MASS-SPECTROMETRIC STUDY OF PHYSIOLOGICALLY ACTIVE β-THIOSEMICARBAZONES OF N-ALKYLISATINS

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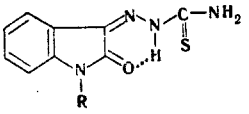
UDC 543.51+547.756

The molecular ions of isatin (I) and N-methyl- (II) and N-ethylisatin (III) β-thiosemicarbazones undergo fragmentation via many pathways with the elimination of NH_3, H_2S, CO, CH_2N_2, CHN_3, CH_2N_2S, CH_2NS, and CHNS particles; this is due to primary localization of the charge on the heteroatoms of the thiosemicarbazone residue. A previously unknown rearrangement, which consists in migration of an HS group to the β-carbon atom of the heteroring with subsequent ejection of a CHN_3 fragment. The $[M - CO]^+$ ions undergo fragmentation with the elimination of CH_2N_2S; in the case of II and III fragmentation is preceded by detachment of a hydrogen atom (II) or a methyl group (III) from the substituent attached to the ring nitrogen atom. The $[M - CO, -H, -CH_2NS]^+$ (II) and $[M - CO, -CH_3, -CH_2N_2S]^+$ (III) ions undergo fragmentation with the ejection of HCN in two ways through both the ring nitrogen atom and the thiosemicarbazone residue. Schemes for the principal pathways of fragmentation and rearrangements are presented. The compositions of the ions were confirmed by the high-resolution mass spectra and the mass spectra of the N-deuteroalkyl derivatives.

N-Alkylisatin β-thiosemicarbazones [1], among which substances with pronounced antivirus activity have been discovered [2], occupy a special place among the physiologically active isatin derivatives. The literature contains references to research devoted to the study of the mass spectrometric behavior of various isatin derivatives [3-8], but the dissociative ionization of compounds with the general formula A have not been studied. Since the β-thiosemicarbazones of lower homologs of N-alkylisatins display the greatest clinical effect against the smallpox virus [1], we investigated the behavior of the most active compounds (I-III) under the influence of electron impact by means of the mass spectra of the deutero derivatives (IV and V) and the high-resolution mass spectra (II and III).



A

I R = H; II R = CH_3; III R = C_2H_5.
IV R = CD_3; V R = CD_2CH_3

The molecular-ion peaks are the maximum peaks in the mass spectra of I-III. In contrast to isatins with different alkyl substituents attached to the nitrogen atom of the heteroring [5, 6], the fragmentation of the molecular ions of I-III proceeds via many pathways (see Scheme 1).

The region of high mass numbers contains low-intensity ion peaks that indicate the loss of an NH_3 molecule by the molecular ions ($M^+ \rightarrow a$). The detachment of an H_2S molecule ($M^+ \rightarrow b$) confirms the existence of the thiol form of the molecular ions. The mass spectra of I-III contains peaks that correspond to ejection of a CO molecule from the molecular ion ($M^+ \rightarrow c$); this is also characteristic for the previously investigated isatins [5, 6]. The relative intensity of the c ion peaks decreases regularly as the length of the alkyl chain increases. Low-intensity ion peaks formed as a result of the loss of a CH_2N_2 group by the molecular ions ($M^+ \rightarrow d$) are also observed in the mass spectra. The relative intensities of the peaks of these ions also decrease on passing from I to III. The detachment of a CH_2N_2 group may proceed via one of the following mechanisms (see Scheme 2), which are also characteristic for the thiosemicarbazones of alicyclic ketones [9].

