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CHROMATOGRAPHIC/MASS-SPECTROMETRIC ANALYSIS OF HETEROCYCLIC TAUTOMERIC FORMS OF NITROGEN-CONTAINING DERIVATIVES OF 1,3-DICARBONYL COMPOUNDS*

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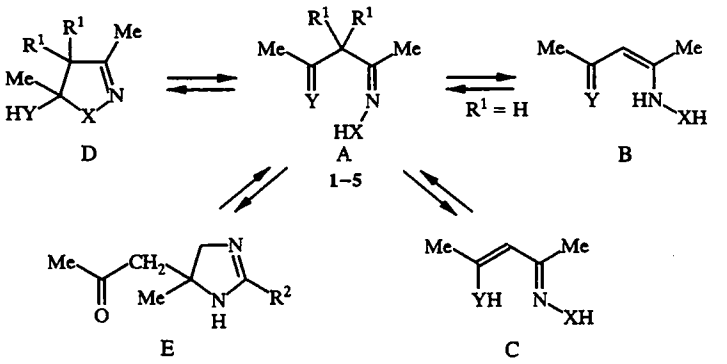
By means of chromatography/mass spectrometry, a quantitative estimate has been made of the gas-phase contents of different tautomeric forms of a monooxime, monoacetylhydrazone, diacetylhydrazone, and monoamidrazonoacetylacetone. In particular, individual tautomeric forms of these compounds were identified: 5-hydroxyoxazoline, 5-hydroxypyrazoline, 5-hydroxylaminopyrazoline, 5-acetylhydrazinylpyrazoline, and 5-acetonyl-2,3,4-triazoline.

The attention of investigators has been attracted in recent years to nitrogen derivatives of carbonyl compounds – which, one would think, had already been studied thoroughly – and also to 1,3-dicarbonyl compounds (oximes, substituted hydrazones, semicarbazones, thiosemicarbazones), for which a tendency has been found not only toward keto–enol (A–C) or imine–enamine (A–B) tautomerism, but also to ring–chain tautomerism (A–D) [1-4] (Scheme 1). However, these studies were performed in solutions, where, it had been shown, the predominance of one tautomeric form or the other is highly dependent on the polarity of the solvent. In the gas phase, with no solvent present, mass-spectrometric studies have identified both cyclic and linear tautomeric forms [5-8]; in those studies, the reliability of interpretation of ion characteristics was not always adequate.

Scheme 1



2) $R^2 = NH_2$, 3) R^2 = Me; 1–4) R^1 = H; 5) R^1 = Me; 1) X = O; 2) XH = N=C$(NH_2)_2$; 3) XH = N=CMeNH_2; 4) X = NCOMe; 5) X = NMe; 1–3) Y = O; 4) Y = N–NHCOMe; 5) Y = N–OH

*We dedicate this article to the memory of I. N. Goncharova.

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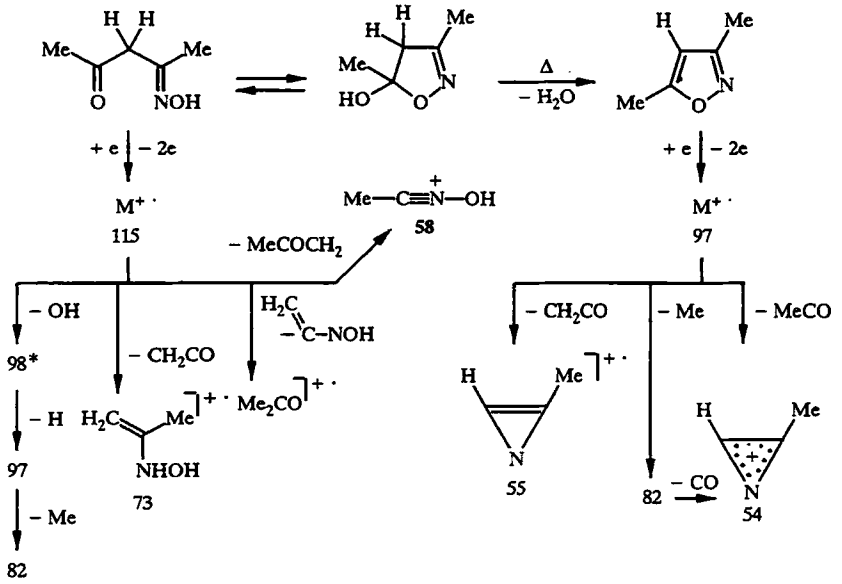
Under certain conditions, some of the tautomeric forms can be isolated as individual compounds. For example, HPLC has been used to separate a tautomeric mixture of keto and enol tautomers of acetoacetic ester and acetylacetone [9], and also 4-aminoisoxazoline-1,2-naphthoquinone [10]. It was shown in [11] that, for the separation and identification of individual keto–enol forms of 1,3-dicarbonyl compounds, chromatography/mass spectrometry may be used; however, there is no information in the literature on any use of this method to investigate compounds that are capable of manifesting ring–chain tautomerism. In view of this background, we investigated the chromatographic/mass-spectrometric behavior of certain derivatives of diacetylacetone with one or two nitrogen-containing groups (compounds **1-5**).

