SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, AND BIOLOGICAL ACTIVITY OF (ACRIDINYL-9-THIO)ACETIC ACID HYDRAZIDES

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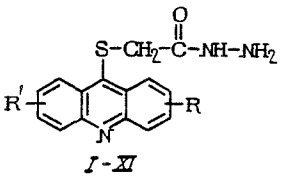
It is known that amides and hydrazides of heterylthioacetic acids, derivatives of five- and six-membered aza-heterocycles are biologically active compounds [3, 4]. Esters and amides of substituted (acridinyl-9-thio)acetic acids, which we have previously studied, have pronounced pharmacological and antimicrobial activity [5-8].

We have carried out the synthesis and a primary biological screening of hydrazides of chloro-, ethoxy-, methoxy-, and nitro-substituted (acridinyl-9-thio)acetic acids. These hydrazides (I-XI) were obtained by treating esters of substituted (acridinyl-9-thio)acetic acids with hydrazine hydrate in an alcoholic medium.



I-XI

The structure of the synthesized compounds was confirmed by IR-spectroscopy, mass spectrometry, and elemental analysis data. In the IR spectra of hydrazides I-XI, an absorption band is recorded of the stretching vibrations of the secondary amino group in the 3350-3170 cm^{-1} region, and a vibration band of the carbonyl group C=O in the 1690-1610 cm^{-1} region. Fragmentary ions are observed in the mass spectra of compounds II-XII, confirming the presence of a hydrazine fragment in the molecule $[M]^+$: $[M - NH_2]^+$, $[M - N_2H_2]^+$, $[M - N_2H_3]^+$. The $[M - CONHNH_2]^+$ ions were recorded as the result of β-decomposition relative to the carbonyl group. The $[M - CH_2 - CO - NHNH_2]^+$ ions are the result of a typical β-decomposition relative to the heteryl ring of the molecule.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in a KBr tablet. The low and high resolution mass spectra were obtained on a "Varian MAT-311a" mass spectrometer. Conditions of running the spectra: ionizing voltage 70 eV, cathode emission current 300 μA, accelerating voltage (3 kV, temperature of exposure 280-310°C). The samples were introduced directly into the ionic source. The results of the elemental analysis correspond to the calculated values.

(2-Chloro-6-nitroacridinyl-9-thio)acetic Acid Hydrazide (IV). A 2.2 g portion (0.04 mole) of hydrazine hydrate was added to a solution of 3.77 g (0.01 mole) of ethyl ester of (2-chloro-6-nitroacridinyl-9-thio)acetic acid in 50 ml of ethanol, and the mixture was heated on a water bath for 25-30 min and evaporated at room temperature. The residue was washed with water on a filter and dried. Yield 2.19 g (65%), red needles (from ethanol).

Compounds I-III (Table 1) were obtained in a similar manner.

Compounds VIII-XI were synthesized in a similar way. On cooling the reaction mixture, the compounds precipitated. They were crystallized from an ethanol–water (2:1) mixture.

Compounds V-VII were synthesized in a similar way, but the duration of heating the reaction mixture varied from 10 to 25 min.

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TABLE 1. Hydrazides of Substituted (Acridinyl-9-thio)acetic Acids

Compound	R	R′	mp, °C	Empirical formula
I	2-Cl	H	160—162	$C_{15}H_{22}ClN_3OS$
II	3-Cl	H	139—141	$C_{15}H_{21}ClN_3OS$
III	4-Cl	H	182—184	$C_{15}H_{21}ClN_3OS$
IV	2-Cl	6-NO_2	280—282	$C_{15}H_{11}ClN_4O_3S$
V	H	H	136—137	$C_{15}H_{13}N_3OS$
VI	2-OEt	H	163—164	$C_{17}H_{17}N_3O_2S$
VII	H	6-NO_2	174—175	$C_{15}H_{12}N_4O_3S$
VIII	2-OMe	H	132—134	$C_{16}H_{15}N_3O_2S$
IX	4-OMe	H	185—187	$C_{16}H_{15}N_3O_2S$
X	2-Me	H	270—272	$C_{16}H_{15}N_3OS$
XI	4-Me	H	285—287	$C_{16}H_{15}N_3OS$

TABLE 2. Acute Toxicity, Neurotropic and Anti-Inflammatory Activity of the Synthesized Compounds

