MASS SPECTRA OF SUBSTITUTED 4-AMINOPIPERIDINES WITH A SHIELDED NITROGEN ATOM*

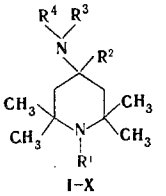
A. I. Ermakov and Yu. N. Sheinker

UDC 547.834.5:545.51

The principal fragmentation pathway of 4-aminopiperidines under the influence of electron impact are determined by charge localization on the nitrogen atom of the piperidine ring or on the nitrogen atom of the substituent in the 4 position. In the case of electron-donor substituents in the 4 position and in the absence of a substituent attached to the nitrogen atom of the polysubstituted piperidine ring the charge is primarily localized on the nitrogen atom of the substituent; this is expressed in the specific fragmentation pathways. The principles found in this research make it possible to establish the structures of nitrogen-containing compounds that are similar to the investigated compounds.

In [2] it was shown that some functionally substituted piperidines, in contrast to the simplest analogs [3, 4], undergo ionization not only at the ring heteroatom but also at the nitrogen or oxygen atom of the substituents; a number of specific principles of the fragmentation of the piperidine ring are observed in this case.

In order to establish the peculiarities of the fragmentation of the piperidine ring as a function of the character of the functional groups attached to the ring nitrogen atoms and in the substituents, in the present research we studied the mass spectra of previously uninvestigated piperidines I-X (Table 1) with substituents attached to a shielded nitrogen atom and attached to the carbon atom in the 4 position. In the investigation of the fragmentation of these compounds we used the spectra obtained at ionizing-electron energies of 70 and 12 eV and the high-resolution mass spectra.



I–X

I—IV $R^1=H$; IV—VII $R^2=CONH_2$, $R^3R^4=N(CH_2)_5$; I $R^2=CH_2NH_2$, $R^3=R^4=H$; II $R^2=CONH_2$, $R^3=H$, $R^4=(CH_2)_3CH_3$; III $R^2=CH_2NH_2$, $R^3=H$, $R^4=CH_2C_6H_5$; V $R^1=CH_3$; VI $R^1=CH_2CH=CH_2$; VII $R^1=CH_2C_6H_5$, VIII $R^1=C_2H_5$, $R^2=H$, $R^3=COCH_3$, $R^4=CH_2C_6H_5$; IX $R^1=CH_3$, $R^2=CONH_2$, $R^3=H$, $R^4=CH_2C_6H_5$; X $R^1=(CH_2)_2C_6H_5$, $R^2=R^3=H$, $R^4=C_6H_5$

We have previously shown [2] that in the case of 4-substituted piperidines (if the substituent does not contain a nitrogen atom) shielding by the α-methyl groups of the unshared electron pair of the nitrogen atom does not suppress the characteristic fragmentation pathway, viz., detachment of a substituent form from the α position with the formation of an $[M - CH_3]^+$ ion. The peak of this fragment has the maximum intensity in the spectra of such α-substituted piperidines at electron energies of 70 and 12 eV.

In contrast to the spectra of the monosubstituted analogs [2], the peaks of the molecular ions (M^+) and cyclic amine $[M - CH_3]^+$ fragments in the mass spectra of 4-disubstituted derivatives I-VII are characterized by low relative intensities; the intensity of the M^+ peak also does not increase as the ionizing voltage is lowered to 10-12 eV. This behavior of I-VII

*Communication 10 in the series "Application of mass spectrometry in structural and stereochemical studies." See [1] for Communication 9.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 72-77, January, 1981. Original article submitted November 21, 1979; revision submitted July 1, 1980.

