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DISSOCIATIVE IONIZATION OF SUBSTITUTED PIPERIDEINES

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The fragmentation of different alkyl(aryl) substituted piperideines [tetrahydropyridines] was studied by analyzing high-resolution mass spectra and DADI [Direct Analysis of Daughter Ions] spectra. It was shown that the retrodiene decomposition of the ring is suppressed by competing processes of elimination of ring substitutents. The nature of the substituents and their mutual disposition on the ring have a substantial influence on the extent of their cleavage from the ring.

The piperideine ring is an important structural element of many natural and synthetic, biologically active substances [1; 2, p. 12]. Determining the position of the double bond in this ring is an important structural/analytical problem, for the solution of which mass spectrometry has been successfully applied [3, 4].

The study of aza analogs of cyclohexane, which are quite unstable compounds, is limited to data on the decomposition of some derivatives of N-acyl substituted 2,3- and 3,4-dehydropiperidines [5-7], the fragmentation of which is basically explained by the cleavage of the acyl group and the localization of the positive charge on it. Here, the fragments, forming via a retrodiene decomposition (RDD), either have these compounds in their mass spectra at low intensities or not at all [6].

It was of interest to investigate the dissociative ionization of alkyl(aryl) substituted piperideines I-IX and also structural analogs of the natural alkaloid anabasine, N-substituted 3-methyl-2-phenyl-6-(3'-methyl-2'-phenylpyridyl-5')-3,4-dehydropiperidines X-XIX, in order to learn the effect of the substituents and their mutual disposition on the ring on the ratio of the fragmentation processes of ring cleavage by an RDD mechanism [8] and elimination of ring substituents. In the present work, the mass spectral behavior of compounds I-IX and XI-XIX are analyzed for the first time; data on the decomposition of X was given in [9].

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TABLE 1. Mass Spectra of Compounds I-XIX*

Compound	m/z Values (I_{rel}, %)
I	56 (16), 91 (9), 128 (10), 129 (21), 143 (4), 144 (5), 170 (4), 184 (4), 186 (100), 200 (9), 201 (M^+, 30); $S_{1/2}=3$
II	91 (13), 115 (17), 128 (21), 129 (16), 143 (82), 158 (28), 170 (6), 184 (11), 186 (100), 200 (8), 201 (M^+, 62); $S_{1/2}=3$
III	56 (19), 77 (7), 91 (13), 128 (11), 143 (13), 158 (9), 170 (9), 184 (8), 186 (100), 200 (8), 201 (M^+, 33); $S_{1/2}=4$
IV	56 (20), 91 (9), 128 (14), 129 (56), 143 (9), 144 (12), 170 (4), 184 (9), 186 (100), 200 (9), 201 (M^+, 58); $S_{1/2}=3$
V	77 (68), 91 (92), 118 (90), 128 (27), 205 (100), 220 (67), 234 (28), 262 (31), 324 (46), 338 (23), 339 (M^+, 63); $S_{1/2}=8$
VI	77 (69), 91 (68), 118 (69), 128 (16), 205 (35), 234 (30), 246 (11), 276 (44), 324 (100), 352 (6), 353 (M^+, 27); $S_{1/2}=6$
VII	51 (20), 77 (31), 91 (68), 118 (82), 205 (45), 219 (22), 246 (13), 248 (29), 290 (18), 324 (100), 367 (M^+, 19); $S_{1/2}=6$
VIII	51 (17), 77 (23), 91 (37), 103 (8), 118 (100), 128 (8), 205 (16), 246 (8), 290 (20), 324 (89), 367 (M^+, 13); $S_{1/2}=6$
IX	77 (25), 91 (45), 118 (63), 205 (32), 220 (62), 234 (22), 248 (45), 262 (65), 324 (23), 338 (29), 339 (M^+, 100); $S_{1/2}=8$
X	65 (3), 77 (6), 91 (5), 104 (3), 115 (6), 128 (21), 129 (100), 144 (63), 170 (3), 197 (10), 340 (M^+, 7); $S_{1/2}=3$
XI	77 (26), 108 (26), 120 (21), 128 (30), 129 (100), 144 (63), 186 (15), 211 (37), 277 (18), 339 (10), 354 (M^+, 19); $S_{1/2}=6$
XII	91 (11), 122 (25), 128 (14), 129 (100), 144 (78), 170 (14), 200 (33), 225 (35), 291 (48), 353 (25), 368 (M^+, 27); $S_{1/2}=6$
XIII	77 (15), 91 (11), 115 (14), 129 (88), 134 (16), 144 (100), 212 (32), 237 (41), 303 (56), 365 (20), 380 (M^+, 79); $S_{1/2}=9$
XIV	77 (27), 91 (19), 115 (21), 128 (41), 129 (100), 144 (35), 195 (21), 323 (80), 324 (31), 339 (49), 382 (M^+, 66); $S_{1/2}=9$
XV	77 (25), 91 (18), 115 (21), 128 (39), 129 (100), 144 (65), 170 (23), 323 (71), 339 (48), 381 (22), 416** (M^+, 43); $S_{1/2}=9$
XVI	77 (14), 91 (11), 115 (12), 128 (23), 129 (100), 144 (33), 194 (23), 323 (19), 324 (11), 339 (17), 436 (M^+, 13); $S_{1/2}=8$
XVII	77 (68), 105 (100), 115 (8), 128 (13), 129 (44), 144 (11), 183 (11), 323 (56), 324 (19), 339 (49), 444 (M^+, 21); $S_{1/2}=5$
XVIII	77 (40), 91 (14), 121 (42), 128 (20), 129 (100), 144 (39), 170 (16), 323 (14), 324 (10), 339 (18), 460 (M^+, 21); $S_{1/2}=6$
XIX	77 (18), 91 (30), 120 (29), 128 (21), 129 (100), 144 (41), 197 (14), 223 (10), 323 (10), 367 (30), 459 (M^+, 6); $S_{1/2}=8$

