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SYNTHESIS OF 5-SUBSTITUTED 2-NITRAMINOPYRIMIDINES AND 2-HYDROXYAMINOPYRIMIDINES

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2-Nitraminopyrimidine and its 5-R derivatives (R = Me, Cl, NO_2, Ph, p-$O_2NC_6H_4$) have been prepared by cyclization of nitroguanidine with 2-methyl-3-dimethylaminoacrolein or bis(dimethylamino)trimethinium salts, and also by nitration of the corresponding aminopyrimidines. By interaction of these nitramino derivatives with hydroxylamine, substituted 2-hydroxyaminopyrimidines have been obtained.

As reported previously [1], we had introduced changes into a known method for the synthesis of hydroxyaminopyrimidines through the interaction of chloropyrimidines with hydroxylamine [2, 3]. By that method, we had obtained a number of phenyl- or methyl-substituted 2- and 4-hydroxyaminopyrimidines and had demonstrated the possibility of their selective oxidation to nitro-, nitroso-, and azoxypyrimidines [4-6]. For certain substituted chloropyrimidines having functional groupings, however, this method of synthesis of hydroxyamino derivatives was not suitable, owing to the limited accessibility of these particular chloropyrimidines, and sometimes owing to low nucleophilic mobility of the chlorine atoms. A search for alternative methods led us to the use of 2-nitraminopyrimidines as the starting materials.

In a π-deficient heterocyclic ring, the nitramino group is comparatively mobile, and it can act as the leaving group under the influence of nucleophilic reagents. We had already demonstrated in two examples the possibility of synthesizing 2-hydroxyaminopyrimidines by nucleophilic substitution of the nitramino group [2]. In comparison with syntheses based on chloropyrimidines, the new method shortens the synthesis of hydroxyaminopyrimidines by one or more stages; also, the new method can be used to synthesize derivatives that would be quite difficult to obtain by other methods.

Thus far, only isolated representatives of the 2-nitraminopyrimidine series have been described in the literature. One such compound had been prepared either by nitration of aminopyrimidines [7, 8] or by cyclization of nitroguanidine with cyanoacetic ester and β-dicarbonyl compounds [2, 9]. In the work reported here, we have broadened the circle of compounds that can be used in the reaction of cyclization with nitroguanidine, and we have verified the possibility of synthesizing 5-substituted 2-hydroxylaminopyrimidines on the basis of 2-nitraminopyrimidines.

By the interaction of nitroguanidine with 2-methyl-3-dimethylaminoacrolein or with bis(dimethylamino)trimethinium salts (Ia,b) in ethanol in the presence of sodium ethylate, we obtained with high yields the corresponding 5-methyl- and 5-aryl-2-nitraminopyrimidines (IIa-c). When the reaction between nitroguanidine and 1,1,3,3-tetraethoxypropane was carried out under analogous conditions, or in ethanol in the presence of HCl, we recovered only the original nitroguanidine. Also unsuccessful were attempts to perform the reaction with the participation of nitroguanidine and the sodium salt of nitromalonic dialdehyde. Therefore, for the synthesis of the 2-nitraminopyrimidines IId-f, we used the reaction of nitration of 2-aminopyrimidines (III). In the nitration of the unsubstituted aminopyrimidine (IIId) in a mixture of concentrated sulfuric and fuming nitric acids under conditions described in [7], we recovered only the original compound. This result can be explained by the double protonation of the aminopyrimidine in sulfuric acid to form a dication, which prevents attack by the nitronium cation. When the nitration reaction was performed in nitric acid (d = 1.52), we obtained 2-nitraminopyrimidine (IId).

Under the same conditions, we synthesized the bromo derivative IIe and the nitro derivative IIf. We obtained 5-(p-nitrophenyl)-2-nitraminopyrimidine IIb not only by cyclization of nitroguanidine with the trimethinium salt Ib, but also by nitration of 5-aryl-2-aminopyrimidines IIIb and IIIa. In the latter case, the action of nitric acid resulted in nitration of not only the amino group, but also the phenyl ring at the para position.

