SYNTHESIS AND REDUCTION OF ESTERS OF N-(4-AMINO-5-NITRO-6-PYRIMIDYL)AMINO ACIDS

V. M. Cherkasov, N. A. Kapran, G. S. Tret'yakova, and V. A. Latenko

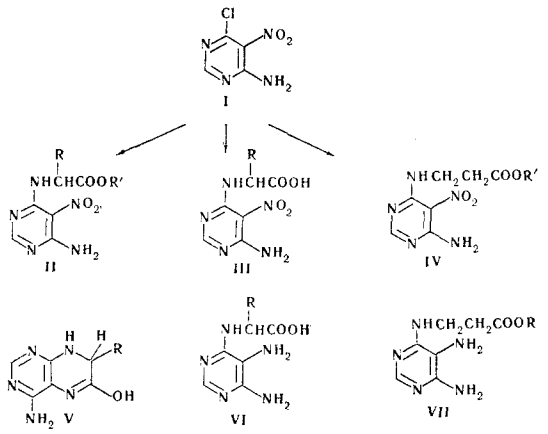
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 124–126, 1969

UDC 547.853.7.466.07:542.942

The reaction of esters of amino acids with 4-amino-6-chloro-5-nitropyrimidine has yielded esters of (4-amino-5-nitro-6-pyrimidyl)amino acids. The reduction of the esters of α-(4-amino-5-nitro-6-pyrimidylamino) acids has yielded 4-amino-6-hydroxy-7,8-dihydropteridines. α-(4-Amino-5-nitro-6-pyrimidylamino) acids and the ester of N-(4-amino-5-nitro-6-pyrimidyl)-β-alanine do not cyclize and on reduction give the corresponding diaminopyrimidine derivatives.

In the preceding communication [1] the preparation of esters of (6-purinyl)amino acids by the condensation of amino acid esters with 6-chloropurine was described. It was of interest to synthesize 8-substituted (6-purinyl)amino acids for investigation as kinins.

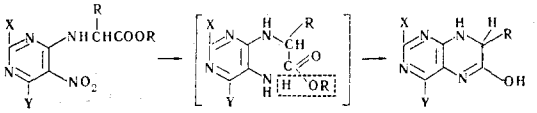
The present work was devoted to the synthesis of esters of (4-amino-5-nitro-6-pyrimidyl)amino acids (II, IV) and their reduction to esters of (4,5-diamino-6-pyrimidyl)amino acids, which are the starting materials for the preparation of esters of 8-substituted (6-purinyl)amino acids.



IIa R=H; R′=CH_3;
IIb R=H; R′=C_2H_5;
IIc R=H; R′=n-C_3H_7;
IId R=H; R′=n-C_4H_9;
IIe R=CH_3; R′=C_2H_5;
IIf R=R′=C_2H_5;
IIg R=i-C_3H_7; R′=C_2H_5;
IIh R=i-C_4H_9; R′=C_2H_5;
IIIa R=H;
IIIb R=CH_3;
Va R=H;
Vb R=CH_3;
Vc R=i-C_3H_7;
Vd R=i-C_4H_9;
VIa R=H;
VIb R=CH_3.

The esters II and IV were obtained by condensing 4-amino-6-chloro-5-nitropyrimidine (I) with freshly vacuum-distilled esters of amino acids taken in excess in order to bind the hydrogen chloride. Under these conditions, condensation takes place more easily than by methods in which the hydrochlorides of the amino acid esters are used [2–4]. Compounds II and IV are colorless crystalline substances sparingly soluble in water and practically insoluble in the usual organic solvents.

According to the literature [3,4] the reduction of esters of α-(5-nitro-6-pyrimidylamino) acids forms dihydropteridines.



The formation of the pteridine ring depends on the nature of the substituents X and Y. All attempts to carry out the reduction of the esters of the nitropyrimidine-α-amino acids (II) in order to obtain the corresponding esters of α-(4,5-diamino-6-pyrimidylamino) acids were unsuccessful. In all cases the 4-amino-6-hydroxy-7,8-dihydropteridines (V) were isolated in the form of high-melting colorless microcrystalline substances sparingly soluble in water and insoluble in the usual organic solvents. When the ester of N-(4-amino-5-nitro-6-pyrimidyl)-β-alanine (IV) and the α-(4-amino-5-nitro-6-pyrimidylamino) acids (III) were reduced under the same conditions, as was to be expected, the formation of the pteridine ring could not take place, and the pyrimidine derivatives VIa,b, and VII were obtained.

EXPERIMENTAL

Esters of (4-amino-5-nitro-6-pyrimidyl)amino acids (IIa–h and IV). A mixture of 0.01 mole of compound I in the form of a suspension, 0.03 mole of freshly vacuum-distilled amino acid ester, and 15 ml of anhydrous ethanol was stirred at room temperature for 2 hr. The product was filtered off and crystallized from ethanol. The properties of the compounds and the yields are given in Table 1.

