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SYNTHESIS OF 3-METHYL-3,7-DIHYDRO-1H-PURINE-2,6-DIONE DERIVATIVES AND INVESTIGATIONS OF THEIR PHYSICOCHEMICAL PROPERTIES

The reaction of alkylation of 3-methyl-8-mercaptoxanthine was studied. Obtained derivatives of purin-2,6-dione were confirmed using methods of IR-, NMR-spectroscopy and mass-spectrometry. Conducted investigations unambiguously confirm the structure of the synthesized compounds.
Key words: synthesis, purine-2,6-dione, physicochemical properties, spectroscopy, spectrometry.

Нами було вивчено реакції алкілування 3-метил-8-меркаптоксантину. Будову отриманих похідних пурин-2,6-діону було підтверджено методами ІЧ-, ПМР-спектрометрії та мас-спектрометрії. Проведені дослідження повністю підтверджують структуру синтезованих сполук.
Ключові слова: синтез, пурин-2,6-діон, фізико-хімічні властивості, спектроскопія, спектрометрія.

Нами была изучена реакция алкилирования 3-метил-8-меркаптоксантина. Строение полученных производных пурин-2,6-диона было подтверждено методами ИК-, ПМР-спектрометрии и масс-спектрометрии. Проведенные исследования полностью подтверждают структуру синтезированных соединений.
Ключевые слова: синтез, пурин-2,6-дион, физико-химические свойства, спектроскопия, спектрометрия.

From the literature resources, it is known, that certain xanthine derivatives possess diuretic, antioxidant, radioprotective activities [1, c. 272; 2, c. 976; 3, c. 645; 4, c. 236]. Earlier reports of the synthesis of 7-alkyl-3-metilthioxanthines [5, c. 2133], which are obtained by reaction of the 7-alkyl-8-bromo-3-methylxanthines with sulfur nucleophiles (KSH, Na_2S). Subsequently, we described the alkylation of 7-substituted 3-methyl-8-thioxanthine [6, c. 3428]. 3-Methyl-8-mercaptoxanthine and its derivatives is the objects of studying their chemical, physico-chemical and biological properties.

The goal of our investigation is to study the reaction of alkylation of 3-methyl-8-mercaptoxanthine (II), which has several reaction centers – N_1, N_7, N_9, SH-group, as well as the search for biologically active compounds amongst obtained compounds.

Materials and methods. The object of this study is 3-methyl-8- mercaptoxanthine (II), which was obtained from 8-bromo-3-methylxanthine (I). By alkylation of compound (II) were synthesized corresponding 8-S-substituted 3-methylxanthines (III-X).

IR spectra were recorded on a spectrophotometer Bruker ALPHA. NMR-spectra were recorded on a Varian device (operating frequency of 200 MHz, the solvent DMSO-d6, TMS internal standard). Mass-spectra of the synthesized compounds were recorded on a Varian MAT-311A with direct sample introduction into the ion source under standard conditions: accelerating voltage of 3 kV, the cathode emission current is 300 mA, an ionizing voltage of 70 eV.

3-Methyl-8-merkaptoksantin (II)

A mixture of 24.5 g (0.1 mol) of 3-methyl-8-bromoxanthine (I), 15,2 g (0.2 mole) of thiourea, 100 ml of 48% HBr heated for 1 hour. Cooled and diluted with 300 ml H_2O. The precipitate was filtered off. Washed with water and alcohol. Dried. Yield: 16.2 g (82%). Mp > 320°C.

Found%: C 36.7; H, 3.3; N 28,6; S 16,1; $C_6H_6N_4O_2S$. Calculated%: C, 36.4; H, 3.1; N 28,3; S 16,2.

