4. N. N. Shapet'ko, S. S. Berestova, V. G. Medvedeva, A. P. Skoldinov, and Yu. S. Andreichikov, Dokl. Akad. Nauk SSSR, 234, 876 (1977).
5. N. N. Shapet'ko, D. N. Shigorin, A. P. Skoldinov, T. S. Ryabchikova, and L. N. Reshetova, Zh. Strukt. Khim., 6, 155 (1965).
6. Ya. F. Freimanis, Chemistry of Enaminoketones, Enaminoimines, and Enaminothiones, Zinatne, Riga (1974).
7. A. Streitwieser, Molecular Orbital Theory for Organic Chemists [Russian translation], Mir, Moscow (1965).
8. B. Pullmann and A. Pullman, Quantum Biochemistry [Russian translation], Mir, Moscow (1965).

# MASS SPECTROMETRY OF NITROGENOUS HETEROCYCLES.

## 1. MASS SPECTROMETRIC EVALUATION OF STABILITY OF TETRAHYDROPYRAZINES ANNELATED TO FIVE- AND SIX-MEMBERED HETEROCYCLES

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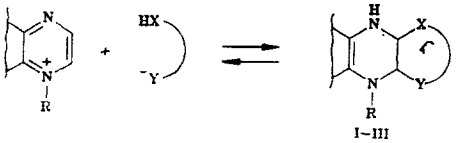
UDC 543.51:547.863

Based on a study of electron impact mass spectra of a large number of tetrahydropyrazines, which are joined to five- and six-membered heterocyclic and carbocyclic residues, the trends which characterize the stability of these condensed systems are found. The proposed criteria can be used for evaluation of the chemical stability of these compounds, for example, their propensity toward the reverse dissociation reaction.

Recently, a series of studies have appeared in which mass spectrometric methods are used for evaluation of the stability of hydrogenated heterocycles and for prediction of reaction directions [1-4]. In the present work, experimental material on mass spectrometry of condensed tetrahydropyrazines is correlated. These data were accumulated during a study of the fragmentation patterns of hydrogenated heterocycles, the cyclization products of 1,4-diazine cations with bifunctional nucleophiles.

Annelation of azines by carbo- and heterocycles through reaction of bifunctional nucleophilic reagents to the two ortho-carbon atoms of the azine ring is a general method for synthesis of pyrazines and condensed systems based on them. Cyclizations of this type are known in a series of pyrazine derivatives, quinoxaline, pyrido[2,3-b]pyrazine, and pteridine, including both 1,4-diazinium cations [5-7] and neutral 1,4-diazines activated by acceptor substituents, in particular, pteridine derivatives [8, 9].



I–III

The cyclizations examined are reversible and, as was shown in a number of works [5-7, 10-12], dissociation of the cycloadducts I-III creates grounds for various types of isomerization which lead to regio- [10, 11] and stereoisomeric compounds [12] as well as to a change in the annelated ring [10]. The result of these complicated reverse reactions which as a rule have a few possible directions is largely determined by the thermodynamic stability of the adducts I-III which are formed. Chemical experiments [10] have shown that dissociation of cyclic adducts occurs with rupture of both C–X and C–Y bonds and leads to final addends, cations of 1,4-diazine and the corresponding dinucleophiles. The tendency of the condensed

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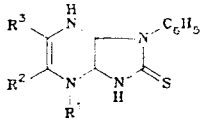
 0009-3122/89/2504-0444 $12.50 

tetrahydropyrazines I-III toward dissociation depends on the carbon-heteroatom bond energies (C–X and C–Y) which in turn are determined by the nature of the heteroatom and the character of the substituents in the 1,4-diazine ring. Analogous effects are related to the synchronous rupture of these bonds and are observed in the first stage of fragmentation of the molecular ions ($M^+$) of compounds I-III as demonstrated by a study of the mass spectra of the metastable ions.

