residue is dissolved in chloroform, and compound I is precipitated by adding a few portions of ether. For compounds V-VIII, the reaction mixture is refluxed for 2 h, and for compounds XI-XIV, 17 h. Phosphoniosulfonamide XXI is obtained similarly to compound I, using DMFA as the solvent; the mixture is refluxed for 5 h. Data for compounds I-XXI are listed in Table 1.

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DERIVATIVES OF AMINOPHENYLACETIC ACID AND THEIR ANTINEOPLASTIC ACTIVITY

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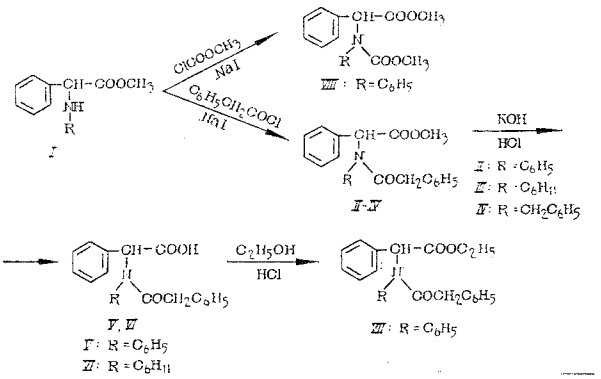
N-Acetyl derivatives of a number of amino acids, possessing antileukemic activity, have been described in the literature [1]. To expand the spectrum of N-acetyl derivatives of amino acids and to seek new substances with antileukemic activity we synthesized N-phenacetyl derivatives of N-substituted aminophenylacetic acids, as well as their methyl and ethyl esters and the methyl ester of N-phenyl-N-carbomethoxyphenylacetic acid (II-VIII), according to the following scheme:



Compounds II-IV were synthesized by the reaction of the methyl ester of N-monosubstituted aminophenylacetic acids I [2] with phenylacetyl chloride. The methyl esters II and III were saponified with an aqueous solution of potassium hydroxide to the corresponding acids V and VI.

Since the ethyl ester of α-aminophenylacetic acid was obtained in a negligible yield, the corresponding N-phenacetyl derivative VII was synthesized by esterification of the acid V. Compound VIII was produced by the reaction of I with the methyl ester of chlorocarbonic acid.

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TABLE 1. Toxicity and Antineoplastic Activity of Derivatives of Aminophenylacetic Acids

Compound	Toxicity for mice, mg/kg			% inhibition of tumor growth				Increase in lifetime of mice with Ehrlich's ascites carcinoma, %
	LD_{100}	LD_{50}	maximum tolerable dose	sarcoma 45	sarcoma 180	Shvets leukemia	Fliss lymphosarcoma	
II	5000	—	—	58,6	57	37	Inactive	36
III	2750	2300	2000	33	46	Inactive	"	22,4*
IV	2750	2350	2000	54	Stimulated	"	31,7	—
V	600	430	150	35,6	33	"	Inactive	40
VII	4500	—	—	32*	Inactive	"	"	—
VIII	400	235	150	Inactive	32,6*	"	33	Inactive
Sarcolysin	30	20	10	95	32	90,7	76	138,6

Note. The significance (α) in all the experiments is 0.95 or more, except for the experiments marked by an asterisk.

EXPERIMENTAL BIOLOGICAL PART

The toxicity and antineoplastic activity of the synthesized substances were studied according to the well-known procedure [3].

The toxicity of the substances was determined on noninbred white mice of both sexes, weighing 18-20 g, with a single intraperitoneal injection. The antineoplastic activity was studied on noninbred white rats with sarcoma 45, Shvets leukemia, and Pliss lymphosarcoma (dose 1/25 of LD_{100}, eight daily injections) and mice with sarcoma 180 and Ehrlich's ascites carcinoma (dose 1/10 of LD_{100}, six daily injections). The compounds in the tested doses were administered to the animals intraperitoneally in the form of a suspension prepared in a 0.5% solution of CM-cellulose. In the experiments we used 256 rats and 300 mice.

The results of a preliminary study of the tested compounds (see Table 1) showed that their LD_{100} ranges from 400 to 5000 mg/kg. In comparison with sarcolysin they proved substantially less toxic. For compound V LD_{100} is 600 mg/kg. Replacement of the N-phenacetyl group by a carboxyl group led to an increase in the toxicity of compound VIII to 400 mg/kg. Its methyl and ethyl esters (II, VII) proved virtually nontoxic.

Most of the compounds studied exhibited the same antineoplastic activity with respect to sarcomas 45 and 180, inhibiting tumor growth by 32-58%. In Shvets leukemia, only one compound, II, exhibited weak inhibiting activity (37%). The same activity was exhibited by compounds VII, VIII, and IV in Pliss lymphosarcoma and two compounds (II, V) in Ehrlich's ascites carcinoma, significantly increasing the average lifetime of the experimental mice by 36-40% in comparison with the indices in the control.

