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Synthesis and physicochemical investigation of thiazoloxanthine derivatives

Emeneka O.J., Vasylyev D.A.
[1]College of Medicine, Lagos State University, Ikeja, Lagos State
[2]Department of Biological Chemistry, Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine
E-mail address: vasylyev.d.a@zsmu.edu.ua

ABSTRACT
Heterocycle containing compounds (xanthines, pyrazoles, thiazoles etc) represent very important structural units in drug discovery. In the design of new pharmaceutical agents, multiple factors need to be adjusted in parallel to discover the best balance of efficacy and safety. After many years of thorough medicinal chemistry investigations on the modification of well-known antibacterial scaffolds, it is becoming increasingly hard to deliver new leads. A survey of literature reveals the biological properties of these substances including hypoglycemic, anticancer, antioxidant, anti-inflammatory, bronchodilator and xanthine oxidase inhibitory effects. In our opinion, combination of several heterocyclic systems in one molecule could improve pharmacological properties. Aim of our work was a development of method of thiazole and triazole containing xanthine derivative synthesis.
KEW WORDS *purine, thiazoloxanthine, synthesis.*

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INTRODUCTION

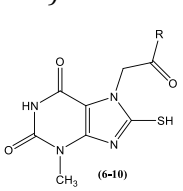
Purine and purindione-2,6 derivatives are valuable drugs. So, theobromine, theophylline, caffeine has a stimulating effect on the central nervous system, have a pronounced effect on the heart muscle, skeletal muscles, and are also used as antispasmodic and diuretic agents. Synthetic drugs - themisal, aminophyllin, diprofillin and many others possess diuretic and bronchodilator activity, dilate cerebral vessels, increase coronary blood flow, etc [1-6]. We have previously reported [6,7] on the synthesis of 6H-thiazolo[3,2-f]xanthines and the study of their pharmacological activity. The purpose of our study is to develop methods for the synthesis of 3- and 2,3-substituted 6H-thiazolo[3,2-f]xanthine and to study the physicochemical properties and biological activity

MATERIALS AND METHODS

The object of the study is 7-aroylmethyl-3-methyl-8-bromoxanthines (1-5), on the basis of which 7-aroylmethyl-3-methyl-8-thioxanthines were obtained (6-10), and the cyclization of the latter leads to the formation of derivatives 8-methyl 6H-thiazolo[3,2-f]xanthine (11-15). The structure of the synthesized compounds (6-20) was established using elemental analysis and physicochemical methods: IR spectroscopy and mass-spectrometry.
IR spectra were recorded on a Bruker ALPHA spectrophotometer. Mass spectra of the synthesized compounds were recorded on a Varian MAT-311A with direct injection of the sample into the ion source. The shooting conditions are standard: accelerating voltage 3 kV, cathode emission current 300 μA, ionizing voltage 70 eV.
7-Aroylmethyl-8-bromo-3-methylxanthines (1-5) were obtained by the previously described methods [7,8].
3-Methyl-7-aroylmethyl-8-thioxanthines (6-10).
Method A. A mixture of 0.01 mol of the corresponding 7-aroylmethyl-8-bromo-3-methylxanthine (1-5), 0.02 mol of Na_2S $9H_2O$, 50 ml of DMF is boiled for 5 hours, cooled, diluted with water, the filtrate is acidified to pH = 3, left overnight, the precipitate is filtered off, washed with water, and purified by crystallization from aqueous DMF.
Method B. A mixture of 0.01 mol 1-5 (0.015 mol) of potassium hydrosulfide in 100 ml of methanol is heated in an autoclave for 6-7 hours at 170-180 °C, cooled, the contents of the autoclave are diluted with water to 200 ml, filtered and acidified to pH = 3. The precipitate is filtered off, washed with water. The constants are shown in Table 1.
6H-8-Methylthiazolo [3,2-f] xanthines (11-15)
Method A. 0.01 mol of the corresponding 3-methyl-7-aroylmethyl-8-thioxanthine (6-10) is dissolved in 20 ml of conc. H_2SO_4 (d = 1.85) and left at room temperature for 24 hours. It is diluted with a threefold amount of water, the precipitate formed is filtered off, washed with water, alcohol, acetone, and dried.