When a solution of the monooxime of acetylacetone **1** in methanol was introduced into the chromatograph, we found only two distinct chromatographic peaks, with an area ratio of 3/1 (Fig. 1*a*), these two peaks differing sharply in the corresponding mass spectra of the compounds (Fig. 1*b,c*). Thus, in the mass spectra of the first of these compounds (Fig. 1*b*), the ion with the maximal mass corresponded to loss of a water molecule from the original monooxime, and fragmentation of such a molecular ion corresponded to a process of dissociative ionization of 3,5-dimethyloxazole [12] (Scheme 2). Thus, the first peak on the chromatogram corresponds to the cyclic form D of the monooxime that was analyzed, with this compound losing water by thermal decomposition, probably even in the injector. The low thermal stability of such hydroxyisoxazolines is well known [13].

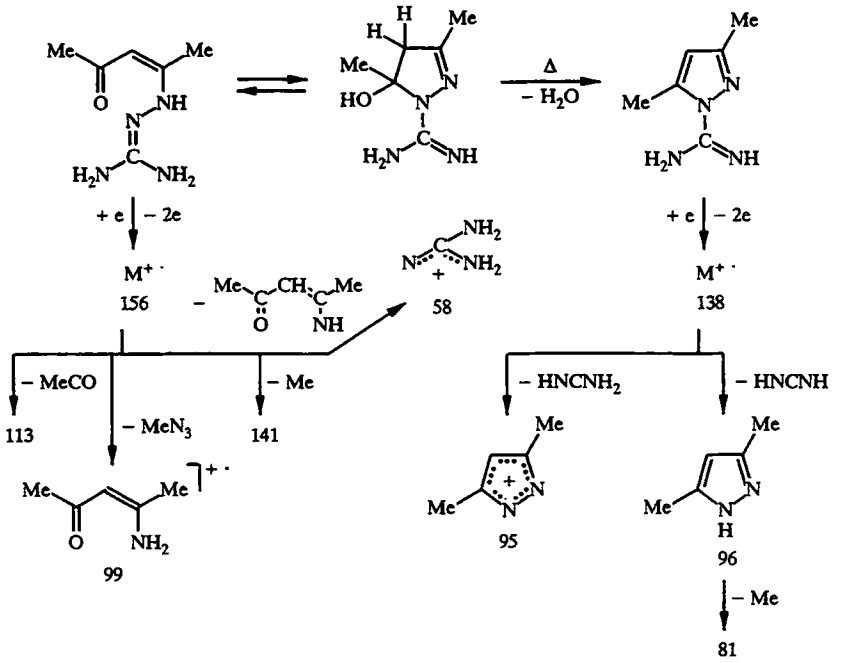
Scheme 2



In the mass spectrum of the compound of the second peak, the molecular ion was present, and the characteristic paths of its decomposition involve the loss of a ketene molecule or an acetonyl fragment, as is typical for the known linear forms of acetylacetone and its derivatives [14, 15] (Scheme 2). Let us note that when compound **1** was introduced into the direct injection system of the mass spectrometer, we obtained a spectrum representing the sum of the mass spectra of the two tautomers (Fig. 1*d*).