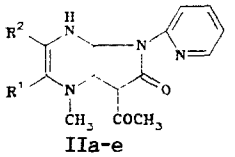
The present work includes a study of the relative stability of the cyclic adducts I-III upon variation of structural elements in order to find correlations between the chemical stability of compounds I-III and the nature of their fragmentation. To this end, mass spectrometric properties of about 30 different condensed tetrahydropyrazines are studied. These form the following series:

– hydrogenated imidazo-1,4-diazines Ia-e with a constant imidazole fragment and variable substituents in the 1,4-diazine ring (Table 1):



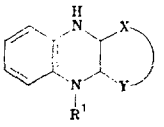
Ia-e

– tetrahydropyrazines IIa-e condensed to a pyrrole ring with various substituents in the pyrazine ring (Table 1):



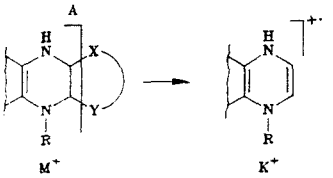
IIa-e

– tetrahydroquinoxalines IIIa-s with a common quinoxaline core, the structure of which is varied due to annelation in the 2 and 3 positions of the quinoxaline nucleus by various carbo- and heterocycles (Table 1):



IIIa-s

The ratio of intensities of molecular ion $M^+$ peaks of the cycloadducts I-III to the 1,4-diazine ion $K^+$ peaks which are formed as a result of retrodecomposition was chosen as a measure of the stability of the annelated tetrahydropyrazines I-III.



The value $I_{M^+}$ characterizes the stability of the molecule to electron impact and is determined by the aromaticity of the molecule as a whole. The value $I_{K^+}$ indicates the probability of fragmentation of the molecular ion $M^+$ of the cycloadducts I-III in the A direction. This fragmentation pattern is characteristic for all compounds of the series studied. Besides this, the ratio of peak intensities of these ions $(I_{M^+}/I_{K^+})\cdot 100 = S$, which characterizes the stability of $M^+$, depends little on sample vaporization temperature and quantity of sample introduced into the ion source for production of the mass spectrum [13, 14] (Table 1, compound Ib). Namely for these reasons, the ratio S is chosen as the analytical indicator of relative stability in the series of annelated tetrahydro-1,4-diazines.

TABLE 1. Mass Spectrometric Data Determining the Stability of Condensed Tetrahydropyrazines Ia-e, IIa-e, and IIIa-s

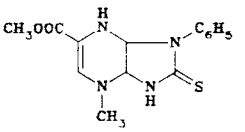
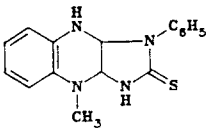
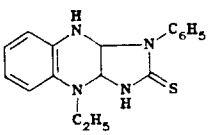
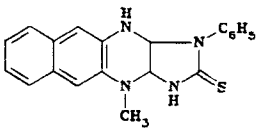
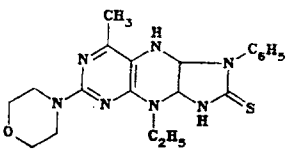
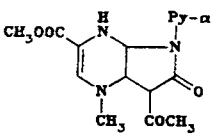
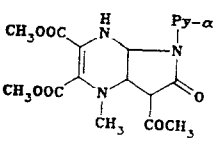
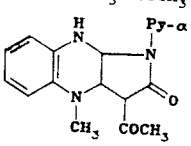
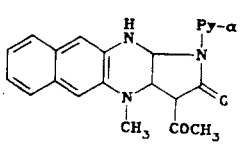
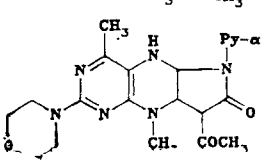
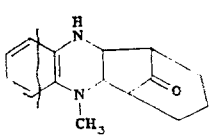
| Compound | Formula | Sample vaporization temp., °C | m/z ($I_{M^+}$) | m/z ($I_{K^+}$) | ($I_{M^+}/I_{K^+}$)×100 = S |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| Ia |  | 60 | 304 (59,2) | 154 (42,6) | 139 |
| Ib |  | 50<br>100 | 296 (51,3)<br>296 (38,2) | 146 (93,7)<br>146 (77,2) | 55<br>49 |
| Ic |  | 100 | 310 (7,8) | 160 (12,5) | 62 |
| Id |  | 150 | 346 (15,3) | 196 (43,4) | 35 |
| Ie |  | 160 | 411 (27,4) | 261 (46,8) | 58 |
| IIa |  | 85 | 315 (2,6) | 139 (2,0) | 130 |
| IIb |  | 90 | 402 (21,3) | 226 (4,8) | 444 |
| IIc |  | 120 | 322 (20,4) | 146 (19,5) | 105 |
| IId |  | 130 | 372 (15,0) | 196 (19,4) | 77 |
| IIe |  | 150 | 423 (23,8) | 247 (20,8) | 114 |
| IIIa |  | 120 | 242 (60,4) | 146 (100) | 60 |

