SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF SULFUR-CONTAINING AMIDES OF DICARBOXYLIC ACIDS

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Derivatives of malonic acid exhibit a wide spectrum of pharmacological properties. There are compounds in this group that exhibit hypotensive, diuretic, spasmolytic, antioxidant, antiinflammatory, and analgetic effects [1 – 5].

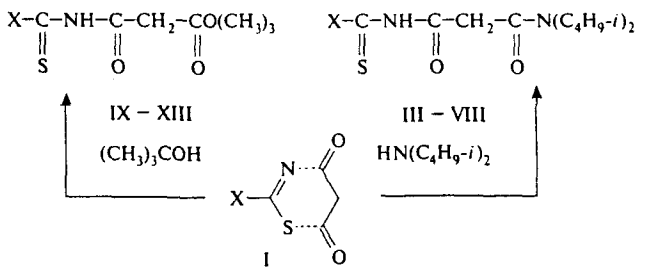
The purpose of this work was to synthesize nonsymmetric sulfur-containing diamides and amidoesters of malonic and oxalic acids and to study their hypotensive, antiarrhythmic, and antihypoxic activity.

For the synthesis of thioaroyl(alkylthio) derivatives of malonic acids (III – XIII) we used the reaction of 1,3-thiazidines (I) with nucleophilic reagents (alcohols, amines), since no other schemes led to the desired target products [6]. Special attention was paid to the interaction of 2-aryl-4,6-dioxo-1,3-thiazines with diisobutylamine, because this amine was known not to give high toxicity of the products while imparting high pharmacological activity [7].

2-Aryl(alkylthio)-4,6-dioxo-1,3-thiazines (I) are relatively strong acids (pK_a 3.0 – 5.0 in 50% ethanol) and readily form salts with amines on mixing the reagents in various solvents at 18 – 20°C. Heating diisobutylammonium salts, as well as the interaction of secondary amines with thiazines I on heating in toluene or dioxane, leads to the formation of diamides III – VIII. Note that replacement of the substituent at C(5) in the thiazine cycle (arylthio group) by an alkylthio group allows the reaction with diisobutylamine to be performed under much softer conditions (in benzene at 60°C) but at a much higher rate.

The reaction with *tert*-butyl alcohol leads to amidoesters of malonic acid (XI – XIII). The *tert*-butyl alcohol for reaction with thiazines I (as well as for aminolysis) must be thoroughly dried because the presence of even minor amounts of water in the reaction mixture would hinder the process, producing destruction of both the initial thiazines and the final products (diamides and amidoesters of malonic acid).

Diamides (XIV) and amidoesters of oxalic acid (XV) were synthesized through the reactions of alcoholysis and aminolysis of 2-aryl-4,5-dioxo-1,3-thiazolidines (II). The latter were obtained by condensation of the corresponding thiobenzamides with excess oxalyl chloride in thoroughly dehydrated solvents. The constants of the thus obtained 1,3-thiazolidinediones II corresponded to those reported in the literature [8]. After the interaction of thiazolidinedione II with diisobutylamine in benzene at 60°C we isolated two products from the reaction mixture: first, by separating the precipitate on filter and second, by evaporating the mother liquor. The products had different colors, melting temperatures, R_f (TLC), and physicochemical characteristics. For example, the IR spectrum of crystalline samples of one of the compounds showed two absorption bands in the region of stretching vibrations of the C=O bond (1710 and 1640 cm^{-1}), whereas the spectrum of the other compound exhibited a single band at 1650 cm^{-1}. Some differences were also observed in the ^{13}C NMR spectra of these compounds. While having similar signals due to carbon nuclei of the aromatic ring (114 – 148 ppm), thiocarbonyl carbon (202 ppm), and alkyl carbon (20 – 26 ppm), the spectra exhibited different numbers of signals due to carbonyl groups (a double signal at 163.7 and 159.6 ppm against a single line at 155.0 ppm). Distinctions were also found in the UV spectra. On this basis, the product obtained upon evaporation of the mother liquor was assigned the structure of N′,N′-diisobutyl-N-thioaroyloxalyldiamide (XIV), while the second product, isolated upon filtration of the precipitate, was attributed the structure of N′,N′-diisobutyl-N-thioaroylurea (XVI). These unusual reaction pathways are explained by the fact that heating of 2-aryl-1,3-thiazolidine-4,5-dione (II) ia accompanied by decarbonylation with the formation of benzylthioisocyanate [9].



