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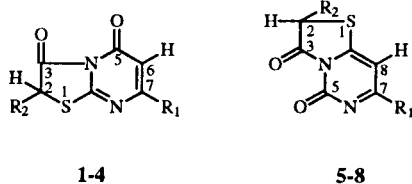
The mass spectral fragmentation of eight new 3-oxothiazolo[3,2-*a*] and [3,2-*c*]pyrimidin-5-ones were investigated. Fragmentation pathways are proposed on the basis of accurate mass and metastable transition measurements. The correlation between the intensities of $M^{+\cdot}$ and the selected fragment ions of these compounds is discussed. The data obtained created the basis for distinguishing isomers and metamers.

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Introduction.

We have previously found that the esters of halocarboxylic acids may be used as reagents for the chemical modification of the thio analogs of the pyrimidine bases [1-3]. The syntheses of thiazolo[3,2-*a*] [3,2-*c*] and [4,5-*d*]pyrimidinones have been reported by a number of workers [4-10], as well as thiazolopyrimidinones with a carbonyl function in the thiazole ring [11,12]. Many compounds of this group have exhibited interesting biological properties as inhibitors of cyclic AMP phosphodiesterase [4,5], or as inotropic antiinflammatory and antidopaminergic agents [13].

In continuation of our research on the spectral analysis of products which have been obtained in these reactions [1-3,14], this paper deals with the mass fragmentation of 3-oxothiazolo[3,2-*a*]pyrimidin-5-ones **1-4** and 3-oxothiazolo[3,2-*c*]pyrimidin-5-ones **5-8**, Figure 1.



- 1,5** $R_1 = H; R_2 = H$
2,6 $R_1 = H; R_2 = CH_3$
3,7 $R_1 = CH_3; R_2 = H$
4,8 $R_1 = CH_3; R_2 = CH_3$

Figure 1. Structures of 3-oxothiazolo[3,2-*a*] and [3,2-*c*]pyrimidin-5-ones.

Mass spectrometry has been used for the identification of isomers having carbonyl groups in position 7 (or 5) of the pyrimidine ring [15,16]. Direct distinction between the thiazolo[3,2-*a*] and [3,2-*c*]pyrimidinones containing carbonyl groups on the thiazole ring has not been reported in the literature.

The correlation between the structures and the intensities of the $M^{+\cdot}$ and the selected fragment ions of 2-alkyl-

thiouracils [17], benzylthiouracils [18] as well as *N*-substituted amino acids and their derivatives [19] has been studied in our laboratory. In continuation of these studies, it would be of interest to determine whether it is possible to establish the structure of a thiazolopyrimidinone, *i.e.* the position of thiazole ring on the thiazolopyrimidine skeleton, on the basis of the differences in the values of μ (*i.e.* the ratio of intensity of the selected ions peaks to that of the molecular ion peak).

Results and Discussion.

Since the first publication, mass spectrometry has been one of the most important techniques in the investigation of thio analogues of pyrimidine bases [20-23]. The mass spectral fragmentation of 2- and 4-alkylthiouracils [17,24-26] as well as 2- and 4-alkoxycarbonylalkylthiouracils [1-2] have been a research subject in our laboratory. In the first step of the mass fragmentation of the molecular ions of 2- and 4-alkoxycarbonylalkylthiouracils [1,2], the odd-electron fragment ions $[M^{+\cdot} - R_2OH]$ have been obtained (Figure 2). These ions have the structure of the molecular ions of a thiazolopyrimidinone which are reported in the present study. In the series of 2- and 4-alkoxycarbonylalkylthiouracils [1,2] the mass fragmentation of $[M^{+\cdot} - R_2OH]$ ions has not been observed.

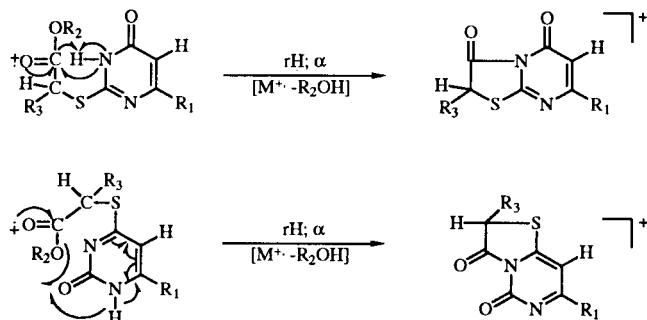


Figure 2. Fragmentation of $[M^{+\cdot} - R_2OH]$ in the series of 2 and 4-alkoxy-carbonylalkylthiouracils [12].

