REACTIONS OF 2,2-DIMETHYL-3-PHENYLAZIRINE WITH HYDRAZINO AND AMINO ALCOHOLS

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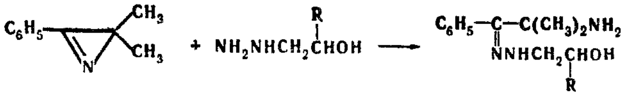
The reaction of 2,2-dimethyl-3-phenylazirine with β-hydrazino alcohols leads to the corresponding β-hydroxyalkylhydrazones of 2-amino-2-methyl-1-phenyl-1-propanone. The reaction of the same azirine with β- and γ-amino alcohols gives primarily substituted oxazolidines and perhydro-1,3-oxazine, respectively, which undergo isomerization to the chain form, viz., the corresponding N-(2-amino-2-methyl-1-phenylpropylidene)amino alcohols; the tendency to undergo isomerization to the chain form is not manifested in the case of β-aminoethanol. A conclusion regarding the preferred conformation of the oxazolidines was drawn on the basis of the data from ^{1}H and ^{13}C NMR spectroscopy. The product of the reaction of azirine with α-aminoethanol is 2,5,5-trimethyl-4-phenyl-3-imidazoline.

Hydrazones are formed in the reaction of 2,2-dimethyl-3-phenylazirine (I) with hydrazine and its serivatives [1], while Schiff bases of 2-amino-2-methyl-1-phenyl-1-propanone are formed in the reaction of I with aliphatic amines [2].

In order to further study the reactivity of azirine I with respect to functionally substituted amines and hydrazines we investigated its reactions with β-hydrazino and α-, β-, and γ-amino alcohols. Absorption bands of stretching vibrations of a C═N bond (1620-1630 cm^{-1}) and bands of stretching vibrations of NH_2, NH, and OH groups (3280-3370 cm^{-1}) are observed in the IR spectra of II and III, which were obtained by the reaction of azirine I with 2-hydrazinoethanol and 1-hydrazino-2-propanol. Broad singlets of protons of NH_2 and OH groups at 2.15-2.46 ppm and of an NH group (4.75 ppm) and multiplets of the protons of an alkyl chain (2.9-3.8 ppm) and of a phenyl ring (7.04-7.35 ppm) are present in their ^{1}H NMR spectra. The ^{13}C NMR spectra contain a singlet at 156 ppm, which can be assigned only to the resonance of the carbon atom of the C═N bond. The equivalence of the methyl groups in the ^{1}H and ^{13}C NMR spectra constitutes evidence for the acyclic structure of II and III. Consequently, 2-amino-2-methyl-1-phenyl-1-propanone β-hydroxyalkylhydrazone structures should be assigned to these compounds on the basis of the spectral and analytical data:



I

II, III

II R=H; III R=CH_3

However, the products of the reactions of azirine I with α-, β-, and γ-amino alcohols in most cases have properties that are extremely different from the properties of the expected N-(2-amino-2-methyl-1-phenylpropylidene)amino alcohols. Thus a singlet of a carbon atom of the C_{quat}—O bond at 105 ppm is observed in the ^{13}C NMR spectra (Table 1) of IV and Va, b, which were obtained by the reaction of azirine I with 2-aminoethanol and 1-amino-2-propanol; however, the signal of an azomethine carbon atom of a C═N bond is absent (which is also confirmed by the IR spectral data, for which see the experimental section). Multiplets of nonequivalent protons of a β-methylene groups of β-amino alcohols (2.35-3.18 ppm) were recorded in the ^{1}H NMR spectra of IV and Va, b (Table 2); this is possible only in the case of a cyclic structure for IV and Va, b. Taking into account the set of spectral and analytical data we arrived at the conclusion that substituted oxazolidines IV and Va, b are formed as

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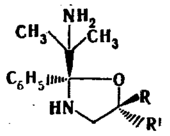
TABLE 1. ^{13}C Chemical Shifts of Oxazolidines IV and Va, b

Compound	C_2	C_4	C_5	C_R	$-\overset{\vert}{\underset{\vert}{C}}-$	CH_3	C_α	C_o	C_m	C_p
IV	103,6	45,8	65,1	—	54,1	28,3, 25,9	140,8	127,1	128,6	127,1
Va	105,7	55,4	76,7	30,3	55,4	28,6, 21,7	144,9	128,6	130,3	128,6
Vb	105,5	54,2	73,2	30,0	56,2	27,6, 22,5	143,1	128,9	130,6	128,9