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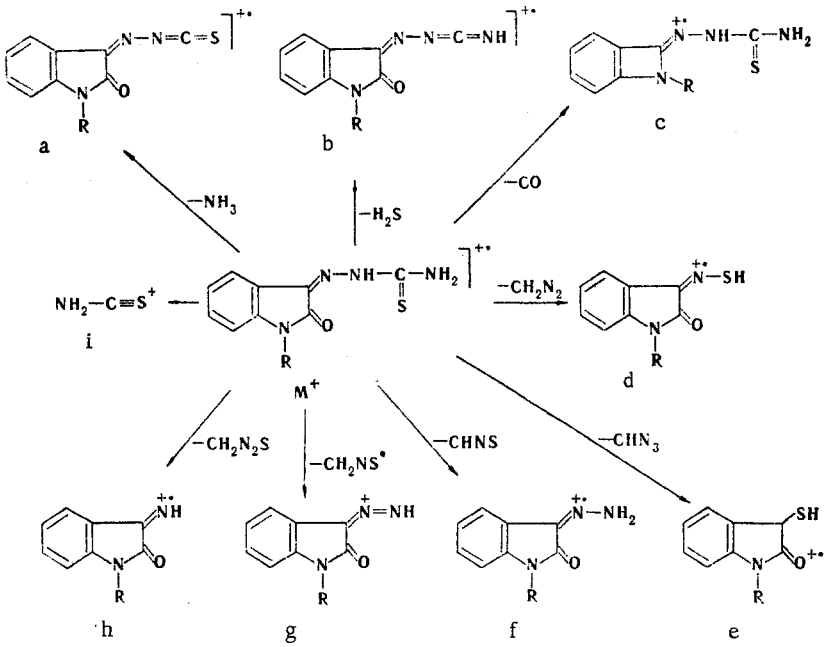
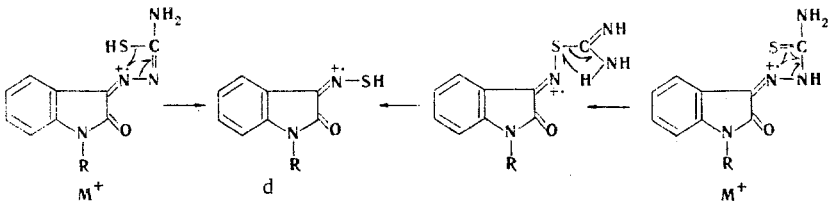
Scheme 1

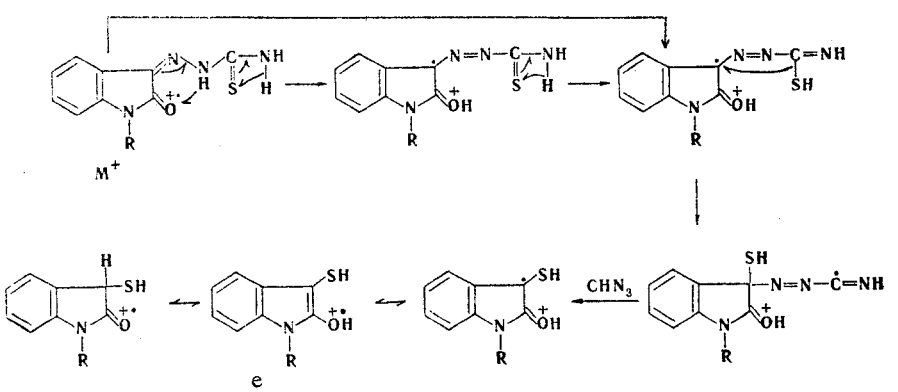


Scheme 2



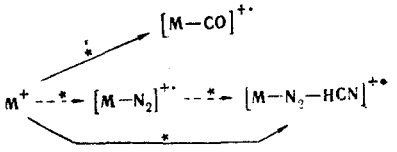
Of greatest interest are the peaks that correspond to the $[M - 55]^+$ fragment (e), the intensity of which increases as the length of the alkyl chain increases. It was established by means of the mass spectra of deutero derivatives IV and V that the atoms of the alkyl substituent attached to the nitrogen atom of the heteroring do not participate in the elimination of 55 amu. Ejection of a CHN_3 group by the molecular ions, which most likely proceeds as shown in Scheme 3, corresponds to the $[M - 55]^+$ ions in the high-resolution mass spectra; it is apparent from Scheme 3 that the formation of ion e may be realized as a result of a rearrangement of the McLafferty type with migration of a hydrogen atom to the sulfur atom, subsequent migration of an SH group to the radical center, and detachment of a CHN_3 group.

