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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF 7-AROYLALKYLXANTHINYL-8-THIOACETIC ACID

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When 7-aroylalkyl-8-bromo-3-methyl- and 1,3-dimethylxanthines are boiled with an excess of thioglycolic acid, a reductive dehalogenation takes place, while reaction with an equimolar amount of thioglycolic acid in DMFA leads to 7-aroylalkyl-3-methyl- and 1,3-dimethylxanthinyl-8-thioacetic acids. Cyclization of the latter with acetic anhydride in the presence of anhydrous sodium acetate results in the formation of 3-aryl-1,4-dihydro-9-methyl- and -7,9-dimethylthiazino[3,2-f]xanthine.

7-Aroylalkyl-8-bromoxanthines are known as convenient synthones for the synthesis of annelated imidazo- [1], oxazolo- [2, 3], thiazolo[f]azoloxanthines [4], or azinoxanthines [5].

In the present work we obtained thiazinoxanthine derivatives from these synthones.

The reaction of 7-aroylalkyl-8-bromoxanthines (VI-X) with an equimolar amount of thioglycolic acid in DMFA results in the formation of derivatives of 7-aroylalkylxanthinyl-8-thioacetic acid (XI-XV). It should be noted that on boiling compounds VI-X in an excess of thioglycolic acid, a reductive dehalogenation of the substrates takes place with the formation of compounds III-V.

This process is most probably related to the reducing properties of thioglycolic acid. Compounds III-V can also be obtained by direct alkylation of the potassium salts of 3-methyl- or 1,3-dimethylxanthine by α-haloketones in DMFA. Samples of compounds III-V obtained by the two methods do not give a mixed melting point depression.

When compounds XI-XV were boiled in acetic anhydride in the presence of anhydrous sodium acetate, we obtained 3-aryl-1,4-dihydro-9-methyl- and -7,9-dimethylthiazino[3,2-f]xanthines (XVI-XIX) (Table 1). It is clear that, in the course of the reaction, after cyclization with the formation of an annelated thiazine ring, a decarboxylation of the intermediately formed acids takes place.

In the IR spectra of acids XI-XV intense absorption bands of the stretching vibrations of the OH group are observed in the 3475-3375 cm^{-1} region and the absorption bands of stretching vibrations of the NH fragment appear in the 3165-3150

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	Yield, %	
			A	Б
III	$C_{14}H_{12}N_4O_3$	326...328	69	78
IV	$C_{15}H_{14}N_4O_3$	189...191	68	81
V	$C_{14}H_{11}ClN_4O_3$	>300(decomp.)	57	73
X	$C_{15}H_{12}BrClN_4O_3$	208...210	65	
XI	$C_{16}H_{14}N_4O_5S$	294...295	80	
XII	$C_{17}H_{16}N_4O_5S$	220...221	64	
XIII	$C_{17}H_{15}ClN_4O_5S$	258...259	76	
XIV	$C_{17}H_{16}N_4O_5S$	271...273	94	
XV	$C_{16}H_{13}ClN_4O_5S$	262...263	81	
XVI	$C_{15}H_{12}N_4O_2S$	285...286	83	
XVII	$C_{16}H_{14}N_4O_2S$	>300(decomp.)	45	
XVIII	$C_{16}H_{14}N_4O_2S$	>300(decomp.)	82	
XIX	$C_{15}H_{11}ClN_4O_2S$	>300(decomp.)	75	

TABLE 2. PMR Spectra of Synthesized Compounds

Compound	Chemical shifts ($CDCl_3$, TMS), δ, ppm					
	$N_{(1)}-CH_3$; $N_{(7)}-CH_3$ (s, 3H)	$N_{(3)}-CH_3$; $N_{(9)}-CH_3$ (s, 3H)	CH (1H)	C–CH_3 (d, 3H)	C_6H_5 (Ar) (5H)	CH_2 (s, 2H)
III		3,35	8,51 s		7,03...7,70 m	5,81
IV	3,36	3,05	8,56 s		7,08...7,73m	5,86
XI		3,25			7,10...7,70 m	3,70; 5,68
XII	3,23	3,01			7,0 br.s	4,0; 5,05
XIII	3,28	3,01			7,10...7,71 m (4H)	3,68; 5,85
XIV		3,1	5,54 q (J=6)	1,39 (J=6)	7,20...7,60 m	4,53
XVI		3,25	6,15 s		6,96 br. s	5,18
XVII		3,25	5,90 q (J=8); 6,10 s	1,26 (J=8)	7,95 br. s	
XVIII	3,25	3,05	6,10 s		6,9 br. s	5,16
XIX		3,33	6,21 s		7,05 br. s (4H)	5,16