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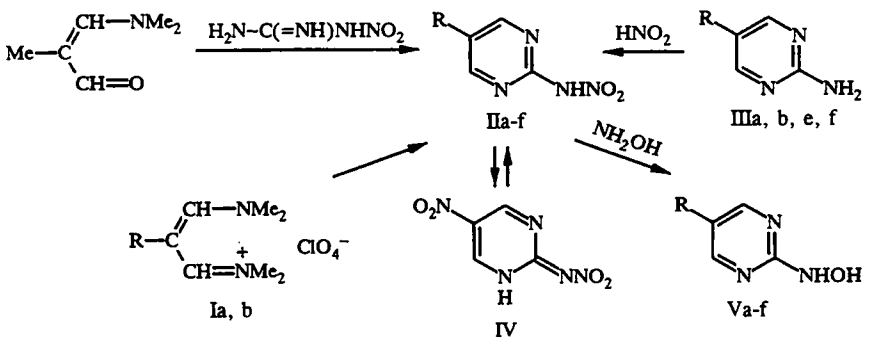

I—III, Va)R = Ph, b)R = *p*-$O_2NC_6H_4$, c)R = Me, d)R = H, e)R = Br, f)R = NO_2

The synthesized 5-substituted 2-nitraminopyrimidines IIa-f are compounds that are stable at room temperature but decompose when heated to the melting point.

The IR spectra of compounds IIa-e contain intense bands of symmetric stretching vibrations of the nitro group in the 1260-1290 cm^{-1} region, similar to those observed for nitraminopyrimidines in [10]. The band of antisymmetric N—O stretching vibrations, for the nitramines IIa-f, has a lower intensity and is shifted toward higher frequencies (up to 1600 cm^{-1} or higher), where N—H bending vibrations and stretching vibrations of the aromatic ring are also manifested [10]. The N—H stretching vibrations are observed at about 3200 cm^{-1} in the form of rather intense bands.

The introduction of NO_2 into the amino group leads to a significant increase of the N—H acidity of the amino group and also to the manifestation of prototropic tautomerism, which is characteristic for nitraminoazines [11]. In determining the structure of the compounds that we obtained, we used UV and PMR spectroscopic data. It is known that nitraminoazines can actually exist in two tautomeric forms [10, 11]. In a series of 5-substituted 2-nitraminopyrimidines, we found the imino form (IV) only for compound IIf, which has the strongly electron-accepting nitro group in the pyrimidine ring. In the PMR spectrum of the 5-nitro derivative IIf in DMSO-d_6, we observed two sets of signals, indicating the presence of both tautomeric forms in solution, in equal quantities. Characteristic for these forms is a broadened signal of the proton for the $NHNO_2$ group at 11.72 ppm and a doublet signal for the endocyclic NH group at 10.79 ppm [12, 13]. In the less polar DMF-d_7, the fraction of the imino form IV is smaller, approximately 35%. Upon dissolution of a sample of IIf in acetone-d_6, we initially observed primarily the tautomer IV, the fraction of which gradually decreased with the passage of time, amounting to no more than 5% after 20 h. This gives us grounds for considering that in the crystalline state, the nitro compound IIf exists in the imino form IV. In the UV spectrum recorded in DMF, the imino form has an intense absorption band at 402 nm. The intensity of this band decreases as the tautomeric equilibrium shifts toward the amino form IIf, as is observed when the polarity of the medium is decreased in a series of mixtures of DMF and $CHCl_3$ (Fig. 1).