*The peaks of M^+ and the 10 most intense ions are given.
**Peak of an ion containing ^{35}Cl.

TABLE 2. Mass Spectra of Piperideines I-IX

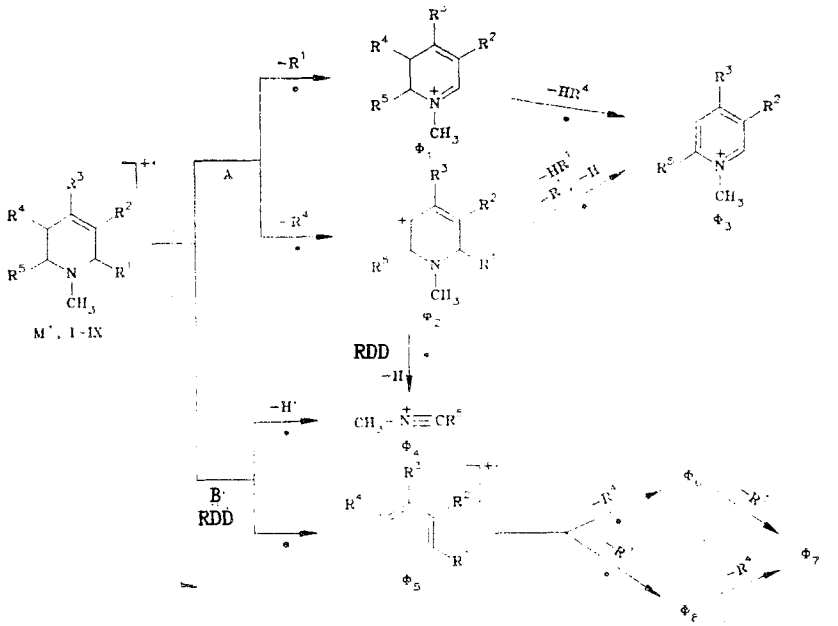
Compound	Intensities of peaks of characteristic ions of the full ion current, % (Σ_{50})								
	M^+	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8
I	11.6	33.0	3.9	1.3	5.3	1.7	1.3	3.3	6.9
II	14.3	1.6	19.8	2.2	—	5.6	16.2	1.2	1.2
III	10.4	13.6	13.6	2.5	—	2.5	1.8	3.0	1.8
IV*	18.7	1.3	1.3	0.6	5.6	3.4	1.3	—	1.3
V	6.6	2.8	4.1	0.7	8.1	6.0	9.0	2.4	0.8
VI	4.7	6.3	14.4	1.6	9.9	4.3	5.0	2.3	0.4
VII	3.3	2.6	14.3	1.9	11.8	4.1	6.5	1.4	1.2
VIII	3.2	3.9	17.6	1.6	19.8	1.0	3.1	1.6	1.2
IX	10.4	6.7	2.9	0.5	6.5	6.3	0.9	0.2	0.3