 0009-3122/81/1701-0058$07.50

TABLE 1. Mass Spectra of I-X at Electron Energies of 70 (a) and 12 eV (b)

Compound	m/e values (relative intensities of the ion peaks in percent relative to the maximum peak)
Ia	185 (0,5), 156 (3), 155 (23), 139 (2), 136 (5), 122 (2), 121 (2), 99 (8), 98 (100), 96 (2), 83 (3), 82 (4), 58 (22), 57 (6), 56 (3), 43 (4), 42 (28), 41 (8)
Ib	185 (0,5), 156 (18), 155 (100), 99 (8), 98 (88), 58 (3)
IIa	256 (2), 255 (12), 240 (2), 212 (4), 211 (25), 168 (2), 167 (16), 154 (5), 153 (2), 139 (4), 122 (4), 114 (14), 99 (10), 98 (100), 82 (5), 81 (2), 58 (12), 57 (6), 56 (4), 42 (16), 41 (10)
IIb	256 (3), 255 (15), 212 (16), 211 (100), 114 (32), 99 (5), 98 (68)
IIIa	246 (2), 245 (10), 188 (2), 156 (2), 155 (22), 121 (2), 107 (4), 106 (8), 99 (8), 98 (100), 92 (2), 91 (20), 58 (18), 57 (2), 56 (2), 55 (2), 42 (10), 41 (5)
IVa	267 (1), 224 (3), 223 (20), 184 (4), 126 (3), 110 (3), 104 (3), 99 (10), 98 (100), 84 (3), 67 (3), 58 (13), 57 (2), 56 (4), 55 (2), 42 (5), 41 (6)
IVb	267 (2), 224 (18), 223 (100), 184 (7), 167 (3), 99 (8), 98 (64)
Va	281 (0,2), 266 (2), 238 (14), 237 (54), 223 (4), 222 (2), 221 (5), 199 (2), 198 (10), 183 (3), 182 (6), 181 (43), 167 (15), 166 (100), 165 (3), 164 (6), 150 (8), 149 (2), 138 (6), 137 (2), 136 (3), 113 (8), 112 (94), 111 (38), 110 (62), 109 (2), 108 (4), 107 (3), 99 (6), 98 (54), 97 (4), 85 (3), 84 (10), 83 (6), 82 (6), 81 (7), 73 (4), 72 (60), 71 (6), 70 (7), 69 (6), 58 (4), 57 (8), 56 (38), 55 (13), 54 (6), 53 (4), 52 (8), 44 (6), 43 (10), 42 (14), 41 (22)
Vb	281 (4), 266 (6), 238 (22), 237 (100), 223 (6), 199 (3), 198 (20), 182 (2), 181 (8), 167 (8), 166 (8), 112 (22), 98 (3), 72 (10)
VIa	307 (0,1), 292 (1), 264 (4), 263 (20), 224 (5), 223 (10), 207 (12), 167 (7), 166 (30), 139 (4), 138 (28), 111 (2), 110 (24), 99 (10), 98 (100), 58 (6), 57 (2), 56 (3), 55 (5), 43 (3), 42 (8), 41 (16)
VIb	307 (0,2), 292 (2), 264 (24), 263 (100), 225 (3), 224 (28), 223 (48), 207 (12), 167 (8), 166 (28), 139 (4), 138 (38), 110 (3), 99 (8), 98 (66), 84 (2)
VIIa	357 (2), 342 (3), 314 (16), 313 (56), 298 (3), 275 (3), 274 (16), 258 (4), 257 (22), 240 (4), 222 (4), 189 (6), 188 (40), 167 (16), 166 (100), 150 (4), 149 (6), 148 (40), 142 (10), 112 (4), 111 (5), 110 (43), 99 (2), 98 (30), 92 (5), 91 (58), 85 (3), 84 (6), 83 (3), 58 (12), 57 (7), 56 (7), 55 (10), 54 (4), 44 (2), 43 (10), 42 (12), 41 (6)
VIIb	357 (2), 343 (2), 342 (6), 315 (4), 314 (26), 313 (100), 275 (6), 274 (36), 257 (6), 222 (5), 189 (4), 188 (14), 167 (6), 166 (20), 148 (2), 98 (4)
VIIIa	317 (1), 316 (3), 301 (2), 287 (2), 274 (1), 273 (2), 261 (1), 260 (2), 259 (1), 245 (3), 243 (1), 242 (2), 225 (4), 217 (19), 216 (70), 203 (20), 202 (100), 167 (2), 166 (16), 162 (6), 161 (16), 160 (26), 146 (6), 141 (2), 140 (8), 134 (20), 133 (1), 132 (12), 126 (22), 124 (10), 123 (2), 113 (3), 112 (30), 111 (2), 100 (18), 99 (4), 98 (26), 92 (10), 91 (84), 86 (7), 85 (2), 84 (18), 83 (8), 82 (8), 77 (8), 76 (20), 72 (3), 70 (16), 59 (4), 58 (38), 43 (24), 42 (22), 41 (16)
VIIIb	317 (1), 316 (4), 302 (1), 301 (2), 287 (2), 274 (1), 273 (2), 261 (2), 260 (1), 245 (1), 226 (1), 225 (6), 218 (3), 217 (20), 216 (100), 203 (5), 202 (32), 166 (10), 161 (8), 160 (8), 135 (3), 134 (22), 126 (8), 112 (8), 98 (4)
IXa	304 (0,2), 303 (0,4), 302 (0,4), 289 (6), 288 (28), 274 (3), 273 (8), 260 (4), 259 (18), 245 (3), 244 (2), 243 (5), 203 (2), 202 (10), 199 (2), 198 (18), 189 (4), 188 (22), 183 (3), 182 (1), 181 (100), 165 (3), 164 (12), 153 (5), 113 (3), 112 (22), 111 (1), 110 (3), 98 (6), 92 (5), 91 (68), 73 (2), 72 (44), 71 (4), 58 (2), 57 (4), 56 (36), 42 (6), 41 (6)
IXb	304 (0,1), 303 (1), 302 (0,5), 289 (20), 288 (95), 274 (8), 273 (32), 260 (10), 259 (60), 246 (4), 245 (14), 199 (12), 198 (100), 189 (3), 188 (12), 182 (6), 181 (60), 112 (16), 98 (7), 91 (2), 72 (23)
Xa	337 (3), 336 (6), 246 (18), 245 (85), 141 (16), 140 (100), 133 (2), 132 (6), 115 (33), 106 (10), 105 (12), 104 (8), 99 (2), 98 (26), 91 (6), 78 (2), 77 (22), 59 (6), 58 (84), 57 (4), 56 (4), 55 (12), 43 (2), 42 (14), 41 (12)
Xb	337 (4), 336 (16), 246 (20), 245 (100), 141 (3), 140 (30)