Upon interaction of the nitramino derivatives IIa-f with hydroxylamine in aqueous solution, the $NHNO_2$ group is readily replaced by the NHOH group; as a result, the corresponding 2-hydroxyaminopyrimidines (Va-f) are formed, giving an intense color with Fe(III) salts. According to UV spectroscopic data, the synthesized 2-hydroxyaminopyrimidines Va-f exist in the amino form. In their PMR spectra (in DMSO-d_6), the signals of the protons of the NH and HO groups are shifted downfield; and the position of the resonance signals is determined by the electron-acceptor properties of the substituent in position 5 of the heterocycle.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer in KBr tablets (concentration 0.25%). The UV spectra of solutions in ethanol were obtained on a Specord UV-Vis spectrophotometer, and the spectra of solutions in a mixture of DMF and chloroform were obtained on a Specord M-40 spectrophotometer. The PMR spectra were recorded on a Bruker WP-200 SY instrument (200.13 MHz) in DMSO-d_6. The magnitudes of the chemical shift were determined relative to the signal of the solvent.

The characteristics of the synthesized compounds are listed in Table 1, and spectroscopic data are presented in Table 2.

TABLE 1. Characteristics of 2-Nitraminopyrimidines IIa-f and 2-Hydroxyamino-pyrimidines Va-f

Compound	Empirical formula	Found, % / Calculated, %			mp (and solvent)	M^+	Yield, % (and method)
		C	H	N (Br)			
IIa	$C_{10}H_8N_4O_2$	55,41 / 55,56	3,73 / 3,73	26,08 / 25,91	210...212 decomp. (EtOH)	216	69(A)
IIb	$C_{10}H_7N_5O_4$	45,80 / 45,98	2,66 / 2,70	26,91 / 26,81	216 decomp. (DMF)	261	92(A), 92(B*), 79 (B†)
IId	$C_4H_4N_4O_2$	34,01 / 34,29	3,01 / 2,88	40,20 / 39,99	190...192 decomp. (MeOH)	140	43 (B)
IIc	$C_5H_6N_4O_2$	38,66 / 38,96	3,82 / 3,92	36,44 / 36,35	185...188 decomp. (H_2O)	154	55 (A)
IIe					195 decomp. (H_2O—EtOH); 189 [7]		64 (B)
IIf	$C_4H_3N_5O_4 \cdot H_2O$	23,70 / 23,65	2,57 / 2,48	34,73 / 34,48	167 decomp. (H_2O)	185	54 (B)
Va					175...179 decomp. (EtOH); 184...185 decomp. [4]		75
Vb	$C_{10}H_8N_4O_3$	51,81 / 51,72	3,50 / 3,47	24,49 / 24,13	> 220 decomp. (DMF) —EtOH)	232	98
Vc	$C_5H_7N_3O$	47,86 / 47,99	5,63 / 5,64	33,41 / 33,58	172...175 decomp. (EtOH)	125	27
Vd	$C_4H_5N_3O$	43,31 / 43,24	4,24 / 4,54	37,37 / 37,82	127...130 decomp.	111	28
Ve	$C_4H_4BrN_3O$	25,28 / 25,28	2,03 / 2,12	21,85(41,50) / 22,12(42,06)	186...187 decomp. (EtOH)	189	60
Vf	$C_4H_4N_4O_3$	30,54 / 30,78	2,56 / 2,58	35,70 / 35,89	196...198 decomp. (EtOH)	156	38

*Obtained from IIa.

†Obtained from IIb.

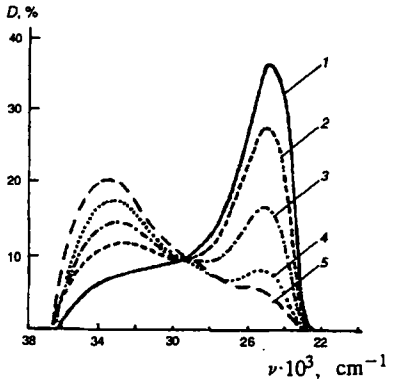

Fig. 1. UV spectra of compound IId* in DMF and in mixtures of DMF and $CHCl_3$ (c = $1 \cdot 10^{-4}$ M, l = 0.5 cm): *1*) DMF; *2-5*) mixtures of DMF and $CHCl_3$ in following ratios: *2*) 75/25; *3*) 50/50; *4*) 25/75; *5*) 10/90. [*As in Russian original; the text states that this is compound IIf — Translator.]