TABLE 2. Parameters of the ^1H NMR Spectra of Oxazolidines IV and Va, b



Compound	R	R′	δ, ppm						J, Hz	
			4-H	5-H	CH_3	NH	H_R	C_6H_5	4,5	4,4
IV	H	H	3,14 (*e*), 2,63 (*a*)	3,64	1,06, 1,12	2,0	—	7,1—7,6	3,4 (5*e*4*e*), 6,8 (5*a*4*e*), 7,6 (4*a*5*e*), 7,6 (5*a*4*a*)	−11,0
Va	CH_3	H	2,14 (*a*), 3,18 (*e*)	3,90	1,06, 1,09	2,0	1,11	7,1—7,6	9,1 (5*a*4*a*), 5,7 (5*a*4*e*)	−11,8
Vb	H	CH_3	2,75 (*a*), 2,35 (*e*)	3,84	1,06, 1,09	2,0	1,06	7,1—7,6	4,1 (5*e*4*e*), 6,7 (5*e*4*a*)	−11,3

TABLE 3. Physicochemical Characteristics of II-Va, b, VII, and IX

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
II	69—70	64,8	8,3	19,1	$C_{12}H_{19}N_3O$	65,1	8,6	19,0	73
III	70—71	66,1	8,6	18,1	$C_{13}H_{21}N_3O$	66,4	8,9	17,9	76
IV	37—38	69,6	8,6	13,5	$C_{12}H_{18}N_2O$	69,9	8,7	13,6	82
Va,b	*	70,7	8,8	12,5	$C_{13}H_{20}N_2O$	70,9	9,1	12,7	78
VII	49—50	70,6	8,9	12,6	$C_{13}H_{20}N_2O$	70,9	9,1	12,7	65
IX	32—33	70,4	8,3	14,7	$C_{12}H_{16}N_2O$	70,6	8,5	14,9	81

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*This compound had bp 121-123°C (5 mm).

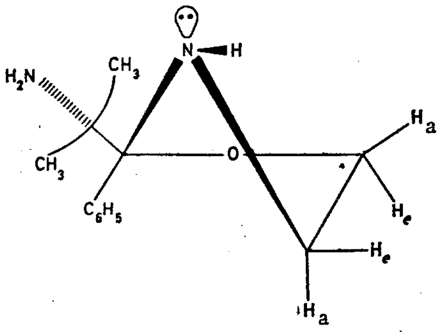


Fig. 1

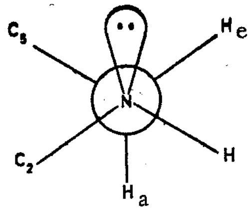
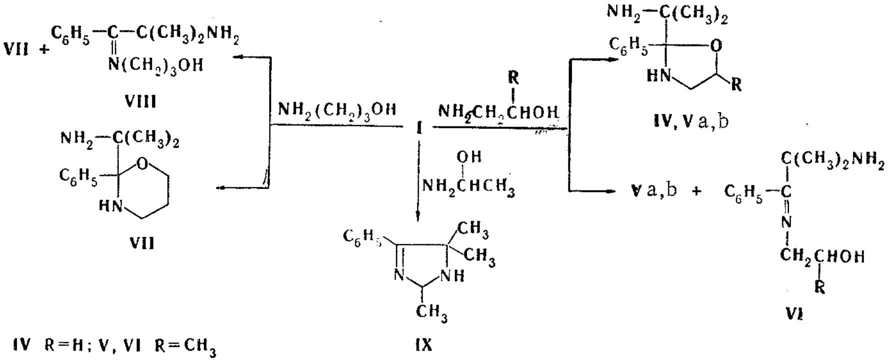


Fig. 2

Fig. 1. Conformation of the oxazolidine ring of IV.

Fig. 2. Newman projection along the N—C_4 bond in oxazolidine IV.

a result of the reaction azirine I with γ-amino alcohols, whereas the corresponding perhydro-1,3-oxazine VII is formed in a similar reaction with γ-aminopropanol (see the experimental section):