TABLE 1 (Continued)

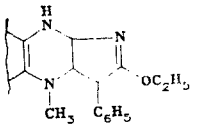
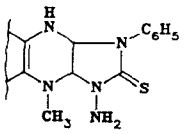
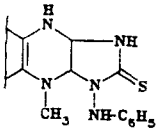
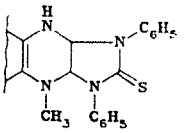
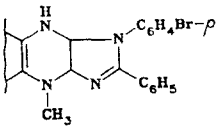
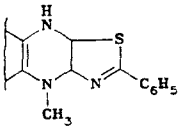
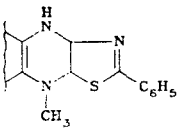
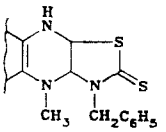
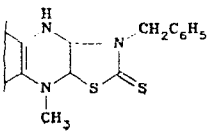
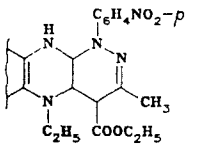
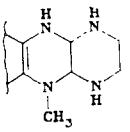
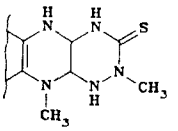
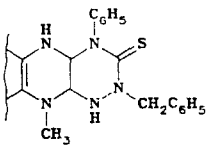
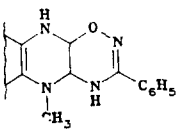
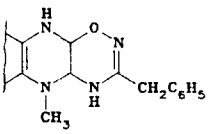
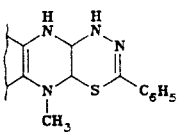
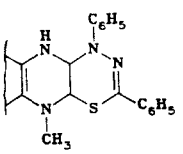
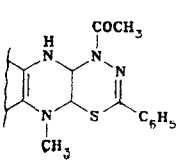
| Compound | Formula | Sample vaporization temp., °C | m/z ($I_{M^+}$) | m/z ($I_{K^+}$) | ($I_{M^+}/I_{K^+}$)×100=S |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| IIIb |  | 160 | 307 (100) | 146 (46,6) | 215 |
| IIIc |  | 175 | 311 (32,9) | 146 (100) | 33 |
| IIId |  | 210 | 311 (44,0) | 146 (78,8) | 56 |
| IIIe |  | 170 | 372 (41,8) | 146 (100) | 41 |
| IIIf |  | 110 | 418 (90,6) for $^{79}Br$<br>420 (83,8) for $^{81}Br$ | 146 (43,4) | 209<br>193 |
| IIIg |  | 40 | 281 (31,9) | 146 (56,1) | 57 |
| IIIh |  | 60 | 281 (100) | 146 (67,2) | 149 |
| IIIi |  | 110 | 327 (12,0) | 146 (100) | 12 |
| IIIj |  | 140 | 327 (28,4) | 146 (100) | 28 |
| IIIk |  | 70 | 423 (12,7) | 160 (100) | 12 |

TABLE 1 (Continued)

| Compound | Formula | Sample vaporization temp., °C | m/z ($I_{M^+}$) | m/z ($I_{K^+}$) | ($I_{M^+}/I_{K^+}$)×100=S |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| III ℓ |  | 50 | 204 (100) | 146 (27,2) | 368 |
| III m |  | 80 | 249 (97,2) | 146 (100) | 97 |
| III n |  | 110 | 401 (12,9) | 146 (80,9) | 16 |
| III o |  | 90 | 280 (7,2) | 146 (48,3) | 15 |
| III p |  | 120 | 294 (25,4) | 146 (100) | 25 |
| III q |  | 100 | 296 (0,99) | 146 (9,9) | 0,1 |
| III r |  | 130 | 372 (1,1) | 146 (100) | 1 |
| III s |  | 150 | 338 (20,3) | 146 (100) | 20 |

Examination of the mass spectra of 1,4-diazines annelated by imidazole and pyrrole rings shows that the stability of the hydrogenated condensed systems I and II depends weakly on the substituents in the 1,4-diazine ring. It is determined mainly by the nature of the C—X and C—Y bonds (Table 1). Also, introduction of acceptor subsituents in the pyrazine ring confers elevated stability to compounds Ia and IIb. The influence of an acceptor substituent on the stability of the heteroannelated system is also followed well in the series of thiadiazino[5,6-b]quinoxalines IIIq-s. The weakly accepting phenyl substituent in the thiadiazine ring increases the stability of compound IIIr by ten times in comparison with thiadiazinequinoxaline IIIq while introduction of an acetyl group in position 4 of the thiadiazine ring (compound IIIs) leads to a 200-fold increase in the S value (Table 1).

