SYNTHESIS AND PROPERTIES OF N-(2-CHLORO-5-FLUORO-4-PYRIMIDYL)- AND N-(2-ETHYLTHIO-5-FLUORO-4-PYRIDMIDYL)-SUBSTITUTED AMINO ACIDS

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Synthetic routes to and the properties of N-(2-chloro-5-fluoro-4-pyrimidyl)- and N-(2-ethylthio-5-fluoro-4-pyrimidyl)-substituted amino acids are shown.

Continuing our study of potential antimetabolites of nuclein-proteinmetabolism, we have described the synthesis and properties of N-(2-oxo-4-pyrimidyl)-substituted amino acids [1, 2]. The corresponding 5-fluoropyrimidyl-substituted amino acids, which contain an amino acid residue instead of an amino group in their molecules, are also of interest as analogs of 5-fluorocytosine.

To synthesize the N-(5-fluoro-4-pyrimidyl)-substituted amino acids we used a method based on the reaction of halopyrimidines with amino acid salts [3, 4]. In the reaction of 2,4-dichloro-5-fluoropyrimidine (I) with the sodium salt of the amino acid in water only the chlorine atom in the 4-position is replaced by an amino acid residue to form the N-(2-chloro-5-fluoro-4-pyrimidyl)-substituted amino acid. The chlorine atom in the 2-position of the pyrimidine ring remains inert under these conditions. Thus, N-(2-chloro-5-fluoro-4-pyrimidyl)glycine (II) is obtained smoothly by the reaction of I with the sodium salt of glycine after acidification with hydrochloric acid. The reaction of I with the sodium salts of phenylalanine, methionine, valine, leucine, tryptophan, and β-alanine proceeds similarly to form III-VIII, respectively.

The synthesis of N-(2-ethylthio-5-fluoro-4-pyrimidyl)-substituted amino acids is accomplished readily on the basis of nucleophilic substitution of chlorine during the reaction of 2-ethylthio-4-chloro-5-fluoropyrimidine with sodium salts of the amino acids. N-(2-Ethylthio-5-fluoro-4-pyrimidyl)valine (IX), -leucine (X), -glycine (XI), -β-alanine (XII), -phenylalanine (XIII), -methionine (XIV), and -tryptophan (XV) were synthesized in this way (Table 1). All of the compounds obtained are colorless, crystalline substances which are only slightly soluble in cold water, ethanol, and nonpolar solvents and quite soluble in hot water and dimethylformamide.

We also studied the hydrolysis of these compounds. We observed the hydrolysis from paper chromatography by comparing the hydrolysate with authentic samples. When both N-(2-chloro-5-fluoro-4-pyrimidyl)- and N-(2-ethylthio-5-fluoro-4-pyrimidyl)-substituted amino acids are refluxed with concentrated hydrochloric acid for 2-4 h, they split out amino acid and form 2-chloro-4-hydroxy-5-fluoropyrimidine and 2-ethylthio-4-hydroxy-5-fluoropyrimidine, respectively. 5-Fluorouracil is formed on prolonged heating. Compounds VIII, X, and XIV were checked for antitumorigenic activity and did not give appreciable inhibition of S-180, HK, and NK tumors and Walker's carcinosarcoma.

The UV absorption spectra of N-(2-ethylthio-5-fluoro-4-pyrimidyl)-substituted amino acids IX-XI and XIV (Table 2), obtained in aqueous solution (pH 7) and 0.1 N NaOH (pH 13), display three absorption bands of different intensities. The first band at 235-237 nm (ε 9700-15,500) and the second band at 249-

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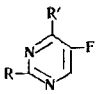
TABLE 1. N-(2-Chloro-5-fluoro-4-pyrimidyl)- and N-(2-Ethylthio-5-fluoro-4-pyrimidyl)-Substituted Amino Acids*