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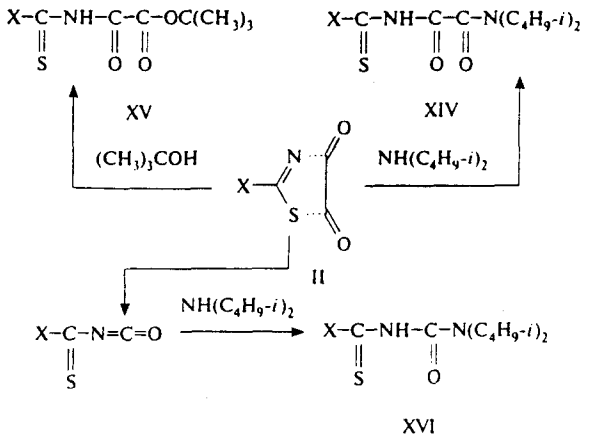

X = *p*-$CH_3OC_6H_4$ (III, IX, XIV);
C_6H_5 (IV, X, XV, XVI);
p-$NO_2C_6H_4$ (V, XI);
p-, *m*-$(CH_3O)_2C_6H_3$ (VI);
$C_6H_5CH_2S$ (VII, XII);
C_2H_5S (VIII, XIII).

For this reason, the interaction of thiazolidone II with diisobutylamine at 60°C involves two competing reactions: (i) decomposition of thiazolidinedione by secondary amine with the formation of oxalic acid diamide and (ii) decarbonylation of compound II followed by nucleophilic addition of amine to isocyanate. By changing the temperature, the direction of the reaction can be shifted toward ureas (70°C) or oxalic acid diamides (20°C). A similar behavior of 2-aryl-1,3-thiazolidine-4,5-dione (II) was observed in their reaction with *tert*-butyl alcohol.

Amides and esters of thiosubstituted malonamides and oxalylamides obtained by the above reactions appear as deep-colored crystalline substances well soluble in organic solvents.

TABLE 1. Physicochemical Characteristics of Synthesized Compounds

Compound	M.p., °C (solvent for crystallization)	R_f*	Empirical formula	Yield, %
III	101 – 102(ethyl ether)	0.35	$C_{19}H_{28}N_2O_3S$	65
IV	94 – 96 (hexane)	0.69	$C_{18}H_{26}N_2O_2S$	70
V	115 – 117 (ethyl ether)	0.40	$C_{18}H_{25}N_3O_4S$	60
VI	123 – 125 (hexane – benzene)	0.24	$C_{20}H_{30}N_2O_4S$	50
VII	116 – 117 (hexane)	0.37	$C_{19}H_{28}N_2O_2S_2$	75
VIII	79 – 80 (hexane)	0.51	$C_{14}H_{26}N_2O_2S$	42
IX	103 – 104 (ethanol)	0.46	$C_{15}H_{19}NO_4S$	52
X	123 – 124 (petroleum ether)	0.65	$C_{14}H_{17}NO_3S$	55
XI	83 – 84 (hexane)	0.61	$C_{14}H_{16}N_2O_5S$	77
XII	84 – 85 (hexane)	0.69	$C_{15}H_{19}NO_3S_2$	65
XIII	52 – 54 (hexane)	0.88	$C_{10}H_{17}NO_3S_2$	58
XIV	110 – 113 (hexane)	0.45	$C_{18}H_{26}N_2O_3S$	40
XV	134 – 135 (hexane)	0.56	$C_{13}H_{15}NO_3S$	60
XVI	119 – 121 (benzene)	0.48	$C_{16}H_{24}N_2OS$	55

* TLC on Silufol UV-254 (Czechoslovakia) with acetone – hexane (1 : 2) eluent mixture.

The x-ray diffraction analysis showed that malonodiamides have a nonplanar structure with intramolecular hydrogen bonds [4].