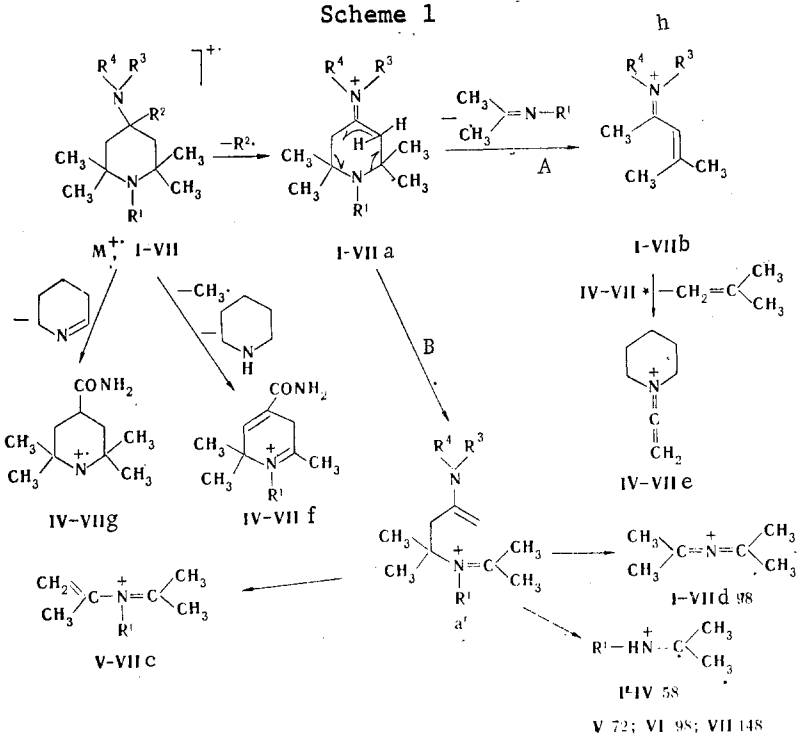
under electron impact constitutes evidence for primary localization of the charge in M^+ on the nitrogen atom of the substituent in the 4 position (Scheme 1).

