The central neurotropic activity of the compounds obtained (influence on the orientational reaction, the muscle tonus, and Corazol induced convulsions) was studied by the generally accepted methods [2] in experiments on white nonpedigree male mice, each weighing 22-25 g. The compounds were introduced intraperitoneally in the form of aqueous solutions in a dose of 50 mg/kg. The control animals were administered the solvent.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF p-SUBSTITUTED ANILIDES OF THIOPROPANOIC ACIDS

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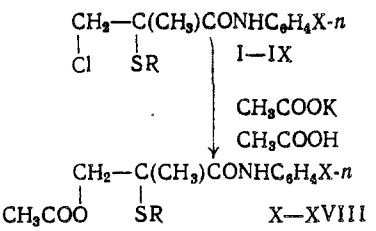
In continuation of our studies on the synthesis of potential antitumorigenic compounds from the group of derivatives of alkylthiocarboxylic acids [1] and the establishment of the relationship between their structure and the biological activity of the corresponding halo-substituted compounds (I-IX), we synthesized p-substituted anilides of 3-acetoxy-2-alkylthiocarboxylic acids (X-XVIII) with electron-donor and electron-acceptor substituents. The consideration for the synthesis of the latter compounds was the presence of pronounced antitumorigenic properties in p-carbethoxyanilide of 3-acetoxy-2-methylthiopropanoic acid (XVIII) [4].



For the meanings of R and X, see Table 1.

The anilides of 3-chloro-2-methyl-2-alkylthiopropanoic acid I-IX were prepared by adding methyl or ethylsulfenyl chlorides to p-substituted anilides of 2-methyl-2-propenoic acid in dry dichloromethane; by reaction with potassium acetate in glacial acetic acid, compounds I-IX gave the p-substituted anilides of 3-acetoxy-2-methyl-3-alkylthiopropanoic acids X-XVIII, and as by-products, the isomeric p-substituted anilides of 2-acetoxy-2-methyl-3-alkylthiopropanoic acid, the amount of which did not exceed 10% (according to the PMR spectroscopy data). The pure isomers X-XVIII were obtained by fractional crystallization. The characteristics of the compounds are given in Table 2, and the PMR spectra in Table 1. The investigation of the PMR spectra also showed that the screening of the NH protons changes depending on the character of the substituent in the aromatic ring, and the equivalency of the methylene protons in these molecules also varies. This shows that the electronic effects of the substituents are transmitted along the entire carbon chain of I-XVIII.

The toxicological investigations of X-XVIII showed that they exhibit slight or moderate (XII, XIV, XVIII) toxicity (Table 3). All of them have little influence on the blood parameters and body weight of the experimental animals. Antitumorigenically, anilides X-XVII were found to be slightly active against a rapidly growing Walker carcinosarcoma (WCS), in contrast

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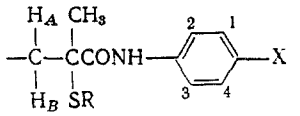
TABLE 1. PMR Spectra of Cl (I-IX) and CH_3OCO (X-XVIII)[a]



Compound	R[b]	X[c]	Chemical shifts of protons δ, ppm						
			of the main skeleton				aromatic[d]		
			CH_3[e]	H_A^f	H_B^f	$\delta_A-\delta_B$	$H_{(1)}H_{(4)}$	$H_{(2)}H_{(3)}$	NH
I	CH_2CH_3	OCH_3	1,53	4,01	3,55	0,46	6,69	7,29	8,37
II	CH_2CH_3	OC_2H_5	1,53	3,94	3,64	0,30	6,60	7,26	8,28
III	CH_2CH_3	H	1,59	3,95	3,71	0,24	g	—	8,53
IV	CH_2CH_3	CH_3	1,53	3,97	3,63	0,34	6,93	7,27	8,43
V	CH_2CH_3	Cl	1,59	3,91	3,71	0,20	7,27	7,42	8,57
VI	CH_2CH_3	$COOCH_3$	1,63	4,18	3,71	0,47	7,87	7,51	9,03
VII	CH_2CH_3	$COOC_2H_5$	1,61	3,99	3,71	0,28	7,86	7,47	8,98
VIII	CH_3[h]	Cl	1,59	3,96	3,70	0,26	7,26	7,46	8,56
IX	CH_3[h]	$COOC_2H_5$	1,60	4,02	3,86	0,16	7,95	7,57	8,78
X	CH_2CH_3	OCH_3	1,53	4,47	4,17	0,30	6,45	7,03	8,13
XI	CH_2CH_3	OC_2H_5	1,53	4,46	4,17	0,29	6,57	7,19	8,31
XII	CH_2CH_3	H	1,52	4,41	4,24	0,17	g	—	8,73
XIII	CH_2CH_3	CH_3	1,47	4,28	4,13	0,13	7,03	7,26	8,51
XIV	CH_2CH_3	Cl	1,52	4,36	4,29	0,07	7,26	7,46	8,62
XV	CH_2CH_3	$COOCH_3$	1,53	4,43	4,40	0,03	7,88	7,68	8,81
XVI	CH_2CH_3	$COOC_2H_5$	1,53	4,28	4,23	0,05	7,96	7,63	8,83
XVII	CH_3[h]	Cl	1,52	4,39	4,28	0,11	7,22	7,47	8,63
XVIII	CH_3[h]	$COOC_2H_5$	1,53	4,33	4,27	0,06	7,91	7,54	8,61

