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NEW METHOD FOR THE SYNTHESIS OF SOME POLYFUNCTIONAL 5-AMINOPYRIMIDINES

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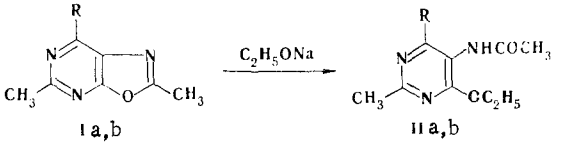
A preparative method for the synthesis of some 5-aminopyrimidines, which consists in the nucleophilic opening of the oxazole ring of 2,5-dimethyl-7-chloro- and 7-amino-substituted oxazole[5,4-d]pyrimidines under the influence of acids and bases, was developed.

5-Aminopyrimidines are the starting compounds for the synthesis of various condensed pyrimidines and are of interest as biologically active substances. The widely known methods for the preparation of compounds of this type are multistep processes and are based on starting compounds that are difficult to obtain [1].

Moreover, the lack of literature data on the stability of the oxazole ring in oxazolo[5, 4-d]pyrimidines compelled us to investigate its behavior in acidic and alkaline media in the case of the readily accessible 2,5-dimethyl-7-chloro- and 7-amino-substituted oxazolo[5, 4-d]-pyrimidines [2, 3].

In contrast to oxazoles, the majority of which are resistant to the action of acids and alkalis [4], the reaction of 2,5-dimethyl-7-chloro- and 7-amino-substituted oxazolo[5,4-d]-pyrimidines with sodium ethoxide leads to opening of the oxazole ring:



I a,b II a,b

I, II a R = Cl; b R = $N(C_2H_5)_2$

The hydrolysis of oxazolo[5,4-d]pyrimidines under the influence of acids proceeds just as readily. 2-Methyl-4-chloro-5-amino-6-hydroxypyrimidine hydrochloride (IIIa) was obtained in high yield by the action of hydrochloric acid on Ia in benzene or alcohol. 2-Methyl-4-chloro-5-acetamido-6-hydroxypyrimidine (IVa), which was deacetylated to give IIIa upon refluxing with hydrochloric acid, was formed when a weaker acid (such as acetic acid) was introduced into the reaction.

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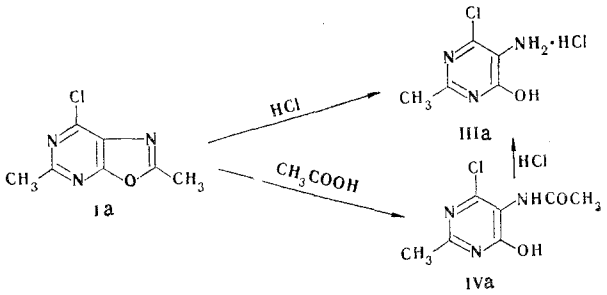
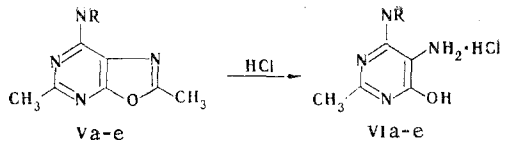
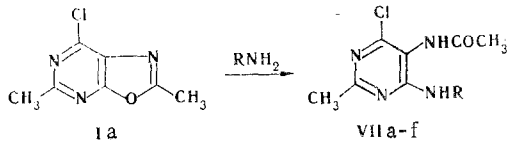


Similarly, the reaction of the previously obtained [3] 2,5-dimethyl-7-dialkylamino-substituted oxazolo[5,4-d]pyrimidines (Va-e) with hydrochloric acid leads to 2-methyl-4-dialkylamino-5-amino-6-hydroxypyrimidine hydrochlorides (VIa-e).



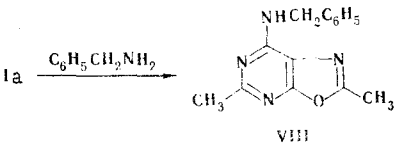
V, VI a NR=N(CH$_3$)$_2$, b N(C$_2$H$_5$)$_2$, c N(C$_3$H$_7$)$_2$, morpholyl, e piperidyl

The reaction of Ia with benzyl- and p-alkoxybenzylamines leads to opening of the oxazole ring to give 2-methyl-4-chloro-5-acetamido-6-benzyl(p-alkoxybenzyl)aminopyrimidines (VIIa-f).



a R=C$_6$H$_5$CH$_2$; b *p*-CH$_3$OC$_6$H$_4$CH$_2$, c *p*-C$_2$H$_5$OC$_6$H$_4$CH$_2$, d *p*-C$_3$H$_7$OC$_6$H$_4$CH$_2$, e *p-iso*-C$_3$H$_7$OC$_6$H$_4$CH$_2$, f *p*-C$_4$H$_9$OC$_6$H$_4$CH$_2$

A side product [R_f 0.52, thin-layer chromatography (TLC)] is formed along with principal product VIIa (R_f 0.67) in the reaction of Ia with excess benzylamine in a low-polarity solvent (hexane, heptane) in the presence of potassium carbonate. It was shown by mass spectrometry that the reaction mixture contains, in addition to VIIa, a compound with a molecular-ion peak at m/z 254, which is the product of replacement of the chlorine atom in Ia by benzylamine. Structure VIII was assigned to this substance.



