CYCLIZATION OF MONOSUBSTITUTED TRIAMINOPYRIMIDINES WITH ACETIC ACID IMINO ESTER HYDROCHLORIDE

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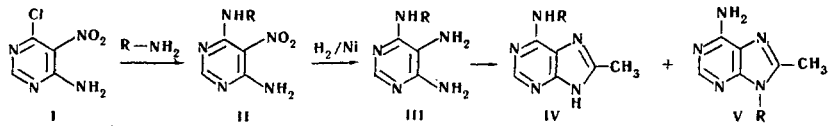
6-N-Substituted 6-amino-8-methylpurines and 6-amino-8-methyl-9-substituted purines were obtained by cyclization of 6-N-substituted 4,5,6-triaminopyrimidines with acetic acid imino ester hydrochloride. The yields of the isomers depend on the different basicities of the secondary amino groups, which are determined by the basicities of the starting amines. The yields of the 6-amino-8-methyl-9-substituted purines increase with decreasing basicity.

In the case of 6-furfuryl- and 6-benzylaminopurines [1], which are taken as standards of cytokinetic activity, it is well known that their 8-methyl derivatives have considerably higher physiological activity; it is therefore of interest to synthesize various 8-methyl-substituted purines. The major method for obtaining 8-methylpurines is cyclization of the corresponding diaminopyrimidines with acetic anhydride or orthoacetic acid ester [2, 3]. The second variant is the most effective since pronounced resin formation occurs during cyclization with acetic anhydride. The literature contains no information regarding the application of acetic acid imine esters as a cyclizing agent for diaminopyrimidines, although this method is widely known for preparing 2-methylbenzimidazoles.

In this paper we have studied the reaction of acetic acid imino ester with triaminopyrimidines (III), obtained from the corresponding 5-nitro-4,6-diaminopyrimidines (II). Attempts to carry out the reaction of III with the acetic acid imino ester free base in various solvents did not give positive results.

The cyclization was carried out by heating triaminopyrimidines III with acetic acid imino ester hydrochloride in a molar ratio of 1 : 2 at 140-150°C. The reactions were also carried out with IIIb and c for comparison with the known methods of cyclization. In all cases the reactions proceed in two directions to form 6-N-substituted 6-amino-8-methylpurines (IVa-g) and 6-amino-8-methyl-9-substituted purines (Va-g), which are separated during treatment of the reaction mixture with aqueous sodium hydroxide.



I II III IV V R

a R=C_6H_{11}; b R=$CH_2C_6H_5$; c R=$CH_2C_4H_3O$-2; d R=C_6H_5; e R=*m*-ClC_6H_4; f R=*p*-$F_3CC_6H_4$; g R=*p*-NCC_6H_4

It is apparent that the different yields of the isomers (Table 1) can depend only on the different basicities of the secondary amino group of the triaminopyrimidines (III), which is determined by the basicity of the starting amines. By comparing the yields of isomers with the pK_a values of the starting amines, one can conclude that the yields of isomers V increase with decreasing basicity of the secondary amino group of the triaminopyrimidines (III), i.e., cyclization occurs primarily at the amino group with the more protonated hydrogen atom. The structures of isomers Va-g are proved by the fact that they are insoluble in aqueous sodium hydroxide and form acetyl derivatives, as shown in the case of the acetylation of Vd, from which 6-acetamido-8-methyl-9-phenylpurine (VI) is obtained.

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TABLE 1. Substituted 6-Amino-8-methylpurines (IV and V)