5-Substituted 2-Nitraminopyrimidines IIa-f. **A.** To a solution of 20 mmoles of sodium methylate in 20 ml of MeOH, there was added 10 mmoles of nitroguanidine and 10 mmoles of 2-methyl-3-dimethylaminoacrolein or the corresponding bis(dimethylamino)trimethinium salt Ia,b. The reaction mixture was refluxed 2.5 h, cooled, poured into water, and filtered, and the filtrate was acidified with concentrated HCl. The resulting precipitate was filtered off and dried.

TABLE 2. Spectral Characteristics of Compounds IIa-f, IV, and Vb,c,e*

Compound	PMR spectrum, δ, ppm (and J, Hz), DMSO-d_6	UV spectrum, λ_{max}, nm (and log ε)
IIa	7,37...7,69 (3H, H_{arom}); 7,69...8,07 (2H, H_{arom}); 9,13 (2H, c, $H_4 + H_6$)	2,80 (3,28), 339 sh (3,48)
IIb	8,08 (2H, s, H_{arom}); 8,31 (2H, s, H_{arom}); 9,21 (2H, s, $H_4 + H_6$)	309 (4,37), 353 sh (3,90)
IIc	2,28 (3H, s, CH_3); 8,68 (2H, s, $H_4 + H_6$); 11,81 (1H, br.s., NH)	263 (3,86), 333 sh (3,08)
IId	7,33 (1H, t, H_5, $J = 5$); 8,79 (2H, d, $H_4 + H_6$, $J = 5$)	255 (3,99), 315 sh (3,32)
IIe	8,97 (2H, s, $H_4 + H_5$)	265 (3,81)
IIf	9,43 (2H, s, $H_4 + H_5$); 11,72 (1H, br.. s, NH)	330 (4,11), 375 sh (3,81)
IV	6,00 (1H, d, H_6, $J = 3,5$); 8,13 (1H, s, H_4); 10,79 (1H, d, NH, $J = 3,5$)	
Vb	7,95 (2H, d, H_{arom}, $J = 9$); 8,19 (2H, d, H_{arom}, $J = 9$); 8,82 (2H, s, $H_4 + H_6$); 9,00 (1H, s, OH); 10,01 (1H, s, NH)	240 (4,11), 330 (4,23)
Ve	8,44 (2H, s, $H_4 + H_6$); 8,85 (1H, s, OH); 9,76 (1H, s, NH)	243 (4,27), 349 (3,31)
Vf	9,05 (2H, s, $H_4 + H_6$); 9,76 (1H, s, OH); 11,36 (1H, s, NH)	220 (3,54), 338 (3,80)
VI	2,09 (3H, s, CH_3); 8,23 (2H, s, $H_4 + H_6$); 8,53 (1H, s, OH); 9,10 (1H, s, NH)	236 (4,26), 302 (3,41)

*As in Russian original; identification of compounds V does not match that given in the body of the table — Translator.

B. To fuming nitric acid (d = 1.52), the aminopyrimidine IIIa,b,d-f was added in small portions while stirring and cooling with ice water. The reaction mass was stirred for an additional 1 h at 20°C and then poured onto ice; the precipitate was filtered off and dried.

5-Substituted 2-Hydroxyaminopyrimidines Va-f. A 14-mmole quantity of $NaHCO_3$ and 15 mmoles of $NH_2OH \cdot HCl$ were dissolved in 20 ml of water, 10 mmoles of compound IIa-f was added, and the mixture was refluxed for 0.5-1.5 h. The course of the reaction was monitored chromatographically (Silufol UV-254, chloroform with the addition of ethanol). The reaction mixture was cooled, and the precipitate was separated and dried. Compound Vd was recovered from an aqueous solution by extraction with ether. In the case of compound Vc, the aqueous solution was evaporated to dryness, the residue was treated with boiling isopropanol, and the material that precipitated upon cooling was separated and dried.

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