Table 1
Elemental Compositions and Relative Intensities of the Ion Peaks in the Spectra of 1-8 According to High Resolution Data

Ion	m/z	Elemental Composition	Relative Intensity							
			1	2	3	4	5	6	7	8
M ⁺	168	C ₆ H ₄ N ₂ O ₂ S	100	—	—	—	3	—	—	—
a	182	C ₇ H ₆ N ₂ O ₂ S	—	100	100	—	—	5	4	—
	196	C ₈ H ₈ N ₂ O ₂ S	—	—	—	100	—	—	—	6
b	128	C ₄ H ₄ N ₂ OS	6	8	—	—	25	34	—	—
	142	C ₅ H ₆ N ₂ OS	—	—	10	23	—	—	15	18
c	95	C ₄ H ₃ N ₂ O	50	73	—	—	3	6	—	—
	109	C ₅ H ₄ N ₂ O	—	—	59	67	—	—	16	20
d	69	C ₃ H ₃ NO	40	10	—	—	8	10	—	—
	83	C ₄ H ₅ NO	—	—	31	23	—	—	5	10
e	140	C ₅ H ₄ N ₂ OS	30	—	—	—	16	—	—	—
	154	C ₆ H ₆ N ₂ OS	—	18	72	—	—	11	3	—
f	168	C ₇ H ₈ N ₂ OS	—	—	—	12	—	—	—	8
	112	C ₄ H ₄ N ₂ S	54	—	—	—	17	—	—	—
	126	C ₅ H ₆ N ₂ S	—	11	10	—	—	9	7	—
	140	C ₆ H ₈ N ₂ S	—	—	—	14	—	—	—	9
g	47	CH ₃ S	52	2	26	2	98	97	99	98
h	45	CHS	52	25	30	45	100	100	100	100

Based on metastable transitions and exact mass determinations the principal mass fragmentations routes of compounds 1-8 are interpreted as shown in Scheme 1. The main mass fragmentation pathways of 3-oxothiazolo[3,2-*a*]pyrimidin-5-ones 1-4 are similar to those of the analogous [3,2-*c*] series, 5-8. The molecular ions of 1-4 however, have 100% of the relative intensities (Table 1). Molecular ions of 5-8 have only 3% 5, 5% 6, 4% 7, and 6% 8 relative intensity (Table 1). The cleavages of the molecular ions of 1-8 deal with the destruction of the bonds of the thiazole ring. The driving force of these destructions is connected with the lower ionization energy (IE) of the fragment ions having in the skeleton pyrimidine ring (Stevenson's Rule [27]).

The first mass fragmentation pathways of the molecular ions of 1-8 are cleavages of the two bonds of the thiazole ring, as well as elimination of neutral fragments of C₂O, 1, 3, 5, and 7, or C₃H₂O, 2, 4, 6, and 8, (Figure 3, Scheme 1). The odd-electron fragment ions **b** have been obtained by this route of mass fragmentation. It is possible, that the decomposition of the thiazole ring is a two-step (noncon-

certed) process [28,29]. The first step is α -cleavage (homolytic dissociation) of the C_{sp2}-N bond and rearrangement of one of the hydrogen atoms to N-3 of the pyrimidine ring, 1-8. This process gives the stable open-ring intermediate ("distonic" radical ion). The second step of this fragmentation is α -cleavage of the C_{sp3}-S bond with simultaneous rearrangement of the second hydrogen atom to the S-2, 1-4 or S-4, 5-8 of the pyrimidine ring (Figure 3). The odd-electron fragment ions **b** lost in the second steps of mass fragmentation *SH radicals (IE = 10.4 eV, Stevenson's Rule [27]). These sigma-bonds dissociations (σ) of the S-C_{sp2} are probably similar to those which have been previously observed in the mass fragmentation processes of the secondary and aromatic thiols [30]. The even-electron fragment ion **c** has been obtained in this way of mass decomposition. In the third step of the mass fragmentation inductive cleavages (i) of the two C_{sp2}-N bonds of the pyrimidine ring with simultaneous eliminations of the *CN radicals give even-electron fragment ions **d**. The ejection of the *CN radicals from even-electron fragment ions **c** is favored because the *CN has

