SYNTHESIS AND STUDY OF THE COVALENT SOLVATION OF 6-NITROAZALOPYRIMIDINES

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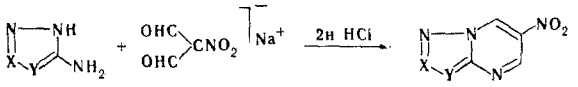
The corresponding 6-nitroazolo[1,5-a]pyrimidines were obtained by the reaction of the sodium salt of nitromalondialdehyde with 3(5)-aminotriazoles and 3(5)-aminopyrazoles. The covalent solvation of the synthesized compounds was investigated by PMR spectroscopy.

Derivatives of azolopyrimidines with a bridged nitrogen atom are finding application as stabilizers of photoemulsions [1], and some of them have bactericidal [2], analgesic, and antiphlogistic activity [3, 4]. The introduction of a nitro group in compounds, particularly compounds of the heterocyclic series, often intensifies the bactericidal activity and also has a substantial effect on the chemical properties of the compounds. Thus nitro derivatives of azolopyrimidines readily form solvates and can serve as good subjects for the investigation of covalent hydration.

The synthesis of both monocyclic and annelated nitropyrimidines by direct nitration is possible only when donor amino or hydroxy groups are present in the molecule [5, 6]. Unsubstituted nitropyrimidine was obtained by oxidation of the 5-nitro-4,6-dihydrazino derivative [7]. Within the framework of a further study of nitro derivatives of six-membered nitrogen heterocycles [8] in the present communication we describe the synthesis of 6-nitroazolo[1,5-a]pyrimidines IIa-H by condensation of aminoazoles Ia-h with nitromalondialdehyde and the results of a study of the properties of the compounds obtained.

The reaction evidently proceeds through a step involving an azomethine. Condensation at the second aldehyde group and the formation of the corresponding azolo[1,5-a]pyrimidines II occur at 30-40°C. After crystallization from alcohol, IIe was isolated in the form of a stable adduct. Free 6-nitro-1,2,4-triazolo[1,5-a]pyrimidine was obtained only after heating at 120°C in vacuo (10 mm, mercury column) for 24 h.



I, II a X=Y=CH; b X=CCH_3, Y=CH; c X=CH, Y=CBr; d X=CH, Y=CCN; e X=CH, Y=N; f X=CCH_3, Y=N; g X=$CSCH_3$, Y=N; h X=CNH_2, Y=N

Absorption bands of stretching vibrations of a nitro group are observed in the IR spectra of the compounds obtained at 1330-1350 cm^{-1} and 1560-1590 cm^{-1} (Table 1). The PMR spectra of IIc,f-h (Table 2 and Fig. 1) contain doublets of pyrimidine protons at 9.29-9.60 and 10.10-10.55 ppm with a meta constant of 2.5 Hz and singlet signals of a 2-H proton (IIc), protons of a methyl group (IIf,g), or protons of an amino group (IIh). The 5-H protons of the pyrimidine ring, which are situated between the nitro group and the pyrimidine nitrogen atom, resonate at weakest field. The 5-H proton in the spectra of IIa,b is split into a doublet of doublets because of long-range spin–spin coupling with the 3-H proton ($J_{2,5}$ = 0.9 Hz). In the spectrum of IIa the meta $J_{2,3}$ - 2.3 Hz and $J_{5,7}$ = 2.5 Hz constants are close in value. The reliability of the assignment of the signals was additionally confirmed by double resonance. In addition to absorption of the principal compound at 8.98 (s, 2-H), 9.67 (d, 7-H), and 10.63 ppm (d, 5-H), signals at 7.91 (s, 2-H), 6.87 (s, 5-H), and 8.47 ppm (s, 7-H) belonging to the covalent hydrate that is formed by reaction with the water present in commercial-

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TABLE 1. 6-Nitroazolo[1,5-a]pyrimidines (IIa-h)

Compound	mp, °C	IR spectrum, cm⁻¹		Found, %			Empirical formula	Calc., %				Formation of an adduct with alcohol, %
		ν_s, NO_2	ν_{as}, NO_2	C	H	N		C	H	N		
IIa	205—206[a]	1350	1560	43,6	2,5	34,1	$C_6H_4N_4O_2$	43,2	2,4	34,1	55	14
IIb	191—192[b]	1350	1570	47,5	3,4	31,4	$C_7H_6N_4O_2$	47,2	3,4	31,4	70	0
IIc	152—153[a]	1350	1568	30,2	1,5	23,3	$C_6H_3BrN_4O_2$	29,6	1,2	23,1	63	25
IId	141—143[c]	1350	1570	44,5	1,7	36,9	$C_7H_3N_5O_2$	44,4	1,6	37,0	70	56 (10)[d]
IIe	165—167[a]	1346	1560	36,5	2,1	42,2	$C_5H_3N_5O_2$	36,4	1,8	42,2	75	74 (30)[d]
IIf	165—166[a]	1350	1570	40,1	3,0	39,0	$C_6H_5N_5O_2$	40,2	2,8	39,1	53	52
IIg	143—145[a]	1350	1560	34,4	2,4	33,2	$C_6H_5N_5O_2S$	34,1	2,4	33,2	70	41
IIh	>300[b]	1350	1560	33,7	2,3	46,6	$C_5H_4N_6O_2$	33,3	2,2	46,6	85	0

[a]From alcohol. [b]From isopropyl alcohol. [c]From 50% aqueous dimethylformamide. [d]Adduct with water.