Compound	R	R′	mp, °C	Empirical formula	N, %* found	N, %* calc.	Reaction time, min	Yield, %
II	Cl	$NHCH_2(COOH)$	169	$C_6H_5Cl_1F_1N_3O_2$	20,42	20,43	40	85
III	Cl	$NHCH(COOH)CH_2C_6H_5$	171	$C_{13}H_{11}Cl_1F_1N_3O_2$	14,43	14,21	40	79
IV	Cl	$NHCH(COOH)CH_2CH_2SCH_3$	159	$C_8H_{11}Cl_1F_1N_3O_2S$	14,75	15,02	40	66
V	Cl	$NHCH(COOH)CH(CH_3)_2$	179	$C_9H_{11}Cl_1F_1N_3O_2$	17,72	17,72	40	84
VI	Cl	$NHCH(COOH)CH_2CH(CH_3)_2$	173	$C_{10}H_{13}Cl_1F_1N_3O_2$	16,27	16,06	40	66
VII	Cl	$NHCH(COOH)CH_2NC_8H_6$	182	$C_{15}H_{12}Cl_1F_1N_4O_2$	16,48	16,74	60	61
VIII	Cl	$NHCH_2CH_2COOH$	132	$C_7H_7Cl_1F_1N_3O_2$	19,47	19,18	60	52
IX	SC_2H_5	$NHCH(COOH)CH(CH_3)_2$	174	$C_{11}H_{16}F_1N_3O_2S$	15,33	15,12	240	45
X	SC_2H_5	$NHCH(COOH)CH_2CH(CH_3)_2$	177	$C_{12}H_{18}F_1N_3O_2S$	14,32	14,63	120	73
XI	SC_2H_5	$NHCH_2COOH$	215	$C_8H_{10}F_1N_3O_2S$	18,13	18,22	180	70
XII	SC_2H_5	$NHCH_2CH_2COOH$	141	$C_9H_{12}F_1N_3O_2S$	17,34	17,14	180	52
XIII	SC_2H_5	$NHCH(COOH)CH_2C_6H_5$	186	$C_{15}H_{16}F_1N_3O_2S$	13,05	13,08	120	67
XIV	SC_2H_5	$NHCH(COOH)CH_2CH_2SCH_3$	173	$C_{11}H_{16}F_1N_3O_2S_2$	13,63	13,27	300	62
XV	SC_2H_5	$NHCH(COOH)CH_2NC_8H_6$	198	$C_{17}H_{17}F_1N_4O_2S$	15,70	16,00	240	69

* See [1] for the results of elementary analysis for C and H.

TABLE 2. UV Absorption Spectra of N-(2-Chloro-5-fluoro-4-pyrimidyl)- and N-(2-Ethylthio-5-fluoro-4-pyrimidyl) -Substituted Amino Acids (sh – shoulder)

Compound	0,1 *N* HCl		H_2O		0,1 *N* NaOH	
	λ, nm	ε	λ, nm	ε	λ, nm	ε
IV	230	9060	243	11720	242—243	11400
	274	7920	280	6800	280	6700
VI	241	10200	243	12800	244—245	11700
	270—271	9650	279—281	7300	280	6730
V	239—240	11400	239—240	11400	—	—
	272—274	10600	280	7180		
IX	252	18100	235	15460	233—234	16200
	sh 290	—	249	15490	sh 249	—
			290	6940	295	6860
X	253	27200	sh 234	—	232—253	16200
	sh 290	—	249—250	15020	sh 250	—
			290	6490	294	6730
XI	250	25100	sh 235	—	231	17300
	sh 285	—	249	15670	sh 247	—
			288	6560	291	6360
XIV	251—254	25800	235	9720	231—232	18800
	sh 290	—	sh 247	—	sh 245	—
			292	4080	294	7390

