SYNTHESIS OF N-(2-CHLORO-5-BROMO-4-PYRIMIDYL)- AND N-(2-CHLORO-5-IODO-4-PYRIMIDYL)AMINO ACIDS

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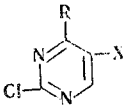
The previously unreported N-(2-chloro-5-bromo-4-pyrimidyl)- and N-(2-chloro-5-iodo-4-pyrimidyl)amino acids were synthesized.

Continuing our investigations of the potential antimetabolites of nucleic acid–protein metabolism, we have undertaken the preparation of N-(5-bromo-4-pyrimidyl)amino acids. We have previously reported [1] the synthesis of derivatives of N-(5-fluoro-4-pyrimidyl)amino acids, which did not display pronounced activity against experimental strains of malignant tumors [2]. There is currently little known about the biochemical activity of derivatives of 5-bromopyrimidines, and there are only indications that 5-bromouracil, like 5-iodouracil, may be partially included in DNA in place of thymine and may thus have an inhibiting action on the sequence of protein synthesis [3, 4]. The known antitumorigenic activity of some 5-bromouracil derivatives has also been pointed out [5, 6]. The synthesis of N-(2-chloro-5-bromo-4-pyrimidyl)amino acids (II-X) and N-(2-chloro-5-iodo-4-pyrimidyl)amino acids (X-XIV) can be readily accomplished by the reaction of 2,4-dichloro-5-bromo(iodo)pyrimidine with amino acid salts [9]. The reaction proceeds only at the chlorine atom in the 4-position of the pyrimidine ring; this chlorine is much more reactive than the chlorine atom in the 2-position, which is under the influence of two adjacent nitrogen atoms. The bromine or iodine atom, by virtue of its inductive effect, increases the reactivity of a halogen in the ortho position with respect to nucleophilic reagents. Compounds II-XIV are crystalline substances. Data regarding their constants and yields are presented in Table 1. The structures of the compounds can be readily proved by alternative transformations. The compounds obtained display the absorption characteristic for pyrimidine compounds in the near UV region.

We prepared the sodium salts of II-XIV for physiological tests.



Ia R=Cl; X=Br; Ib R=Cl; X=I; II R=NHCH(CH$_3$)CO$_2$H (DL-); X=Br; III R=NHCH[CH$_2$CH(CH$_3$)$_2$]CO$_2$H (DL-); X=Br; IV R=NHCH[CH$_2$CH(CH$_3$)$_2$CO$_2$H (L-); X=Br; V R=NHCH[CH(CH$_3$)$_2$]CO$_2$H (DL-); X=Br; VI R=NHCH[CH(CH$_3$)$_2$]CO$_2$H (L-); X=Br; VII R=NHCH[(CH$_2$)$_2$SCH$_3$]CO$_2$H (DL-); X=Br; VIII R=NHCH(CH$_2$NC$_8$H$_6$)CO$_2$H (DL-); X=Br; IX R=NHCH[CH(CH$_3$)CH$_2$CH$_3$]CO$_2$H (L-); X=Br; X R=NHCH$_2$CO$_2$H (DL-); X=Br; XI R=NHCH[CH$_2$CH(CH$_3$)$_2$]CO$_2$H (L-); X=I; XII R=NHCH[CH$_2$CH(CH$_3$)$_2$]CO$_2$H (DL-); X=I; XIII R=NHCH[CH(CH$_3$)$_2$]CO$_2$H (DL-); X=I; XIV R=NHCH(CH$_3$)CO$_2$H (DL-) X=I.

EXPERIMENTAL

2,4-Dichloro-5-bromopyrimidine and 2,4-Dichloro-5-iodopyrimidine. These were obtained by the methods in [7, 8].