Compounds (11-15) are obtained. For analysis, compounds 11-15 were purified by crystallization from aqueous DMF (Table 1).
Method B. 0.01 mol (6-10) in 30 ml of 48% HBr is boiled for 2 hours, cooled and worked up as described above. Properties (11-15) crystalline substances, soluble in organic solvents and mineral acids, insoluble in water. Elemental analysis data and yields in% are shown in Table 1.

3-methyl-7-aroylmethyl-8-mercaptoxanthines (6-10)
6H-Thiazolo [3,2-f] xanthines (11-15)


(6-10)

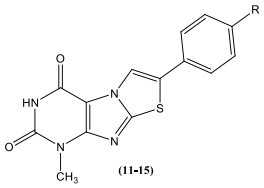
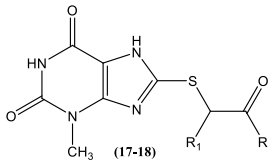
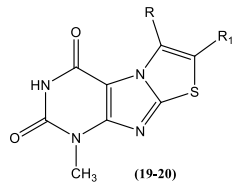

(11-15)

Table 1.

№	R	Mp., °C	Found, %				Formula	Calcd, %				Yield, %
			C	H	N	S		C	H	N	S	
6	C_6H_5	283-284	50,3	3,6	17,5	10,0	$C_{14}H_{12}N_4O_3S$	53,2	3,8	17,7	10,1	82(A)80(B)
7	C_6H_4F	300-301	50,5	3,5	16,7	9,3	$C_{14}H_{12}FN_4O_3S$	50,3	3,3	16,8	9,6	80(A)85(B)
8	C_6H_4Cl	304-305	48,3	3,4	16,1	9,0	$C_{14}H_{12}ClN_4O_3S$	48,0	3,2	16,0	9,1	84(A)75(B)
9	C_6H_4Br	307-308	42,8	3,2	16,1	9,0	$C_{14}H_{12}BrN_4O_3S$	42,5	3,2	14,2	8,1	73(A)80(B)
10	$C_6H_4NO_2$	298-299	46,4	3,1	19,6	8,8	$C_{14}H_{12}N_5O_5S$	46,5	3,0	19,4	8,8	60(A)70(B)
11	C_6H_5	302-304	56,2	3,2	18,6	10,5	$C_{14}H_{10}N_4O_2S$	56,4	3,4	18,8	10,8	60(A)72(B)
12	C_6H_4F	>300	53,4	3,0	17,4	10,4	$C_{14}H_9FN_4O_2S$	53,1	2,8	18,8	10,8	53(A)65(B)
13	C_6H_4Cl	>300	50,9	2,4	16,3	9,7	$C_{14}H_9ClN_4O_2S$	50,5	2,7	16,8	9,6	66(A)80(B)
14	C_6H_4Br	>300	44,1	2,7	14,5	10,0	$C_{14}H_9BrN_4O_2S$	44,5	2,4	14,8	9,5	60(A)65(B)
15	$C_6H_4NO_2$	>300	48,6	2,3	20,6	9,2	$C_{14}H_9N_4O_4S$	48,9	2,2	20,4	9,4	64(A)80(B)

3-methyl-8-mercaptoxanthine (16) was obtained according to the method [6].
8-Aroylmethylthio-3-methylxanthines (17.18, Table 2)
Method A. To a solution of 1.98 g (0.01) mole of 16 and 0.01 mole of sodium ethylate in 100-150 ml of ethanol, 0.01-0.015 mole of α-halogenketone is added. The mixture is heated for 1 hour at 60-65 °C, cooled, the precipitate is filtered off, washed with water, and dried.
Method B. A mixture of 1.98 g (0.01) mol of 16, 0.01 mol of NaOH is dissolved in 150 ml of aqueous ethanol, then 0.01-0.015 mol of α-haloketone is added and heated for 1 hour in a boiling water bath. Cool. The precipitate is filtered off, washed with water, acetone, and dried. Compounds (17, 18) are obtained. Purified by crystallization from aqueous DMF.
Cyclization of 8-aroylmethylthio-3-methylxanthines (17,18) to 6H-8-methylthiazolo[3,2-f]xanthine derivatives (19,20) containing substituents at positions 3- and 2,3 (Table 2).
A solution of 3.16 g (0.01) mol (17) in 50 ml in ice-cold CH_3COOH is refluxed for 3-4 hours. Cooled. Poured into 150 ml of water. Filtered off. Washed with water, acetone. Dried. Purified by crystallization from aqueous DMF. Compound (19) is obtained.
A solution of 3.92 g (0.01) mole (18) in 50 ml of 85% HCOOH is heated at reflux for 3 hours. Poured into 150 ml of water. Filtered off. Wash with water, alcohol. Compound (20) is obtained.
Table 2