One's attention is directed to two features in the ^1H NMR spectra of oxazolidine IV: the large difference in the chemical shifts and the decreased value for the geminal spin-spin coupling constants of the protons of the C_4 methylene group. In the spectra of oxazolidines the $^2J_{HH}$ value for the CH_2N protons should have a value close to −9.0 Hz [3]. The decreased $^2J_{HH}$ value of −11 Hz (Table 2) can be explained only by assuming the preferred conformation presented in Fig. 1 for the oxazolidine ring of IV. The Newman projection along the $N-C_4$ bond is depicted in Fig. 2. According to the dependence presented in [4] for this conformation, one can expect $^2J_{HH}$ values close to −11 Hz. In addition, in this conformation the phenyl ring is oriented close to the 4-H proton. Calculation of the anisotropic effect of the aromatic ring by the method in [5] shows that in the conformation indicated above the resonance of the 4-H_a proton should be observed at stronger (by 0.4 ppm) field than the resonance of the 4-H_e proton, which, if one takes into account the approximate character of the estimate, is extremely close to the experimental data (0.51 ppm). The preferred orientation of the unshared electron pair of the nitrogen atom may undoubtedly make a certain contribution to the difference in the shielding of the methylene protons of the NCH_2 group, as indicated by the $^2J_{HH}$ value, but this contribution is not amenable to an accurate evaluation.

The reaction of azirine I with 1-amino-2-propanol leads to two oxazolidines Va and Vb, which differ with respect to the orientation of the CH_3 group. We carried out an analysis of the two $ABMX_3$ spin systems in the ^1H NMR spectrum of a mixture of the two isomers by the INDOR method. The assignment of the signals to a specific isomer was made by a comparison of the $^3J_{45}$ SSCC obtained by an analysis of unsubstituted IV (Table 2). The correctness of the assignment was verified by means of the ^{13}C spectra, in which a shift to strong field of the C_α resonance is observed for Vb, whereas a shift of the resonance of the quaternary carbon atom is observed for Va (Table 1). Such shifts are usually associated in the literature [6] with a nonvalence interaction of groupings. The certain change in $^3J_{45}$ in the spectra of oxazolidines Va and Vb as compared with IV probably constitutes evidence for freezing out of the individual conformation transitions in the oxazolidine ring. The changes in the shielding of the 4-H_a and 4-H_e protons in oxazolidines Va and Vb as compared with IV are evidently associated not only with the different anisotorpic effect of the phenyl ring and the change in the conformational equilibrium but also with the anisotropy of the C_5-CH_3 bond.

A mixture of the cyclic and chain forms, viz., oxazolidines Va, b and 1-[N-(2-amino-2-methyl-1-phenylpropylidene)amino]-2-propanol (VI), in a ratio of 69:31 according to the PMR spectral data, is formed when azirine I is heated with 1-amino-2-propanol in an ampul at 70°C for 5 h. Bands of stretching vibrations of a $C=N$ bond (1630 cm^{-1}) and of vibrations of NH_2 and OH groups (3290-3390 cm^{-1}) are present in the vibrational spectrum of the isolated mixture. Signals of nonequivalent groups that belong to oxazolidines Va, b (1.05 and 1.11 ppm) are observed along with the signal of equivalent gem-methyl groups in azomethine VI (1.26 ppm) in its PMR spectrum. Consequently, it might be assumed that the substituted oxazolidines Va, b that are formed under mild conditions are converted to the chain form, viz., azomethine VI, under more severe conditions.

In attempts to realize a similar reaction of azirine I with β-aminoethanol we obtained oxazolidine IV, whereas in the case of γ-aminopropanol we isolated, according to the PMR spectral data, a mixture of perhydro-1,3-oxazine VII and 3-[N-(2-amino-2-methyl-1-phenylpropylidene)amino]-1-propanol (VIII) in a ratio of 77:22. The PMR spectrum of the mixture indicates the preponderant formation of precisely the cyclic form: an intense doublet of gem-CH_3 groups at 0.97 and 1.02 ppm and a considerably less intense singlet at 1.26 ppm (the protons of the gem-CH_3 groups in VIII) are observed. A band of a C=N bond at 1640 cm^{-1} is noted in the vibrational spectrum of the mixture as compared with the IR spectral data for VII (see the experimental section).

Bands of stretching vibrations of a C=N bond (1610 cm^{-1}) and of an NH group (3400 cm^{-1}) are present in the IR spectrum of IX, which was obtained in the reaction of azirine I with α-aminoethanol, whereas nonequivalence of the gem-CH_3 groups is observed in the PMR spectrum) this constitutes evidence for its cyclic structure. Thus on the basis of the spectral and analytical data it may be assumed that 2,5,5-trimethyl-4-phenyl-3-imidazoline IX is formed in the reaction of azirine I with α-aminoethanol.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol and of the pure liquids were obtained with a Specord spectrometer. The ^1H NMR spectra of 5% solutions of the compounds were recorded with Perkin—Elmer R 12A (60 MHz) and Brucker WH-90 spectrometers with tetramethylsilane as the internal standard. The chemical shifts were measured relative to tetramethylsilane. The physicochemical characteristics of II-Va, b, VII, and IX are presented in Table 3.