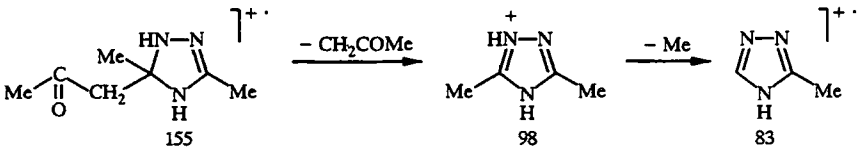
When the monoamidrazone of acetylacetone **2** was introduced into the chromatograph injector, two chromatographic peaks were obtained, with a 1/5.5 area ratio (Fig. 2*a*). Analysis of the mass spectrum of the minor component of the mixture (Fig. 2*b*) indicated that this compound has the structure of 3,5-dimethyl-1-amidinopyrazole, which was formed, the same as in the first case, as a result of thermal dehydration of the oxypyrazoline tautomeric form. The molecular ion of this pyrazole eliminates either the amidine group (m/z 95) or a cyanamide molecule (m/z 96) (Scheme 3). In the mass spectrum of the major component (Fig. 2*c*), we observed an intense peak of the molecular ion, losing methyl or acetyl groups or the MeN_3 fragment (Scheme 3). Such a character of the fragmentation indicates a linear ketoenehydrazine tautomeric structure of the compound [14]. A summation of the mass spectra of these two compounds coincides with the mass spectrum of the original amidrazone **2** (Fig. 2*d*) that was obtained by direct introduction of the substance into the ion source; and the proposed scheme of fragmentation is supported by analysis of the mass spectrum of the deuterium-labeled compound. According to IR and PMR spectroscopic data, compound **2** in the solid phase, and also in solution in chloroform or DMSO, has the linear enehydrazine structure; and only upon acidification (HCl) does the cyclic pyrazoline form become more stable [1, 5].

Scheme 3



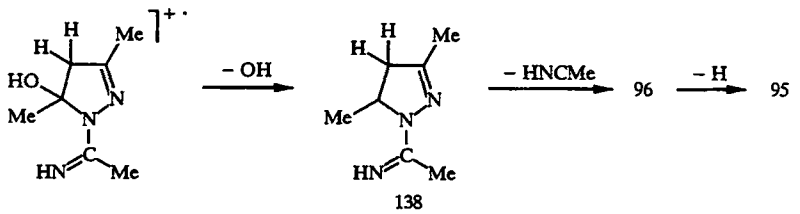
The most complicated chromatogram was obtained in the case of compound **3** (Fig. 3*a*). According to the GLC data, this compound exists in the gas phase in four tautomeric forms (ratio of peak areas 2.3/1.0/5.4/2.3), namely the ketohydrazone form A (peak *3*), the ketoenehydrazine form B (peak *4*), and two cyclic forms, the hydroxypyrazoline D (peak *2*) and 2,5-dimethyl-5-acetonyl-1,3,4-triazoline E (peak *1*). This tautomer was formed as a result of attack of the terminal amino group on the C=N bond of the hydrazone part of the molecule. This sort of tautomeric cyclization has been described for a number of thiosemicarbazones of monocarboxyl compounds [16]. The structures of these compounds were established on the basis of analysis of their mass spectra (Fig. 3*b,c,d,e*). In the first of these, the peak with the greatest mass corresponded to loss of an acetonitrile fragment from the molecular ion; this is possible only in case of the tautomeric triazoline structure E (Scheme 4).

Scheme 4



In the mass spectrum of the highest-boiling compound (peak *2*), there was likewise no molecular ion, and the ion with the greatest mass corresponded to splitting of a hydroxyl group from the molecular ion. The resulting pyrazolyl cation successively eliminates a methylimine group and a hydrogen radical (ions m/z 96 and 95) (Scheme 5).