(17-18)

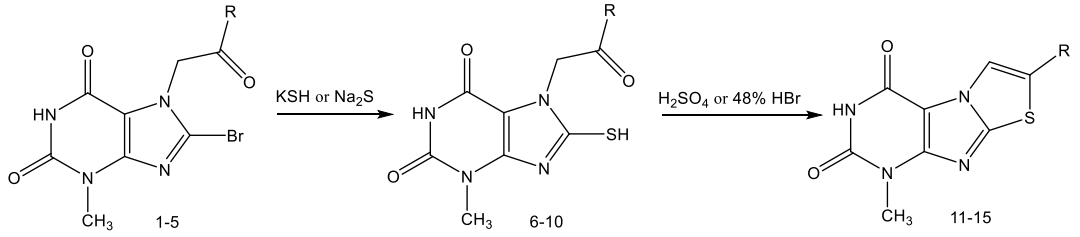

(19-20)

№	R	R_1	Mp., °C	Found, %				Formula	Calcd, %				Yield, %
				C	H	N	S		C	H	N	S	
17	C_6H_5	H	241-243	53,4	3,9	17,4	9,7	$C_{14}H_{12}N_4SO_3$	53,2	3,8	17,7	10,1	82(A)83(B)
18	C_6H_5	C_6H_5	243-245	60,9	4,4	14,4	8,5	$C_{20}H_{16}N_4SO_3$	61,2	4,1	14,3	8,2	85(A)82(B)
19	H	C_6H_5	305-307	56,5	3,6	18,9	10,6	$C_{14}H_{10}N_4SO_2$	56,4	3,4	18,8	10,7	87
20	C_6H_5	C_6H_5	313-315	64,1	4,0	14,8	8,5	$C_{20}H_{14}N_4SO_2$	64,2	3,7	14,9	8,6	92

RESULTS AND DISCUSSION

We studied the reaction of 3-methyl-7-aroylmethyl-8-bromoxanthines (1-6) with sulfur-containing nucleophiles (NaSH, Na_2S $9H_2O$) leads to the production of 3-methyl-7-aroylmethyl-8-thioxanthines (6-10, Table 1, scheme. 1).

3-Methyl-7-aroylmethyl-8-thioxanthines (6-10) are SH-acids that allow synthesis at the 8th position of the xanthine ring, as well as the transition to 2-substituted 6H-thiazolo[3,2-f]xanthine (11-15, table. 1, scheme. 1) and the study of their physicochemical and biological properties.