Note. a) δ CH_3OCO 2.03-2.05 ppm s (3H); b) δ CH_2CH_3 2.56-2.66 ppm, m (2H); 1.18-1.23 ppm t (3H) J = 8 Hz; c) the parameters of PMR spectra of X are close to those given in [2]; d) A_2B_2-multiplet with J_{O+M} = 8-9 Hz; e) CH_3 s (3H); f) AB-quartet J_{AB} = 11-12 Hz; g) ABX-multiplet H_2H_3 = 7.42, $H_{(1)}H_{(4)}$ = 7.01-7.05 ppm; h) δ SCH_3 2.07-2.09 ppm, s (3H).

TABLE 2. p-Substituted Anilides of 3-Chloro-(I-VIII) and 3-Acetoxy-(X-XVIII)-2-methyl-2-alkylthiopropanoic Acids

Compound	mp, °C	Empirical formula
I	51,5—53	$C_{13}H_{16}ClNO_2S$
II	77—78	$C_{14}H_{20}ClNO_2S$
III	70,5—71	$C_{12}H_{16}ClNOS$
IV	58—59	$C_{13}H_{18}ClNOS$
V	83—84	$C_{12}H_{15}Cl_2NOS$
VI	120—121	$C_{14}H_{18}ClNO_3S$
VII	106—107	$C_{15}H_{20}ClNO_3S$
VIII	93,5—95	$C_{11}H_{13}Cl_2NOS$
X	87—88	$C_{15}H_{21}NO_4S$
XI	71,5—72	$C_{16}H_{23}NO_4S$
XII	64,5—65	$C_{14}H_{19}NO_3S$
XIII	42—44	$C_{15}H_{21}NO_3S$
XIV	72—73	$C_{14}H_{18}ClNO_3S$
XV	94—94,5	$C_{16}H_{21}NO_5S$
XVI	78,5—79	$C_{17}H_{23}NO_5S$
XVII	87—88	$C_{13}H_{16}ClNO_3S$

Note. Compounds III, VII, VIII were recrystallized from CCl_4, VI — from ethyl acetate, XIV, XV, XVI, XVII — from CCl_4 and pentane, the remainder from ethyl acetate and hexane.

TABLE 3. Toxicity and Antitumorigenic Activity of Compounds X-XVIII and Their Action on Blood Parameters in Tumor-Carrying Rats