(4-Amino-5-nitro-6-pyrimidyl)amino acids (IIIa,b). A mixture of 0.01 mole of I, 0.01 mole of the appropriate amino acid, and 20 ml of ethanol was stirred for 30 min, and then 0.005 mole of sodium carbonate was added and the mixture stirred for another 1 hr 30 min. The product was filtered off and purified with two reprecipitations from 1 N NaOH solution with dilute hydrochloric acid. Compounds **IIIa,b** are colorless substances not melting below 300° C. They are very sparingly soluble in water and insoluble in organic solvents.

N-(4-Amino-5-nitro-6-pyrimidyl)glycine (IIIa). Yield 77.0%. Found, %: C 33.36; H 3.21. Calculated for $C_6H_7N_5O_4$, %: C 33.80; H 3.30. **N-(4-Amino-5-nitro-6-pyrimidyl)-α-alanine (IIIb)**—yield 81%. Found, %: C 37.48; H 4.02. Calculated for $C_7H_9N_5O_4$, %: C 37.48; H 3.99

Reduction of the esters IIa,b,g,h. A mixture of 0.01 mole of the compound II, 3.5 g of Raney nickel catalyst, and 40 ml of ethanol was hydrogenated at an overpressure of 200–250 cm water at room temperature for 3–4 hr (until the cessation of the absorption of hydrogen). At the end of the reduction, the product passed into solution (if the substance was not completely soluble, it was separated from the catalyst by decantation). The solution was filtered, the ethanol was filtered off in vacuum, and the product was purified by crystallization from ethanol. The yields and properties of the substances obtained are given in Table 2.

Table 1

Esters of (4-Amino-5-nitro-6-pyrimidyl)amino Acids (II, IV)

Compound	R	R′	Mp, °C	Empirical formula	Found, %		Calculated, %		Yield, %
					C	H	C	H	
IIa	H	CH_3	191	$C_7H_9N_5O_4$	37.68	4.15	37.00	3.99	63
IIb*	H	C_2H_5	167—168	$C_8H_{11}N_5O_4$	40.04	4.61	39.83	4.56	72
IIc	H	n-C_3H_7	238—240	$C_9H_{13}N_5O_4$	42.52	5.38	42.31	5.09	54
IId	H	n-C_4H_9	112	$C_{10}H_{15}N_5O_4$	44.80	5.67	44.61	5.57	45
IIe	CH_3	C_2H_5	153	$C_9H_{13}N_5O_4$	42.37	5.12	42.31	5.09	71
IIf	C_2H_5	C_2H_5	135	$C_{10}H_{15}N_5O_4$	44.94	5.65	44.61	5.57	58
IIg	i-C_3H_7	C_2H_5	94	$C_{11}H_{17}N_5O_4$	46.49	6.33	46.64	6.00	56
IIh	i-C_4H_9	C_2H_5	74—76	$C_{12}H_{19}N_5O_4$	48.39	6.28	48.48	6.39	62
IV	—	C_2H_5	141	$C_9H_{13}N_5O_4$	42.28	5.06	42.31	5.09	65

*Reported in the literature [4].

Table 2

4-Amino-6-hydroxy-7,8-dihydropteridines (V)

Compound	R	Mp, °C	Empirical formula	Found, %		Calculated, %		Yield, %
				C	H	C	H	
Va*	H	Does not melt below 300° C	$C_6H_7N_5O$	43.35	4.28	43.63	4.24	50
Vb	CH_3	" "	$C_7H_8N_5O$	46.96	5.19	46.92	5.02	90
Vc	i-C_3H_7	" "	$C_9H_{13}N_5O$	52.39	6.40	52.06	6.17	82
Vd	i-C_4H_9	" "	$C_{10}H_{15}N_5O$	54.70	6.72	54.28	6.83	62

*Reported in the literature [4].

The reduction of the ester IV and the amino acids IIIa, b was carried out under the conditions of the procedure given above. The products were crystallized from water: colorless needles sparingly soluble in water and insoluble in organic solvents.

Ethyl ester of N-(4, 5-diamino-6-pyrimidyl)-β-alanine (VII). Yield 85%, mp 101° C. Found, %: C 48.32; H 6.66. Calculated for $C_9H_{15}N_5O_2$, %: C 48.00; H 6.67.

N-(4, 5-Diamino-6-pyrimidyl)glycine (VIa). Yield 90%, not melting below 300° C. Found, %: C 37.14; H 5.12. Calculated for $C_6H_9N_5O_2 \cdot H_2O$, %: C 35.82; H 5.47.

N-(4, 5-Diamino-6-pyrimidyl)-α-alanine (VIb). Yield 77%, not melting below 300° C. Found, %: C 41.84; H 5.30. Calculated for $C_7H_{11}N_5O_2$, %: C 42.04; H 5.58.

REFERENCES

1. V. M. Cherkasov, G. S. Tret'yakova, N. A. Kapran, and N. A. Nedel'kina, KhGS [Chemistry of Heterocyclic Compounds], **3**, 170, 1967.

2. M. Polonovski and H. Jirome, C. r., **230**, 392, 1950.

3. J. Clark and A. Layton, J. Chem. Soc., 3411, 1959.

4. W. Boon, W. Jones, and G. Ramage, J. Chem. Soc., 96, 1951.

15 November 1966

Institute of Organic Chemistry
AS UkrSSR, Kiev