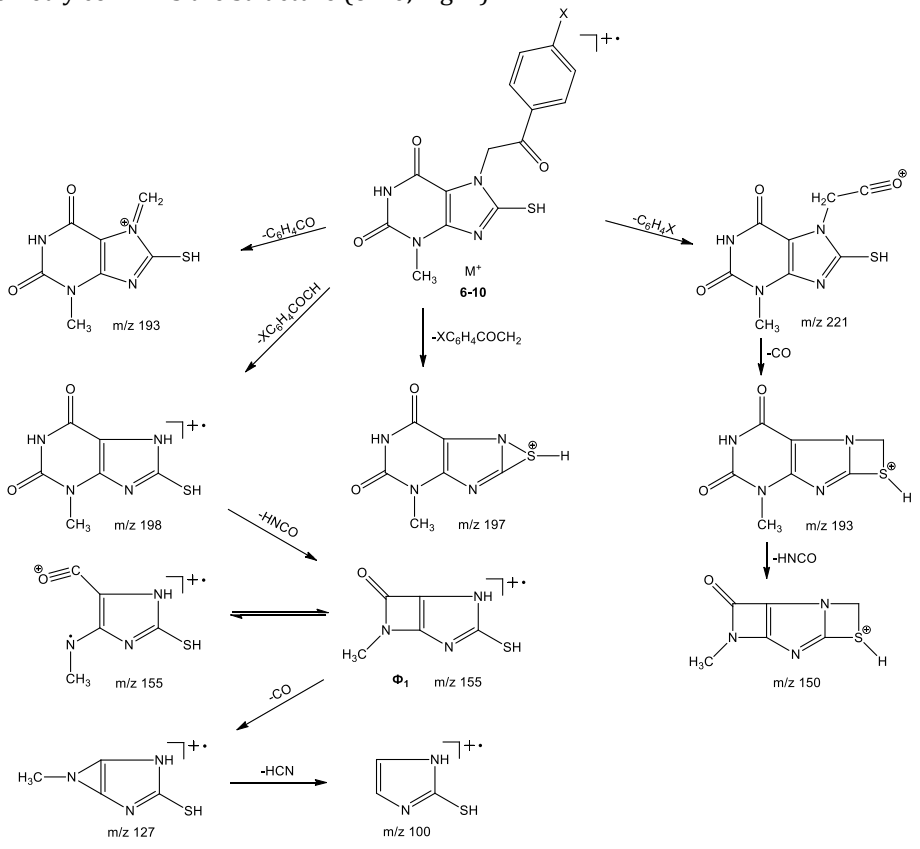


1,6,11 - R = C_6H_5; 2,7,12 - R = C_6H_4F; 3,8,13 - R = C_6H_4Cl; 4,9,14 - R = C_6H_4Br; 5,10,15 - R = $C_6H_4NO_2$

Fig1. Scheme of synthesis condensed xanthine derivatives

In the IR spectra (6-10), characteristic bands of stretching vibrations of non-associated at 3470-3400 cm^{-1} and associated at 3200-3170 cm^{-1} amide groups are observed, the bands of stretching vibrations of carbonyl groups lie in the region of 1700-1690 cm^{-1}, the band absorption of ketone carbonyl appears in the range of 1730-1700 cm^{-1}, 2600 cm^{-1} (SH).

The mass spectra (6-10) recorded peaks M^+ with m / z 298 (6), M^+ with m/z 316 (7), M^+ with m/z 332 (8), M^+ with m/z 376 (9) , M^+ with m/z 343 (10), which corresponds to the calculated molecular weights (Fig. 2). The decomposition of M^+ compounds (6-10) is accompanied by the elimination of C_6H_4X particles (X = H, F, Cl, Br, NO_2) with the formation of $[M - C_6H_4X]^+$ m/z 221, $[M - C_6H_4CO]^+$ m/z 193, $[M - XC_6H_4COCH]^+$ m/z 198, $[M - C_6H_4COCH_2]^+$ m/z 197. Thus, these fragment ions prove the presence of a substituent at the 7th position (6-10). The emission of HNCO particles (by the type of retrodiene decay) is specific for uracil derivatives $[\Phi - HNCO]^+$ m/z 155, $[\Phi1 - CO]^+$ m/z 127, $[\Phi1 - CO\text{-}HCN]^+$ m/z 100. Mass data -spectrometry confirms the structure (6-10, Fig. 1).

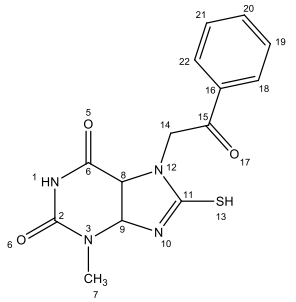


(6) - X = H, M^+ 298; (7) - X = F, M^+ 316; (8) - X = Cl, M^+ 332; (9) - X = Br, M^+ 376; (10) - X = NO_2, M^+ 343

Fig. 2. Mass-decay scheme of compounds (6-10)

Treatment of compounds 6-10 with concentrated H_2SO_4 (d = 1.85) gives 11-15 (method A).
Heating 6-10 in 48% HBr is realized by the formation of 11-15 (method B, Table 1, Scheme 1).
To describe the supposed mechanism of cyclization (6-10) under the action of acids, we carried out a quantum-chemical calculation of charges according to Hückel (6, Table 3).

