MASS-SPECTRAL INVESTIGATION OF PYRROLO[3,2-c]PIPERIDINES

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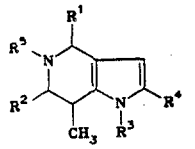
The dissociative ionization of derivatives of pyrrolo[3,2-c]piperidines and their deutero analogs was studied. The successive elimination of the substituents in the piperidine ring, which leads to its aromatization, and cleavage of this ring via a retrodiene fragmentation mechanism are the principal pathways of fragmentation of these substances. The principles found make it possible to determine the position and character of the substituents in the piperidine ring of derivatives of pyrrolo[3,2-c]piperidines.

Pyrrolo[3,2-c]piperidine derivatives [1] are of interest as potentially biologically active substances. Their aromatic analogs – azaindoles – have a broad spectrum of physiological activity [2]. In the present research we examined the mass-spectral fragmentation of compounds I-VII of this series and their deutero analogs and elicited the structural-analytical possibilities of a method for the determination of the structures of these substances.



I-VII

I—V $R^1=CH_3$, VI, VII $R^1=R^2=C_6H_5$; I—V $R^2=H$; I, II, IV—VI $R^3=H$, III, VII $R^3=CH=CH_2$, I—III, V—VII $R^4=H$, IV $R^4=CHO$; I $R^5=H$, II—IV, VI, VII $R^5=CH_3$, V $R^5=C_6H_5CO$

Molecular-ion peaks ($M^{+\cdot}$) of medium and low intensity are observed in the mass spectra of I-VII (Table 1). A comparison of the stabilities (W_{M^+}) of the molecular ions of I-VII shows that an increase in the number of substituents in the piperidine ring, as well as their presence in the pyrrole ring, leads to a decrease in W_{M^+} (Table 2).

The principal pathways of the fragmentation of I-VII can be represented by a general scheme. Peaks of $(M - H)^+$ ions, the intensities of which vary symbatically with the magnitudes of the peaks of the $M^{+\cdot}$ ions, are observed in the mass spectra of pyrrolopiperidines I-VII. A second pathway of fragmentation of I-VII (pathway B) is the elimination of radical R^1 from the 4 position, which increases the number of conjugated π bonds in ion F_2, which leads to its stabilization. The indicated process is typical for the mass-spectral behavior of α-substituted piperidines [3-5]. This fragmentation pathway is confirmed by the metastable ions in the mass spectra of all of the compounds and the 2-amu shift of the peak of the F_2 fragment to the higher-mass region in the fragmentation of the deutero analog of I and the 1-amu shift for the deutero derivatives of II, V, and VI. The formation of the $(M - R^1)^+$ ion leads to the maximally intense peak in the mass spectra of pyrrolopiperidines I-IV, for which $R^1 = CH_3$, with the exception of V, which contains a benzoyl radical attached to the piperidine nitrogen atom. Fragmentation pathway B makes it possible to determine the nature of the substituent in the 4 position of pyrrolopiperidines I-VII.

Fragment F_2 undergoes further fragmentation via pathways B_1 and B_2 with the formation of ions F_3 and F_4, which have an azaindole structure. The intensity of the peak of the F_4 fragment is higher by a factor of 2-3 than that of the F_3 ion in the case of I-IV, which do not contain substituents in the 6 position; this is due to the more facile loss of a methyl

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TABLE 1. Mass Spectra of Pyrrolo[3,2-c]piperidines I-VII

Compound	Mass spectra* (relative intensities, %)
I	57 (10), 93 (17), 106 (83), 108 (17), 119 (24), 121 (80), 133 (18), 135 (100), 149 (19), 150 (44)
II	57 (10), 84 (8), 93 (7), 106 (30), 121 (32), 133 (24), 147 (8), 149 (100), 163 (7), 164 (8)
III	57 (9), 117 (9), 132 (33), 145 (5), 147 (15), 159 (15), 173 (7), 175 (100), 189 (4), 190 (7)
IV	57 (6), 58 (5), 106 (4), 134 (35), 149 (32), 161 (13), 175 (5), 177 (100), 191 (3), 192 (5)
V	57 (17), 77 (66), 105 (100), 106 (34), 121 (22), 133 (11), 149 (22), 237 (3), 239 (19), 254 (25)
VI	77 (10), 91 (8), 118 (13), 119 (19), 168 (43), 182 (28), 183 (100), 225 (11), 301 (3), 302 (5)
VII	77 (11), 91 (16), 118 (15), 119 (21), 132 (10), 194 (85), 209 (100), 235 (5), 251 (16), 328 (5)

*The 10 most intense peaks are presented.