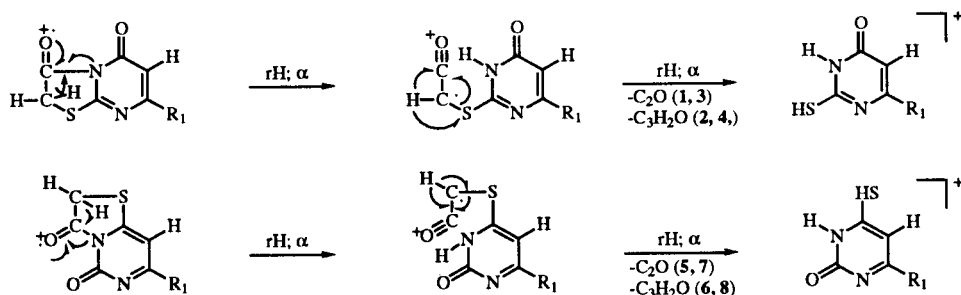


Figure 3. Fragmentation of [M⁺ - C₃H₂O] 2,4,6,8 ions.

Table 2

The Values of μ_1 - μ_3 Calculated from the EI Spectra Recorded at 75 eV of 3-oxo-5*H*-thiazolo[3,2-*a*] and [3,2-*c*]pyrimidin-5-ones 1-8

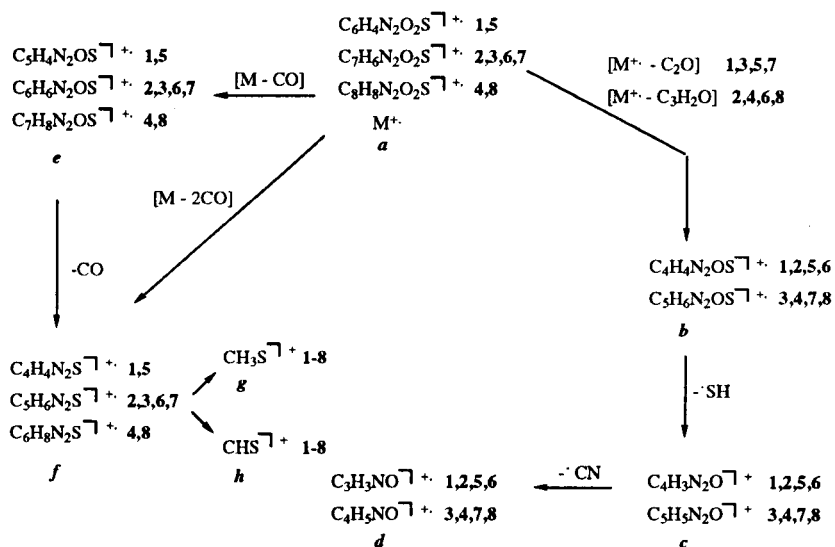
Compound	R	$\mu_1 = \text{int.}[\text{M}-\text{C}_2\text{O}]^+ / \text{int.} \text{M}^+;$ $\mu_1 = \text{int.}[\text{M}-\text{C}_3\text{H}_2\text{O}]^+ / \text{int.} \text{M}^+;$ $\mu_2 = \text{int.}[\text{M}-\text{CO}]^+ / \text{int.} \text{M}^+;$ $\mu_3 = \text{int.} [\text{M}-2\text{CO}]^+ / \text{int.} \text{M}^+;$			Compound	R	$\mu_1 = \text{int.} \text{b}^{\cdot+} / \text{int.} \text{a}^{\cdot+} \quad 1, 3, 5, 7$ $\mu_1 = \text{int.} \text{b}^{\cdot+} / \text{int.} \text{a}^{\cdot+} \quad 2, 4, 6, 8$ $\mu_2 = \text{int.} \text{e}^{\cdot+} / \text{int.} \text{a}^{\cdot+} \quad 1-8$ $\mu_3 = \text{int.} \text{f}^{\cdot+} / \text{int.} \text{a}^{\cdot+} \quad 1-8$		
		μ_1	μ_2	μ_3			μ_1	μ_2	μ_3
1	R ₁ = H, R ₂ = H	0.1	0.3	0.5	5	R ₁ = H, R ₂ = H	8.3	5.3	5.7
2	R ₁ = H, R ₂ = CH ₃	0.1	0.2	0.1	6	R ₁ = H, R ₂ = CH ₃	6.8	2.2	1.8
3	R ₁ = CH ₃ , R ₂ = H	0.1	0.7	0.1	7	R ₁ = CH ₃ , R ₂ = H	3.8	0.8	1.8
4	R ₁ = CH ₃ , R ₂ = CH ₃	0.2	0.1	0.1	8	R ₁ = CH ₃ , R ₂ = CH ₃	3.0	1.3	1.5

