were separated off, triturated with aqueous sodium acetate solution, filtered off again, and washed with water.

Method C. Compounds **IIIb** and **IIIc** were triturated with acetone and concentrated HCl (or HBr) and washed with acetone.

Method D. A mixture of 5mM of **IIIa–IIIc**, 10 ml of a carboxylic acid, and 7.5 mM of its anhydride was boiled for 2 hr and was then diluted with water, and the precipitate was filtered off.

Method E. A solution of 6 mM of chloroacetyl chloride in 6 ml of dry benzene was slowly added to 5 mM of **IIIa** in 100 ml of dry benzene and the mixture was boiled for 4 hr; after a day the precipitate was filtered off.

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NEW α-(PYRIMID-4-YLAMINO)ACIDS

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The reaction of 4-methylthiothymine with amino acids has given α-(2-hydroxy-5-methylpyrimid-4-ylamino)acids. Similarly, 4-methylthiouracil forms α-(2-hydroxypyrimid-4-ylamino)acids the halogenation of which gives α-(5-halogeno-2-hydroxypyrimid-4-ylamino)acids.

In recent years, interest has arisen in the study of pyrimidylamino acids as possible anticarcinogenic substances [1, 2]. Some representatives of the α-(pyrimid-4-ylamino)acids such as, for example, N-(2-hydroxypyrimid-4-yl)α-alanine and its 5-halogeno derivatives have been described by Ueda and Fox [1].

We have synthesized a number of new N-substituted α-amino acid derivatives of uracil, thymine, and 5-halogenouracils. For the synthesis of the α-(2-hydroxypyrimid-4-ylamino)acids (I) and the α-(2-hydroxy-5-methylpyrimid-4-ylamino)acids (II) we used a recently developed method [1]—the reaction of 2-hydroxy-4-methylthiopyrimidine and 2-hydroxy-5-methyl-4-methylthiopyrimidine, respectively, with amino acids in an aqueous alkaline medium.

The products obtained are white crystalline substances with high melting points which are readily soluble in hot water, less readily in ethanol, and insoluble in ether and benzene.

The treatment of compound I with elementary bromine or N-bromosuccinimide in acetic acid gave the α-(5-bromo-2-hydroxypyrimid-4-yl)amino acids (III) and the reaction of compound I with elementary iodide in an aqueous alkaline medium yielded the α-(2-hydroxy-5-iodopyrimid-4-yl)amino acids (IV).

The compounds obtained were characterized by their UV absorption spectra, their R_f values in two systems of solvents, elementary analyses, and melting points.

We shall publish information concerning their antiblastic activity separately.

EXPERIMENTAL

Chromatography was carried out on paper of type "chromatograficheskaya B" ["chromatographic fast"] of the Volodarskii Leningrad mill by the ascending method. The following systems of solvents were used: n-butanol—acetic acid—water (4 : 1 : 5, upper layer) (system 1); n-butanol—water (86 : 14) (system 2); n-butanol—ethanol—water (4 : 1 : 5, upper layer) (system 3); n-butanol—saturated NH_3 (system 4). The substances were detected on the chromatograms by their absorption of UV light.

The UV absorption spectra were recorded on an SF-4 spectrophotometer in 0.1 N HCl, 0.1 N caustic soda, and water with concentrations of the order of 10^{-3} g-mole/l.

N-(2-Hydroxypyrimid-4-yl)valine (Ia). A mixture of 1.0 g (7 mM) of 4-methylthiouracil, 0.91 g (7.8 mM) of valine, 0.42 g (3.9 mM) of sodium acetate, and 20 ml of water was boiled for 22 hr. The cooled solution was acidified with dilute formic acid to pH 3 and was left overnight in the refrigerator. The precipitate that had deposited was filtered off, washed with water, and dried. Compounds **Ib** and **Ic** and **IIa–IId** were obtained similarly.

N-(5-Bromo-2-hydroxypyrimid-4-yl)glycine (IIIa). A solution of 0.32 g (4 mM) of bromine in 5 ml of acetic acid was added dropwise to a suspension of 0.34 g (2 mM) of N-(2-hydroxypyrid-4-yl)glycine in 15 ml of glacial acetic acid. After 30 minutes' stirring, the solid matter was dissolved, and the solution was left overnight at room

α-(2-Hydroxypyrimid-4-ylamino)acids, α-(2-Hydroxy-5-methylpyrimid-4-yl)acids, and α-(5-Halogeno-2-hydroxypyrimid-4-ylamino)acids