cm^{-1} region. The stretching vibration absorption bands of the carbonyl group of the carboxyl fragment appear at 1725-1720 cm^{-1}, while those of the carbonyl groups of the dioxopyrimidine fragment are shifted to the low-frequency region and appear at 1675-1700 cm^{-1} [6].

The structure of the synthesized compounds is adequately confirmed by the PMR spectroscopy and mass spectrometry data.

The set of signals in the PMR spectra (Table 2) and their integral intensity correspond to the proposed structures.

Peaks of $M^{+\cdot}$ are seen in the mass spectra of acids XI-XIII, which correspond to their molecular weight. The structure of the substituent at $N_{(7)}$ can be easily monitored from the presence of fragmentary ions Ar^+, $ArCO^+$, and CH_3COAr^+. The occurrence of the last of these is due to steric factors, which may be effective in the case of o-disposition of the substituents in the xanthine ring and when migration of the mobile α-hydrogen atom to the oxygen atom of the carbonyl group is possible. The presence of a substituent at the $C_{(8)}$ atom is monitored by the peaks of the $[M - CO_2]^{+\cdot}$ (which is a typical process for acids) and $[M - CH_2COO]^+$ ions – a β-decomposition relative to the xanthine ring; moreover, an ion with the structure $[SCH_2COOH]^+$ is recorded. A characteristic ion $[(M - CO_2) - CH_3COAr]^+(F_3)$ is also recorded (see Scheme 1).

Highly intense peaks of molecular ions, which correspond to their empirical formulas, are recorded in the mass spectra of compounds XVI-XVIII. The presence of a dioxopyrimidine fragment in the structure of XVI-XVIII is confirmed by the recorded ions $[(M - R^1) - RNCO]^+$, $[(M - R^1) - RNCO - Co]^+$ (E_2), $[F_2 - HCN]^+$, and $[(M - SH) - RNCO]^+$, which is characteristic for methylated xanthines [2, 7]. The 4H-1,3-thiazine part of the molecule is monitored by ions $[S{=}CHC(C_6H_5){=}CR^1]^+$ (a), $[\overline{SCH{=}C}{-}\ C_6H_5]^+$ (b), and $[R^1\overline{CCH{=}C}C_6H_5]^+$ (c) [8]. In addition, ions are recorded confirming the presence of a sulfur atom $[M + 2]^+$ (the ^{34}S isotope) and $[M - H]^+$ [9].