The peaks of the principal fragments in the mass spectra of derivatives I-VII are due to fragmentation of the α ($[M - R^2]^+$) ions. The contribution of these ions to the total ion current increases sharply as the ionizing voltage is lowered to 12 eV (Table 2), while the intensity of the peak of the fragment α increases to a maximum value.

TABLE 2. Relative Intensities (in percent relative to ΣJ_{39}) of the Peaks of the Characteristic Fragments in the Mass Spectra of I-VII

Compound	Ion a		b		e		c		d	
	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV
I	11	46	—	—	—	—	—	—	44	40
II	9	42	2	0,5	—	—	—	—	36	28
III	5	—	1	0,3	—	—	—	—	45	
IV	11	53	2	1	2	—	—	—	53	49
V	7	45	12	5	8	—	12	10	7	2
VI	7	17	10	8	9	—	9	10	33	18
VII	10	41	17	8	8	—	7	6	5	2

Scheme 1

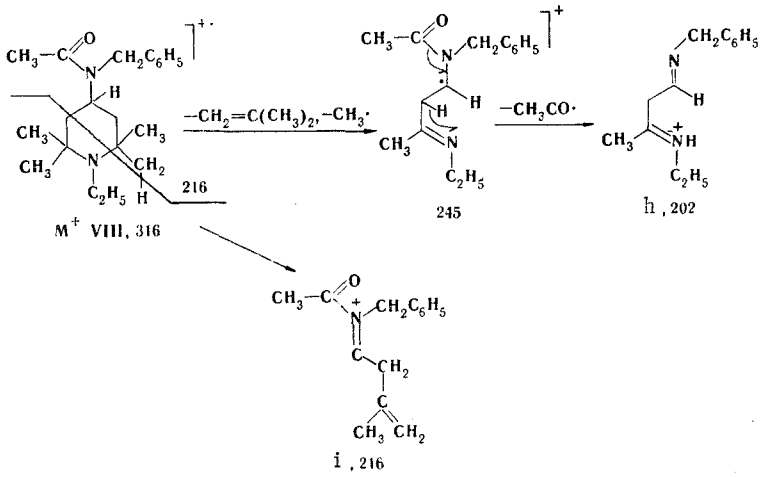


V 72; VI 98; VII 148

Ia 155; IIa 211; IIIa 245; IVa 223; Va 237 $[C_{15}H_{29}N]^*$; VIa 263; VIIa 313; Ib 98; IIb 154; IIIb 188; IVb 166; Vb 166 $[C_{11}H_{20}N]$; VIb 166 $[C_{11}H_{20}N]$; VIIb 166; Vc 112 $[C_7H_{14}N]$; VIc 138; VIIc 188; IVd, VId $[C_6H_{12}N]$; I—VIIe 110 $[C_7H_{12}N]$; IVf 167; Vf 181 $[C_{10}H_{17}N_2O]$; VIf 207; VIIf 257; IVg 184; Vg 198; VIg 224; VIIg 274

