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MASS-SPECTROMETRIC STUDY OF 2- AND 4-THIOBARBITURIC ACID DERIVATIVES

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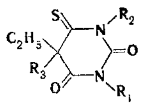
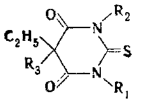
UDC 547.854.5'718:543.51:541.61.63

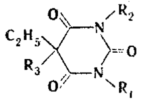
The mass spectra of 2- and 4-thiobarbituric acids and some of their close analogs at ionizing voltages of 70 and 14 eV are compared. Qualitative and quantitative differences in the behavior of these compounds under the influence of electron impact were established. It is shown that the position of the thione group in the ring and the tautomeric transformations have a substantial effect on the character of the fragmentation of the investigated compounds. The established fragmentation principles make it possible to distinguish the structural isomers in a series of 2- and 4-thiobarbituric acids from their mass spectra.

The mass spectra of barbituric acid derivatives have been studied by many investigators [1-7]. However, the peculiarities of the behavior of compounds of this class under the influence of electron impact have not been completely evaluated, inasmuch as the high-resolution spectra, the spectra at low ionizing-electron energies, and model analogs with isotopic and chemical labels have not been studied systematically in the early papers [1-3] and the later papers [6, 7].

In the present paper we present a comparison of the mass spectra of 2- and 4-thiobarbituric acids (I-X) and their close analogs (XI, XII) with the application of deuterium labeling, metastable ions, and data from high-resolution mass spectrometry and mass spectrometry with low-energy electrons. The mass spectra of 4-thiobarbituric acid derivatives I-VII were obtained for the first time. It should be noted that the spectra of VIII and X-XII also have practically not been discussed previously [1].


I-VII


VIII-X


XI-XII

I $R_1=R_2=H$; $R_3=C_2H_5$; II $R_1=R_2=D$; $R_3=C_2H_5$; III $R_1=R_2=H$; $R_3=C_3H_7$; IV $R_1=R_2=H$; $R_3=\begin{matrix}C_3H_7\\H_3C\end{matrix}\!\!>\!CH$; $V=R_1=H$; $R_2=CH_3$; $R_3=C_2H_5$; VI $R_1=CH_3$; $R_2=H$; $R_3=C_2H_5$; VII $R_1==R_2=H$; $R_3=C_6H_5$; VIII $R_1=R_2=H$; $R_3=C_2H_5$; IX $R_1=R_2=D$; $R_3=C_2H_5$; X $R_1=R_2=H$; $R_3=\begin{matrix}C_3H_7\\H_3C\end{matrix}\!\!>\!CH$; XI $R_1=R_2=H$; $R_3=C_6H_5$; XII $R_1=C_6H_5{-}CO$; $R_2=H$; $R_3=C_6H_5$

The behavior under electron impact of structural isomers I, VIII and IV, X can be compared with respect to the W_M* values and the relative intensities of the peaks of the characteristic fragments. The differences in the fragmentation under electron impact of I, VIII and IV, X are manifested primarily in the W_M values. We found that the W_M value for I is 5 at 70 eV and increases to 35 as the ionizing voltage is lowered to 14 eV. In the case of VIII this parameter under the same conditions is characterized by higher values of, respectively,

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* The W_M value is the relative stability of the molecule with respect to electron impact and is equal to $I[M^{+\cdot}]/\Sigma I$; $[M^{+\cdot}]$ is the intensity of the molecular ion peak, and ΣI is the total ion current.