2-Amino-2-methyl-1-phenyl-1-propanone β-Hydroxyethylhydrazone (II). A 2.28-g (0.03 mole) sample of β-hydrazinoethanol was added dropwise to a solution of 4.74 g (0.03 mole) of azirine I [7] in 30 ml of methanol, and the mixture was stirred at room temperature for 2 h. The alcohol was then removed by distillation, and the residue was recrystallized from petroleum ether to give 4.84 g (73%) of product. IR spectrum: 1625 (C=N); 3275, 3360 cm^{-1} (NH, NH_2, OH). ^1H NMR spectrum ($CDCl_3$), δ: 1.23 (6H, s, C—CH_3), 2.52 (3H, s, NH_2 and OH), 3.12 (2H, t, N—CH_3), 3.65 (2H, t, O—CH_2), 4.78 (1H, s, NH), 7.09 (2H, m, H_o), and 7.36 ppm (3H, m, H_m and H_p). ^{13}C NMR spectrum ($CDCl_3$), δ: 29.6 (C—CH_3), 53.0 (N—CH_2), 55.0 (C_{quat}), 61.2 (O—CH_2), 129.2 (C_o and C_m), 129.8 (C_p), 134.4 ($C_α$), and 156.3 ppm (C=N).

2-Amino-2-methyl-1-phenyl-1-propanone β-Hydroxypropylhydrazone (III). This compound was similarly obtained. IR spectrum: 1620 (C=N); 3280, 3370 cm^{-1} (NH, NH_2, OH). ^1H NMR spectrum ($CDCl_3$), δ: 1.10 (3H, d, J = 5.4 Hz, CH_3), 1.22 (6H, s, C—CH_3), 2.15 (3H, s, NH_2 and OH), 2.91 (2H, d, CH_2), 3.88 (1H, m, CH), 4.77 (1H, s, NH), 7.04 (2H, m, H_o), and 7.35 ppm (3H, m, H_m and H_p). ^{13}C NMR spectrum ($CDCl_3$), δ: 21.1 (CH_3), 29.3 (C—CH_3), 55.2 (CH_2), 57.8 (C_{quat}), 67.7 (CH), 129.1 (C_o and C_m), 129.9 (C_p), 134.2 ($C_α$), and 155.6 ppm (C=N).

2-(2-Amino-2-propyl)-2-phenyloxazolidine (IV). A 1.83-g (0.03 mole) sample of β-aminoethanol was added to 4.74 g (0.03 mole) of azirine I, and the mixture was stirred at 70°C for 3 h. The product was recrystallized from petroleum ether to give 5.06 g (82%) of purified substance. IR spectrum: 3280, 3370 cm^{-1} (NH_2, NH).

Compounds Va, b and VII were similarly obtained.

5-Methyl-2-(2-amino-2-propyl)-2-phenyloxazolidine (Va, b). IR spectrum: 3290 and 3390 cm^{-1} (NH_2, NH).

2-(2-Amino-2-propyl)-2-phenylperhydro-1,3-oxazine (VII). IR spectrum: 3305 and 3385 cm^{-1} (NH_2 and NH). PMR spectrum ($CDCl_3$), δ: 0.83 and 0.90 (3H and 3H, s, C—CH_3), 1.48 (5H, m, 5-CH_2, NH_2 and NH), 2.48 (2H, m, 4-CH_2), 3.30 (2H, m, 6-CH_2), and 6.59 ppm (5H, m, C_6H_5).

2,5,5-Trimethyl-4-phenyl-3-imidazoline (IX). A mixture of 4.74 g (0.03 mole of) azirine I and 1.83 g (0.03 mole) of α-aminoethanol was heated in an ampul at 70°C for 10 h, after which the product was recrystallized from petroleum ether to give 4.99 g (81%) of pure substance. IR spectrum: 1610 (C=N) and 3400 cm^{-1} (NH). PMR spectrum ($CDCl_3$), δ: 1.41 and 1.52 (3H and 3H, s, C—CH_3), 1.47 (3H, d, J = 6 Hz, CH_3), 1.78 (1H, s, NH), 4.94 (1H, q, J = 6 Hz, CH), 7.36 (3H, m, H_m and H_p), and 7.72 ppm (2H, m, H_o). ^{13}C NMR spectrum ($CDCl_3$), δ: 22.8 (CH_3), 26.3 and 28.1 (C—CH_3), 69.6 (C_{quat}), 80.9 (CH), 128.5 (C_o), 128.9 (C_m), 130.5 (C_p), 131.6 ($C_α$), and 177.0 ppm (C=N).