The IR spectra of crystalline samples of compounds III – VIII (Table 2) have two absorption bands of equal intensities in the region of stretching vibrations of C=O bonds (1750 and 1630 cm^{-1}), the low-frequency component being asymmetric due to an additional absorption at 1660 cm^{-1}. The region of stretching vibrations of the NH bond contains weak bands at 3300 cm^{-1} and complex bands at 3200 cm^{-1}. The IR spectra of dilute solutions of diamides III – VIII in $CHCl_3$ and DMSO show evidence that the molecules are not associated and exist in the form of chelate cycles with intramolecular hydrogen bonds [10]. The IR spectra of esters IX – XIII differ but little from the spectra of diamides, showing two absorption bands ν_{NH} in the region of 3400 and 3160 cm^{-1},

TABLE 2. UV, IR, and ^1H NMR Characteristics of Synthesized Compounds III – XVI

Compound	UV spectrum: λ_{max}, nm ($E \times 10^4$)	^1H NMR spectrum ($CDCl_3$), δ, ppm			IR spectrum (nujol mulls), ν_{max}, cm^{-1}	
		X	NH(1H)	$COCH_2CO$	C=O	NH
III	240(1.050)				1720	3175
	345(0.925)	7.44(4H)	12.5	3.86(2H)	1630	3400
	476(0.100)					
IV	272(0.800)				1740	3200
	312(0.600)	7.52(5H)	12.6	3.75(2H)	1630	3368
	484(0.145)					
V	273(1.200)				1630	3180
	312(0.875)	8.17(4H)	12.7	3.78(2H)	1750	3300
	490(0.043)					
VI	270(1.150)				1640	3180
	295(0.830)	7.33(3H)	12.3	3.93(2H)	1720	3340
VII	263(1.375)				1620	3215
	310(0.940)	7.4(5H)	12.6	3.70(2H)	1730	3300
VIII	260(1.375)				1610	3200
	312(0.900)	–	12.5	3.50(2H)	1705	3350
IX	292(1.087)				1680	3220
	345(1.187)	7.85(4H)	11.8	3.47(2H)	1745	3350
	476(0.050)					
X	272(0.512)				1720	3275
	315(0.250)	7.60(5H)	11.3	3.75(2H)	1745	3400
	484(0.160)					
XI	272(1.263)				1680	3200
	312(0.625)	7.3(4H)	11.0	3.60(2H)	1725	3368
	496(0.225)					
XII	263(1.200)				1690	3215
	312(1.062)	7.34(5H)	11.3	4.40(2H)	1735	3300
XIII	260(1.420)				1690	3200
	310(1.200)	–	11.2	3.30(2H)	1735	3300
XIV	295(1.440)				1650	3120
	345(1.470)	7.5(4H)	12.2	–	1710	3225
	470(0.032)					
XV	245(0.790)				1680	3215
	300(1.060)	7.5(5H)	11.8	–	1750	3350
	465(0.023)					
XVI	405(0.088)	7.7(5H)	11.2	–	1650	3190

$\nu_{C=O}$ at 1740 and 1680 cm^{-1}, and the bands due to ester groups.

The ^1H NMR spectra of dimethylsulfoxide and chloroform solutions of compounds III – XVI (Table 2) show signals due to protons of methylene groups (malonic acid derivatives), NH, isobutyl (*tert*-butyl) groups, and aromatic ring (alkylthio groups).

The electronic absorption spectra (Table 2) of aroylthiodiamides III – V and aroylthioamidoesters IX – XI of malonic acid, as well as the spectra of analogous derivatives of the oxalic acid (XIV, XV), show two maxima in the UV range at 240 – 295 and 300 – 345 nm, and a band in the visible range at 465 – 490 nm. The UV spectra of alkylthiomalonodiamides VI and VII exhibit two maxima in the region of 260 – 312 nm, and the spectrum of urea derivative (XVI) has a band at 255,405 nm.

EXPERIMENTAL CHEMICAL PART

The electronic absorption spectra of ethanol solutions of the compounds studied were recorded on an SF-20 spectrophotometer. The ^1H and ^{13}C NMR spectra of the sample solutions in $CDCl_3$ and DMSO-d_6 were measured on a Bruker AP200 spectrometer (operated at 200 MHz in the ^1H regime) using HMDS as the internal standard. The IR spectra of the synthesized compounds prepared as vaseline oil suspensions were measured on a Specord IR-75 spectrophotometer. The completion of reactions and the purity of the target products were checked by thin-layer chromatography using Silufol UV-254 plates. The data of elemental analyses agreed with the results of analytical calculations for the empirical formulas proposed (Table 1).