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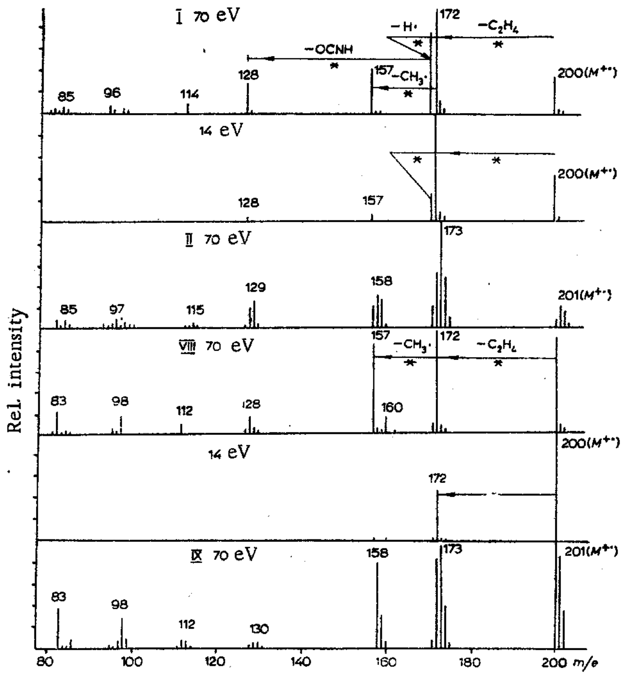

Fig. 1. Mass spectra of I, II, and VIII, IX at 70 and 14 eV.

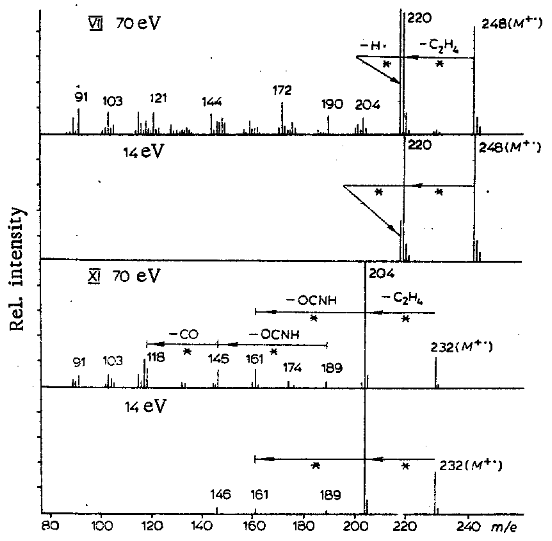

Fig. 2. Mass spectra of VII and XI at 70 and 14 eV.

15 (70 eV) and 70 (14 eV). An even sharper difference in the W_M values is observed for isomers IV and X, which have branched substituents [3 (70 eV) for IV and 0.07 (70 eV) for X]. Thus 4-thiobarbituric acid derivatives are less stable with respect to electron impact than the corresponding isomers with a thione group attached to C-2.

The primary fragmentation process of 5,5-diethyl derivatives of barbituric acid, as assumed in [1, 6], is manifested by olefinic fragmentation with splitting out of C_2H_4 from the molecular ion. A study of the high-resolution mass spectra of I and VIII shows that the formation of ions with m/e 172 in the spectra of I and VIII is actually due, on the whole, to splitting out of C_2H_4. We also observe that the peak with m/e 172 in the spectrum of I is of maximum intensity at 70 and 14 eV, whereas the intensity of the peak with m/e 172 is only 50% for VIII at 14 eV. In the spectrum of I at 70 and 14 eV one subsequently observes an intense ion peak with m/e 171, the formation of which may be realized from the fragment with m/e 172 by loss of a hydrogen atom. This process is confirmed by the presence of a metastable ion (m* =170) in the spectrum of I at 70 and 14 eV.

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*The m/e values are presented in parentheses.