This regularity is also characteristic for the fragments that are formed when a substituent is split out from the α position relative to the ion-radical center. In addition to fragment *a*, in the fragmentation of I-VII one observes ions that, according to the elementary composition found from the high-resolution spectra (see the scheme), contain a ring nitrogen atom and four α,α'-methyl groups. The formation of fragments **c** and **d** can be conceived of as being the result of charge transfer to the shielded nitrogen atom in accordance with the processes $a \rightarrow a_1 \rightarrow$ **c**, **d**. The fact that the nitrogen atoms in ion *a* are para-oriented relative to one another may promote charge transfer. The formation of ion a_1 is therefore energically favorable, since in this case cleavage of the C_2—C_3 or C_5—C_6 bond should be regarded as α cleavage with respect to the double bond attached to the quaternary nitrogen atom. A similar process is observed in the fragmentation of piperazineindoles [5]. Subsequent fragmentation of ion *a* via pathways A and B leads, respectively, to fragments **b**, **e** and **c**, **d**. Splitting out of a neutral $(CH_3)_2C{=}N{-}R^1$ molecule from ion *a* is characteristic for the 2,2,6,6-tetramethylpiperidine ring [2]. Detachment of nitrogen-containing substituents is observed only from the M^+ ions of IV-VII (ions **f** and **g**). The intensities of the peaks of these fragments in the spectra and their contribution to the total ion current depend on the character of the substituents in the 4 position, on the substituents attached to the ring nitrogen atom, and on the ionizing-electron energy (Table 2). The intensities of the peaks of ions **c** and **d** are determined by the ability of substituent R^1 to be split out in the form of a radical and also by the stabilizing effect of α substituents in charge localization on the shielded nitrogen atom. In the spectra of unsubstituted analogs I-IV the peak of ion **c** (or **d**) is maximal at an ionizing voltage of 70 eV and retains its high intensity as the electron energy is lowered to 12 eV.

Scheme 2



Both an ion with structure c (112) and an ion with structure d (98) are observed in the fragmentation of N-methyl analog V. However, in contrast to fragment d, the peak of ion c is one of the maximum peaks in the spectrum at an electron energy of 70 eV and has an appreciable intensity in the low-voltage spectrum. Ion d is primarily formed in the fragmentation of derivative VI, evidently as a consequence of facile splitting out of a stable allyl radical from the nitrogen atom. Ion d has low intensity in the case of N-benzyl analog VII, evidently as a consequence of the primary formation of a tropylium ion. The changes in the relative intensities of the peaks of the α-e ions in the spectra of I-VII as a function of the ionizing-electron energy are presented in Table 2.

The principal peaks in the spectra of derivative VIII at electron energies of 70 and 12 eV correspond to fragments with charges on the nitrogen atoms of the substituent or the ring (Scheme 2).

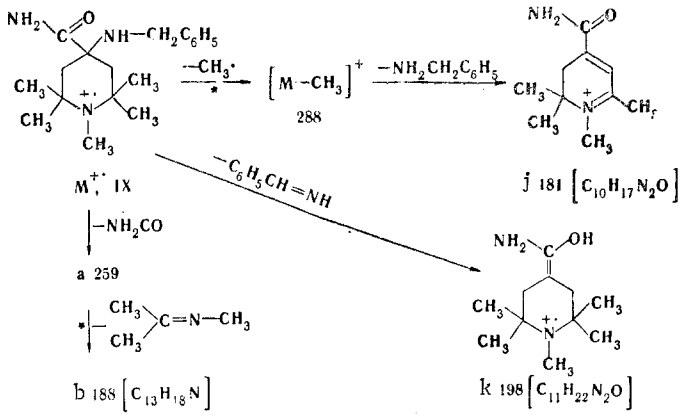
In analogy with the previously investigated tetramethyl-substituted [2] piperidines, the formation of ion h with 202 is realized as a result of the two-step process $M^+ \rightarrow 245 \rightarrow h$. Fragment i (216) is formed directly from M^+ (m* = 147.9). The maximum peak in the spectrum at an electron energy of 70 eV corresponds to ion h. The peak of fragment i becomes the most intense peak at a low ionizing voltage.