N',N'-Diisobutyl-N-*para*-methoxythiobenzoylmalonodiamide (III). To a suspension of 4.25 mmole of 4-hydroxy-2-*para*-methoxyphenyl-6-oxo-6H-1,3-thiazine (I) [11] in 50 ml of anhydrous toluene is added 7.2 mmole diisobutylamine. The reaction mixture is stirred for 30 min at 20 – 25°C and heated for 20 min at 115°C. Then toluene and excess amine are evaporated in vacuum (15 Torr) at 60 – 65°C, and the oily residue is crystallized by adding ethyl ether. Compounds IV – VIII are obtained by a similar procedure.

***tert*-Butyl ester of N-*para*-methoxythiobenzoylmalonamic acid (IX)** [11]. To a suspension of 4.25 mmole of 4-hydroxy-2-*para*-methoxyphenyl-6-oxo-6H-1,3-thiazine (I) [11] in 100 ml of anhydrous toluene is added 8.5 mmole of anhydrous *tert*-butyl alcohol. The reaction mixture is heated for 3 h at 90°C. Then toluene and excess alcohol are evaporated in vacuum (15 Torr) at 50°C. The oily residue is crystallized by triturating with ethyl ether and recrystallized from absolute ethanol. A similar procedure is used for the synthesis of compounds IX and XI.

***tert*-Butyl ester of N-*para*-benzyldithioformylmalonamide (XII).** A suspension of 4 mmole of 2-benzylthio-4,6-dioxo-5,6-dihydro-4H-1,3-thiazine (I) in 15 ml of *tert*-butyl alcohol is heated for 2 h at 80°C. Then the excess alcohol is evaporated in vacuum (20 Torr) at 40 – 50°C. The oily residue is crystallized by adding ethyl ether and recrystallized from hexane. A similar procedure is used for the synthesis of compound XIII.

N',N'-Diisobutyl-N-*para*-methoxythiobenzoyloxalyldiamide (XIV). To a suspension of 10 mmole of 2-*para*-methoxyphenyl-1,3-thiazolidine-4,5-dione [8] in 50 ml of anhydrous benzene is added 11 mmole diisobutylamine. The reaction is carried out for 2 h at 20 – 25°C. The course of the reaction is monitored by thin-layer chromatography using Silufol UV-254 plates. Then benzene and excess amine are evaporated in vacuum (20 Torr) at 20°C, The oily residue is triturated with hexane and recrystallized from hexane.

***tert*-Butyl ester of N-thiobenzoyloxalamic acid (XV).** To a suspension of 5.2 mmole of 2-phenyl-1,3-thiazolidine-4,5-dione [8] in 15 ml of anhydrous toluene is added 5.5 mole of *tert*-butyl alcohol. The reaction is carried out by stirring for 2 h at 20 – 25°C. The course of the reaction is monitored by thin-layer chromatography using the Silufol UV-254 plates. Then toluene and excess alcohol are evaporated in vacuum at 40°C, The oily residue is triturated with hexane and recrystallized from hexane.

N',N'-Diisobutyl-N-thioaroylurea (XVI). To a suspension of 10 mmole of 2-phenyl-1,3-thiazolidine-4,5-dione in 50 ml of anhydrous is added in one portion 11 mmole diis-

TABLE 3. Hypotensive and Antihypoxic Activity of Compounds III – XV

Compound	LD_{50}, mg/kg	Maximum hypotensive effect, % of control ($M \pm m$)	Rat survival at 12 km 'altitude'	
			min ($M \pm m$)	% to control
III	1209 (1365 – 1053)	– 36 ± 1.5	4.7 ± 0.97	+ 15
IV	1367 (1472 – 1262)	– 22 ± 8.3	4.7 ± 1.1	+ 17
V	533 (604 – 462)	– 25 ± 0.88	9.65 ± 2.8	+ 135
VI	1000 (1285 – 725)	– 26 ± 2.4	7.9 ± 2.4	+ 93
VII	1733 (1802 – 1665)	Inactive	9.65 ± 3.1	+ 135
VIII	1005 (1140 – 970)	– 19 ± 8.1	7.5 ± 1.7	+ 83
IX	642 (720 – 564)	– 30 ± 4.3	5.9 ± 0.9	+ 44
X	600 (708 – 492)	– 22 ± 1.8	11.5 ± 3.2	+ 180
XI	250 (298 – 202)	– 12 ± 1.6	8.3 ± 1.9	+ 102
XII	868 (996 – 740)	– 22 ± 3.0	7.3 ± 1.7	+ 78
XIII	267 (314 – 220)	– 28 ± 1.1	6.95 ± 1.4	+ 70
XIV	1000 (1055 – 945)	– 26 ± 5.6	4.7 ± 0.9	+ 14
XV	975 (1039 – 891)	– 20 ± 4.9	5.1 ± 1.1	+ 25
Gutimine (50 mg/kg i.p.)	1440 (1260 – 1620)	–	7.8 ± 2.1	+ 90
Amtizole (25 mg/kg i.p.)	–	–	9.36 ± 3.4	+ 105
Nifedipine (5 mg/kg)	750 (795 – 705)*	– 24 ± 3.7	–	–
Control	–	–	4.1 ± 0.8	–