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MASS-SPECTROMETRIC STUDY OF 6-METHYL-2-ARYL-7-BENZYLINDOLIZINES

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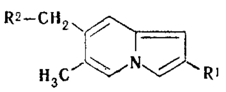
The mass-spectral behavior of 15 compounds from the 6-methyl-2-aryl-7-benzylindolizine series was investigated, and it was shown that the peculiarities of their dissociative ionization are due to the formation of stable resonance-stabilized ions that contain a quaternized nitrogen atom in the heteroring.

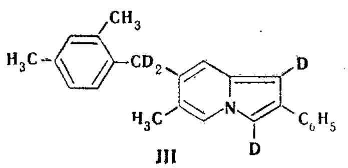
In contrast to the isomeric indoles [1], little study has been devoted to the dissociative ionization of indolizines. Only three reports have been devoted to a systematic study of the fragmentation of compounds of this series [2-4], whereas this problem is deserving of serious attention.

The nitrogen atom in the indolizine ring is found simultaneously in the pyridine and pyrrole rings. This position of the nitrogen atom in the fragmentation of indolizines may lead to the formation of resonance-stabilized ions that contain a quaternized nitrogen atom. The hypothetical electronic effect of the indolizine ring should be similar to the effect of electron-donor substituents of the OH, OR, NH_2, OCH_3, and $N(CH_3)_2$ type in the ortho or para positions of aromatic and heteroaromatic rings [5, 6]. It is known that these substituents markedly change the character of fragmentation under the influence of electron impact of the atomic groups included in the aromatic or heteroaromatic ring. Consequently one might also expect anomalous mass-spectrometric behavior for indolizine derivatives.

In the present research we studied the dissociative ionization of 6-methyl-2-aryl-7-benzylindolizines I-XV in order to establish the chief principles of their fragmentation and to verify the assumption indicated above.



I, II, IV – XV



III

I $R^1=C_6H_5$, $R^2=C_6H_5$; II $R^1=C_6H_5$, $R^2=2,4\text{-}(CH_3)_2C_6H_3$; IV $R^1=C_6H_5$, $R^2=3,4\text{-}(CH_3)_2C_6H_3$; V $R^1=4\text{-}CH_3C_6H_4$, $R^2=3,4\text{-}(CH_3)_2C_6H_3$; VI $R^1=C_6H_5$, $R^2=2,4,5\text{-}(CH_3)_3C_6H_2$; VII $R^1=4\text{-}CH_3C_6H_4$, $R^2=4\text{-}C_2H_5C_6H_4$; VIII $R^1=4\text{-}CH_3C_6H_4$, $R^2=2,4,5\text{-}(CH_3)_3C_6H_2$; IX $R^1=4\text{-}OCH_3C_6H_4$; $R^2=2,4,5\text{-}(CH_3)_3C_6H_2$; X $R^1=4\text{-}BrC_6H_4$, $R^2=C_6H_5$; XI $R^1=4\text{-}BrC_6H_4$, $R^2=4\text{-}C_2H_5C_6H_4$; XII $R^1=4\text{-}BrC_6H_4$, $R^2=2,4,5\text{-}(CH_3)_3C_6H_2$; XIII $R^1=C_6H_5$, $R^2=4\text{-}NO_2C_6H_4$; XIV $R^1=4\text{-}NO_2C_6H_4$, $R^2=C_6H_5$; XV $R^1=4\text{-}NO_2C_6H_4$, $R^2=4\text{-}NO_2C_6H_4$

The molecular-ion peaks (M^+) are the most intense peaks in the mass spectra of I-XV (Table 1). The stabilities of indolizines with respect to electron impact (W_M, Table 2) are approximately equal to the stabilities of the M^+ ions of 6-methyl-2,7-diarylindolizines [4]. The W_M value changes only slightly when the electron-donor substituents CH_3, C_2H_5, OCH_3, and Br are present in 7-benzylindolizines I-XII (Table 2) but decreases appreciably (by a factor of 1.5-2) in the case of XIII-XV, which contain an electron-acceptor NO_2 group.

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