The relative stability of annelated tetrahydropyrazines practically does not depend on replacement of the N-methyl group in the pyrazine ring (compound Ib) by an N-ethyl. The determining influence on the stability of the annelated tetrahydropyrazine system is the presence of bulky substituents on atoms which are directly bonded to the core. Thus, introduction of a phenyl substituent in position 3 of the imidazole ring lowers the stability index of compound IIIc in comparison to compound IIId. For the same reason, the cyclization product of the N-methylquinoxaline cation with diphenylthiourea, 1,3-diphenyl substituted imidazo[4,5-b]quinoxaline IIIe, has a lower stability coefficient S in comparison to the monophenylsubstituted analog Ib. Analogous rules are observed in the series of 1,4-diazines condensed with six-membered heterocycles. Thus, the values of S for pyrazinoquinoxaline IIIℓ and triazinoquinoxaline IIIm are equal to 368 and 97, respectively, while for 4-phenylsubstituted triazinoquinoxaline IIIn the value is substantially lower and equal to 16 (Table 1).

The accuracy of evaluation of the stability of annelated tetrahydropyrazines using the proposed mass spectrometric criteria is confirmed by chemical experiments. Earlier it was shown [10] that thiazoloquinoxaline IIIo is formed as a kinetic cyclization product of the quinoxalinium cation with thioamide and that this compound converts into the thermodynamically more stable product IIIh under the influence of acid. The large stability of thiazoloquinoxaline IIIh presages the mass spectrometric data: the S value for compound IIIh is equal to 149, i.e., almost three times greater than for compound IIIg (S = 57). These same rules are obeyed even in the pair of regioisomeric thiazoloquinoxaline-2-thiones IIIi and IIIj. The kinetic product IIIi has a smaller stability coefficient (S = 12) in comparison to the thermodynamic product IIIj (S = 28).

Comparison of the mass spectrometric data for the series of compounds I-III shows that thiazoloquinoxalines IIIi, j are less stable than imidazoquinoxalines IIb, c and IIIc-e, and that imidazoquinoxalines Ia-e in turn are less stable than their pyrrole annelated analogs IIa-e. From the mass spectrometric data it can be expected that reactions of annelated pyrrole rings to 1,4-diazines will be very favored since they lead to cyclic adducts which are more stable. In fact, amides of acetoacetic acid undergo cyclization reactions with a wide range of 1,4-diazinium salts, including pteridinium cations and 1,2,4-triazinium [15, 16], while N,S-dinucleophiles form comparatively stable cyclic adducts primarily with quinoxalinium salts.

In general, the following conclusions can be made based on the data given in Table 1:

– the stability of tetrahydropyrazines condensed with various heterocycles depends both on the type of bonds to the annelated fragment, i.e., on the nature and orientation of the heterocycle and on the nature and size of the substituent,

– the successive change of some structural elements by others allows the succession of changes in bond stability of the condensed tetrahydropyrazines to be placed in order based on mass spectrometric criteria:

$$C—S<C—O<C—NR\lesssim C—C<C—N=$$

– bulky substituents on atoms directly bonded to the core lower the stability of cycloadducts and the presence of acceptor substituents conversely increases their stability.

## EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-311A instrument. Standard conditions were: acceleration potential 3 kV, cathode emission current 1 mA, and ionizing electron energy 70 eV. Direct insertion was used for introduction of samples into the ion source. Mass spectra of metastable ions were recorded using DADI [17].

Compounds Ib, c, e; IIa-e; and IIIa-s were synthesized by methods given earlier in the literature (see reviews [5-7]) and also were donated by coworkers M. G. Ponizovskii and L. M. Naumova of the Organic Chemistry Faculty of S. M. Kirov Ural Polytechnic Institute, for which the authors are sincerely thankful.