8-methylthio (III); 8-ethylthio (IV); 8-propylthio (V); 8-poxythio- (VI); 8-allylthio- (VII); 8-isobutylthio (VIII); 8-isopentiltio- (IX); 8-benziltio-(X)-3-methylxanthines

A mixture of 0.01 mole of 3-methyl-8-thioxanthine (II), 0,01 mole sodium hydroxide and 0.01 mole of the corresponding alkyl halide dissolved in 50 ml of an aqueous alcohol was heated at reflux for 2 hours. The mixture is cooled, diluted with an equal volume of water. The precipitate was filtered off and washed with acetone. Dried. The data on the compounds (III-X) shown in Table 1.

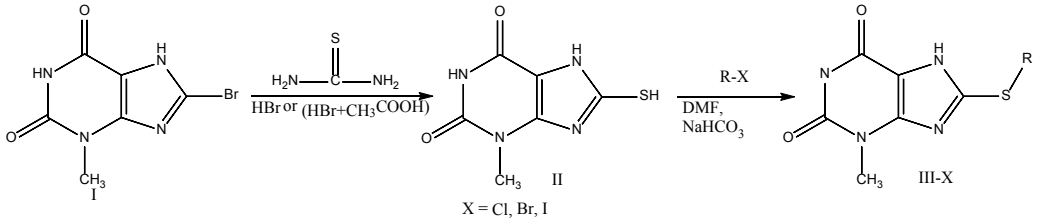
Results and its discussion. 3-Methyl-8-mercaptoxanthine (II) is a typical SH-acid, which give a possibility to create a large set of its derivatives, although we do not exclude the opportunity of alkylation at N_1 and N_7. In this connection, we performed quantum-chemical calculation of charges for Huckel (II, Table 2).

In the uracil moiety on the N_1 positive charge is prevailed (+0.282994), in the imidazole moiety at the pyrrole N_7 deficit of electrons (+0.375876), and pyridine atom N_9 (-0.534601) and sulfur atom in 8 position of xanthine cycle acquires a slight positive charge due to the influence of the imidazole ring (+0.0286981).

We can conclude, relying on quantum-chemical calculations that SH-group must be the primary site of electrophilic attack. Subsequent alkylation proceeds at N_7 atom and then N_1 (II).

We have studied the reaction of 8-bromo-3-methylxanthine (I) with thiourea in HBr (HBr + CH3COOH in the ratio 1:1), leading to the production of 8-mercapto-3-methylxanthine (II, Scheme 1). The proposed method for the synthesis favors previously described [8], because laborious processes of autoclaving and

Scheme 1

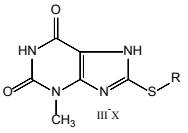


X = Cl, Br, I

III: R= CH_3; IV: R = C_2H_5; V: R = C_3H_7; VI: R = $CH_2CH(O)CH_2$; VII: R = $CH_2CH{=}CH_2$; VIII: R = i-C_4H_9; IX: R = i-C_5H_{11}; X: R = $CH_2C_6H_5$

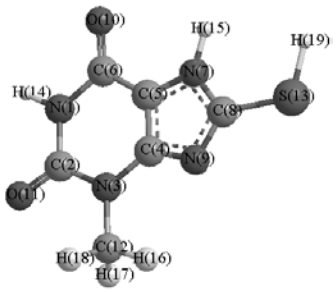
Table 1

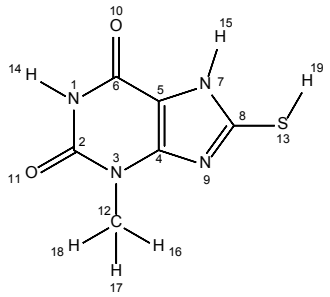
8-substitued derivatives of 3-methyl-8-mercaptoxanthine