TABLE 1. , Mass Spectra of III-VI, X, and XII* at 70 eV

Compound	Mass spectra
III	39 (12), 41 (45), 42 (6), 43 (12), 44 (13), 55 (22), 69 (13), 70 (6), 96 (8), 97 (7), 114 (15), 157 (90), 171 (7), 187 (60), 186 (100), 187 (9), 214 (0,7)
IV	39 (20), 41 (44), 55 (36), 56 (6), 69 (14), 70 (8), 82 (10), 85 (4), 86 (6), 97 (8), 98 (5), 113 (4), 114 (12), 128 (10), 139 (4), 141 (6), 142 (3), 156 (6), 157 (62), 158 (10), 170 (8), 171 (46), 172 (100), 213 (18), 242 (3), 243 (0,5)
V	39 (6), 41 (12), 42 (8), 55 (6), 69 (10), 70 (4), 82 (8), 83 (4), 84 (3), 85 (6). 110 (7), 114 (5), 128 (10), 130 (5), 142 (20), 171 (70), 172 (5), 185 (44), 186 (100), 187 (12), 188 (7), 214 (44), 215 (6)
VI	39 (28), 41 (48). 42 (8), 55 (16), 69 (21), 70 (7), 82 (4), 83 (4), 84 (4), 85 (7), 96 (20), 97 (4), 114 (18), 128 (54), 142 (5), 171 (60), 172 (6), 185 (64), 186 (100), 187 (14), 188 (4), 214 (30), 215 (6)
X	41 (31), 43 (50), 55 (14), 69 (17), 97 (12), 98 (8), 129 (5), 157 (66), 171 (5), 172 (100), 173 (54), 174 (10), 213 (4), 242 (21), 243 (3)
XII	51 (5), 77 (26), 78 (3), 103 (4), 104 (2), 105 (100), 106 (8), 114 (2). 117 (7), 146 (25), 147 (3), 204 (2), 232 (2), 309 (2), 336 (5), 337 (1)

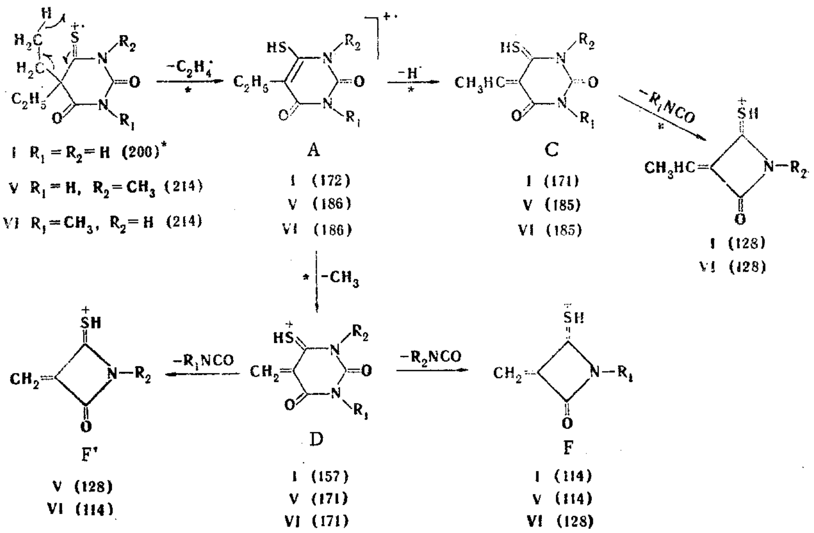
*The mass numbers of the fragments, the relative intensities (in parentheses) of which exceed 2%, are presented.

The fact that a fragment with m/e 171 is absent at high and low ionizing voltages in the fragmentation of VIII is important.

The formation of an ion with m/e 171 in the fragmentation of I might have been conceived of as simple detachment of the $C_2H_5^{\cdot}$ radical directly from $M^{+\cdot}$. However, the metastable ion corresponding to the process $M^{+\cdot} - C_2H_5^{\cdot}$ is not observed in the spectrum of I. In addition, in this case it is difficult to explain the absence of a similar process in the fragmentation of VIII. A choice between the probable processes for the formation of m/e 171 can be made from a comparison of the spectra of I and VIII.