*In the spectrum, peaks are also present from ions $[M-CH_3]^+$ 186 (27.9) and $[\phi_5 - CH_3]^+$ 129 (15.6).

TABLE 3. Elemental Composition of the Characteristic Ions of Compounds I, II, V-VII, XVII, and XIX from High Resolution Mass Spectra

Compound	M	Exact ionic mass		Elemental composition of the ion	
		determined	calculated		
I	144	144.0935	144.0936	$C_{11}H_{12}$	(Φ_5)
II	158	158.1095	158.1092	$C_{12}H_{14}$	(Φ_5)
V	205	205.1027	205.1014	$C_{16}H_{13}$	(Φ_6)
VI	128	128.0618	128.0624	$C_{10}H_8$	(Φ_7)
VII	118	118.0661	118.0655	C_8H_8N	(Φ_4)
XVII	323	323.1567	323.1544	$C_{23}H_{19}N_2$	(Φ_{16})
	339	339.1842	339.1856	$C_{24}H_{23}N_2$	(Φ_{14})
XIX	144	144.0929	144.0936	$C_{11}H_{12}$	(Φ_5)

Scheme 1



Scheme 2

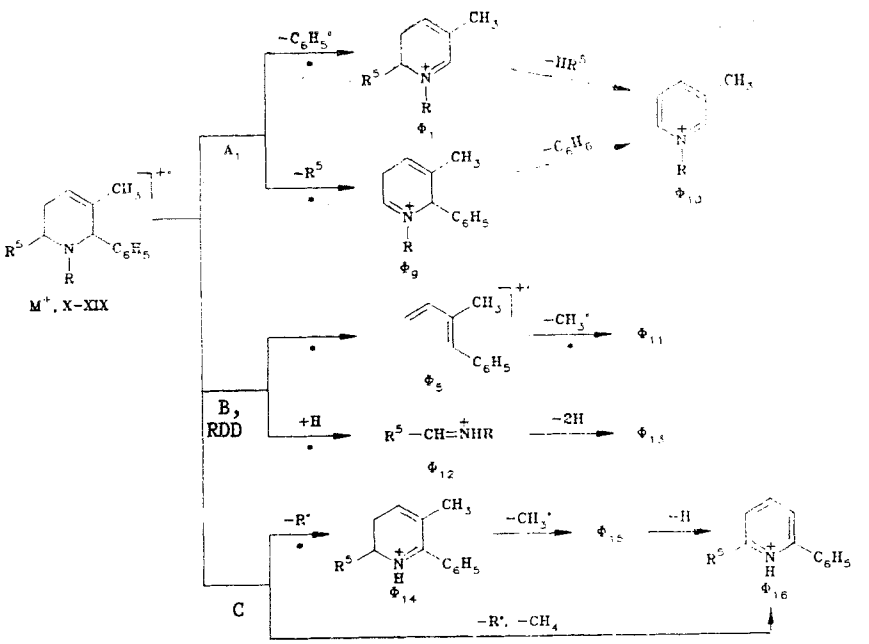
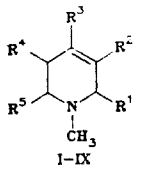


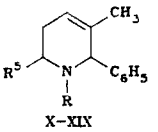
TABLE 4. Mass Spectra of Compounds X-XIX