№	R	M.p., °C	Found, %				Gross formula	Calculated,%				Yield, %
			C	H	N	S		C	H	N	S	
III	CH_3	>300	39,8	3,9	26,2	15,0	$C_7H_8N_4O_2S$	39,6	3,8	26,4	15,1	63
IV	C_2H_5	283-284	42,7	4,6	24,9	14,4	$C_8H_{10}N_4O_2S$	42,5	4,4	24,8	14,2	74
V	C_3H_7	276-277	44,9	5,1	4,4	24,7	$C_9H_{12}N_4O_2S$	44,7	5,3	44,3	24,6	71
VI	$CH_2CH(O)CH_2$	>300	42,7	4,0	22,1	12,7	$C_9H_{10}N_4O_2S$	42,5	3,9	22,0	12,6	65
VII	$CH_2CH{=}CH_2$	251-252	45,3	4,4	23,6	13,6	$C_9H_{10}N_4O_2S$	45,4	4,2	23,5	13,4	68
VII	i-C_4H_9	258-259	47,2	5,3	22,2	12,0	$C_{10}H_{13}N_4O_2S$	47,4	5,1	22,1	12,7	63
IX	i-C_5H_{11}	234-235	49,4	6,1	20,9	12,0	$C_{11}H_{15}N_4O_2S$	49,2	6,0	20,9	11,9	71
X	$CH_2C_6H_5$	252-253	54,0	4,7	19,4	11,2	$C_{13}H_{13}N_4O_2S$	53,9	4,5	19,3	11,1	55

Table 2





Atom	Type	Charge	Atom	Type	Charge
N(1)	N Amide	+0.282994	O(11)	O Carbonyl	-0.900634
C(2)	C Carbonyl	+0.385209	C(12)	C Alkane	-0.0561881
N(3)	N Amide	+0.389089	S(13)	S Thiol	+0.0286981
C(4)	C Alkene	+0.165686	H(14)	H Amide	+0.0976268
C(5)	C Alkene	-0.0867212	H(15)	H Amine	+0.0748273
C(6)	C Carbonyl	+0.31083	H(16)	H	+0.0349657
N(7)	N Pyrrole	+0.375876	H(17)	H	+0.0373516
C(8)	C Alkene	+0.204567	H(18)	H	+0.0377401
N(9)	N Imine	-0.534601	H(19)	H Thiol	+0.0299772
O(10)	O Carbonyl	-0.877294			

prolonged heating are excluded. 3-Methyl-8-mercaptoxanthine (II), it is a convenient starting material for the synthesis of 8-S-, N_1- and N_7-substituted derivatives (Scheme 1).

Structure II is confirmed by elemental analysis, IR-, NMR-spectroscopy and mass spectrometry. The IR spectrum of (II) has bands of stretching vibrations of the amide carbonyl in the 1715-1695 cm^{-1}, the absorption of NH-groups 3190-3160 cm^{-1} in the form of broadened lines of medium intensity. Characteristic absorption bands of the groups C=N, C=C shown at 1670-1640 and 1630-1600 cm^{-1}, C-SH at 800 cm^{-1}.

NMR spectrum of compound II following proton signals: 11.36 (s, 1H, N_1H.); 3,66 (c, 3H, N_3CH_3.); 10,35 (c., 1H, N_7H). The mass spectrum II has a peak M^+ with m/z 198. The measurement of mass of compound II shows the mass number of 198.0258, which corresponds to the gross composition $C_6H_4N_4O_2S$. In the first stage, cleavage fragmentation particles HNCO, which is typical for uracil cycle (of the type "retrodiene