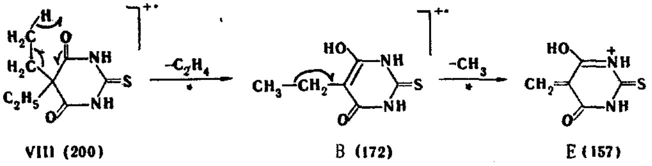
The splitting out of C_2H_4 from the molecular ions of I and VIII is realized from the ethyl groups with migration of a hydrogen atom to the charged fragment. The anomalous dependence of the intensity of the peak with m/e 172 on the magnitude of the ionizing voltage and the presence of a peak with m/e 171 only in the spectrum of I indicate that the mechanisms of the $M^{+\cdot} - C_2H_4$ rearrangement process should be different in the fragmentation of I and VIII.

Scheme 1



It is known that barbituric acid derivatives in solution are capable of tautomeric transformations. As previously assumed in [1], this feature may be expressed to an even greater degree in the gas phase, especially during excitation by electron impact. Data on the fragmentation of 4-aminouracils, for example, also provide evidence for this. On the basis of everything stated above, we proposed the most probable mechanisms of fragmentation of 2- and 4-thiobarbituric acid derivatives I and VIII:

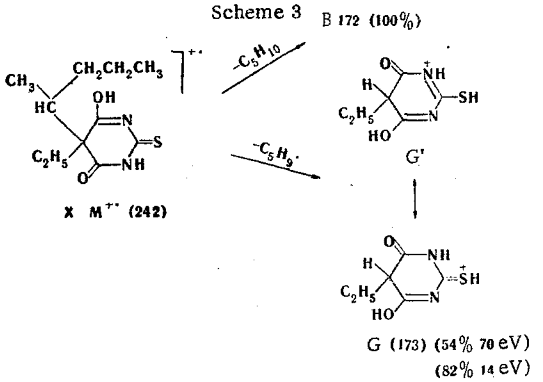
Scheme 2



It follows from an examination of the above scheme that the differences in the fragmentation of I and VIII are due, on the one hand, to tautomeric transformations, with which the probability of localization of the charge on the various atoms of the rings of I and VIII is evidently linked, and, on the other hand, to migrations of hydrogen atoms to six- and four-membered transition states with the formation of ions A and B. In fact, the subsequent fragmentation of fragment A to give ions with m/e 171 (C) and 157 (D) is represented as the result of two possible stabilizations of the radical center at C-5 with splitting out of a hydrogen atom and a methyl group. The absence of this center in fragment B (for VIII) leads to splitting out of only CH_3, which is accomplished with an energically favorable rearrangement of the structure and the formation of fragment E with conjugated bonds. It is interesting to note that the intensity of the peak with m/e 157 in the spectrum of VIII is higher than the intensity observed for ion D (for I). The fragmentation processes for I and VIII presented in the scheme correspond to deuterium redistribution in the fragmentation of II and IX, and the elementary composition of ions A-E is confirmed by the high-resolution mass spectrum. The first act in the fragmentation of III is detachment of C_2H_4. The effect of the propyl group is manifested by splitting out from the molecular ion of an ethyl radical to give a fragment of the D type with m/e 157. As in the case of I, IV, and V, the fragmentation of III is characterized by an intense $(M^{+\cdot} - C_2H_4) - H\cdot$ process.

The ion peak with m/e 172 $(M^{+\cdot} - C_5H_{10})^{+\cdot}$ for IV and X is the principal peak in the spectrum at 70 and 14 eV. On the other hand, the $(M^{+\cdot} - C_2H_4)^{+\cdot}$ fragment typical for I and VIII is characterized by an extremely low intensity. Consequently, loss of the more branched group attached to C-5 is preferable in the fragmentation of 5,5-dialkyl derivatives of 2- and 4-thiobarbituric acids. The $(M^{+\cdot} - C_5H_{10} - H\cdot)^+$ ion peak is observed only in the spectrum of IV. A distinctive feature of the fragmentation of X is manifested in turn by the presence in the spectrum of an ion with m/e 173, the formation of which can be represented by the scheme