* Peroral.

TABLE 4. Antiarrhythmic Activity of Compounds III – XV for the Model of Calcium Chloride Induced Arrhythmia

Compound	Number of animals tested	Rat survival lifetime, min ($M \pm m$)	Tolerable amount of $CaCl_2$, mg/kg	Frequency of ventricular fibrillation cases, %
Control	25	0.66 ± 0.08	220	100
III	10	2.0 ± 0.38	352 ± 48	89
IV	12	1.61 ± 0.36	286 ± 33	90
V	12	1.75 ± 0.24	286 ± 44	70
VI	12	2.3 ± 0.29	308 ± 42	72
VII	12	1.8 ± 0.3	308 ± 48	71
VIII	10	2.3 ± 0.18	308 ± 53	82
IX	10	4.7 ± 2.0	418 ± 77	39
X	12	1.8 ± 0.33	330 ± 62	79
XI	12	2.9 ± 0.51	638 ± 88	56
XII	10	2.1 ± 0.93	396 ± 18.5	49
XIV	8	0.67 ± 0.09	220	100
XV	8	1.1 ± 0.12	220	100
Quinidine	6	2.6 ± 0.21	420 ± 81	62
Novocainamide	6	4.9 ± 0.19	488 ± 42	60

obutylamine. The mixture is allowed to stand for 30 min and cooled. The precipitate is filtered and recrystallized from benzene.

EXPERIMENTAL PHARMACOLOGICAL PART

The acute toxicity of the synthesized compounds was studied by intraperitoneal injections to white mice weighing 16 – 20 g. The LD_{50} values and confidence intervals were determined by the graphical Miller – Teinter method [12].

The hypotensive activity was determined on a group of 80 cats weighing 2.5 – 3.5 kg. The animals were narcotized with sodium pentobarbital (50 mg/kg). The arterial pressure was measured in the common carotid artery. The test preparations were introduced by intramuscular injections at a dose of 15 mg/kg.

The antiarrhythmic activity was studied on a group of 190 urethane-narcotized (1 g/kg) rats with a model arrhythmia induced by 10% calcium chloride solution (200 mg/kg i.v.). The test compounds were introduced at a dose of 7 mg/kg with Tween solution 5 min before the calcium chloride injection. The heart rhythm was monitored with the aid of an ELKAR electrocardiograph using type II standard leads. The antiarrhythmic activity was evaluated by the survival lifetime, the frequency of ventricular fibrillation cases, and the tolerable amount of arrhythmogenic agent.

We have also studied animals with aconitine-induced (40 μg/kg) model arrhythmia, whereby the test compounds were introduced at a dose of 7 mg/kg either as prophylactic injections (40 – 45 min before aconitine) or as therapeutic injections (immediately after the arrhythmia development). The antiarrhythmic activity was evaluated for the therapeutic injections by the duration of arrhythmia and the number of lost animals, and for the prophylactic injections, by the onset of arrhythmia, the length of latent period, the duration of arrhythmia, and the number of lost anumals.

TABLE 5. Antiarrhythmic Activity of Compounds III, VI, VIII, IX, and XI for the Model of Aconitine Induced Arrhythmia (Therapeutic Effect)

Compound	Duration of arrhythmia, min ($M \pm m$)	Loss of anumals, %
III	21.3 ± 3.4	0
VI	35.4 ± 2.7	0
VIII	29.6 ± 3.1	0
IX	32.6 ± 2.3	0
XI	37.2 ± 1.9	0
Quinidine	29.8 ± 4.2	8
Novocainamide	40.9 ± 8.3	12
Control	47.3 ± 4.9	15

Hypobaric hypoxia was studied on rats by lifting the animals in an altitude chamber and monitoring their lifetime at an effective altitude of 12 km during a 20 min observation period. The test compounds were injected (25 mg/kg i.p.) 1 h before the lift start.