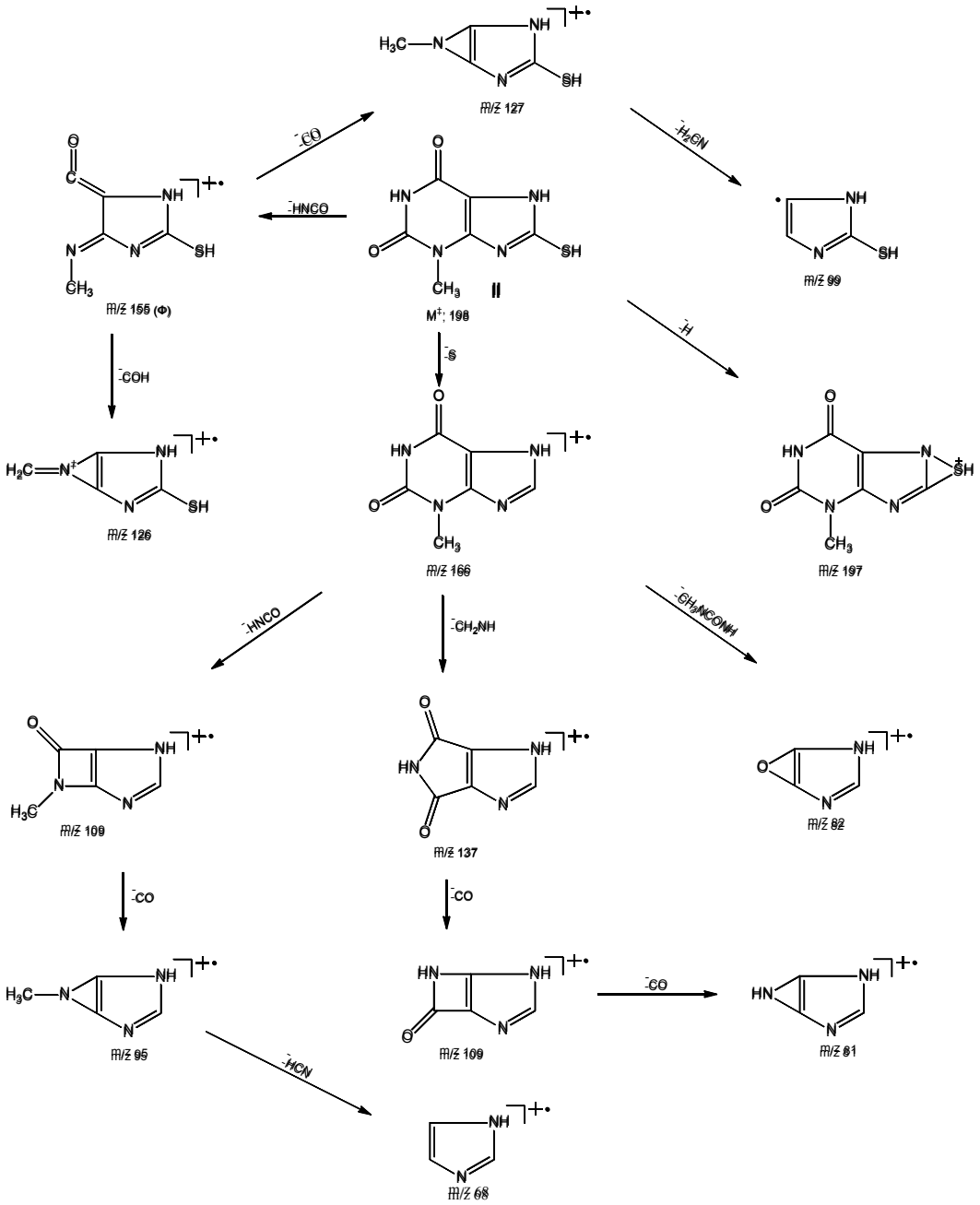


Fig. 1. Schematic mass-decay of compound (II)