Compound	Intensities of peaks of characteristic ions, % to Σ_{50}															
	M^+	$[M-H]^+$	$[M-CH_3]^+$	Φ_1	Φ_9	Φ_{10}	Φ_5	Φ_{11}	Φ_{12}	Φ_{13}	Φ_{14}	Φ_{15}	Φ_{16}	R^+	77	91
X	2,9	0,3	0,7	0,8	0,8	0,7	22,6	35,8	3,6	1,8	—	—	—	—	2,2	1,8
XI	3,9	1,2	1,8	3,2	2,6	4,6	11,0	17,5	6,5	2,3	—	—	—	—	4,6	2,5
XII	4,8	1,4	3,5	6,8	4,7	3,6	11,1	14,2	5,0	2,1	—	—	—	—	1,4	1,6
XIII	11,1	1,7	2,2	6,0	3,4	1,7	10,8	9,5	4,4	1,2	—	—	—	—	1,6	1,2
XIV	9,7	1,0	0,5	0,3	—	—	4,0	11,3	0,9	0,3	5,6	3,5	9,1	—	3,1	2,1
XV	6,5	0,3	0,1	0,3	—	—	6,2	9,5	0,6	0,3	4,5	1,2	6,7	—	2,4	1,7
XVI	3,0	1,0	0,5	0,5	—	—	5,7	17,1	0,3	0,4	3,0	1,9	3,3	1,0	2,4	1,9
XVII	5,0	0,7	0,3	0,4	—	—	2,0	7,9	0,8	0,5	8,8	3,4	10,0	17,9	12,2	1,2
XVIII	5,0	0,6	0,4	0,3	—	—	6,9	17,8	0,7	0,5	3,2	1,8	2,5	7,5	7,1	2,5
XIX*	1,5	0,3	0,3	0,3	—	—	7,6	18,6	0,3	0,4	1,5	0,7	1,9	5,4	3,3	5,6

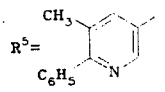
*The $[M - C_6H_5NH]^+$ ion 367 (5.6), is present in the spectrum.



I-IX



X-XIX



I, III $R^1=CH_3$, II, IV $R^1=H$, V—IX $R^1=C_6H_5$; I, III, V—IX $R^2=H$; II, IV $R^2=CH_3$; I—VIII $R^3=C_6H_5$, IX $R^3=o$-$CH_3C_6H_4$; I, IV, IX $R^4=H$, II, III, IV $R^4=CH_3$, VI $R^4=C_2H_5$, VII $R^4=n$-C_3H_7, VIII $R^4=i$-C_3H_7; I, IV $R^5=CH_3$, II, III $R^5=H$, V—IX $R^5=C_6H_5$; X R=H, XI $R=CH_3$, XII $R=C_2H_5$, XIII $R=CH_2CH=CH_2$, XIV $R=COCH_3$, XV $R=COCH_2Cl$, XVI $R=COCF_3$, XVII $R=COC_6H_5$, XVIII $R=COC_6H_4OH$-*o*, XIX $R=CONHC_6H_5$

In the mass spectra of piperideines I-IX, the peaks of the molecular ions (M^+) are present with high or medium intensity, and their decomposition is characterized by a selectivity of $S_{\frac{1}{2}} = 3...8$ (Table 1). A comparison the stabilities (W_M) of M^+ in this series shows that for substances V-IX, which contain phenyl substituents in the 2 and 6 positions, W_M decreases, but that the pesence of a methyl group at the double bond in compounds II and IV causes, contrariwise, an increase in the stability of M^+. An increase in the bulk of substituent R^4 in the allylic position, leads to a sharp drop in W_M in the series of compounds V-IX (Table 2).

The fragmentation of piperideines I-IX can be represented by Scheme 1, which is confirmed by high-resolution mass spectral data (Table 3) and the DADI spectra of compounds VII and VIII. Their decomposition is characterized by the occurrence of two, competing, fundamental processes. The first (path A) involves the elimination of substituents R^1 and R^4 from the allylic position and the subsequent aromatization of the ions resulting from this. The other path of decomposition (path B) involves the cleavage of the piperideine ring by an RDD mechanism [8].