Scheme 5



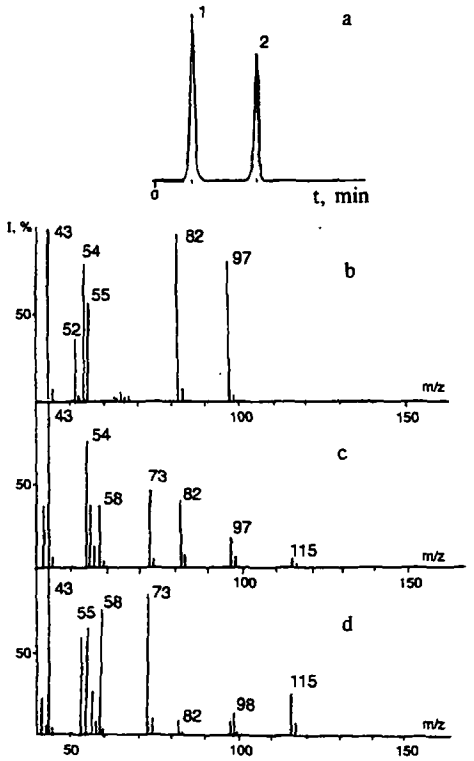
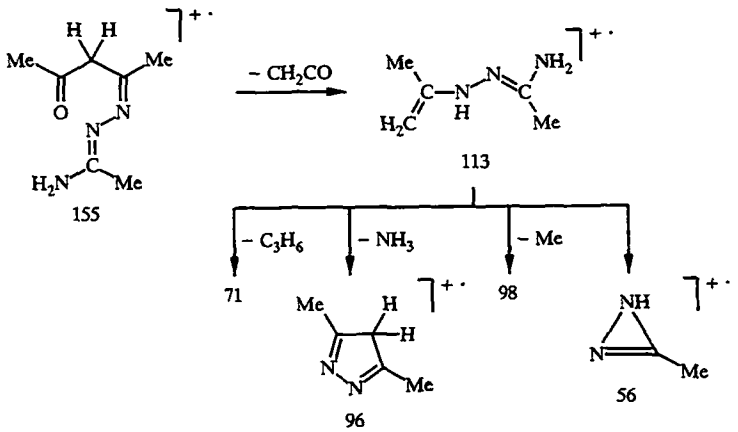


Fig. 1. Results of chromatographic/mass-spectrometric analysis of mixture of tautomers of compound **1**: *a*) Chromatogram of mixture; *b*) mass spectrum of tautomer D (peak *1*); *c*) mass spectrum of tautomer A (peak *2*); *d*) mass spectrum of compound **1**, taken by the direct injection method.

In the mass spectra of both tautomeric forms with the linear structure (peaks *3* and *4*), we observed molecular ions with significant intensity; however, the character of fragmentation differed for these two forms (Fig. 3*d,e*). Thus, the ion radical of the ketohydrazone, like other derivatives of acetylacetone [14], readily ejected a ketene molecule to form an ion with m/z 113, which then lost a methyl group (m/z 98) or an ammonia molecule (m/z 96), propylene (m/z 71) or aminopropene (m/z 56) (Scheme 6). Dissociative ionization of the molecular ion of the enehydrazine proceeded with preferential cleavage of an "allyl" bond N–N and localization of charge on the nitrogen-containing fragment with m/z 57 (Scheme 7).