7-Methyl-3-phenyl-5-methoxycarbonyl-2,3,3a,4,7,7a-hexahydro-1H-imidazo[4,5-b]pyrazine-2-thione (Ia) and 11-methyl-3-phenyl-2,3,3a,4,11,11a-hexahydro-1H-imadazo[4,5-b]benzo[3,4]quinoxaline-2-thione (Ic) were prepared by the method of [18] especially for these studies. Elemental analyses for C, H, and N corresponded to those calculated.

Ia, $C_{14}H_{16}N_4O_2S$. mp 180-181°C, yield 90%. PMR spectrum (DMSO-$D_6$): 2.88 (3H, s, N-$CH_3$); 3.49 (3H, s, $OCH_3$); 4.71 (1H, d. d, $J_{7a,NH}$ = 2.5 Hz, $J_{7a,3a}$ = 6.5 Hz, 7a-H); 5.72 (1H, d. d, $J_{3a,NH}$ = 3.0 Hz, 3a-H); 6.78 (1H, br. s, NH); 6.9-7.5 (5H, m, $C_6H_5$); 9.48 ppm (1H, br. s, NH).

Ic, $C_{20}H_{18}N_4S$. mp 219-220°C, yield 70%. PMR spectrum (DMSO-$D_6$): 3.00 (3H, s, N—$CH_3$); 5.51 (1H, d, $J_{3a,11a}$ = 9.2 Hz, 11a-H); 5.98 (1H, d.d, $J_{3a,NH}$ = 2.8 Hz, 3a-H); 6.76 (1H, d, 4-H); 6.8-7.8 (11H, m, aromatic protons); 9.42 ppm (1H, br. s, 1-H).

## LITERATURE CITED


1. V. P. Williams and J. E. Ayuling, J. Heterocycl. Chem., 10, 827 (1973).
2. J. H. Bowie, Mass Spectrom. Rev., 3, 1 (1984).
3. Yu. V. Shurukhin, N. A. Klyuev, and I. I. Grandberg, Khim. Geterotsikl. Soedin., No. 6, 723 (1985).
4. T. Kametani, Yakugaku Zasshi, 101, 1 (1981).
5. V. N. Charushin and O. N. Chupakhin, Usp. Khim., 53, 1648 (1984).
6. V. N. Charushin, M. G. Ponizovskii, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., No. 8, 1011 (1985).
7. V. N. Charushin and O. N. Chupakhin, Izv. Sev.-Kavk. Nauch. Tsentra Vyssh. Shk., No. 3, 88 (1987).
8. A. Albert and H. Mizuno, J. Chem. Soc., Perkin Trans. I, 1615 (1973).
9. J. Clark and F. S. Gates, J. Chem. Soc. C, No. 2, 371 (1971).
10. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, and V. N. Drozd, Khimn. Geterotsikl. Soedin., No. 3, 396 (1985).
11. V. G. Baklykov, V. N. Charushin, O. N. Chupakhin, and V. N. Drozd, Khim. Geterotsikl. Soedin., No. 4, 557 (1987).
12. O. N. Chupakhin, V. N. Charushin, L. M. Naumova, and A. I. Rezvukhin, Dokl. Akad. Nauk SSSR, Ser. Khim., 261, 384 (1981).
13. N. A. Klyuev, A. K. Sheinkman, and V. G. Zhil'nikov, Dokl. Akad. Nauk SSSR, 232, 618 (1977).
14. V. A. Zamureenko, N. A. Klyuev, L. B. Dmitriev, and I. I. Grandberg, J. Chromatogr., 303, 105 (1984).
15. I. V. Kazantseva, V. G. Baklykov, V. N. Charushin, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., No. 3, 420 (1986).
16. S. G. Alexeev, V. N. Charushin, O. N. Chupakhin, and G. G. Alexandrov, Tetrahedron Lett., 29, 1431 (1988).
17. N. A. Klyuev, É. N. Istratov, R. A. Khmel'nitskii, V. P. Suboch, V. L. Rusinov, and V. A. Zyryanov, Zh. Org. Khim., 13, 1501 (1977).
18. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, N. N. Vereshchagina, L. M. Naumova, and N. N. Sorokin, Khim. Geterotsikl. Soedin., No. 12, 1684 (1983).