Table 3.



Atom	Type	Charge	Atom	Type	Charge
N(1)	N Amide	0.284011	C(18)	C Alkene	0.0146206
C(2)	C Carbonyl	0.389401	C(19)	C Alkene	-0.0271647
N(3)	N Amide	0.386997	C(20)	C Alkene	0.00897776
C(4)	C Carbonyl	0.330275	C(21)	C Alkene	-0.0262203
O(5)	O Carbonyl	-0.846349	C(22)	C Alkene	0.00310193
O(6)	O Carbonyl	-0.898753	H(23)	H Amide	0.0977491
C(7)	C Alkane	-0.0564971	H(24)	H	0.0352148
C(8)	C Alkene	-0.118128	H(25)	H	0.0377879
C(9)	C Alkene	0.166886	H(26)	H	0.0372339
N10)	N Imine	-0.525741	H(27)	H Thiol	0.0378266
C(11)	C Alkene	0.147781	H(28)	H	0.0369844
N(12)	N Pyrrole	0.517606	H(29)	H	0.0585536
S(13)	S Thiol	-0.0189518	H(30)	H	0.0166713
C(14)	C Alkane	-0.0601779	H(31)	H	0.0204593
C(15)	C Carbonyl	0.465745	H(32)	H	0.0203239
C(16)	C Alkene	0.00827446	H(33)	H	0.0199779
O(17)	O Carbonyl	-0.588332	H(34)	H	0.0238536

There is a deficit of electrons on carbonyl carbon (+0.4601779), on oxygen (-0.588332), and on N9 (-0.525741).
A slight negative charge (-0.0189518) is concentrated on the sulfur atom in position 8 of the imidazole ring of the xanthine system.
Based on the quantum-chemical calculation (6), it can be assumed that in an acidic medium (H_2SO_4 conc. or HBr - 48%) protonation proceeds at N9 and oxygen of the carbonyl group. Subsequently, a nucleophilic attack of the electron pair of the sulfur atom of the formed carbocation proceeds, followed by cyclization into the thiazole ring (11, Fig. 3).

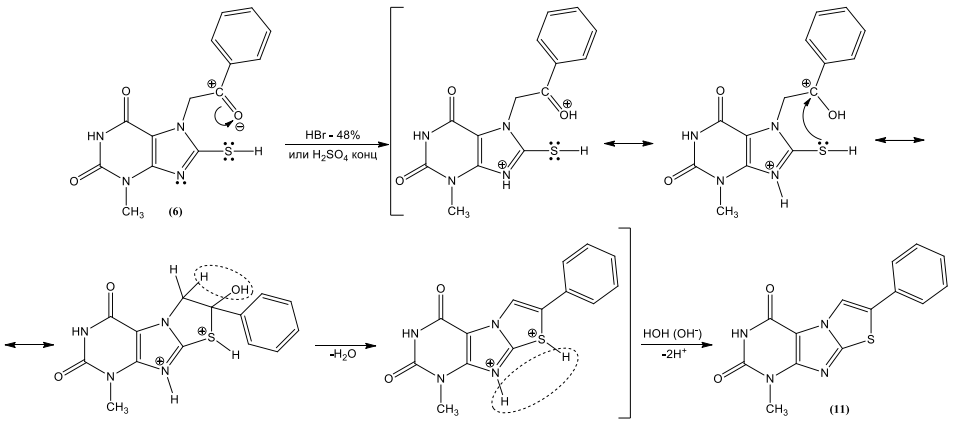


Fig 3. Scheme of the putative mechanism of cyclization (6) to the 6H-thiazolo[3,2-f]xanthine derivative (11)

In IR spectra 11-15 there are absorption bands that refer to stretching vibrations of NH-groups at 3190-3175 cm^{-1}, absorption bands of amide carbonyls of the uracil fragment appear in the region of 1710-1700 cm^{-1} and 1695-1690 cm^{-1}.