Scheme 6



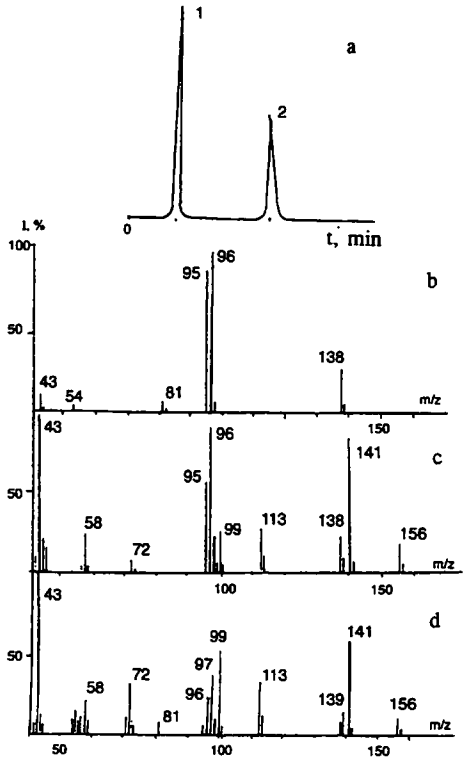
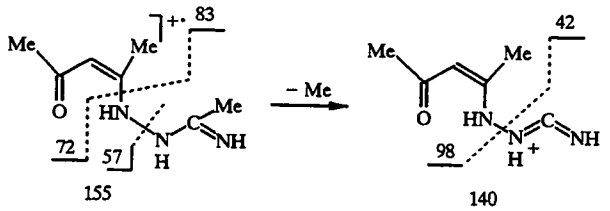


Fig. 2. Results of chromatographic/mass-spectrometric analysis of mixture of tautomers of compound **2**: *a*) Chromatogram of mixture; *b*) mass spectrum of tautomer D (peak *1*); *c*) mass spectrum of tautomer B (peak *2*); *d*) mass spectrum of compound **2**, taken by direct introduction method.

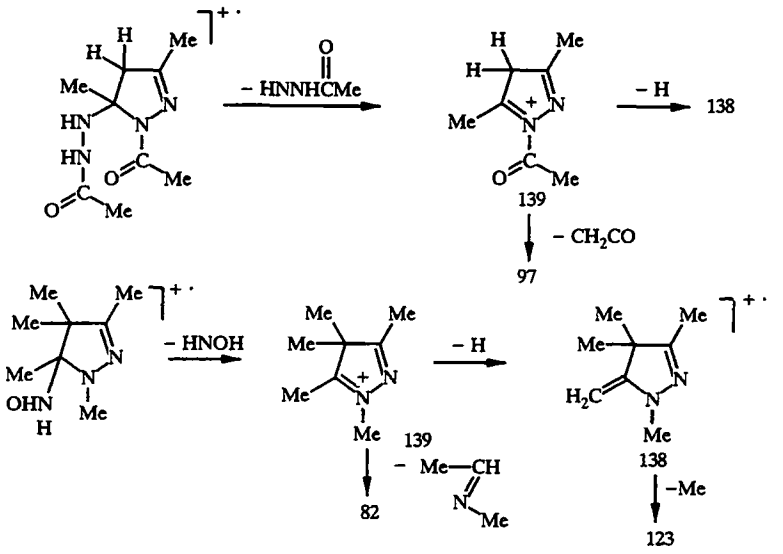
Scheme 7



The same as in all of the preceding cases, the mass spectrum obtained when compound **3** was introduced into the direct injection system contained peaks of ions of all four components (Fig. 3*f*). By analogy with compound **2**, the PMR spectrometric data provide us with grounds for stating that in polar or weakly polar solvents, compound **3** exists primarily in the two linear forms A and B [1, 5].