250 nm (ε 9000-16,000) are caused by $\pi \rightarrow \pi^*$ transitions of the electrons of the neutral and protonated (in the 3-position) forms of the 2-ethylthio-5-fluoropyrimidine ring, respectively [5, 7]. This is confirmed by the spectra of IX-XI and XIV in acid (pH 1) and base (pH 12); in acid the band at 231-235 nm disappears completely and the intensity of the band at 245-250 nm increases sharply, while just the opposite is observed in alkali. The approximately equal intensities of both bands at pH 7 indicates the considerable basicity of IX-XI and XIV as compared with the basicity of pyrimidine. This is explained by the presence of such strong electron donors as SC_2H_5 in the 2-position and the nitrogen atom of the amino acid residue (R'). The amino acid residues (R') have virtually no affect on the position of the $\pi \rightarrow \pi^*$ bands of the compounds and only slightly increase their intensities in the order XIV < X < XI < IX. A third, less intense band (ε 4000-7000) at 288-294 nm appears due to $n \rightarrow \pi^*$ transitions of the ring [6]. The disappearance of this band in acid solutions also speaks in favor of this assumption [5].

At pH 7 the UV spectra of IV-VI (Table 2) contain two absorption bands which arise due to $\pi \quad \pi^*$ transitions of the electrons of the 2-chloro-5-fluoropyrimidine ring in two forms: neutral at 243-244 nm

(ε 11,720-14,240) and protonated at 280 nm (ε 6800-7300). Replacement of the SC_2H_5 group by a chlorine atom shifts the $\pi \rightarrow \pi^*$ bands strongly to the long-wave region of the spectrum ($\Delta\lambda_{neut}$ 8 nm, $\Delta\lambda_{prot}$ 30 nm) and thereby masks the $n \rightarrow \pi^*$ band, whose position is only slightly affected by the substituent in the 2-position.

Changing the pH of the medium from 7 to 12 has absolutely no effect on the UV spectra of IV-VI, and only lowering the pH to 1 causes a decrease in the intensity of the band of the neutral molecule and an increase in the intensity of the protonated form. This attests to the extremely low basicity of IV-VI as compared with that of IX-XI and XIV.

EXPERIMENTAL

2-Ethylthio-4-chloro-5-fluorouracil. This compound was synthesized according to the method in [6].

2,4-Dichloro-5-fluoropyrimidine (I). Dry pyridine (16.2 ml) was added with cooling to 132 ml of phosphorus oxychloride. A white precipitate was formed. Stirring was continued, 11.85 g of 5-fluorouracil was added in small portions to the reaction mixture, and the resulting mixture was refluxed on a water bath for 1.5 h. The excess phosphorus oxychloride was distilled at reduced pressure. The residue was dissolved in benzene (or ether) and poured over ice. The organic layer was separated, washed twice with cold water, and dried over calcium chloride. The benzene was removed by distillation at reduced pressure. The residue crystallized rapidly to give 10.6 g (62%) of a product with mp 38 deg (mp 38.5 deg [8]).

N-(2-Chloro-5-fluoro-4-pyrimidyl)glycine (II). Sodium hydroxide [0.8 g (0.02 mole)] and 1.5 g (0.02 mole) of glycine were dissolved in 80 ml of water, 1.67 g (0.01 mole) of I was added, and the mixture was refluxed on a water bath for 40 min. The cooled solution was acidified with 5 ml of acetic acid; and the resulting precipitate was filtered, washed with water, and dried to give 3.0 g (79%) of II.

Amino acids II-VIII were similarly obtained.

N-(2-Ethylthio-5-fluoro-4-pyrimidyl)valine (IX). Sodium hydroxide [0.64 g (0.016 mole)] and 1.87 g (0.016 mole) of valine were dissolved in 60 ml of water, 3.2 g (0.016 mole) of 2-ethylthio-4-chloro-5-fluoropyrimidine was added to the solution, and the mixture was refluxed for 3 h. The cooled reaction solution was acidified with 7 ml of acetic acid, and the precipitate was filtered and washed with water to give 2.39 g (52%) of IX.

Amino acids X-XV were similarly obtained.

The UV absorption spectra of IV-VI, IX-XI, and XIV were obtained with an SF-4 spectrophotometer in water (pH 7), in 0.1 N NaOH (pH 13), and in 0.1 N HCl (pH 1) at concentrations of 10^{-4} mole/liter and an absorbing layer thickness of 1 cm. The pH of the solutions was monitored with an LPP-01 meter.

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