Scheme 3



The mass spectra of I-V contain metastable peaks that indicate the existence of $M^+ \rightarrow [M - 28]^+$, $M^+ \rightarrow [M - 55]^+$, and $[M - 28]^+ \rightarrow [M - 55]^+$ transitions. The elementary compositions of the starting and resulting ions determined by means of high-resolution mass spectrometer indicate ejection of a CO molecule (Scheme 4) in the first case and detachment of a CHN_3 fragment in the second case. The problem is more complex in the case of the metastable $[M - 28]^+ \rightarrow [M - 55]^{+\cdot}$ transition, since the parent ion with the composition $[M - CO]^+$ cannot be associated with the daughter ion with the composition $[M - CHN_3]^+$. The assumption that a two-step process with the preliminary loss of a nitrogen molecule, as shown by means of the dash line in Scheme 4, is also possible in addition to the direct ejection of a CHN_3 group is not confirmed by the high-resolution spectra.

Scheme 4



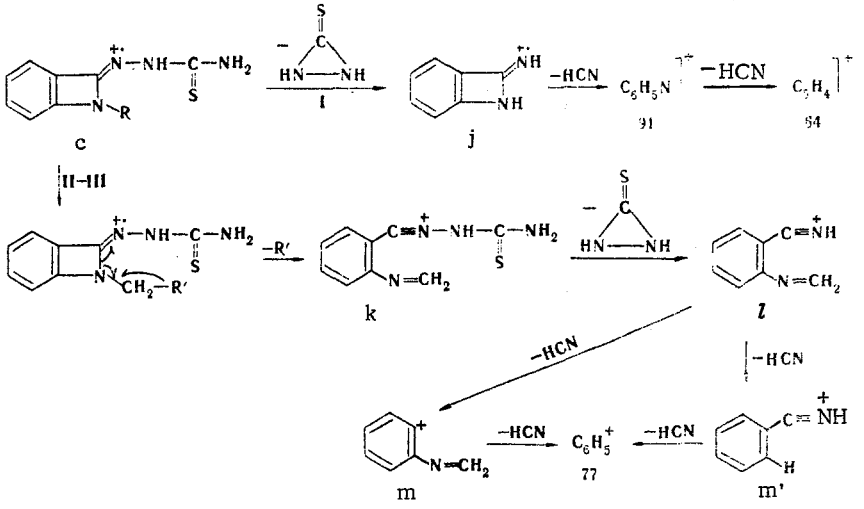
It should be noted that the fragmentation of the molecular ion, which is accompanied by elimination of a CHN_3 group, is not observed in the mass-spectrometric fragmentation of the thiosemicarbazones of aromatic aldehydes and ketones and alicyclic ketones [9]. Its occurrence in the case of the compounds that we studied is most likely associated with the peculiarities of their structures, viz., the existence of the syn form of A [10] and the possibility of charge localization on the oxygen atom.

The molecular ion also undergoes fragmentation with the elimination of 59 and 60 amu to give ions f and g (Scheme 1). Fragments with m/e* 60 ($M^+ \rightarrow$ i), the intensity of the peak of which is 20-30%, are formed in the case of localization of the charge on the sulfur atom. Finally, intense ion h peaks are formed as a result of cleavage of the N-N bond with migration of a hydrogen atom through a five-membered transition state ($M^+ \rightarrow$ h).

As we have already noted above, the elementary compositions of all of the ions presented above were established by means of the high-resolution mass spectra of II and III.

Rather intense peaks in the medium- and low-mass ranges of the m/e values are formed as a result of subsequent fragmentation of some of the ions presented above. Thus, for example, a CH_2N_2S group is detached from ion c in the case of I to give ion j (Scheme 5). Ions with m/e 91 and 64 are formed by subsequent ejection of two HCN molecules from ion j. In the case of II and III a hydrogen atom (II) or a methyl group (III, confirmed by the spectra of deutero derivatives IV and V) is lost after elimination of a CO molecule to give ion k (Scheme 5). The k ions lose a CH_2N_2S group to give l ions, which in turn lose two HCN molecules to give m or m' ions and an ion with m/e 77. The ejection of two HCN molecules pro-

Scheme 5



*Here and subsequently, the numbers that characterize the ion are the mass-to-charge ratios.

ceeds via two pathways, as shown in Scheme 5 ($l \rightarrow m$ and $l \rightarrow m'$); this was also confirmed by the mass spectra of the deutero derivatives, from which it is apparent that two peaks with m/e 106 (m) and 105 (m') in the mass spectra of IV and V correspond to the peaks with m/e 104 in the mass spectra of II and III.