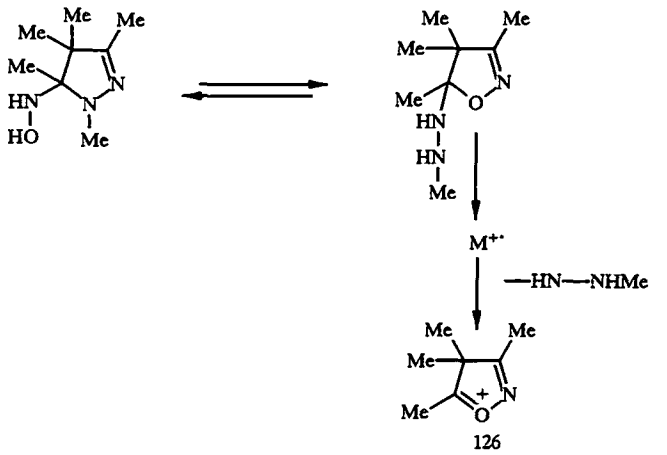
Our chromatographic/mass-spectrometric investigation of the diaza-substituted derivatives of acetylacetone **4** and of 3,3-dimethylacetylacetone **5** proved unambiguously that in the gas phase, these compounds exist entirely in one cyclic tautomeric form, respectively 1-acetyl-5-acetylhydrazino-3,5-dimethylpyrazoline and 1,3,4,4,5-pentamethyl-5-hydroxylamino-pyrazoline. The mass spectra of these compounds were similar in many respects, since they did not contain molecular ions, and the ion with maximal mass corresponded to loss from the M^+ ion of a hydroxyaminyl or (correspondingly) an acetylhydrazyl group. The isobaric ions that are formed in this case (1-acetyl-3,5-dimethylpyrazolium and 1,3,4,4,5-pentamethylpyrazolium (m/z 139) lose a molecule of ketene (compound **4**, ion m/z 97) or lose successively a hydrogen radical and a methyl group (ions m/z 138 and 123). Since there are no peaks of molecular ions in these spectra, we took their mass spectra with chemical ionization, in which we observed intense peaks of ions (M + H), thereby confirming the structure of the original molecules. In the chemical-ionization mass spectra, the most intense peaks (other than that of the protonated molecular ion) were those of the fragments with m/z 139, 138, and 123 (Scheme 8).

Scheme 8



According to PMR spectroscopic data [17, 18], compounds **4** and **5** exist in the crystalline state exclusively in the pyrazoline form, whereas in solution in DMSO, chloroform, or pyridine, it was established for compound **5** that an equilibrium exists between two cyclic forms, the pyrazoline and 5-methylhydrazinoisoxazoline forms (Scheme 9). For either of the compounds in solution, not even traces of any linear tautomeric forms could be detected, so it could be concluded tentatively that ring–ring tautomerism is manifested in this case [19].

Scheme 9



In the investigation of compound **5** by means of secondary ion mass spectrometry in a thioglycerol matrix, in addition to the peaks of the protonated molecular ion and the characteristic ions m/z 139 and 123, the spectrum exhibited a peak for an ion m/z 126, corresponding to loss of a methylhydrazinyl group by the molecular ion. This proved that the isoxazoline form was present in the gas phase of the ionization chamber, this form having been created in the polar medium of the thioglycerol matrix. Such results enable us to state that after ionization, there are no processes of tautomeric isomerization that take place in the molecular ion, at least none that are significant. In this event, the observed mass spectrum is "an ionized imprint" of the tautomeric equilibrium that had been established in the gas phase before ionization.

Thus, chromatography/mass spectrometry has proved to be highly informative and sensitive as a method of investigation of both prototropic and ring–chain tautomeric systems, making it possible in a number of cases to detect in the gas phase, in the absence of any influence of solvents or other external media, new tautomeric forms that could not be observed in solutions.

