Based on the established absolute configurations of the "a" and "b" diastereomer we conclude, within the framework of the steric control model [17, p. 122], that imine I reacts preferentially in the conformation from the sterically less hindered pro-R-face.



We have thus discovered as new assymetric synthesis of diaziridines which proceeds with a high degree of diastereoselectivity. The stereochemical result of this synthesis also clarifies certain details in the mechanisms of epimination and oxidation of imines, while the reaction products, diastereomeric diaziridines, provide a convenient model for developing the principle of absolute configuration assignment of diastereomers using NMR.

EXPERIMENTAL

NMR spectra were recorded for kinetic mixtures of diastereomers IIa,b and IIIa,b on a Bruker WM-400 (^1H, 400.13; ^{13}C, 100.62 MHz) spectrometer using $CDCl_3$ solutions versus TMS as internal standard; optical rotation angles (for IIa,b and IIIa,b in $CHCl_3$) and CD spectra (in heptane), for pure diastereomers were measured on a JASCO J-20A spectropolarimeter. Preparative separation of the mixtures of diastereomers was achieved by liquid chromatography on a Bruker LC-31B.

Potential energy surface profiles for rotation about the angle φ_a were calculated using the Momany and Scheraga atom-atomic potential method [18]; partial atomic charges were obtained from CNDO/2 ($\varepsilon = 2$) quantum mechanical calculations, torsional potentials from data for similar compounds [19]. The rigid valence geometries of the diastereomeric oxaziridines IIIa,b and CH(Me)Ph fragments in diaziridines IIa,b were assumed based on the data in [13]. The following geometric parameters for the diaziridine ring in IIa (IIb) were assumed (bond lengths, A°; bond angles, deg): $N_{(1)}N_{(2)}$ 1.500 (1.481), $N_{(1)}C_{(3)}$ 1.454 (1.445), $N_{(2)}C_{(3)}$ 1.464 (1.451), $< C_{\alpha}N_{(1)}C_{(3)}$117 (110), $< C_{\alpha}N_{(1)}N_{(2)}$109 (119), $< HN_{(2)}N_{(1)}$ 108 (109), $< HN_{(2)}C_{(3)}$ 113 (113), $< C_{Me}C_{(3)}C_{Me}$ 113 (114).

1(S)-α-Phenylethyldiaziridine (II). To a mixture of a solution of 1.61 g (10 mmole) imine I [8] in 25 ml benzene and a solution of 2.76 g (20 mmole) K_2CO_3 and 0.1 g triethylbenzylammonium chloride in 10 ml water cooled to 10°C was added with stirring 2.23 g (20 mmole) hydroxylamine-O- sulfonic acid in portions; stirring was continued for 10 h at 20°C. The benzene layer was separated and dried over anhydrous K_2CO_3. After evaporation of the benzene the residue was analyzed by PMR and distilled under vacuum. Yield 1.61 g 991%) of diaziridine II, bp 89-90°C (1 mm Hg). Found: C 74.7; H 9.3; N 15.7%. $C_{11}H_{16}N_2$. Calculated: C 75.0; H 9.1; N 15.9%. Diastereomers IIa and IIb were separated on an IBM Silica 10 × 250 mm column with hexane + 5% i-PrOH as eluent.

Kinetics of Epimerization of Diastereomer IIb. A solution of diastereomer IIb in $C_6H_5CD_3$(c 2 %) was placed in a thermostated curvette (ℓ = 1 cm, heat transfer agent, water) at 70 ± 0.1°C in a spectropolarimeter and the change in optical rotation was recorded over a h period at 400 nm. The optical rotation of an equilibrium mixture of diastereomers was measured after the solution had been maintained for 20 min at 70°C. The equilibrium ratio of diastereomers IIa/IIb was measured by PMR spectroscopy.

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