The structure of the synthesized compounds (11-15) is confirmed in more detail by mass spectrometry data. In mass spectra (11-15) peaks of molecular ions corresponding to their gross composition are recorded. The mass spectrum 13 recorded an M^+ peak with m/z 332, which corresponds to the calculated molecular weight (Fig. 3). The decay of M^+ is accompanied by the elimination of the HNCO particle (by the type of "retrodienic decay"), which is typical for uracil derivatives, respectively, the ion $[M - HNCO]^+$ m/z 289 (ion F). Subsequently, the [Φ] ion undergoes destruction associated with the elimination of HCN, CO, H, H_2CN, as evidenced by the ions with m/z 288, 262, 260, 233, 231, respectively.
The presence of ions with m/z 233, 234 confirms that compound 13 is a thiazolo[3,2-f]xanthine derivative (Fig. 4).

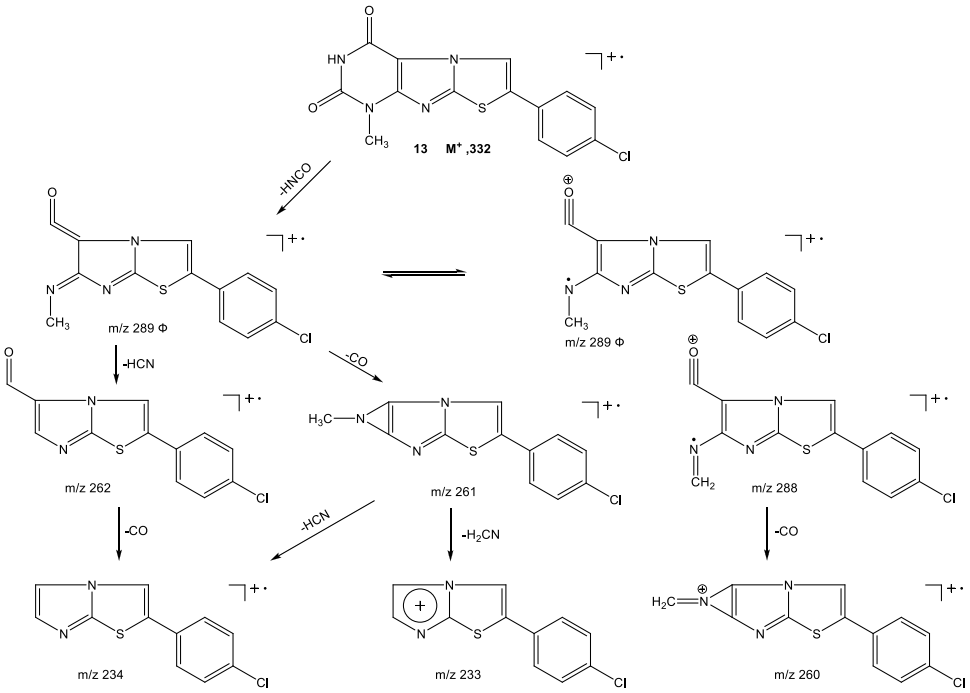


Fig 4. Mass decay of compound (13)

The fragmentation pattern of M^+ compounds 13, 15 corresponds to their structure.
To study the pharmacological activity and establish the structure-action relationship, we have synthesized 3- and 2,3-substituted 8-methyl-6H-thiazolo[3,2-f]xanthine (11-15, 19, 20).
Compounds (17, 18), in contrast to the method [6], were obtained by interaction with α-halogenketones in alcohol or in aqueous alcohol in the presence of an alkaline agent; cyclization (17, 18) in conc. CH_3COOH, 85% HCOOH is realized by the formation of 3- and 2,3-substituted thiazoloxanthine 19, 20.

CONCLUSION

1. Methods for the synthesis of 7-aroylmethyl-3-methyl-8-thioxanthines and 6H-thiazolo[3,2-f]xanthine derivatives have been developed and improved.
2. The physicochemical properties of 2-substituted 6H-thiazolo[3,2-f]xanthine were studied.
3. A probable mechanism for the cyclization of 7-aroylmethyl-3-methyl-8-thioxanthines to 6H-thiazolo[3,2-f]xanthine derivatives has been proposed.
4. The structure of the synthesized compounds was established using IR-spectroscopy and mass spectrometry.

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