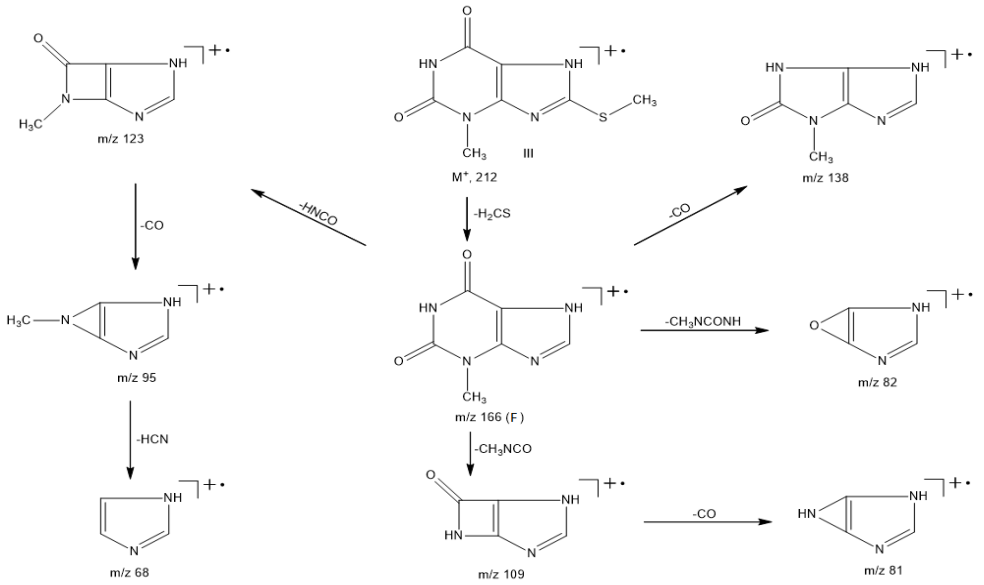


Fig. 2. Scheme mass-decay of compound (III)