In contrast to derivatives I-VIII, in the ionization of IX the ion-radical center is formed primarily on the shielded ring nitrogen atom (Scheme 3).

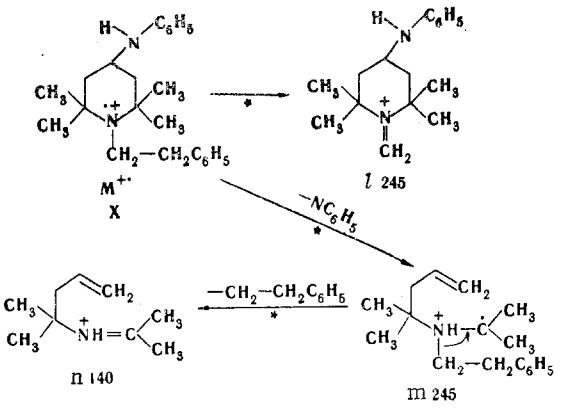
As in the fragmentation of 2,4,6-substituted piperidines [4], the fragmentation of derivative IX proceeds via three pathways. Splitting out of a methyl group from the molecular ion and subsequent ejection of a benzylamine molecule lead to cyclic [1, 4] ion j (181). In contrast to I-VIII, in the fragmentation of derivative IX the process $M^+ \rightarrow \alpha \rightarrow b$, which is determined by localization of the charge on the nitrogen atom of the substituent, is expressed weakly. This can be explained by the higher ionization potential of the nitrogen atom in the aminobenzyl group as compared with the nitrogen atoms of the substituents in I-VIII. Data that indicate that the presence of a benzyl group attached to a nitrogen atom significantly increases the ionization potentials of some aliphatic and cyclic amines are available [6]. The McLafferty rearrangement leads to the formation of k ions. The fragmentation processes presented in Scheme 3 were confirmed by the high-resolution mass spectra and the corresponding peaks of metastable ions. The fact that in the fragmentation of some quinuclidine derivatives ions with such structures give high-intensity peaks in the spectra at electron energies of 70 and 12 eV constitutes evidence in favor of the formation of k ions [7]. The peak of the k ion has the maximum intensity when the ionizing voltage is lowered to 12 eV.

A characteristic peculiarity of the mass spectrum of X is the presence of only two intense peaks of ions with m/e 245 and 140. The peak of the ion with m/e 245 has the maximum intensity at a low ionizing voltage. The subsequent fragmentation of this ion with the splitting out of an ion with m/e 105 and the formation of ions with m/e 140 (confirmed by a metastable transition) constitutes evidence that the ion with m/e 245 is a composite ion (l and m, Scheme 4). The peak of the ion with m/e 140 is the maximum peak in the spectrum at an ionizing

Scheme 3



Scheme 4



voltage of 70 eV and retains its rather high intensity when the electron energy is lowered to 12 eV.

Thus in the present research we have established the principal regularities in the fragmentation of substituted 4-aminopiperidines with a shielded nitrogen atom. We demonstrated that localization of the charge on the shielded nitrogen atom or on the nitrogen atom of the substituents is determined by the electronic properties of the functional groups attached to both nitrogen atoms. In the case of electron-donor substituents [NH_2, $NH(CH_2)_3CH_3$, CH_2NH_2, and $N(CH_3)_2$] in the 4 position and in the absence of substituents attached to the shielded ring nitrogen atom, ionization of the molecule is realized at the nitrogen atom of the substituent.

The relative intensities of the peaks of the characteristic ions are determined by the ability of the substituents attached to the ring nitrogen atom to be split out in the form of a radical or to stabilize the charge on the ring heteroatom and on the substituent itself.

The $NHCH_2C_6H_5$ and NHC_6H_5 substitutents in the 4 position promote rearrangements with cleavage of the ring bonds and charge localization on the shielded nitrogen atom.

The observed fragmentation regularities can be used to establish the structures of nitrogen-containing saturated compounds that are similar to derivatives I-X.