high ionization energy (IE = 14.1 eV), but low proton affinity (PA = 5.4 eV, Field's Rule [31]). The even-electron fragment ions *c* are of 50-73% relative intensity in the series of thiazolo[3,2*a*]pyrimidin-5-ones 1-4 and 3-20% relative intensity in the series of thiazolo[3,2-*c*]pyrimidin-5-ones 5-8.

The second route of mass decomposition of the molecular ions of 1-8 are the successive ejections of two neutral molecules of carbon monoxide. In these routes of mass fragmentation, odd-electron fragment ions *e* and *f* are obtained. According to the Stevenson's Rule [27] the first molecule of carbon monoxide is probably ejected from the thiazole ring. This ejection is connected with inductive cleavage (*i*) and homolytic dissociation α of the two bonds, N-C_{sp3}; C_{sp3}-C_{sp2} 1-8. The ejection of the mole-

cules of carbon monoxide follows probably according to the mechanism of elimination of CO from the molecular ion of cyclohexanone [30] (Figure 4). The odd-electron fragment ions *f* have also been obtained by the third route of the fragmentation, *i.e.* simultaneous (or subsequent) ejections from the molecular ions of two neutral molecules of carbon monoxide. The fragment ions *f* decompose further by two possible pathways creating two characteristic even-electron fragment ions *h* (CHS⁺) and *g* (CH₃S⁺). The peaks of ions *h* are the base peaks in mass spectra of 5-8. Even-electron fragment ions *g* are of 2-26% relative intensity in the series of 1-4 and 97-99% relative intensity in the series of 5-8 (Table 1, Scheme 1). These routes of the mass decomposition of the ions *f* are similar to those observed in thiophenes [30] and in the

Scheme 1



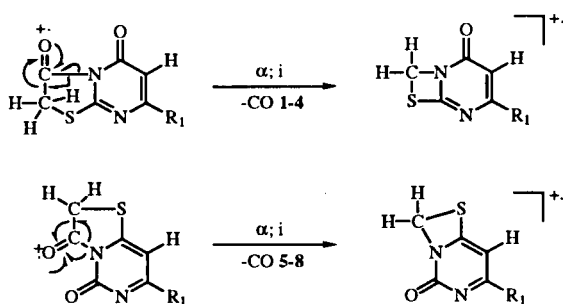


Figure 4. Fragmentation of $[M^+ - CO]$ ions of 1-8.

cases of thiazolopyrimidines without the carbonyl function in the thiazole ring [16,32-34].

In Table 2 are presented the measured values of μ_1 - μ_3 *i.e.* of intensity of the **b**, **e**, **f** ion peaks to that of the parent ion peak for all investigated compounds 1-8. The correlation between the relative intensity of the selected fragment ions **b**, **e**, **f** and M^+ **a** ions peaks *i.e.* the values of μ_1 - μ_3 and structure of the thiazolo[3,2-*a*] and [3,2-*c*]pyrimidin-5-ones is considered below. The regularities resulting from Table 2 can be classified as follows: (i) In the series of 3-oxothiazolo[3,2-*a*]pyrimidin-5-ones 1-4 and 3-oxothiazolo[3,2-*c*]pyrimidin-5-ones 5-8 the values of μ_1 - μ_3 are listed below:

$\mu_1; \mu_2; \mu_3$ 5-8	>	$\mu_1; \mu_2; \mu_3$ 1-4
μ_1 3.0-8.3		μ_1 0.1-0.2
μ_2 0.8-5.3		μ_2 0.1-0.7
μ_3 1.5-5.7		μ_3 0.1-0.5

(ii) In the series metameric 3-oxothiazolo[3,2-*a*]pyrimidin-5-ones 2-3 having elemental composition of $C_7H_6N_2O_2S$ the value of μ_2 is as follows:

μ_2 3	>	μ_2 2
$R_1 = CH_3; R_2 = H$		$R_1 = H; R_2 = CH_3$
0.7	>	0.2

(iii) In the series of metameric 3-oxothiazolo[3,2-*c*]pyrimidin-5-ones 6,7 having elemental composition of $C_7H_6N_2O_2S$ the values of μ_1 and μ_2 are as follows:

μ_1 6	>	μ_1 7
$R_1 = H; R_2 = CH_3$		$R_1 = CH_3; R_2 = H$
6.8	>	3.8
μ_2 6	>	μ_2 7
$R_1 = H; R_2 = CH_3$		$R_1 = CH_3; R_2 = H$
2.2	>	0.8

It should be mentioned that the presence of a methyl group on the thiazole ring as well as on the pyrimidine ring of the thiazolopyrimidinone skeleton has a strong influence on the values of calculated μ_1 - μ_3 . This influence is seen in the ranges of μ_1 - μ_3 listed below:

(i) In the series of 1-4

μ_1 4	>	μ_1 3	>	μ_1 2	>	μ_1 1
$R_1 = R_2 = CH_3$		$R_1 = CH_3; R_2 = H$		$R_1 = H; R_2 = CH_3$		$R_1 = R_2 = H$
		μ_2 1 and μ_2 3	>	μ_2 4 and μ_2 2		
		$R_2 = H$		$R_2 = CH_3$		
		0.3; 0.7	>	0.1; 0.2		
		μ_3 1	>	μ_3 2-4		
		$R_1 = R_2 = H$				
		0.5	>	0.1		

(ii) In the series of 5-8

μ_1 5	>	μ_1 6	>	μ_1 7	>	μ_1 8
$R_1 = R_2 = H$		$R_1 = H; R_2 = CH_3$		$R_1 = CH_3; R_2 = H$		$R_1 = R_2 = CH_3$
8.3	>	6.8	>	3.8	>	3.0
		μ_2 5 and μ_2 6	>	μ_2 7 and μ_2 8		
		$R_1 = H$		$R_2 = CH_3$		
		5.3; 2.2	>	0.8; 1.3		
		μ_3 5	>	μ_3 6-8		$R_1 = R_2 = H$
		5.7	>	1.5 - 0.8		

Conclusions.

1. The basic mass fragmentation of compounds 1-8 is due to cleavage of the S- C_{sp3} , C_{sp2} -N and C_{sp2} -N, C_{sp2} - C_{sp3} bonds of the thiazole ring.

2. The position of the thiazole ring in the thiazolopyrimidinone skeleton may be deduced on the basis of the presence and the intensity of the molecular and analytical fragment ions **a**, **c**, **g** and **h** (Table 1).

3. The values of μ_1 - μ_3 (*i.e.* the ratio of the intensities of the selected fragment ions to that of the molecular ions M^+) depend on the structure of thiazolopyrimidinone and are higher in the series of 3-oxothiazolo[3,2-*c*]pyrimidin-5-ones 5-8 than in the series of 3-oxothiazolo[3,2-*a*]pyrimidin-5-ones 1-4.

4. In the series of 3-oxothiazolo[3,2-*a*]pyrimidin-5-ones 1-4, compound 3 bearing the methyl substituent on the pyrimidine ring has the higher value of μ_2 than its metamer 2 bearing the methyl group on the thiazole ring.

5. In the series of 3-oxothiazolo[3,2-*c*]pyrimidin-5-ones 5-8 compound 6 bearing the methyl group on the thiazole ring has higher values of μ_1 and μ_2 than its metamer 7 bearing the methyl group on the pyrimidine ring.

EXPERIMENTAL

Low and high resolution mass spectra were recorded on a Jeol JMS-D-100 mass spectrometer linked to a Texas Instruments 980B computer (ionizing voltage 75 eV, ionizing current 300 μ A, accelerating voltage 3 KV, resolution 6000). The elemental composition of the ions was also determined by peak matching relative to perfluorokerosene. All measured masses agreed with those of the compositions listed in column 3 of Table 1 to within ± 2 ppm. Metastable transitions were measured in the first field-free region on the same instrument with a metastable ion detector using a high-voltage scan. The values of μ_1 - μ_3 were calculated as averages of two to four measurements.

Compounds 1-8 were obtained according to the literature [12].

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