TABLE 3. Mass Spectra of Compounds XI-XIII, XVI-XVIII

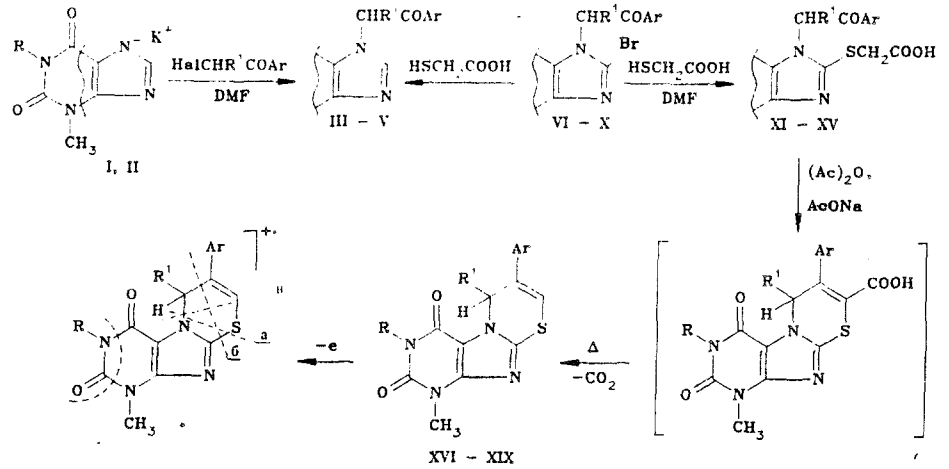
Compound	m/z (I, % of the maximal peak)*																				
	$[M+2]^+$	$[M+1]^+$	$[M]^{+\cdot}$	$[M-CO_2]^{+\cdot}$, Φ_1	$[M-CH_3COO]^+$	$[M-Ar]^+$	$[M-SH]^+$	$[(M-R^1)-RNCO]^+$	$[(M-SH)-RNCO]^+$	$[\Phi_1-CH_2COAr]^+$	$[\Phi_1-CH_3COAr]^+$, Φ_3	$[\Phi_3-RNCO]^+$	[a]$^+$	[b]$^+$	[c]$^+$	$[CH_3COAr]^+$	$[COAr]^+$	$[C_6H_5C{\equiv}CH]^+$	$[SCH_2COOH]^+$	$[Ar]^+$	$[RNCO]^+$
XI		375 (5)	374 (31)	330 (60)	316 (5)	—	—	—	—	211 (25)	210 (24)	225 (21)	—	—	—	120 (7)	105 (100)	—	91 (8)	77 (23)	—
XII	—	389 (11)	388 (51)	334 (5)		—	—	—	—	225 (32)	224 (18)	224 (20)	—	—	—	120 (8)	105 (100	—	91 (10)	77 (22)	—
XIII	424**(12)	423**(8)	422**(30)	378**(15)	364 (7)	—	—	—	—	225 (21)	167 (7)	167 (10)	—	—	—	154**(10)	139**(100)	—	91 (9)	111**(15)	—
XVI***	314 (8)	313 (22)	312 (100)			311 (22)	279 (10)	268 (8)	236 (10)				147 (16)	134 (9)	115 (32)			102 (6)		77 (7)	43 (15)
XVII	328 (4)	327 (16)	326 (60)			311 (100)	293 (5)	268 (6)	—				161 (7)	134 (5)	129 (10)			102 (6)		77 (5)	43 (10)
XVIII	328 (7)	327 (21)	326 (100)			325 (22)	293 (8)	268 (5)	236 (8)				147 (11)	134 (6)	115 (16)			102 (7)		77 (8)	57 (9)

*Peaks of ions with intensity of ≥5% are given.

**Ions containing the ^{35}Cl isotope.

***$[\Phi_2]^+$ 240 (10); $[\Phi_2 - HCN]^+$ 213 (6).

Scheme 1



I, III, V, VI, VIII, IX, XI, XIV—XVII, XIX R=H; II, IV, VII, X, XII, XIII XVIII R=CH_3; III—VII, IX—XIII, XV, XVI, XVIII, XIX R^1=H; VIII, XIV, XVII R^1=CH_3; III, IV, VI—VIII, XI, XII, XIV, XVI—XVIII Ar=C_6H_5; V, IX, X, XIII, XV, XIX . Ar=C_6H_4Cl-p

EXPERIMENTAL

The IR spectra were obtained on a Specord IR-75 spectrophotometer (in KBr tablets), the PMR spectra on a Tesla BS-467 spectrometer (60 MHz) in CF_3COOD solutions, using HMDS as internal standard. The mass spectra were obtained on a Varian MAT-311A spectrometer with the direct introduction of the sample into the ionic source, at an evaporation temperature of 100-150°C, using an accelerating voltage of 3 kV, cathode emission current of 1 mA, and energy of the ionizing electrons of 70 eV, in a low resolution regime.

The characteristics of the synthesized compounds are given in Tables 1-3. The results of the elemental analyses correspond to the calculated data.