EXPERIMENTAL

The investigated compounds were synthesized, purified, and placed at our disposal by E. S. Nikitskaya and co-workers. The methods used to synthesize the compounds were published in [8].

The mass spectra were obtained with an LKB-9000 mass spectrometer by direct introduction of the samples into the ion source. The ionizing voltages were 12 and 70 eV, the temperature of the ionization chamber was 250-290°C, and the emission current was 60 μA. The high-resolution mass spectra were recorded with a JMS-01-SG-2 mass spectrometer.

LITERATURE CITED

1. A. I. Ermakov and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 1, 65 (1981).
2. A. I. Ermakov, Zh. K. Torosyan, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 4, 507 (1979).
3. H. Budzikiewicz, C. Djerassi, and D. Williams, Mass Spectrometry of Organic Compounds, Holden–Day, San Francisco (1967), p. 297.
4. A. I. Ermakov, Yu. N. Sheinker, Zh. K. Torosyan, and V. A. Zamureenko, Khim. Geterotsikl. Soedin., No. 12, 1647 (1975).
5. A. I. Ermakov, Yu. N. Sheinker, V. I. Shvedov, L. B. Altukhova, É. S. Krichevskii, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 6, 827 (1978).
6. Energies Required to Cleave Chemical Bonds. Ionization Potentials and Electron Affinities [in Russian], Nauka, Moscow (1974), p. 261.
7. A. I. Ermakov, Yu. N. Sheinker, and V. K. Potapov, Khim. Geterotsikl. Soedin., No. 7, 970 (1974).
8. E. S. Nikitskaya, L. M. Alekseeva, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 12, 1672 (1972).

DUAL REACTIVITY OF 1,2-DISUBSTITUTED DIHYDRO-N-HETEROAROMATIC SYSTEMS.

2.* MECHANISM OF THE DEHYDROGENATION OF N-ACYLDIHYDROQUINOLINES AND ISOQUINOLINES WITH 2,2,6,6-TETRAMETHYL-1-OXOPIPERIDINIUM PERCHLORATE

Z. M. Skorobogatova, V. A. Golubev, and A. K. Sheinkman

UDC 541.124:542.941.8:547.751.831.833

The mechanism of the heterolytic dehydrogenation of various N-acyl derivatives of α-substituted 1,2-dihydroquinolines and isoquinolines with 2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate was investigated.

In a previous communication we demonstrated [1] that the aromatization of partially hydrogenated nitrogen heterocycles can be realized by means of various organic and inorganic cations, during which the heterocycles are converted to aromatic systems both as a result of splitting out of hydrogen and as a consequence of the loss of a geminal substituent [2, 3].

New selective dehydrogenating agents for the aromatization of α-substituted N-acyldihydroquinolines and isoquinolines, viz., oxo ammonium salts, were recently discovered [1, 4]. To obtain information regarding the mechanism of dehydrogenation by these salts and to develop the optimum methods for the synthesis of previously difficult-to-obtain α-substituted N-acylquinolinium and isoquinolinium salts we investigated the reactions of N-benzoyl-α-(3-indolyl)-1,2-dihydroquinoline (I) and the corresponding isoquinoline II with 2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate (III).

The stoichiometry and kinetics of oxidation of dihydrobenzopyridines (DHP) I and II were studied in acetonitrile solution, in which both the starting reagents and the final products are stable. The experiments were carried out in air or in an oxygen or argon atmosphere.

Dihydrobenzopyridines I and II are dehydrogenated quantitatively by oxopiperidinium salt III to the corresponding benzopyridinium cations (BP^+) IV and V. Oxopiperidinium

*See [1] for Communication 1.

Donetsk State University, Donetsk 340055. Branch of the Institute of Chemical Physics, Academy of Sciences of the USSR, Chernogolvka 142432. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 78-84, January, 1981. Original article submitted December 6, 1979.

0009-3122/81/1701-0063$07.50