The structures of all of the compounds obtained were confirmed by data from the mass spectra. The purity and individuality of VIIa-f were confirmed by TLC.

Possible mechanisms of the acidic hydrolysis of oxazoles that depend on cleavage of the ring as a result of nucleophilic attack at the carbon atom or in the 2 or 5 position have been described [4]; preference is given to the second assumption.

Our results make it possible to assert that the C$_{(5)}$ atom of the oxazole ring undergoes nucleophilic attack in opening of the oxazole ring in oxazolo[5,4-d]pyrimidines, since the formation of the reaction products presented above is excluded in the case of attack at the C$_{(2)}$ atom.

The toxicity and antitumorigenic activity of the synthesized compounds with respect to sarcoma 45, Walker carcinosarcoma, and Erlich's ascitic carcinoma were studied by the method in [5]. It was established that VI display weak and VII display moderate antitumorigenic activity, inasmuch as they depress the growth of solid tumors by a factor of 30 to 60%.

TABLE 1. 2-Methyl-4-chloro(dialkylamino)-5-amino(acetamido)-6-hydroxy(ethoxy)pyrimidines

Compound	mp, °C (from alcohol)	M (by mass spectrometry)	Found, %				Empirical formula	Calc., %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
IIa	200—201	229	46,6	5,3	14,9	17,9	$C_9H_{12}ClN_3O_2$	47,1	5,2	15,4	18,3	49,7
IIb	138—140	266	58,8	8,1	—	21,1	$C_{13}H_{22}N_4O_2$	58,6	8,3	—	21,0	87,1
III	241—242	159*	30,9	4,2	35,7	21,7	$C_5H_7Cl_2N_3O$	30,6	3,6	36,2	21,4	86,1
IV	>300	201	42,0	4,1	17,5	20,6	$C_7H_8ClN_3O_2$	41,7	4,0	17,5	20,8	72,7
VIa	220—221	201*	41,5	6,9	17,3	27,1	$C_7H_{13}ClN_4O$	41,1	6,4	17,6	27,8	61,0
VIb	243—244	232*	46,5	7,1	14,7	24,2	$C_9H_{17}ClN_4O$	46,4	7,4	15,2	24,1	52,4
VIc	174—175	260*	50,2	8,4	14,0	21,4	$C_{11}H_{21}ClN_4O$	50,7	8,1	13,6	21,5	41,2
VId	219—220	246*	43,9	6,3	14,2	22,1	$C_9H_{15}ClN_4O_2$	43,8	6,1	14,4	22,7	85,6
VIe	231—232	244*	49,6	6,8	14,7	23,0	$C_{10}H_{17}ClN_4O$	49,1	7,0	14,5	22,9	53,8

*Ion peaks corresponding to the bases (M^+ — HCl) were obtained in the case of the hydrochlorides of the compounds.

TABLE 2. 2-Methyl-4-chloro-5-acetamido-6-benzyl(p-alkoxybenzyl)aminopyrimidines (VIIa-f)

Compound	mp, °C (from alcohol)	R_f	M (by mass spectrometry)	Found, %				Empirical formula	Calc., %				Yield, %
				C	H	Cl	N		C	H	Cl	N	
VIIa	195—197	0,67	290	57,6	4,8	12,5	19,8	$C_{14}H_{15}ClN_4O$	57,8	5,2	12,2	19,3	86,2
VIIb	199—200	0,75	320	56,0	5,8	10,6	17,4	$C_{15}H_{17}ClN_4O$	56,2	5,3	11,0	17,5	63,1
VIIc	195—196	0,75	334	57,8	5,5	11,0	17,2	$C_{17}H_{19}ClN_4O$	57,4	5,7	10,6	16,7	85,1
VIId	224—225	0,78	348	58,2	5,7	10,6	15,9	$C_{17}H_{21}ClN_4O$	58,5	6,1	10,2	16,1	83,1
VIIe	169—171	0,81	348	59,2	6,1	10,5	15,9	$C_{17}H_{21}ClN_4O$	58,5	6,1	10,2	16,1	88,8
VIIf	180—182	0,89	362	60,0	6,4	9,3	15,2	$C_{18}H_{23}ClN_4O$	59,6	6,4	9,8	15,4	58,0

EXPERIMENTAL

The mass spectra of the compounds were recorded with an MKh-1303 spectrometer at an ionization energy of 30 eV and at temperatures 30-40°C below the melting points of the investigated compounds with direct introduction of the samples into the ion source. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in an absolute ethanol—water system (2:1) with development in UV light.