In addition to the fragmentation pathways presented above, we also determined several others, which were confirmed by metastable peaks. These other pathways include:

in the mass spectrum of II

$$174\ (g) \longrightarrow 146\ [C_9H_8ON_3]^+ \longrightarrow [C_9H_8ON]^+;$$

$$160\ (h) \longrightarrow 132\ [C_9H_8ON_2]^+ \longrightarrow [C_8H_8N_2]^+;$$

$$118 \longrightarrow 91\ (C_8H_8N \longrightarrow C_7H_7);$$

in the mass spectrum of III

$$188\ (g) \longrightarrow 160 \longrightarrow 132\ [C_{10}H_{10}ON_3]^+ \longrightarrow [C_{10}H_{10}ON]^+ \longrightarrow [C_9H_{10}N]^+;$$

$$145 \longrightarrow 117 \longrightarrow 90\ [C_8H_7N_3]^+ \longrightarrow [C_8H_7N]^+ \longrightarrow [C_7H_6]^+$$

The peak with m/e 132 in the high-resolution spectrum of III is split into two peaks of approximately equal intensity, one of which corresponds to the elementary composition $C_9H_{10}N$, the other of which corresponds to the elementary composition C_8H_6ON. The ion with m/e 104 is a composite peak due to fragmentation via the pathways $l \rightarrow m$ (Scheme 5) and $[C_8H_6ON]^+ \rightarrow [C_7H_6N]^+$.

It is apparent from the data presented in this paper that, in contrast to the previously investigated isatins [3-8], the fragmentation of which is due to primary localization of the charge on the nitrogen atom of the heteroring, the fragmentation of the molecular ions of I-III is realized via many pathways and is due to primary localization of the charge on the heteroatoms of the thiosemicarbazone residue and the oxygen atom.

The investigations of series of higher N-alkyl homologs of isatin β-thiosemicarbazones from $C_{(3)}$ to $C_{(6)}$ showed that fragmentation is realized via a monotypic mechanism in conformity with the pathways presented in the schemes and is sufficiently characteristic to make it possible to use mass spectrometry for the identification of compounds of this class.

EXPERIMENTAL

β-Thiosemicarbazones I-III were obtained by the methods described in [1]; IV and V were obtained by similar methods. The mass spectra were recorded with an MKh-1303 spectrometer equipped with a glass system for direct introduction of the samples. The vaporization temperature in the tube was the minimum value of 85-105°C, the ionization-chamber temperature

TABLE 1. Mass Spectra of I-III

Compound	m/e values (relative intensities, %)
I	220 (100), 203 (1), 192 (92), 186 (4), 178 (6), 165 (4), 161 (16), 160 (8), 159 (6), 150 (12), 146 (20), 145 (7), 144 (31), 133 (15); 132 (32), 131 (10), 119 (7), 118 (38), 117 (10), 116 (10), 105 (11), 104 (41), 103 (12), 102 (7), 91 (14), 90 (16), 89 (6), 77 (24), 76 (25), 65 (12), 64 (12), 60 (28), 51 (16), 50 (12), 43 (24)
II	234 (100), 217 (1), 206 (25), 205 (8), 200 (9), 192 (2), 179 (29), 175 (17), 174 (10), 173 (11), 160 (28), 159 (7), 147 (15), 146 (56), 145 (14), 144 (8), 132 (22), 131 (44), 130 (9), 119 (9), 118 (37), 117 (39), 116 (12), 105 (7), 104 (19), 103 (11), 102 (12), 91 (39), 90 (21), 89 (14), 77 (28), 76 (24), 75 (16), 65 (12), 64 (8), 63 (11), 60 (23), 51 (19), 50 (13), 43 (53)
III	248 (100), 231 (1), 220 (12), 214 (3), 205 (21), 193 (25), 189 (8), 188 (7), 187 (3), 174 (13), 173 (2), 161 (6), 160 (33), 159 (4), 146 (14), 145 (32), 144 (13), 132 (22), 131 (21), 130 (8), 118 (6), 117 (21), 116 (4), 105 (3), 104 (9), 103 (7), 102 (10), 91 (15), 90 (10), 89 (6), 77 (13), 76 (11), 75 (8), 65 (5), 64 (3), 63 (5), 60 (17), 51 (7), 50 (3), 43 (12)