Comp.	R	pK_a RNH_2	mp	Crystallization solvent	Empirical formula	Found, %			Calc., %			Yield, %
						N	C	H	N	C	H	
Va	C_6H_{11}	10.8 [10]	216—217	Benzene	$C_{12}H_{17}N_5$	30,4	62,5	7,3	30,3	62,3	7,4	63
IVa	C_6H_{11}		182—184*	Benzene	$C_{12}H_{17}N_5$	30,2	62,0	7,5	30,3	62,3	7,4	23
Vb	$CH_2C_6H_5$	9.62 [11]	238—240	Methanol	$C_{13}H_{13}N_5$	—	65,1	5,4	—	65,3	5,5	70(17)
Vc	$CH_2C_4H_3O$	8.89 [11]	223—224	Ethanol	$C_{11}H_{11}N_5O$	30,6	57,6	4,8	30,5	57,6	4,8	72(17)
Vd	C_6H_5	4.58 [12]	257—259	Methanol	$C_{12}H_{11}N_5$	—	64,1	4,9	—	64,0	4,9	85
IVd	C_6H_5		298—299	Ethanol	$C_{12}H_{11}N_5$	31,0	63,8	4,9	31,1	64,0	4,9	6
Ve	*m*-ClC_6H_4	3.34 [12]	222—223	Chloroform	$C_{12}H_{10}N_5Cl$	26,9	—	Cl 13,4	27,0	—	Cl 13,6	84
IVe	*m*-ClC_6H_4		237—238	Chloroform	$C_{12}H_{10}N_5Cl$	26,2	—	Cl 13,1	27,0	—	Cl 13,6	7
Vf	*p*-$F_3CC_6H_4$	2.6 [12]	283—284	„ „	$C_{13}H_{10}N_5F_3$	24,0	—	F 19,3	23,9	—	F 19,4	86
IVf	*p*-$F_3CC_6H_4$		279—281	„ „	$C_{13}H_{10}N_5F_3$	23,1	—	F 19,4	23,9	—	F 19,4	5
Vg	*p*-NCC_6H_4	1.74 [12]	303—305	Ethanol	$C_{13}H_{10}N_6$	—	62,4	4,1	—	62,4	4,0	85

*The capillary was placed in a bath heated to 170°.

† The yields of IVb and IVc are indicated in parentheses.

TABLE 2. 6-Arylamino-4-amino-5-nitropyrimidines (IIe-g) and Trimaminopyrimidines (IIIe-g)

Comp.	R	mp	Empirical formula	Found, %			Calc., %			Yield, %
				N	C	H	N	C	H	
II e	*m*-ClC_6H_4	230—231	$C_{10}H_8N_5O_2Cl$	26,3	45,2	3,0	26,4	45,2	3,0	99
II f	*p*-$F_3CC_6H_4$	263—265	$C_{11}H_8N_5O_2F_3$	23,1	—	F 18.9	23,4	—	F 19,0	90
II g	*p*-NCC_6H_4	334—335	$C_{11}H_8N_6O_2$	32,6	51,7	3,0	32,4	51,6	3,1	97
III e	*m*-ClC_6H_4	156—158	$C_{10}H_{10}NCl$	29,8	—	Cl 14,8	29,7	—	Cl 15,0	81
III f	*p*-$F_3CC_6H_4$	171—173	$C_{11}H_{10}N_5F_3$	26,1	—	F 20,9	26,1	—	F 21,2	72
III g	*p*-NCC_6H_4	253—254	$C_{11}H_{10}N_6$	—	58,0	4,3	—	58,4	4,4	70

EXPERIMENTAL

4,6-Diamino-5-nitropyrimidines (IIa-g, Table 2). These were obtained via the method described in [4]. Compounds IIa-d were identified from the literature melting points [4, 5].

4,5,6-Triaminopyrimidines (IIIa-f, Table 2). Compounds IIa-f (2 g) were suspended in 100-150 ml of methanol, 2-2.5 g of active Raney nickel was added, and the starting materials were hydrogenated with vigorous shaking at low pressure (about 200 mm H_2O) until hydrogen absorption ceased. The catalyst was removed by filtration, the methanol was evaporated to dryness, and the residue was crystallized (IIIe and g from water, IIIf from water). Compounds IIIa-d were identified from their melting points [5, 6].

4,5-Diamino-6-(p-cyanophenyl)aminopyrimidine (IIIg). This compound is not reduced with a nickel catalyst. The reduction was carried out via the preceding method but with a platinum catalyst prepared according to the method described in [7].

Cyclization of IIIa-g. A mixture of 0.015 mole of III and 0.03 mole of acetic acid imino ester hydrochloride was heated for 1 h at 140-150°, during which a melt formed. The reaction mass was treated twice with 2 N NaOH. 6-N-Substituted 6-amino-8-methylpurines (IVa-f) were precipitated from the filtrate with acetic acid and were filtered and crystallized. The 6-amino-8-methyl-9-substituted purines (Va-g) that precipitated were insoluble in alkali; they were washed with water, dried, and crystallized. Compound IVg was not isolated in pure form. Compounds IVb and c were identified from their melting points [8, 9].

6-Acetamido-8-methyl-9-phenylpurine (VI). Compound Vd was acetylated by heating in acetic anhydride for 1 h. The product was obtained in the form of colorless needles from ethanol with mp 184-186°. Found %: C 62.9; H 4.9. $C_{14}H_{13}N_5O$. Calculated %: C 62.90; H 4.9.

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