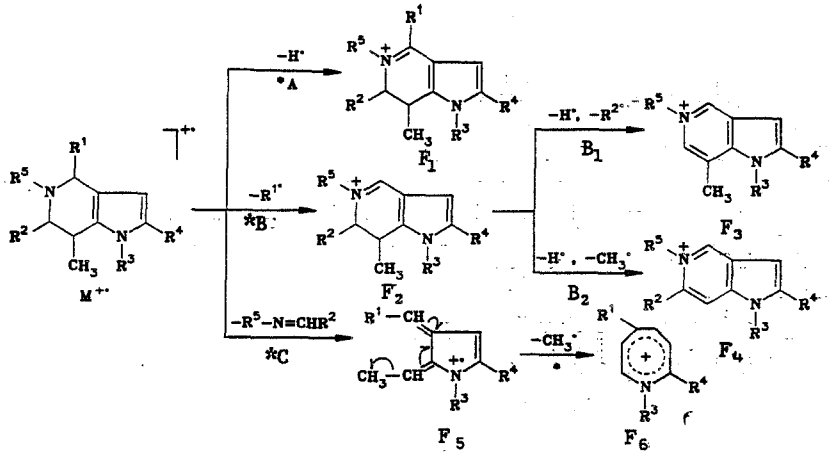
TABLE 2. Characteristic Ions and Their Relative Intensities (in percent relative to Σ_{50}) in the Mass Spectra of Pyrrolo-[3,2-c]piperidines I-VII

Compound	W_M	F_1	F_2	F_3	F_4	F_5	F_6
I	10,7	149 (4,4)	135 (23,3)	133 (4,2)	119 (5,6)	121 (18,6)	106 (19,3)
II	3,2	163 (2,8)	149 (40,0)	147 (3,2)	133 (9,6)	121 (12,8)	106 (12,0)
III	3,2	189 (1,6)	175 (40,0)	173 (2,8)	159 (6,0)	147 (6,0)	132 (13,2)
IV	2,1	191 (1,2)	177 (41,7)	175 (2,1)	161 (5,4)	149 (13,3)	134 (14,6)
V*	7,6	253 (0,7)	239 (5,0)	237 (0,8)	223 (0,5)	121 (5,8)	106 (8,9)
VI	2,1	301 (1,7)	225 (3,9)	147 (0,7)	209 (0,9)	183 (35,7)	168 (15,4)
VII	2,0	327 (1,0)	251 (5,3)	173 (0,7)	235 (1,7)	209 (33,3)	194 (28,3)

*In addition, peaks of $C_6H_5CO^+$ (26.3%) and $C_6H_5^+$ (17.4%) ions are observed.

radical from the allyl position as compared with a hydrogen atom. The metastable peaks detected in the mass spectra of I-VII also correspond to $F_2 \rightarrow F_3$ and $F_2 \rightarrow F_4$ transitions. The 1-amu shift of the peaks of fragments F_3 and F_4 to the higher-mass region in the case of the fragmentation of the deutero analogs of II, V, and VI confirms the mechanism of elimination of hydrogen atoms from the 6 and 7 position of the F_2 ion. The formation of F_3 and F_4 ions makes it possible to establish the presence of a methyl radical in the 7 position and, from the combination of fragmentation pathways B, B_1, and B_2, to determine the nature of all of the substituents in the piperidine ring.

A characteristic feature of the dissociative ionization of the examined compounds, which is of great structural-analytical value, is the retrodiene fragmentation of their molecular ions (pathway C). The genetic relationship of all of the ions formed in the splitting out of an $M^{+\cdot}$ ion via the retrodiene-fragmentation mechanism is confirmed by the presence in the mass spectra of I-VII of metastable ions for the $M^{+\cdot} \rightarrow F_5$ and $F_5 \rightarrow F_6$ transitions, by the value of the precise mass of the F_5 ion in the mass spectrum of III (for empirical formula $C_{10}H_{13}N$ measured m = 147.1035, while calculated m = 147.1047), and by the 1-amu shift to the higher-mass region of the peaks of the F_5 and F_6 ions in the mass spectra of the deutero analogs of I, II, V, and VI. Retrodiene fragmentation proceeds most intensively in the case of VI and VII (Table 2), which contain phenyl substituents in the 4 and 6 positions; the positive charge is also localized on the $[R^5{-}N{=}CH{-}R^2]^{+\cdot}$ fragment with m/z 119, the intensity of the peak of which is considerably higher than in the retrodiene fragmentation of substances that do not contain a phenyl substituent in the 6 position. The presence of a vinyl



radical attached to the pyrrole nitrogen atom in III and VII leads to a decrease in the intensity of the F_5 fragment by a factor of 1.5-2, while the presence of a formyl group in the 2 position (IV) does not affect the intensity of the peak of this ion. The competitive detachment of the benzoyl radical attached to the nitrogen atom of the piperidine ring in V sharply decreases the probability of the occurrence of retrodiene fragmentation. The F_5 ion readily loses a CH_3 group to form an F_6 fragment with a high-intensity peak; this is evidently due to the azatropylium structure of the F_6 ion. The retrodiene fragmentation of the molecular ions of I-VII gives valuable information regarding the structures of the investigated substances, since with it one can readily establish the presence and character of substituents in the 4, 6, and 7 positions of these compounds.