Compound	R	R′	Reaction time, hr	Mp, °C	Empirical formula	Found, %				Calculated, %				R_f				UV spectrum						Yield, %
																		0.1 *N* HCl		H_2O		0.1 *N* NaOH		
						C	H	N	halogen	C	H	N	halogen	I	II	III	IV	λ_{max}, nm	log ε	λ_{max}, nm	log ε	λ_{max}, nm	log ε	
Ia	$CH(CH_3)_2$	H	22	280—281	$C_9H_{13}N_3O_3$	51.10	5.95	19.75	—	51.20	6.19	19.90	—	0.67	—	—	0.16	280	3.794	273	3.776	280	3.612	74
Ib	$CH_2CH(CH_3)_2$	H	20	198	$C_{10}H_{15}N_3O_3$	53.12	6.82	18.95	—	53.32	6.71	18.65	—	0.77	—	—	0.10	280	3.720	270	3.766	280	3.672	76
Ic	$CH_2CH_2SCH_3$ (*d*)	H	20	175	$C_9H_{13}N_3O_3S$	44.14	5.89	17.27	—	44.45	5.38	17.28	—	0.53	—	—	—	—	—	—	—	—	—	35
IIa	H	CH_3	3	230(decomp.)	$C_7H_9N_3O_3$	45.84	4.98	22.61	—	45.92	4.95	22.95	—	0.18	—	0.06	—	285	3.857	275	3.700	275	3.638	77
IIb	$CH(CH_3)_2$	CH_3	40	202	$C_{10}H_{15}N_3O_3$	52.99	6.65	18.39	—	53.32	6.71	18.65	—	0.74	—	0.27	—	—	—	—	—	—	—	83
IIc	CH_2—$CH(CH_3)_2$	CH_3	34	192	$C_{11}H_{17}N_3O_3$	55.00	6.95	18.00	—	55.21	7.12	17.52	—	0.81	0.35	—	—	287	3.836	273	3.697	275	3.696	66
IId	CH_2—COOH	CH_3	24	228(decomp.)	$C_9H_{11}N_3O_5$	45.08	4.87	17.69	—	44.81	4.59	17.42	—	—	—	—	—	285	3.755	277	3.704	275	3.582	60
IIIa	H	Br	—	210(decomp.)	$C_6H_6BrN_3O_3$	29.07	2.66	17.30	31.70	29.05	2.43	16.94	32.21	0.29	—	—	—	290	3.683	278	3.465	292	3.705	78
IIIb	$CH_2CH(CH_3)_2$	Br	—	Not charact.	$C_{10}H_{14}BrN_3O_3$	39.95	4.68	13.96	26.04	39.49	4.63	13.81	26.27	—	—	—	—	285	3.786	—	—	292	3.678	92
IIIc	$CH(CH_3)_2$	Br	—	223	$C_9H_{12}BrN_3O_3$	—	—	14.88	27.93	—	—	14.48	27.54	0.83	—	—	0.22	—	—	280	3.521	292	3.560	80
IVa	CH_2—$CH(CH_3)_2$	I	—	206	$C_{10}H_{14}IN_3O_3$	34.63	4.39	12.22	35.88	34.22	4.02	11.96	36.14	0.84	—	—	0.84	—	—	—	—	—	—	45

temperature. The mass was evaporated to dryness in vacuum and the residue was recrystallized from water, giving white crystals.

Compounds **IIIb** and **IIIc** were obtained similarly.

N-(2-Hydroxy-5-iodopyrimid-4-yl)leucine (IVa). With stirring at room temperature, 0.51 g (4 mM) of iodine was added to a solution of 0.47 g (2 mM) of **Ib** in 20 ml of 1 N NaOH. After the completion of the reaction, the solution was evaporated in the water bath to small bulk and, with careful cooling, was acidified with HCl. After recrystallization from water, white crystals were obtained.

Information on compounds **I–IV** is given in the table.

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THE METALLATION OF 1, 2-DIMETHYLIMIDAZOLE

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Under the action of butyllithium, 1,2-dimethylimidazole is metallated in position 5. The reactions of 5-lithio-1,2-dimethylimidazole with N-bromodiethylamine, benzaldehyde, benzophenone, dimethylformamide, and ω-iodophenylacetylene have been performed.

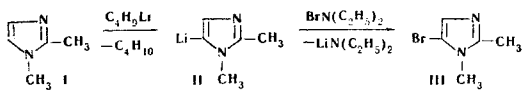
As is well known, when α-picoline, quinaldine, and 2-methylbenzothiazole react with metallating agents,

Table 1

Found and Calculated Values of the Dipole Moments of Imidazole Derivatives

Compound	Dipole moment, D	
	found	calculated
VIII	3.81	—
I	3.74	—
IX	—	4.7
X	—	2.9
III	3.37	—

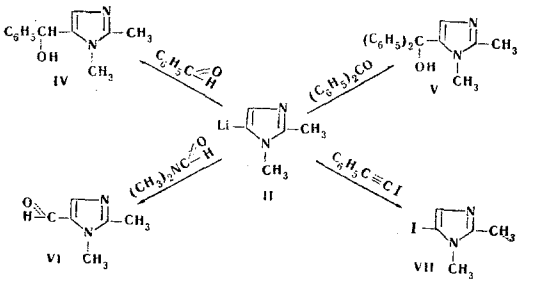
the hydrogen of the methyl group is replaced by a metal [1, 2]. 2-Benzyl-4-methylthiazole behaves similarly [3]. It could be expected that 1, 2-dimethylimidazole (I) will undergo a similar reaction; however, it has been found that the action on it of butyllithium followed by N-bromoethylamine forms a compound with the composition $C_5H_7N_2Br$ differing in properties from 2-bromomethyl-1-methylimidazole. It was concluded from this that in this case the heterocyclic ring is metallated.



To elucidate the structure of compound **II**, we have calculated the dipole moments of 4-bromo-1, 2-dimethylimidazole (**IX**) and 5-bromo-1, 2-dimethylimidazole (**X**) by the vectorial scheme and have compared the figures obtained with the moment of compound **III** obtained experimentally. In the calculation the imidazole molecule was considered as a regular pentagon. The di dipole moments of CH_3 and Br were taken as 4.4 and 1.5 D, respectively. The direction of the vector of the dipole moment of **I** was determined approximately from the experimental magnitudes of the moments of 1-methylimidazole (**VIII**) and of compound **I** (Table 1).

The figures of Table 1 show that compound **II**, which is converted into the bromine derivative **III**, is 5-lithio-1, 2-dimethylimidazole.

Besides its reaction with N-bromodiethylamine, we studied the following reactions of 5-lithio-1, 2-dimethylimidazole:



EXPERIMENTAL

1,2-Dimethylimidazole (I). This was obtained by the methylation of 2-methylimidazole with methyl iodide in liquid ammonia by analogy with Roe's work [4]. Colorless crystals with mp 35–36.5° C,