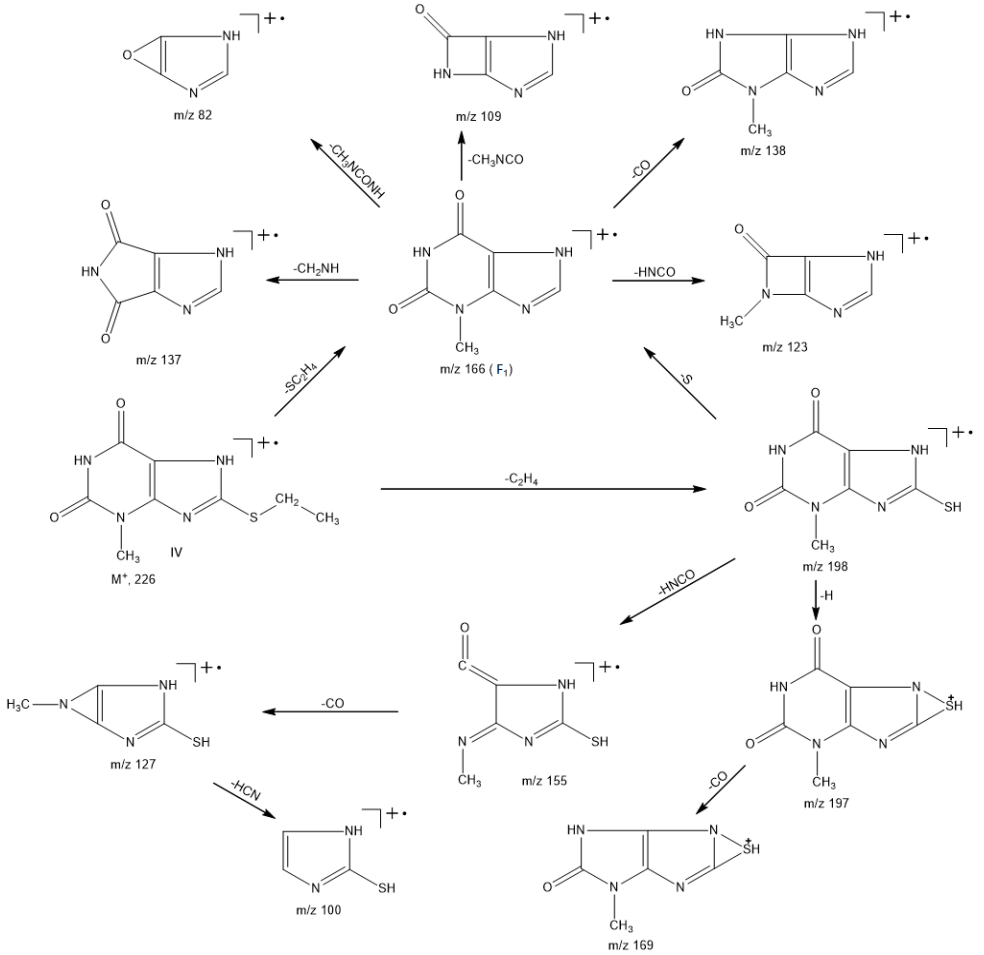


Fig. 3. Scheme mass-decay of compound (IV)