In addition to common pathways of dissociative ionization, characteristic fragmentation pathways that are associated with the peculiarities of the structures of the substituents that enter into their compositions are realized in the mass spectra of some pyrrolopiperidines. Thus the presence of a benzoyl radical attached to the nitrogen atom of the piperidine ring in V gives rise to the appearance of a maximally intense peak of a $C_6H_5CO^+$ fragment with m/z 105, which is diagnostic in the case of detection of this radical in the molecules of many benzoyl-containing substances [6]. An $(M - R^5)^+$ ion with m/z 149, which is not observed in the fragmentation of other pyrrolopiperidines, is also observed in the mass spectrum of V. The indicated ion then successively loses H· and CH_3· radicals to give a fragment with m/z 133 (for empirical formula $C_8H_9N_2$ measured m = 133.0770, while calculated m = 133.0765), which has an azaindole aromatic structure. In the case of pyrrolopiperidines VI and VII, which contain phenyl substituents in the 4 or 6 position, retrodiene fragmentation proceeds without transfer and with transfer of a hydrogen atom from the detached fragment to the principal part of the molecule. The probability of the second process increases and leads to the appearance of an $[R^5{-}N{\equiv}C{-}R^2]^+$ ion with m/z 118 in the fragmentation of VI and VII; this ion is not observed in the mass spectra of the other pyrrolopiperidines I-V.

Thus the dissociative ionization of pyrrolo[3,2-c]-piperidines I-VII is realized via three principal pathways. The first two pathways are accompanied by aromatization of the piperidine ring, which is the driving force of this process, due to the localization of the positive charge on the nitrogen atom of the saturated ring. The occurrence of retrodiene fragmentation via the third pathway is caused to a significant degree by localization of the positive charge on the pyrrole nitrogen atom. The mass spectra of pyrrolo[3,2-c]piperidines convey valuable information regarding their structures, making it possible to determine the position and character of the substituents bonded to the piperidine ring.

EXPERIMENTAL

The mass spectra of I-VII [1] were obtained with an MKh-1303 spectrometer equipped with a system for direct introduction of the samples into the ion source at an ionizing voltage of 70 V and admission temperatures 10-15°C below the melting points of the substances. The mass spectra of the deutero analogs of I, II, V, and VI were obtained under conditions of deuterium exchange of vapors of the investigated substances with CD_3OD vapors directly in the ionization chamber of the apparatus. The precise masses of the ions were measured with an MAT-311 A spectrometer.

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QUANTUM-CHEMICAL INVESTIGATION OF THE DIELS—ALDER REACTION IN CONDENSED ISOINDOLES WITH A NODAL NITROGEN ATOM

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On the basis of calculated data on the electron structures of condensed isoindoles with a nodel nitrogen atom it is hypothesized that these compounds may act as dienes in the Diels—Alder reaction. Conclusions regarding the relative activities and the peculiarities of cycloaddition in the investigated structures were drawn from the static reactivity indexes obtained within the Pariser—Parr—Pople approximation.

Computational methods, together with kinetic studies, are currently the chief sources of information regarding the reactivities of dienes and dienophiles in the Diels—Alder reaction and its stereochemistry and mechanism. Data obtained in recent years [1-5] show that the Woodward—Hoffmann theory [6], which is acknowledged by organic chemists, is not absolute. More thorough and elegant experimental investigations have demonstrated the possibility of the realization of "forbidden" (from the point of view of the theory of orbital symmetry) processes [7], as well as a two-step mechanism of the Diels—Alder reaction, in contrast to the classical one-step synchronous process [1, 3, 5, 8].

Chiefly butadiene, polyenes, benzene, polyacenes, and cyclopentadiene have been included among the dienes that have been investigated by quantum-chemical methods. However, calculations of heterocyclic dienes began to be realized only recently [9, 10]. In particular, several explanations were proposed in [11, 12].

In the course of a systematic study of the chemistry of isoindole and its condensed derivatives we calculated the electron structures of isoindole [13] and a number of azino- [14] and azoloindoles [15]. It was established that the bond orders, π charges, $(\sigma + \pi)$ charges, and valence activities of the bonds and fragments [16] in the isoindole part of the condensed systems change little, and, consequently, it is logical to assume that, with respect to chemical properties, they all* will resemble isoindole; in particular, they should undergo the Diels—Alder reaction that is characteristic for the latter. The aim of the present research was to evaluate the relative activities of a number of condensed isoindoles I-XVII in this reaction by means of calculated data.

*The numbering of the atoms differs from that generally used for a more concise exposition of the material in this paper.

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