In a comparison of the antineoplastic properties of the compounds obtained with sarcolysin, it was established that with respect to sarcoma 180 only one compound (II) somewhat surpasses it, while compounds III, V, and VIII exhibit antineoplastic activity equal to it on this tumor strain. The remaining compounds are inferior to sarcolysin in antiblastic activity. Thus, various modifications of the chemical structure of 1-(N-phenyl-N-phenacetyl)phenylacetic acid have no significant effect on the antineoplastic properties of the substances obtained.

EXPERIMENTAL CHEMICAL PART

Thin-layer chromatography was conducted on Silufol UV-254 plates, developed with iodine vapors. The mass spectra were taken on a MX 1303 instrument with direct introduction of the sample into the region of ionization.

Methyl Esters of N-Substituted N-Phenylacetylaminophenylacetic Acid (II-IV). To a solution of 3.09 g (0.02 mole) phenylacetyl chloride and a catalytic amount of sodium iodide in 50 ml dry benzene, a benzene solution of 9.64 g (0.04 mole) of the methyl ester of α-anilinophenylacetic acid was added dropwise with mixing. The mixture was left overnight, then boiled for 18 h. After cooling the hydrochloride of the initial amine formed was filtered off, the solvent removed, and the residue crystallized. mp 79-80°C, reprecipitation: alcohol—ice water, yield 4.57 g (65%), R_f 0.63 (chloroform, ether 1:1), m/e 359. Found, %: C 76.51; H 5.65; N 3.83. $C_{23}H_{21}NO_3$. Calculated, %: C 76.88; H 5.85; N 3.90.

The remaining N-phenacetyl derivatives were produced analogously. The R, melting point yield, R_f, m/e, and elementary analysis are cited.

C_6H_{11} (cyclohexyl): 91-92°C; 62.1%; 0.62 (hexane–ether–acetone 1:1:1); 365. Found, %: C 75.67; H 7.61; N 4.24 $C_{23}H_{27}NO_3$. Calculated, %: C 75.67; H 7.40; N 3.84.

$CH_2C_6H_5$: 66–67°C; 57%: 0.59 (chloroform–ether 1:1); 373. Found, %: C 77.59; H 5.76; N 4.13. $C_{24}H_{23}NO_3$. Calculated, %: C 77.21; H 6.16; N 3.75.

N-Phenyl-N-phenacetylphenylacetic Acid (V). A mixture of 3.6 g (0.01 mole) II and 50 ml of a 15% aqueous solution of potassium hydroxide were boiled for 6-8 h. After cooling the mixture was extracted several times with ether to remove the unreacted initial methyl ether, then treated with diluted hydrochloric acid (1:1), and the precipitate of compound V formed filtered off, mp 164-165°C; reprecipitation: alcohol–ice water, yield 3.1 g (91.9%); R_f 0.53 (benzene–chloroform 1:1), m/e 345. Found, %: C 76.48; H 6.00; N 4.35. $C_{22}H_{19}NO_3$. Calculated, %: C 76.52; H 5.51; N 4.06.

N-Cyclohexyl-N-phenacetylphenylacetic acid (VI) This was produced analogously; mp 181-182°C yield 85.2%; R_f 0.75 (chloroform–benzene–alcohol 4:4: 1); m/e 351. Found, %: C 75.62; H 7.35; N 3.54. $C_{22}H_{25}NO_3$. Calculated, %: C 75.21; H 7.12; N 3.99.

Ethyl Ester of N-Phenyl-N-phenacetylphenylacetic Acid (VII). Gaseous HCl was passed through a solution of 1.9 g (0.0055 mole) V in 40 ml of ethanol with mixing for 6 h. Then, continuing passage of a slow stream of HCl, the mixture was heated on a water bath for 3-4 h. The alcohol was filtered off, water added, and neutralized with Na_2CO_3. The oil that separated was extracted with ether and dried. After the solvent was distilled off, the residue was dissolved in a small quantity of alcohol and precipitated with ice water. mp 67-68°C yield 1.58 g (77.1%); R_f 0.56 (hexane–ether 1:1); m/e 373. Found, %: C 77.05; H 6.35; N 3.97. $C_{24}H_{23}NO_3$. Calculated, %: C 77.21; H 6.17; N 3.75.

Methyl Ester of N-phenyl-N-carbomethoxyphenylacetic Acid (VIII). This was produced analogously to compounds II-IV by the interaction of I and the methyl ester of chlorocarbonic acid; mp 79-80°C; yield 67.5%; R_f 0.66 (chloroform–ether 1:1); m/e 299. Found, %: C 68.07; H 5.71; N 4.54. $C_{17}H_{17}NO_4$. Calculated, %: C 68.23; H 5.68; N 4.68.

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