The reference preparations were represented by nifedipine (5 mg/kg i.v.) for the hypotensive activity tests, novocainamide (40 mg/kg i.v.) and quinidine (20 mg/kg i.v.) for the experiments with arrhythmia, and gutimine (50 mg/kg i.p.) and amtizole (25 mg/kg i.p.) for the study of antihypoxic activity [13 – 19].

Below we summarize data on the pharmacological activity of compounds III – XV. The urea derivative XVI exhibited no significant biological activity within the framework of the models studied, while its acute toxicity was 1.5 – 2 times that of the malonic and oxalic acid derivatives.

The data of Table 3 give evidence that all the studied compounds are low-toxic substances: the LD_{50} values are in most cases close to or exceeding 1000 mg/kg.

Observation of the arterial pressure variations showed that all compounds except VII possess a hypotensive activity. In most cases, the arterial pressure starts decreasing in 15 – 20 min after the injection of the test preparations, and the effect reaches a maximum in 1 – 2 h. The hypotensive action is retained during a time period exceeding 5 h. For nifedipine, the maximum hypotension is observed in 30 – 50 min after the injection, and in 5 h the arterial pressure is close to the initial value.

The synthesized compounds also exhibit an antihypoxic activity, but the effect varies within wide limits (Table 3). The maximum efficiency is offered by compounds V, VII, X, and XI, which ensured a 30% survival of the test rats against the complete loss of animals in the control group.

The compounds studied also produced some antiarrhythmic effect with respect to the calcium chloride model of ar-

TABLE 6. Antiarrhythmic Activity of Compounds III, VI, VIII, IX, and XI for the Model of Aconitine Induced Arrhythmia (Prophylactic Effect)

Compound	Onset of arrhythmia, %	Latent period, min ($M \pm m$)	Duration of arrhythmia, min ($M \pm m$)	Loss of anumals, %
III	67	7.3 ± 2.1	22.4 ± 1.8	0
VI	71	7.0 ± 2.2	26.1 ± 2.9	0
VIII	40	11.0 ± 2.3	38.8 ± 3.7	0
IX	50	7.2 ± 1.8	46.2 ± 4.2	0
XI	72	7.0 ± 1.6	29.5 ± 2.9	0
Quinidine	100	10.8 ± 3.8	43.8 ± 2.7	7
Novocainamide	100	7.3 ± 2.9	49.4 ± 3.2	8
Control	100	4.6 ± 1.9	47.3 ± 4.9	15

rhythmia (Table 4). As is seen, injection of compounds III and VI – XII allowed the animals to survive upon the injection of 2 – 4 lethal doses of the arrhythmogenic agent.

In the tests with aconitine-induced arrhythmia, compounds III, VI, VIII, IX, and XI exhibited a pronounced antiarrhythmic action for both the prophylactic and therapeutic injections. In both cases, the injections eliminated the loss of animals and reduced the duration of arrhythmia (Tables 5 and 6). After the preventive injections of the tested compounds, the arrhythmia was observed only in 40 – 70% animals and the latent period increased by more than 50% against the control. Quinidine and novocainamide increased the latent period 2 – 3 times, but in no single case did these drugs prevent the development of arrhythmia.

Thus, the results of our experiments with substituted malonic acid derivatives showed that *tert*-butyl esters (IX – XIII) are two times as toxic as diisobutylamides (III – VIII). The hypotensive effect of the compounds studied is only slightly affected by variations of their structure. The antiarrhythmic action is most pronounced in amidoesters of the malonic acid (IX – XIII), but is completely absent in derivatives (XIV, XV) of the oxalic acid. The antihypoxic action of the oxalic acid derivatives (XIV, XV) is inferior to that of the malonic acid derivatives. In the latter group, the antiarrhythmic effect is most pronounced in the same compounds (VI, VII, IX, XI) that exhibit a high activity with respect to hypoxia.

The entire body of data obtained suggest good prospects in the search for new cardiovascular drugs and antihypoxants in the series of substituted sulfur-containing amides of malonic acid.

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