7-Aroylalkyl-3-methyl- and -1,3-dimethylxanthines (III-V). **(A).** A mixture of 10 mmoles of a potassium salt of 3-methyl- or 1,3-dimethylxanthine (I, II) and 11 mmoles of α-phenacyl bromide or p-chloro-α-phenacyl bromide in 50 ml of DMFA was boiled for 30 min, then cooled and diluted with 200 ml of water, and the precipitate that separated out was filtered off. Compounds III-V were crystallized from a H_2O–DMFA (1:1) mixture.

(B). A mixture of 10 mmoles of the corresponding 7-aroylalkyl 8-bromo-3-methyl- or 1,3-dimethylxanthine, and 30 ml of thioglycolic acid was boiled for 6-8 h. It was then cooled, diluted with 100 ml of water, and the precipitate that separated out was filtered off and dried.

7-p-Chlorobenzoyl-methyl-8-bromo-1,3-dimethylxanthine (X). A mixture of 14.9 g (50 mmoles) of a potassium salt of 8-bromotheophylline, and 11.7 g (50 mmoles) of p-chlorophenacyl bromide in 100 ml of DMFA was boiled for 20 min. The mixture was cooled and diluted with 100 ml of water. Compound X was crystallized from a H_2O–DMFA (1:2) mixture.

7-Aroylalkyl-3-methyl- and -1,3-dimethylxanthinyl-8-thioacetic Acids (XI-XV). A mixture of 30 mmoles of the corresponding 7-aroylalkyl-8-bromo-methyl- or -1,3-dimethylxanthine (VI-X) [5, 10, 11], and 4.2 ml (30 mmoles) of thioglycolic acid in 70-100 ml of DMFA was boiled for 2 h. The mixture was cooled, poured into 200-300 ml of water, and the precipitate that separated out was filtered off. It was reprecipitated from an aqueous solution of sodium hydrocarbonate by hydrochloric acid and dried. Compounds XI-XV were crystallized from a DMFA–H_2O (1:1) mixture.

3-Aryl-1,4-dihydro-9-methyl- and 7,9-Dimethylthiazino[3,2-f]xanthines (XVI-XIX). A mixture of 20 mmoles of the corresponding 7-aroylalkyl-3-methyl- or -1,3-dimethylxanthinyl-8-thioacetic acid (XI-XV) and 5-8 g of anhydrous sodium acetate in 50 ml of acetic anhydride was boiled for 5-6 h. The mixture was cooled and poured into 250-300 ml of water. After 12 h, the precipitate that separated out was filtered off, dried, and crystallized from a DMFA–H_2O (3:1) mixture.

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CYANOACETYLATION OF 6-AMINOURACILS. SYNTHESIS OF 7-AMINOPYRIDO[2,3-d]PYRIMIDINE-2,4,5-TRIONES

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6-Aminouracils and N-substituted derivatives are cyanoacetylated to give 5-cyanoacetyl-6-aminouracils. In the presence of bases these are converted to pyrido[2,3-d]pyrimidine-2,4,5-triones in high yields.

It is known that oxo pyrido[2,3-d]pyrimidines have antitumor activity [1]. With previous work on the acylation of 6-aminouracils and N-substituted derivatives in mind the aim of this study has been the cyanoacetylation of 6-aminouracils and subsequent conversion to trioxopyrido[2,3-d]pyrimidines.

Reaction of 1-methyl or 3-methyl-6-aminouracils Ia, b with cyanoacetic acid in acetic anhydride with pyridine gives the corresponding 5-cyanoacetyl-6-aminouracils IIa, b in high yields. 1-Butyl- (Ih), 1-phenyl- (Ig), and 1,3-disubstituted 6-aminouracils (Ic-f, i-k) are also readily cyanoacetylated without the pyridine. The unsubstituted 6-aminouracil (I*l*) could be converted to the 5-cyanoacetyl derivative (II*l*) only by phosphorus oxychloride in DMF. Evidently the acylation conditions are determined by the differences in electron density on pyrimidine atom $C_{(5)}$, due to the electron-donor substituents on the nitrogen atoms. It follows that the unsubstituted 6-aminouracil demands a more vigorous acylating medium.

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