Scheme 3

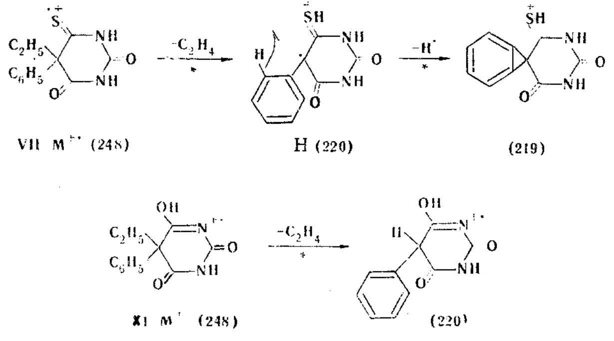


It should evidently be assumed that the formation of the ion with m/e 173, to which structures G and G' can be assigned, is due to the presence of an alkyl substituent with a long chain. In this case there are necessary conditions for the migration of yet another hydrogen atom to the remote ion-radical center at CS-2 or N-3.

From an examination of the scheme one should expect that substituents in the N-1 and N-3 positions will also affect the character of the fragmentation of thiobarbituric acid derivatives. The stabilities of structural isomers V and VI with respect to electron impact are practically identical ($W_M = 9\%$). As in the case of I, intense $M^{+\cdot} - C_2H_4$, $M^{+\cdot} - C_2H_4 - H\cdot$, and $M^{+\cdot} - C_2H_4 - CH_3\cdot$ processes are characteristic for V and VI. The mass spectra of V and VI differ only with respect to the intensities of the peaks with m/e 128 (ions F and F' in scheme 1), which are characterized by values of, respectively, 54% (V) and 10% (VI). The formation of fragments with m/e 128 in the fragmentation of V and VI is associated with cleavage in the ring of, respectively, the 4-CS=NH or 6-CO=NH bonds with splitting out of NHCO. Hence one should assume that the first of these bonds is more labile with respect to electron impact than the second bond.

From the point of view of the peculiarities of the fragmentation of 4-thiobarbituric acid derivatives, it seems of interest to compare the mass spectra of VII, XI, and XII. As in the case of the fragmentation of I and VIII, the $(M^{+\cdot} - C_2H_4 - H)^+$ ion peak is observed only in the spectrum of VII. Moreover, splitting out of a hydrogen atom from the ion with m/e 220 is accompanied by the appearance of an intense peak of a metastable ion (m^* =218). On the basis of an analysis of the spectra of I, VIII and IV, X, the fragmentation of VII and XI can be represented by the scheme

Scheme 4



The detachment of a hydrogen atom from the ortho position of the phenyl (ion H, scheme 4) and other aromatic rings is also an intensive process in the fragmentation of some other classes of compounds [9, 10]. In the spectrum of VII at 70 eV the ion peak with m/e 219 is of maximum intensity.

In contrast to the fragmentation of XI, the fragmentation of XII at 70 and 14 eV is realized with the primary formation of a benzoylium ion with m/e 105. The stability of VII with respect to electron impact is much higher (W_M=10%) than that of I, and this may be explained by the stabilizing properties of the phenyl ring attached to the C-5 radical center. The stability to electron impact of XI is characterized by W_M=5%. One's attention should be directed to the fact that in the spectrum of XI at 70 and 14 eV the relative intensities of the $M^{+\cdot}$ and $(M^{+\cdot}-C_2H_4)$ peaks, as well as their ratios, remain practically constant. This anomalous behavior of XI under the influence of electron impact and the low W_M value of this compound as compared with VII can be explained by, for example, fragmentation from the isolated electronic state of the molecular ion [11, 12].

Thus qualitative and quantitative differences in the behavior of 2- and 4-thiobarbituric acids under the influence of electron impact have been found in the present research. The observed fragmentation principles can be used for the establishment of the structures of other compounds similar to I-XII or their metabolic products.