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TABLE 1. Characteristics of the Compounds Obtained

Comp.	Mp, °C (dec.)	R_f in the system *			UV absorption at 250 nm		Empirical formula	Found, %				Calculated, %				Yield, %
		n-C_4H_9OH—C_2H_5OH—H_2O, 5 : 1 : 4	n-C_4H_9OH—H_2O—CH_3CO_2H 4 : 5 : 1	n-C_4H_9OH sat. with H_2O + sev. drops NH_4OH	pH 7 (H_2O) λ_{max} (lg ε)	pH 13 (0.1N NaOH) λ_{max} (lg ε)		C	H	N	halogen	C	H	N	halogen	
II	162	0,794	0,909	0,468	243(3,99)	248(3,85)	$C_7H_7BrClN_3O_2$	30,23	2,85	15,10	41,12	29,95	2,49	14,98	41,15	31,5
III	161	0,908	0,944	0,686	248(3,74)	250(3,79)	$C_{16}H_{13}BrClN_3O_2$	37,45	4,39	13,32	35,67	37,22	4,06	13,09	35,76	38,8
IV	120—122	0,830	0,952	0,712	248(3,75)	248(3,68)	$C_{16}H_{13}BrClN_3O_2$	37,11	4,14	13,26	35,69	37,22	4,06	13,09	35,76	40,6
V	162	0,919	0,935	0,635	250(3,78)	250(3,74)	$C_9H_{11}BrClN_3O_2$	34,91	3,87	13,92	37,00	35,03	3,59	13,61	37,39	48,7
VI	158	0,901	0,933	0,074	250(3,79)	250(3,84)	$C_9H_{11}BrClN_3O_2$	34,55	3,53	13,63	37,92	34,95	3,56	13,59	37,40	31,3
VII	154—156	0,872	0,927	0,594	250(3,81)	250(3,62)	$C_9H_{11}BrClN_3O_2S$†	32,13	3,39	12,67	—	31,74	3,26	12,34	—	38,2
VIII	162	0,944	0,931	0,610	253(4,03)	253(4,12)	$C_{15}H_{12}BrClN_4O_2$	46,15	3,21	14,29	29,39	45,53	3,05	14,16	29,15	48,1
IX	145	0,965	0,951	0,714	245(4,24)	250(3,66)	$C_{10}H_{13}BrClN_3O_2$	37,67	4,25	12,88	35,89	37,22	4,06	13,09	35,76	36,0
X	170	0,741	0,884	0,379	260(3,85)	250(3,75)	$C_6H_5BrClN_3O_2$	27,48	2,44	16,00	43,25	27,28	1,87	15,76	43,37	31,0
XI	100	0,826	0,984	0,810	—	245(3,57)	$C_{10}H_{13}Cl_1N_3O_2$	32,62	3,87	11,71	—	32,49	3,54	11,37	—	31,1
XII	178	0,860	0,990	0,764	—	250(3,67)	$C_{10}H_{13}Cl_1N_3O_2$	32,86	3,65	11,69	—	32,49	3,54	11,37	—	50,0
XIII	166	0,816	0,950	0,764	—	248(3,66)	$C_9H_{11}Cl_1N_3O_2$	30,79	3,06	11,88	—	30,39	3,12	11,81	—	42,8
XIV	198	0,595	0,974	0,670	—	248(3,62)	$C_7H_7Cl_1N_3O_2$	25,76	2,13	13,48	—	25,66	2,15	12,83	—	35,3

* The R_f values were determined by means of ascending chromatography on "Leningrad B" paper.
† Found %: S 9.79. Calculated %: S 9.41.

N-(2-Chloro-5-bromo-4-pyrimidyl)-DL-alanine (II). A mixture of 2.4 g (0.06 mole) of sodium hydroxide in 50 ml of water, 2.72 g (0.03 mole) of DL-alanine, and 6.0 g (0.026 mole) of Ia was refluxed until everything dissolved (~5 h), the solution was cooled with ice, and 5 ml of glacial acetic acid was added dropwise. Crystals precipitated after 5-10 min. The solution was allowed to stand at room temperature for 12 h, and the precipitate was filtered, washed with cold water, and dried to give a colorless compound which was reprecipitated from aqueous alkaline solution with glacial acetic acid.

Compounds II-X were similarly obtained.

N-(2-Chloro-5-iodo-4-pyrimidyl)-L-Leucine (XI). A mixture of 0.4 g (0.01 mole) of sodium hydroxide in 25 ml of water, 0.65 g (0.005 mole) of L-leucine, and 1.3 g (0.005 mole) of Ib was refluxed until everything dissolved. The solution was cooled with ice, and glacial acetic acid was added dropwise to precipitate crystals of the product. The mixture was allowed to stand at room temperature for 12 h. The precipitate was filtered, washed with water, and dried to give a yellowish substance which was purified by repeated precipitation from aqueous alkaline solution with glacial acetic acid.

Compounds X-XIV were similarly obtained.

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