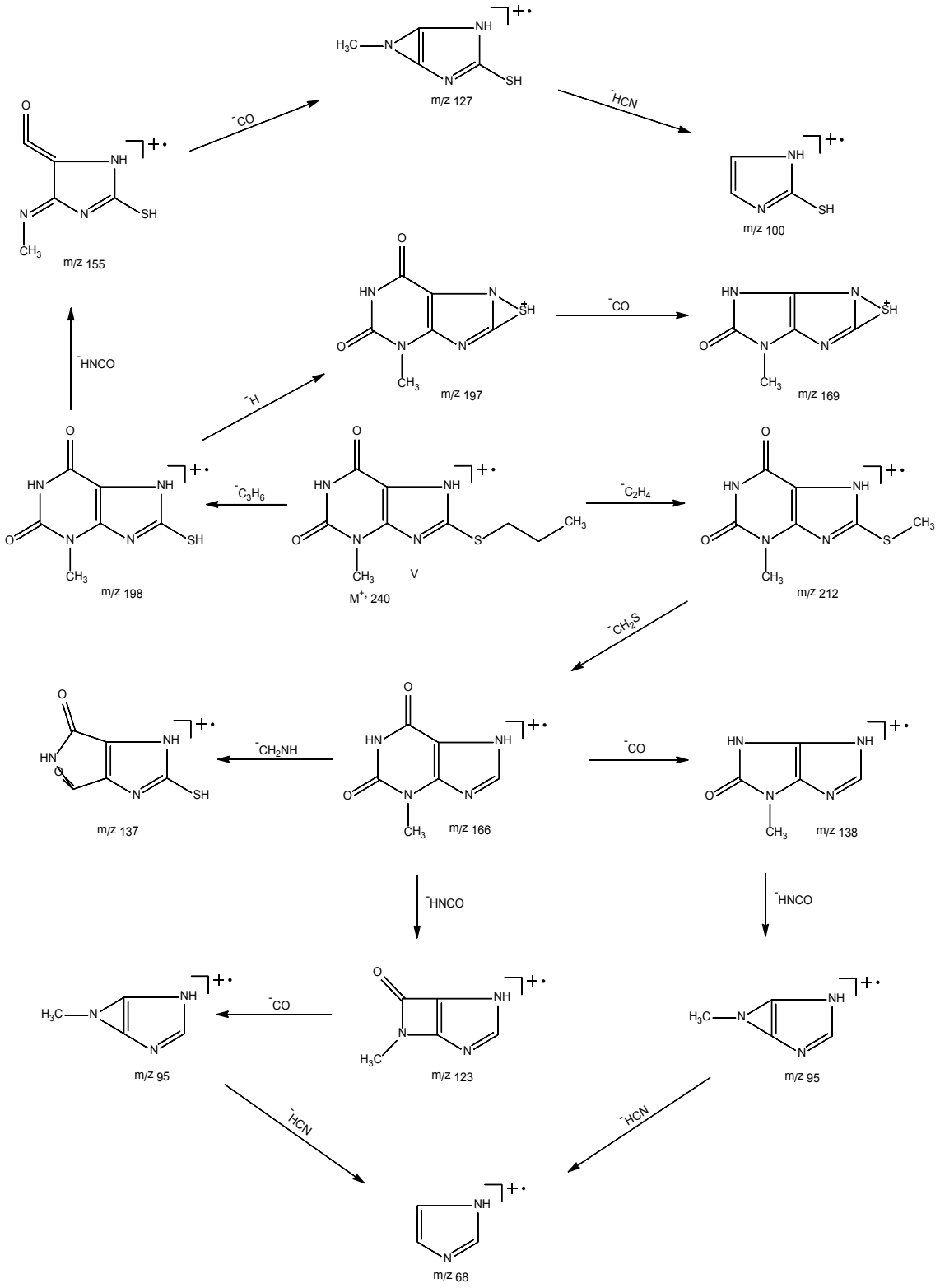


Fig. 4. Scheme mass-decay of compound (V)

decay") into hypoxanthine. This fact confirms the measured mass of 155.0105 (F ion). The next stage begins with elimination of CO (measured – 127.0204) and COH (measured – 126.0125) from $[M\text{-}HNCO]^+$ (F). H_2CN ion with m/z 99 is the result of the further decomposition of the uracil nucleus. There were found two ions with m/z 166 (low intensity) and the ion with m/z 197 – $[M\text{-}H]^+$, indicating thiol group is present. The obtained mass-spectrum fully confirm the structure of interest.

The IR spectra of compounds III-X are characterized by present amide carbonyl stretching vibrations in the region 1690-1730 cm^{-1}, and characteristic absorption bands of C=N group at 1640-1660 cm^{-1}, CS – 630-750 cm^{-1}, S-CH2 – 1410-1425 cm^{-1}.

NMR spectrum of 3-methyl-8-methylmercaptoxanthine (III) the following signals are recorded protons (δ-scale, ppm) 10.35 (s, 1H, N_7H.); 11,36 (c, 1H, N_1H.); 3,29 (c, 3H, N_3CH_3); 2,80 (c., 3H, S-CH_3) with fixed peak with M^+ m/z 212, which corresponds to the calculated molecular mass. Fragmentation M^+ (III) is associated with the elimination of the substituent at position 8 xanthine cycle with ion m/z 166 (F). Then ion (F) undergoes degradation associated with elimination of particles CH_3, NCONH, HNCO, CO, HCN and formation of the corresponding ions m/z 82, 95, 109, 123, 138 and others. Further decay molecular ions by electron impact is depicted in Scheme (Fig. 2).

The mass spectrum of compound IV with M^+ peak m/z 226 corresponds the calculated molecular mass. Mass-spectrometric studies have shown that fragmentation M^+ (IV) is associated with the elimination of the substituent in the 8-position of the molecule with ions with m/z 198 $[M\text{-}C_2H_4]^+$, m/z 166 $[M\text{-}SC_2H_4]^+$. Subsequently ion (F_1) which has the structure 3-methylxanthine, cleaves to particles CH_3NCONH, NHCO, CO, HCN resulting ions with m/z 82, 123, 137, 138 (Fig. 3.). The mass spectra of V, VI with recorded peaks of molecular ions (M^+, 240; M^+, 254) match their gross composition.

Fragmentation M^+ (V) and M^+ (VI) proceeds and uniquely associated with the elimination of the substituent in position 8 xanthine cycle. The uracil fragment cleavage gives CH3NCONH fragments, CH_2NH, CO et al. (Fig. 4, 5). Mass spectrometry data unambiguously confirm the structure of the synthesized compounds II-X.

Conclusions:

1. The reaction of 3-methyl-8-mercaptoxanthine with alkyl halides yields 3-methyl-8-alkylmercaptoxanthines.
2. Alkylation of 3-methyl-8-alkylmercaptoxanthines give 3-methyl-7-alkyl-8-alkylmercaptoxanthines.
3. Reactions of 3-methyl-7-alkyl-8-alkylmercaptoxanthines with methyl iodide give appropriates 1,3-dimethyl-7-benzyl-8-methylmercaptoxanthines.
4. A mass-spectrometric study of the synthesized compounds was carried out.

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