In the series of compounds I-IX, an increased intensity of the ϕ_1 ion is observed in the mass spectra of the α-substituted piperideines. This is due to the coincidence of the fragmentation paths involving allylic cleavage and [10, p. 14] α-decomposition characteristic of the fragmentation of α-alkyl substituted piperideines [11, 12]. The intensity of $[M-R^1]$ in the mass spectra of compounds I-IX increases in dependence on the nature of the substituent R^1: $CH_3 > C_6H_5 > H$.

The fragmentation of piperideines I-IX can be represented by Scheme 1 (see next page) which is confirmed by high-resolution mass spectral data (Table 3) and the DADI spectra of compounds VII and increased fraction of Φ_2 ions in the mass spectra of V-IX, in the sequence: i-C_3H_7 > n-C_3H_7 > C_2H_5 > CH_3 > H. From path A of the decomposition, one can obtain information on the nature of the substituents located in the allylic positions.

Path B of the fragmentation of compounds I-IX occurs via the RDD of the ring and allows one to determine the position of the double bond in the ring. From the appearance of characteristic ions ϕ_4 and Φ_5 in the mass spectra resulting from the RDD of the ring, one can easily distinguish the isomeric pairs I and III, II and IV, and III and IV. In conjunction with the decomposition by path A, one can identify mass spectroscopically all of the isomeric piperideines I-IV. In the mass spectra of these isomers, obtained at 12 eV, one observes

primarily fragments forming from the decomposition of M^+ via path A. For α-methyl substituted piperideines I and III, intensity maxima characteristically appear at the $[M - CH_3]^+$ fragments while in the mass spectra of piperideines II and IV, the M^+ peaks are the major ones.

Substituents at the double bond of the piperideine ring facilitate its decomposition via RDD cleavage. On the contrary, alkyl radicals in the 2 and 5 positions suppress RDD the more, the more readily the competing process of their elimination takes place (Table 2).

As noted, RDD is accompanied by the formation of Φ_4 ions resulting from the migration of a hydrogen atom onto the hydrocarbon part of the molecule and the localization of the positive charge on a nitrogen atom. The specific weight of the Φ_4 fragments in the mass spectra of V-IX increases in proportion to the increase in the bulk of substituent R^4 in position 5, and the contribution of Φ_5 ions to the total ion current correspondingly falls (Table 2). The alternative path of formation of fragments Φ_3, Φ_4, and Φ_7 (Scheme 1)in the decomposition of piperideines I-IX is confirmed by the corresponding, metastable peaks in the DADI spectra of compound VII and VIII.

The fragmentation of N-substituted compounds X-XIX is characterized by the presence in their mass spectra of medium intensity M^+ peaks (Table 1), and the values W_M vary over a wide range (Table 4). The high resolution spectral data and analysis of the mass spectra of the deuterated analog of compound X allow one to predict the fragmentation of compounds X-XIX via general Scheme 2 (see previous page).

As in the decomposition of piperideines I-IX, the dissociative ionization of compounds X-XIX is accompanied by the parallel cleavage of substituents from the α-position of the piperideine ring (path A_1). The ions forming, Φ_1 and Φ_9, then split off radicals from the 6 and 2 positions, respectively, and a hydrogen atom, leading to the appearance of aromatic fragment Φ_{10}. It is of interest to note that the occurrence of ions Φ_9 and Φ_{10} is characteristic only of the decomposition of N-alkyl substituted compounds X-XIII. Their absence from the mass spectra of compounds XIV-XIX is evidence, obviously, of a change in the site of the localization of positive charge in the M^+ of these compounds. At the same time, the elimination of a phenyl radical enables the fragmentation paths due to α-decomposition and allylic cleavage to coincide.