EXPERIMENTAL METHOD

Compounds IX and X were obtained by the methods in [13, 14].* Deuterium analogs II and VIII were obtained by dissolving I and VII in CD_3OD. The mass spectra of I-XII were recorded with an LKB-9000 mass spectrometer at ionizing voltages of 70 and 14 eV, an emission current of 20 uA, and an ion-source temperature of 250°. The temperature of admission of the substances into the ion source was 20-50°. The high-resolution spectra were recorded with a JMS-01-SG-2 spectrometer with an automatic system for processing of the information.

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*The synthesis of I and III-VII will be published separately.

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REACTION OF SUBSTITUTED 5-AMINOPYRIMIDINES WITH OXALYL CHLORIDE

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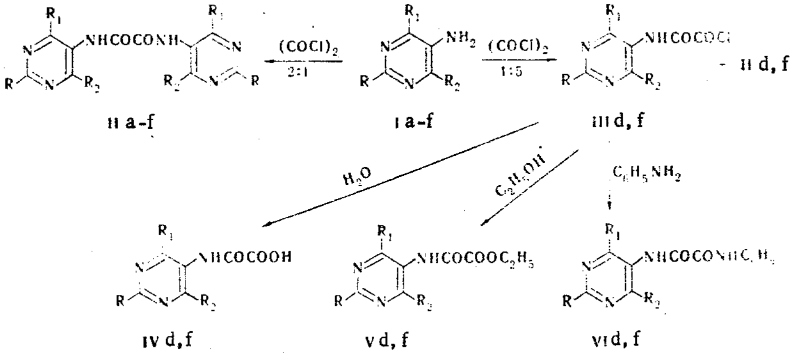
UDC 547.853.7'461.2

Depending on the reaction conditions and the substituents, N-(2,4,6-substituted 5-pyrimidinyl)oxamyl chlorides and N,N'-di(2,4,6-substituted 5-pyrimidinyl)oxamides are formed in the reaction of 5-aminopyrimidines with oxalyl chloride.

Pyrimidinyl isocyanates have been obtained as a result of the reaction of oxalyl chloride with 2- and 4-aminopyrimidines [1, 2]. It is known that the reactions of amino groups with oxalyl chloride proceed in different ways as a function of the basicities of the amino groups. In the present research we have studied the reaction of oxalyl chloride with 5-aminopyrimidines (I). Inasmuch as the amino groups attached to C-5 have higher basicities than the amino groups in the 2 and 4 positions, one might have expected the production of stable 5-pyrimidinyloxamyl chlorides (III).



a $R=R_1=R_2=H$; b $R=CH_3$, $R_1=R_2=H$; c $R=C_6H_5$, $R_1=R_2=H$; d $R=H$, $R_1=R_2=Cl$;
e $R=CH_3$, $R_1=R_2=Cl$; f $R=C_6H_5$, $R=R_2=Cl$

N,N'-Di(5-pyrimidinyl)oxamides (II) or N-(5-pyrimidinyl)oxamyl chlorides (III) mixed with II were obtained under conditions close to those described in [1, 2] with 1 equivalent or with excess oxalyl chloride, respectively. Compounds Id, f with two chlorine atoms adjacent to the amino group form primarily acid chlorides IIId, f (70%) and oxamides IId, f in 25% yields, in contrast to amine Ic, which gives primarily oxamide IIc (80%). The structure of IIId, f was proved by hydrolysis, alcoholysis, and aminolysis to give, respectively, N-(5-pyrimidinyl)oxamic acids (IVd, f), oxamic acid esters (Vd, f), and N,N'-substituted oxamides (VId, f). In addition, N,N'-di(5-pyrimidinyl)oxamide IId, identical to the compound obtained by reaction of Id with one equivalent of oxalyl chloride, was obtained from acid chloride IIId and starting amine Id.

Two absorption bands at 3200-3500 cm^{-1} (NH_2 group) are observed in the IR spectra of starting aminopyrimidines Ia-f, whereas the spectra of the reaction products contain only one such absorption band (NH group) and an absorption band at 1720-1780 cm^{-1} (C=O group).

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