Compound	LD_{50}	Neurotropic activity (sleep duration)		Increment in volume of the rat's paw, % of initial value		
		min	%	after 1 h	after 3 h	after 5 h
II	224	Not tested		33±2,8	29±2,4	23±3,9
III	355	120±9,4	133	51±3,1	67±4,2	42±3,8
V	70	92±5,5	113	42±7,4	32±3,4	24±3,5
VI	205	91±13,4	112	12±6,7	18±6,6	12±6,3
VII	180	—	—	24±4,1	26±3,3	14±1,5
VIII	310	92±7,7	113	23±4,8	35±7,2	38±4,6
IX	310	104±10,6	128	20±3,7	36±1,7	26±3,5
X	230	150±6,6	161	—	—	—
XI	300	112±13	137	—	—	—
Aminazine, 5 mg/kg	—	112±14,0	137	—	—	—
Butadione, 100 mg/kg	—	—	—	24±10,0	37±14,0	31±10,0

EXPERIMENTAL (BIOLOGICAL)

The acute toxicity was determined on mice by the V. B. Prozorovskii et al. method with intraperitoneal administration of the compounds [9]. The anti-inflammatory action was studied on a formalin model of aseptic inflammation in white rats [10].

The influence of the synthesized compounds on ethaminal sodium induced sleep was studied according to [2] (Table 2).

The antihypoxic properties of the synthesized compounds were studied under conditions of hypoxic hypoxia on male rats of the Wistar line, each weighing 150-200 g and on male mice each weighing 18-20 g. The preparations studied were administered intraperitoneally in a dose of 1/20 LD_{50}, 30 min before placing the animals in a barochamber. The elevation was brought to a height of 10,000 m in the course of 10 min. The life time of the animals was recorded to which the synthesized compounds, dibasol in a dose of 1 mg/kg or gutymin in a dose of 100 mg/kg were administered. The results obtained are presented in Table 3.

The antimicrobial activity was determined by the method of serial dilutions in a liquid culture medium (aminopeptide) on 8 strains of pathogenic microorganisms and fungi (Staphylococcus aureus, Escherichia coli, Bacillus pyocyaneus, anthracoid, yeast-like fungus). The experimental results were examined 18-20 h after placing the samples in a thermostat at a temperature of 37°C.

Analysis of the results of biological investigations showed that the hydrazides of chloro-, ethoxy-, methoxy-, and nitro-substituted acridinyl-9-thioacetic acids are moderately toxic compounds according to the K. K. Sidorov classification, and display pronounced neurotropic, anti-inflammatory, analgesic, antihypoxic, antimicrobial and fungistatic properties, in several cases surpassing the activity of preparations used as reference standards (see Tables 2, 3).

TABLE 3. Antihypoxic and Analgesic Activity of Compounds I-XI

Compound (dose)	Life time under hypoxia conditions		Change in pain threshold					
	min	%	after 30 min	after 60 min	after 90 min	after 120 min	after 150 min	after 180 min
V	21±2,6 (rats)	81	143±7,7	203±15,2	230±14,7	207±16,7	198±7,9	183±12,7
VI	35±6,1 (rats)	134	—	—	—	—	—	—
VII	—	—	118±7,5	140±9,1	173±16,5	216±22,7	224±14,5	200±12,8
VIII	27±4 (mice)	675	148±19,6	193±32,7	205±33,9	195±28,1	169±17,7	144±15,9
IX	42±5 (mice)	1050	123±8,4	140±6,8	130±12,3	117±9,1	102±7,3	104±7,6
Dibasol (1 mg/kg)	49±5,9	188	—	—	—	—	—	—
Gutymin (100 mg/kg)	52±7,0	200	—	—	—	—	—	—
Analgin	—	—	137±20	165±40	179±32	155±35,2	150±20,2	127±26

Note. In the study of the antihypoxic activity, the compounds were administered intraperitoneally to rats in a dose of 1/20 LD_{50} per 1 kg body weight of the animal, in the remaining cases — 1/10 LD_{50}.

The antimicrobial activity of the compounds studied is clearly pronounced with respect to Staphylococcus aureus, the anthracoid spores and Candida Albicans fungi. The compounds have this action in concentrations of 62.5, 31.2, 15.6, 7.8 μg/ml, respectively.

Considering the relationship between the structure of the (acridinyl-9-thio)acetic acid hydrazides and the character of their biological activity, it should be noted that blocking of the ester group in the molecules of (monochloroacridinyl-9-thio)acetic acid esters by a hydrazine residue results in a substantial decrease in the acute toxicity of the compounds and intensification of the anti-inflammatory and anti-hypoxic activity. Replacement of the methoxy group in the 2- and 4-positions of the molecules of (acridinyl-9-thio)acetic acid hydrazides by an ethoxy group results in a decrease in the acute toxicity. In the series of ethoxy-, methoxy-, chloro-substituted hydrazides of (acridinyl-9-thio)-acetic acids, the analgesic and anti-inflammatory activity is most strongly pronounced for the ethoxy derivatives.

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