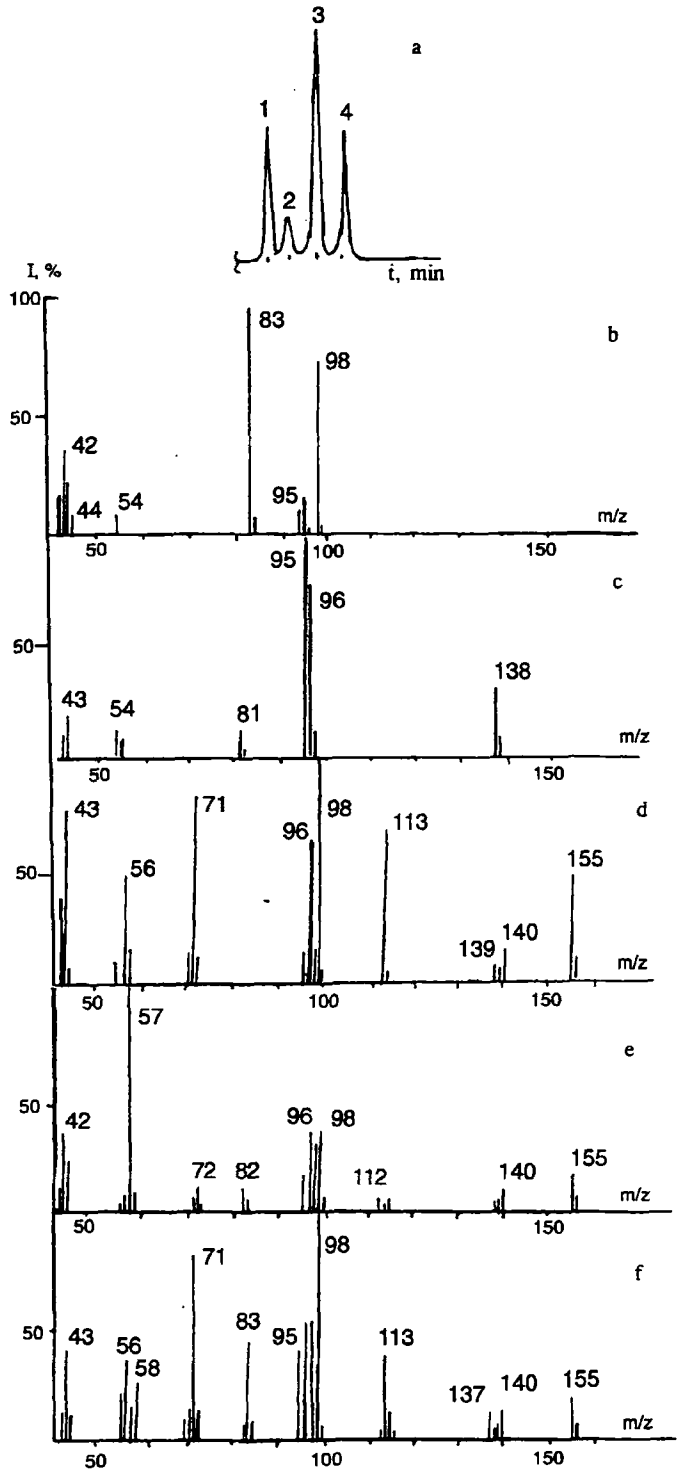


Fig. 3. Results of chromatographic/mass-spectrometric analysis of mixture of tautomers of compound **3**: *a*) Chromatogram of mixture; *b*) mass spectrum of tautomer E (peak *1*); *d*) mass spectrum of tautomer A (peak *3*); *e*) mass spectrum of tautomer B (peak *4*); *f*) mass spectrum of compound **3**, taken by direct introduction method.*

*No information is given in the Russian original on the "c" spectrum—Translator.

EXPERIMENTAL

All of the substances investigated in this work were synthesized at the Department of Organic Chemistry of the Military Medical Academy in St. Petersburg, by means of procedures given in [4, 13, 18, 19]. The chromatographic/mass-spectrometric studies were performed in Varian MAT-111 instruments with direct introduction of the substance into the ion source with an ionization energy of 80 eV, and also using gas-chromatography introduction (packed column with a length of 1.5 m, containing 15% SE-30 phase on Poropak), with the temperature programmed from 50° to 250°C at a rate of 10°C/min), and also in a Finnigan-4615 chromatograph/mass spectrometer with a capillary column, length 25 m, with liquid phase SE-54 and OV-101, with a programmed temperature rise. In this same instrument, mass spectra were obtained with chemical ionization (reagent gas ammonia). Mass spectra were taken in a Hitachi M-80 A instrument, using a Xe^+ ion bombarding beam with an energy of 5-10 keV (for this, we express our thanks to Candidate of Chemical Sciences V. L. Sadovskaya). The values of m/z (and relative intensity, %) for the ten most intense peaks are as follows: Compound **4**: 139(28), 116(3), 97(100), 96(4), 95(4), 74(20), 57(5), 56(12), 43(65), 41(17); compound **5**: 139(43), 138(31), 137(21), 123(100), 82(12), 67(10), 56(28), 55(17), 51(16), 42(43).

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