Compound	MID (minimally inhibiting dose)	TD (toxic dose)	Inhibition of tumor growth, %				Hemoglobin		Leukocytes	
	mg/kg		S-45	WCS	B_{16}	LIAC	g %	c*, %	thous/mm^3	c*, %
X	2000	500	12,5	3,0	21,5 ($P<0,05$)		c 13,2±0,8 13,9±0,6	+5,3	16,6±0,9 19,5±1,3	+17,5
XI	2000	500	33,0 ($P<0,05$)	7,4	38,0 ($P<0,02$)		c 14,4±0,1 13,9±0,2	—3,5	20,2±0,9 22,2±1,9	+9,9
XII	1000	200	20,6 ($P<0,5$)	25,6 ($P<0,05$)	5,0		c 12,7±0,5 12,6±0,2	—1,0	22,9±0,8 22,1±1,6	—3,5
XIII	1800	250	58,6 ($P<0,01$)	17,0	16,3 ($P<0,5$)		c 12,6±0,3 14,5±0,3	+15,0	23,4±3,5 22,3±2,4	+4,7
XIV	700	300	11,1	22,8 ($P<0,05$)	46,1 ($P<0,02$)	61,5 ($P<0,01$)	c 10,5±0,6 9,0±1,2	—13,9	33,1±5,9 44,2±5,4	+33,5
XV	2000	500	53,6 ($P<0,05$)	20,0	25,9 ($P<0,05$)		c 14,4±0,1 13,9±0,4	—3,5	20,2±0,9 19,6±1,4	—3,0
XVI	2000	500	37,7 ($P<0,001$)	24,0	30,0 ($P<0,05$)	34,6 ($P<0,05$)	c 10,5±0,6 10,7±0,7	—1,9	33,1±5,9 35,5±4,4	+7,3
XVII	900	200	16,0	0	0	44,6 ($P<0,05$)	c 12,3±0,2 12,0±0,4	—2,5	20,7±3,2 24,1±1,8	+16,4
XVIII	2000	300	41,0 ($P<0,01$)	53,8 ($P<0,01$)	27,2 ($P<0,05$)		c 13,1±0,2 11,2±0,3	—14,5	18,5±1,6 19,6±2,7	+5,9

Note. c — Control, c* — compared with control. LD_{100}, mg/kg; XII — 1500, XIV — 1000, XVII — 1300. Inhibition of tumor growth, %: X — S-180 — 42.5% ($P < 0.05$); XIV — Pliss LS — 44.5% ($P < 0.05$); XV — LL — 21% ($P < 0.5$).

to XVIII (53.8%). The most active with respect to sarcoma-45 (S-45) are compounds having CH_3 (XIII) and $COOCH_3$ (XV) groups as substituents in the aromatic ring (they suppress tumors by 58 and 53.6%, respectively). Compound X containing the OCH_3 group has low activity. A substituent with an electron-acceptor character $COOCH_3$ (XV) increases the antitumorigenic activity (ATA) to a lesser extent than the CH_3 group (XIII); on the contrary, the anilide with the OCH_3 group (X) is very slightly active. The anilide containing Cl (XIV) inhibited the growth of the Pliss lymphosarcoma (LS) by 44.5%. It was also found to be most effective in its action on the grafted tumors in mice – melanoma B_{16} (by 46.6%) and large intestine adenocarcinoma (LIAC) (by 61.5%).

The above data show that the ATA of p-substituted anilides X-XVIII does not correlate with the electron-donor or electron-acceptor properties of substituents in the aromatic ring, and possibly depends on fine changes in the structure by the action of substituents having definite influence on the vitally important processes of the tumor cells.

EXPERIMENTAL (CHEMICAL)

The PMR spectra of the compounds were recorded on a "Hitachi R-22" spectrometer (90 MHz, Japan) in CCl_4 [$(CD_3)_2CO$ (VI)], using HMDS as internal standard. The analysis the PMR spectra was carried out according to the rules of the first order perturbation theory and methods described for the AB, ABX and A_2B_2 spin systems [2].

The course of the reactions and the chemical homogeneity of the compounds was monitored by the TLC method on Silufol UV-254 plates (CSSR) in an ethyl acetate–benzene–hexane (1:1:1) system, with development by UV light.

The results of the elemental analysis satisfactorily corresponded with the calculated values.

p-Substituted Anilides of 2-Methyl-2-alkylthio-3-chloropropanoic Acid (I-IX). A 1.65 g portion (20 mmoles) of methylsulfenyl chloride or 1.98 g (20 mmoles) of ethylsulfenyl chloride in 15 ml of dry CH_2Cl_2 was added dropwise at 0-15°C, with stirring, to 20 mmoles of a p-substituted anilide of 2-methyl-2-propenoic acid in 40 ml of dry CH_2Cl. The reaction mixture was allowed to stand for 20-48 h at room temperature. The solvent was evaporated under vacuum, and the residue was recrystallized. Yield, 68-78%.