2-Methyl-4-chloro- and 4-Diethylamino-5-acetamido-6-hydroxypyrimidines (IIa, b). A 0.01-mole sample of Ia, b [2, 3] was added to sodium ethoxide, prepared from 0.23 g (0.1 mole) of sodium metal and 20 ml of absolute ethanol, and the mixture was refluxed for 3 h. The solvent was removed by distillation, 2-3 ml of water was added to the residue, and the precipitate was removed by filtration (Table 1).

2-Methyl-4-chloro-5-amino-6-hydroxypyrimidine Hydrochloride (III). A mixture of 1.83 g (0.01 mole) of Ia and 2 ml of concentrated HCl was refluxed in 30 ml of ethanol or benzene for 1 h, after which the precipitate was removed by filtration, washed with alcohol, and dried (Table 1).

2-Methyl-4-chloro-5-acetamido-6-hydroxypyrimidine (IVa). A 3.8-g (0.04 mole) sample of monochloroacetic acid was added to 1.83 g (0.01 mole) of Ia in 30 ml of benzene, and the mixture was refluxed for 2 h. The precipitated crystals were removed by filtration and washed thoroughly with ether (Table 1).

2-Methyl-4-chloro-5-acetamido-6-benzyl- and 6-(p-Alkoxybenzylamino)pyrimidines (VIIa)f). A mixture of 1.83 g (0.01 mole) of Ia and 0.01 mole of the corresponding amine in 30 ml of absolute benzene was refluxed for 2 h, after which the precipitate was removed by filtration and recrystallized from ethanol (Table 2).

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SYNTHESIS OF INDOLE DERIVATIVES OF PYRIDO[2,3-d]PYRIMIDINE

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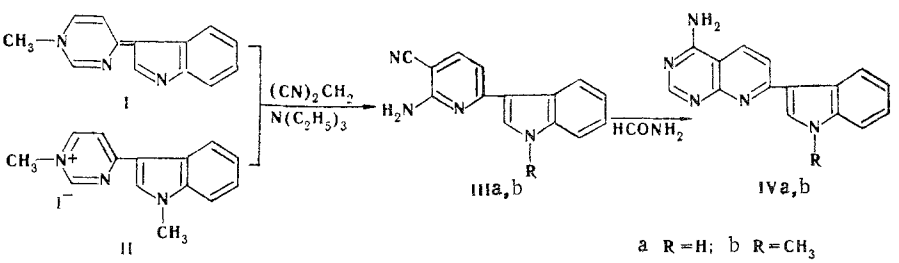
Recyclization of the pyrimidine ring with inclusion of the reagent in the newly formed ring to give indole derivatives of 2,3-disubstituted pyridines occurs in the reaction of the anhydro base of 4-(3-indolyl)pyrimidine with CH acids in the presence of triethylamine. The products react with formamide to give the pyrido[2,3-d]pyrimidine heterocyclic system.

Indole derivatives of condensed heterocyclic systems with nitrogen atoms in different rings are difficult to obtain and are limited to a few representatives, since there is no convenient method for their preparation. Isomeric indolyl-1,2-dihydro-1,5-naphthyridines and indolyl-1,2-dihydro-1,8-naphthyridines, which are obtained by direct reaction of indole with naphthyridines in the presence of benzoyl chloride [1], and the indole derivative of 2,3-dihydropurine, which is formed via a similar pathway [2], constitute exceptions. These dihydro structures could not be aromatized, whereas both indole and condensed heterocycles, viz., purine, pteridine, etc., are important structural fragments of many natural and synthetic physiologically active substances. In this connection the search for new convenient methods for the synthesis of such structures is an urgent task.

We have previously reported [3] the synthesis of 2-amino-3-cyano-6-(3-indolyl)pyridines (III) in the recyclization of anhydro base I or quaternary salt II under the influence of the anion of malonic acid dinitrile. The ortho orientation of the functional groups in pyridylindoles III makes it possible to regard these compounds as promising starting compounds for the subsequent construction of new heterocyclic systems. It is known that o-amino nitriles readily give condensed 4-aminopyrimidines in high yields when they are heated briefly in excess formamide [4]. This reaction lies at the foundation of one of the rather widely used methods for the synthesis of a pyrimidine ring and is regarded as a qualitative reaction for vicinal amino nitriles.

Compounds III [3] also react readily with formamide to give indole derivatives (IV) of pyridopyrimidine:



Absorption bands at 3300 cm^{-1}, which correspond to ν_{NH_2} vibrations, and a series of intense absorption bands at 1650-1670 cm^{-1}, which we assigned to the absorption ($\nu_{C=N}$) of the

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