The RDD of the piperideine ring of X-XIX leads to the appearance in their mass spectra of fragments Φ_5 and Φ_{12}. It should be noted that the positive charge, in contrast to its distribution in the RDD of piperideines I-IX, is predominantly localized on the hydrocarbon part of the molecule. The fragmentation of the Φ_5 ion is then accompanied by the ejection of a methyl radical and leads to the appearance of high-intensity fragment Φ_{11} (129)*. The Φ_{12} ions form as the result of the migration of a hydrogen atom from the hydrocarbon part of the molecule onto the amine fragment and not the reverse, as in the RDD of piperideines I-IX. The fraction of Φ_5 and Φ_{12} in the mass spectra is markedly diminished on going from N-alkyl substituted piperideines X-XIII to the N-acyl substituted analogs, XIV-XIX (Table 4). In the mass spectrum of deuterated compound X, the Φ_1, Φ_9, Φ_{10}, and Φ_{12} peaks of the fragments are shifted by 1 amu to greater m/z values.

Similarly, decomposition path B is only realized in the fragmentation of N-acyl substituted piperideines XIV-XIX [5-7] and is characterized by the formation of $[M - R]^+$ (339). Substituent R can obviously take apart in the redistribution of positive charge in M^+, because when the N-R bond is broken, the charge is partly preserved on the substituent; in the mass spectrum of the N-benzoyl derivative, XVII, the peak of the C_6H_5CO ion (105) has the maximum intensity (Table 4). Analysis of the DADI spectra of XVI and XVII shows that fragment Φ_{16} is formed both by way of the sequential loss of CH_3 and H particles from ion Φ_{14} and as a result of the synchronous cleavage of the acyl radical and a CH_4 molecule from M^+. The appearance of fragments Φ_{14}-Φ_{16} in the mass spectra of N-acy substituted 3,4-dehydropiperidines XIV-XIX can serve as a mass spectroscopic criterion differentiating the latter from N-alkyl substituted analogs, X-XIII.

EXPERIMENTAL

Compunds I-IX were synthesized by the procedure in [13], and compounds X-XIX by that in [14]. The mass spectra were obtained on an LKB-2091 instrument using direct introduction of the sample into the ion source. The programmed temperature regime was 40 to 250°C (10°C/min); the energy of the ionizing electrons, 70(12) eV; and the emission current, 50 μA. The exact ionic masses were determined relative to PFK [perfluorokerosene] on a Varian MAT-311A instrument with resolution 10,000. The DADI spectra obtained on a Varian MAT-112 instrument with direct introduction of the sample into the source. The electron energy was 70 eV; the temperature of the ionization chamber, 180°C. The mass spectrum of deuterated

*Here and elsewhere, values of m/z are given.

compound X was obtained on a series MX-1303 instrument under conditions for deutero exchange between the vapor of the compound under study with the vapor of CD_3OD directly in the ionization chamber of the instrument. The ionization voltage was 70 V; the inlet temperature, 100°C.

The elemental analyses for N correspond to the calculated values.

1,2,5-Trimethyl-4-phenylpiperideine-3 (III, $C_{14}H_{19}N$) and 1,3,6-trimethyl-4-phenylpiperideine-3 (IV, $C_{14}H_{19}N$). A mixture of compounds III and IV (2.18 g), obtained by the procedure in [13] was chromatographed on a column (55×3 cm) with Al_2O_3 II st. akt. The eluent was a 1:20 ethyl acetate/heptane mixture. A mixture of substances (0.8 g) was isolated (R_f 0.79 and 0.58, 1:1 ether/heptane, alophol), and then 0.72 g (33%) of compound IV (an oil, R_f 0.58. PMR spectrum (250 MHz, $CDCl_3$, TMS): 1.13 (3H, d, 6-CH_3, J = 6.0 Hz); 1.55 (3H, s, 3-CH_3); 2.35 (3H, s, N-CH_3), and 7.00-7.40 ppm (5H, m, C_6H_5)]. The mixture obtained (0.8 g) was repeatedly chromatographed on a column (55×2.5 cm) with heptane and then with a mixture of 20:1 heptane/ethyl acetate to isolated 0.1 g (4.6%) of compound III [an oil, R_f 0.79. PMR spectum (80 MHz, $CDCl_3$, TMS): 1.07 (3H, d, 5-CH_3); 1.19 (3H, d, 2-CH_3); 2.35 (3H, s, N-CH_3); 5.67 (1H, d, =CH); and 7.24-7.40 (5H, m, C_6H_5)] and also 0.46 g of compound IV. The total yield of compound IV was 54%.

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