p-Substituted Anilides of 3-Acetoxy-2-methyl-2-alkylthiopropanoic Acid (X-XVIII). A 2.06 g portion (21 mmoles) of CH_3COOK was added to 20 mmoles of a p-substituted anilide of 3-chloro-2-methyl-2-alkylthiopropanoic acid I-IX in 20 ml of glacial acetic acid. The reaction mixture was allowed to stand at room temperature for 3-48 h. After the complete disappearance of the starting compound (according to TLC), the solvent was evaporated under vacuum and the residue was dissolved in CCl_4. Potassium chloride was filtered off, CCl_4 was evaporated under vacuum, and the residue was recrystallized. Yield, 75-82%. The PMR spectra of the reaction mixtures and pure compounds were recorded after isolation.

EXPERIMENTAL (BIOLOGICAL)

The experiments were carried out on nonlinear white rats each weighing 90-110 g, and nonlinear and linear mice each weighing 18-25 g/kg. In all, 400 rats and 260 mice were used, in separate groups of 6-15 animals. The animals were divided into groups according to the body weight and mean diameter of the tumor. The strains of tumors that were grafted were obtained from the All-Union Oncological Scientific Center of the Academy of Sciences of the USSR.

In the study of the ATA, the following tumor strains were used: in rats S-45, WCS, melanoma B_{16}, LIAC, Pliss LS, and Lewis epidermoidal lung carcinoma (LL).

The treatment was started 24-96 h after grafting. The compounds were introduced intraperitoneally daily for 5-10 days in a suspension in mineral oil. The ATA of the compounds was indicated from the weight of the tumor at the end of the experiment or from the increase in the life span of the animal. The results of the investigations were processed statistically [3].

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SYNTHESIS AND CHOLINE ESTERASE HYDROLYSIS OF O-ACYLATED ALKYLCHLOROFORMOXIMES

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The wide spectrum of their biological activity permits classifying oximes and their derivatives as a promising group of physiologically active compounds for practical utilization in human and veterinary medicine. Up to the present time, a fairly large number of O-substituted oximes containing various substituents in the oxime part of the molecule have been synthesized and their biological activity has been studied. At the same time, the question of the synthesis and biological activity of the simplest representatives structurally of these compounds, the O-substituted alkylchloroformoximes still remains unanswered, which, we believe, is due to absence of fairly reliable methods of synthesis, because of the low stability of the starting alkylchloroformoximes.

In the present work, we discuss a fundamentally new approach to the synthesis of O-substituted oximes, based on the use of available α-chloronitrosoalkanes, with which we were able to obtain various O-substituted alkylchloroformoximes. Their biological activity was tested: the toxicity and the action on the key enzyme of the parasympathic nervous system, acetylcholine esterase (ACE) and butyrylcholine esterase (BCE), the binding with which may cause loss of inhibitors at the pharmacokinetic stage of the bioresponse formation. The structure–activity relationship was analyzed for the series of O-acylated alkylchloroformoximes.

We believe that the biological activity of O-substituted alkylchloroformoximes is to a great extent determined by the acceptor properties of the oxime group, and therefore it seemed productive to evaluate the contribution of this group, taking as an example the O-acylated oximes of the general formula

$$RC(O)ON{=}C(Cl)R^1,$$

I—VII

where R = Me (I—III), Et (IV, V), Pr (VI), CH_2Cl (VII, VIII); R′ = Me (I, IV), Et (II), Pr (III, VII), *i*-Pr (V, VI, VIII).

Compounds I-VIII were obtained in a yield of 11-46% by reacting 1,1-dichloro-1-nitrosoalkanes with acid chlorides of the corresponding carboxylic acids in the presence of an equimolar amount of zinc dust.

$$O{=}N{-}CCl_2{-}R' + RCOCl \xrightarrow{Zn} \longrightarrow RC(O)ON{=}C(Cl)R'$$

EXPERIMENTAL (CHEMICAL)

The PMR spectra were recorded in $CDCl_3$ on a CXP-200 spectrometer ("Bruker", FGR) with a working frequency of 200 MHz, using TMS as internal standard.

O-Propylchloroformiminoacetate (III). A 15.6 g portion (0.1 mole) of 1,1-dichloro-1-nitrosobutane was added with stirring at 20°C to a suspension of 6.2 g (0.1 mole) of zinc

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