TABLE 2. Parameters of the PMR Spectra of IIa-h

Compound	Free compound, δ, ppm				Adducts with deuteromethanol,[a] δ, ppm			
	2-H	5-H	7-H	other signals	2-H	5-H	7-H	other signals
IIa	8,65 d	10,34 dd	9,29 d	7,03 dd (3-H)	7,72 d	6,75 s	8,70 s	6,10 d (3-H)
IIb	—	10,42 dd	9,43 d	2,50 s (CH_3)	—	—	—	—
				7,09 d (3-H)				
IIc	8,78 s	10,39 d	9,35 d	—	7,12 s	6,70 s	8,45 s	—
IId	9,40 s	10,78 d	9,73 d	—	8,82 s	6,95 s	8,75 s	—
					(8,25 s)	(6,95 s)	(8,58 s)	
IIe	9,03 s	10,68 d	9,72 d	—	8,05 s	6,85 s	8,65 s	—
					(7,95 s)	(6,92 s)	(8,52 s)	
IIf	—	10,60 d	9,65 d	2,65 s (CH_3)	—	6,75 s	8,60 s	2,35 s (CH_3)
IIg	—	10,60 d	9,65 d	2,85 s (CH_3)	—	6,75 s	8,60 s	2,80 s (CH_3)
IIh	—	10,20 d	9,40 d	7,15 s (NH_2)	—	—	—	—

[a]The δ values of the adducts of IId,e with water are given in parentheses.

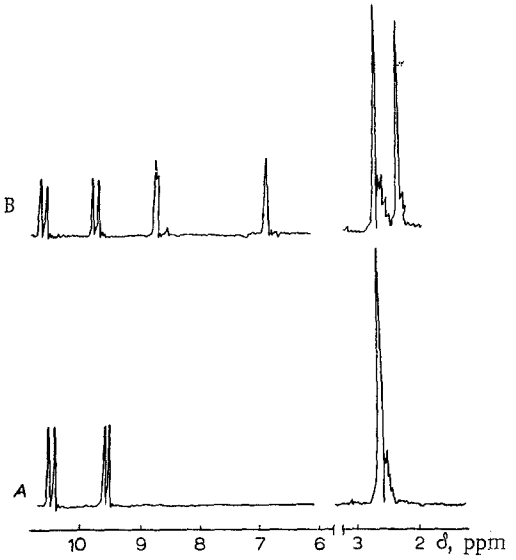

Fig. 1. PMR spectrum of 2-methyl-6-nitro-1,2,4-triazolo[1,5-a]-pyrimidine (IIf): A) in d_6-DMSO; B) in d_6-DMSO + CD_3OD.

grade d_6-DMSO are observed in the spectrum of IIe. It is known that 5-nitropyrimidine [6] and 5-nitro-2-pyrimidone [7], which has an orientation of the multiple bonds that is similar to that in the investigated compounds, also readily form covalent hydrates. The formation of the latter disrupts the aromatic character of the system, and this leads to a shift of the signals to strong field; the proton of the geminal node experiences the greatest shift [7]. The assignment of the lines in the spectrum is facilitated by the fact that the 5-H proton, in addition, gives a broad signal as a consequence of unresolved constants of spin-spin coupling with the 7-H and hydroxy protons. The assignment of the signals to the 2-H and 7-H protons was made by means of double resonance. When the sample is irradiated at the frequency of the absorption of the 5-H proton, the amplitude of the signal at 8.47 ppm (7-H)

increases as a consequence of a decrease in the line width, while the signal at 7.91 ppm (2-H) remains unchanged. As expected, the 2-H proton undergoes the smallest shift to strong field in the case of the formation of a covalent hydrate. The relative amounts of the adducts formed were determined from the integral intensities of the signals. Compound IIe undergoes 30% hydration in a 0.5 M solution in d_6-DMSO containing 0.6% H_2O. Similar character of the spectrum is also observed for 3-cyano-6-nitropyrazolo[1,5-a]pyrimidine (IId) (Table 2). The compound underwent 10% hydration under the same conditions.

As we have already noted, the synthesized 6-nitroazolo[1,5-a]pyrimidines are capable of forming stable adducts with alcohol. This process is conveniently observed by means of PMR spectroscopy. When 0.1 ml of CD_3OD is added to 0.4-ml samples of 0.5 M solutions of the nitropyrimidines, the spectra of IIb,h remain unchanged, additional signals of products of the reaction with alcohol appear in the spectra of IIa,c,f,g (Fig. 1 and Table 2), and the formation of an adduct with both water and alcohol is observed in the case of IId,e. It is apparent from the data presented in Table 1 that the amount of adduct increases from 14% to 25 and 56% when Br and CN acceptor substituents are introduced in the 6-nitropyrazolo[1,5-a]pyrimidine (IIa) molecule. Replacement of the CH fragment in IIa by a nitrogen atom (IIe) leads to a significant increase in the π-deficient character of the system, and 6-nitro-1,2,4-triazolo[1,5-a]pyrimidine gives 74% of the adduct with deuteromethanol under the investigated conditions. Donor CH_3 and SCH_3 substituents in this system (IIf,g) decrease the ability to form adducts (52 and 41%), whereas a product of reaction with alcohol is not detected when an NH_2 group is introduced (IIh).

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO and CD_3OD were recorded with a Perkin-Elmer R12B spectrometer with hexamethyldisiloxane (δ = 0.05 ppm) as the internal standard.

6-Nitroazolo[1,5-a]pyrimidines (IIa-c) (Table 1). A 0.01-mole sample of the amine was dissolved in 7 ml of 2 N HCl, an aqueous solution of 1.3 g (0.01 mole) of the sodium salt of nitromalondialdehyde was added, and the mixture was maintained at 20°C for 15 min. The precipitated II was removed by filtration and crystallized from a suitable solvent.

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