was 150°C, the ionizing voltage was 70 V, and the emission current was 1.0 mA. The high-resolution mass spectra were recorded with an MS-902 spectrometer. The mass spectra are presented in Table 1.

LITERATURE CITED

1. G. I. Zhungietu and M. A. Rekhter, Isatin and Its Derivatives [in Russian], Shtiintsa, Kishinev (1977), pp. 109, 131.
2. P. W. Sadler, Ann. New York Acad. Sci., 130, 71 (1965).
3. I. A. Ballantine, R. G. Fenwick, and M. Alam, Org. Mass Spectrom., 1, 467 (1968).
4. I. A. Ballantine, R. G. Fenwick, and F. D. Popp, Org. Mass. Spectrom., 5, 1003 (1971).
5. M. Butcher, Org. Mass Spectrom., 5, 759 (1971).
6. Kh. Sh. Khariton, G. I. Zhungietu, M. A. Rekhter, B. T. Oloi, and N. I. Chmykhova, Khim. Geterotsikl. Soedin., No. 7, 957 (1975).
7. G. I. Zhungietu, N. I. Chmykhova, M. A. Rekhter, Kh. Sh. Khariton, B. T. Oloi, and N. P. Dormidontova, Khim. Geterotsikl. Soedin., No. 5, 639 (1977).
8. G. I. Zhungietu, N. I. Chmykhova, V. I. Gorgos, M. A. Rekhter, and Kh. Sh. Khariton, Khim. Geterotsikl. Soedin., No. 5, 642 (1977).
9. I. M. Sheikh, A. M. Duffield, and C. Djerassi, Org. Mass Spectrom., 1, 633 (1968).
10. A. B. Tomchin, I. S. Ioffe, Yu. V. Lepp, and A. I. Kol'tsov, Zh. Org. Khim., 9, 1081 (1973).

SYNTHESIS OF 5-SUBSTITUTED 6-METHOXY-1,2,3,4-TETRAHYDRO-β-CARBOLIN-1-ONES

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The nitration and bromination of 6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one were studied. 5-Nitro and 5-bromo derivatives were obtained. 5-Acetyl-1,2,3,4-tetrahydrocarbolin-1-one oxime was obtained, and its Beckmann rearrangement was studied. The use of lithium aluminum hydride leads to reduction of the 5-acetyl group to give an alcohol group, whereas reduction of the acetyl group to an ethyl group occurs in the case of reduction with a palladium catalyst. Saponification of 5-substituted carbolin-1-ones with alcoholic alkali makes it possible to obtain 4-substituted tryptamines with a carbonyl group in the 2 position. The structures of the compounds were established by means of the PMR and mass spectra.

Studies of the electrophilic substitution reactions of 5-methoxyindole and its derivatives by a number of researchers [1-5] have shown that the direction of attack by the electrophilic reagent in this case is determined mainly by the methoxy group of the benzene ring in the para position relative to the indole nitrogen atom. Instead of the electrophilic substitution in the 3 position that is classical for other indoles, the new substituent enters the 6 position in 5-methoxyindole compounds.

In the opinion of Yudin, Kost, and co-workers [5], realization of the process in acidic media, in which indoles that are protonated at the pyrrole nitrogen atom undergo substitution, is decisive for this sort of reaction pathway. According to the data in [4], the introduction in the 2 position of 5-methoxyindoles of an additional alkoxycarbonyl group, which changes the electron density distribution and evidently the site of protonation of the molecule, has a substantial effect on the direction of electrophilic attack. Thus, for example, the bromination of 2-ethoxycarbonyl-5-methoxyindole in acidic media leads to the formation of a 4-bromo derivative rather than a 6-bromo derivative in high yield.

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