SYNTHESIS OF 2- AND 4-AZIDOPYRIMIDINES CONTAINING AN o-HYDROXYPHENYL GROUP AND THEIR REACTION WITH ACETYLENE DERIVATIVES

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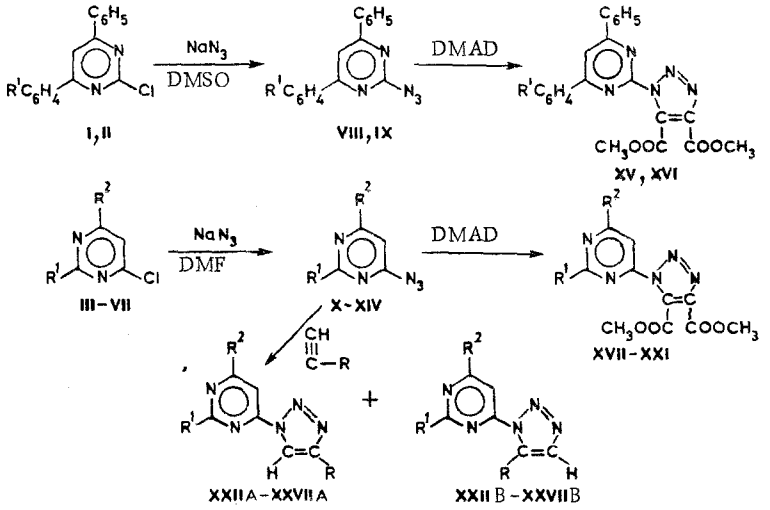
2- and 4-Azidopyrimidines that contain a phenyl and (or) o-hydroxyphenyl group were synthesized. Substituted 1-pyrimidyl-1,2,3-triazoles were obtained by the reaction of azidopyrimidines with acetylenes. Mixtures of isomeric 1,4- and 1,5-disubstituted triazoles, the ratios of which were determined from PMR-spectral data, were formed in the case of unsymmetrical acetylenes.

Intensive study has been devoted in recent years to aromatic and heteroaromatic azides both in the synthesis of diverse heterocyclic systems and for practical utilization in light-sensitive compositions [1, 2]. Nitrogen heterocycles that contain an o-hydroxyphenyl group are of great interest as light stabilizers and complexing agents [3]. However, virtually no study has been devoted to azido azines with an o-hydroxyphenyl group.

It has been reported [4] that the azido-tetrazole equilibrium in o-hydroxyphenyl-substituted azidopyrimidines is shifted to favor the formation of azido derivatives due to the formation of an intramolecular hydrogen bond (IHB). Continuing our study of the effect of a pyrimidine fragment with an o-hydroxyphenyl group on the reactivity of the azido group we investigated the behavior of 2- and 4-azidopyrimidines that contain phenyl and o-hydroxyphenyl groups in reactions involving cycloaddition to acetylenic compounds. This reaction is widely used to obtain substituted 1,2,3-triazoles [5-8]; however, the information regarding this reaction in the pyrimidine series is limited [9, 10].



I, VIII, XV R^1=H; II, IX, XVI R^1=o-HO; III, X, XVII R^1=H, R^2=C_6H_5; IV, XI, XVIII R^1=H, R^2=o-HOC_6H_4; V, XII, XIX R^1=C_6H_5, R^2=H; VI, XIII, XX R^1=o-HOC_6H_4; R^2=H; VII, XIV, XXI R^1=o-HOC_6H_4, R^2=C_6H_5; XXII R=R^1=C_6H_5, R^2=H; XXIII R=C_6H_5, R^1=o-HOC_6H_4, R^2=H; XXIV R=CH_2OH, R^1=C_6H_5, R^2=H; XXV R=CH_2OH, R^1=o-HOC_6H_4, R^2=H; XXVI R=CH_2OH, R^1=H, R^2=C_6H_5; XXVII R=CH_2OH, R^1=H, R^2=o-HOC_6H_4

Aryl-substituted 2- and 4-azidopyrimidines VIII-XIV were synthesized by nucleophilic substitution of the corresponding chloropyrimidines I-VII with sodium azide in dimethyl

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TABLE 1. Characteristics of Substituted 2- and 4-Azidopyrimidines

Compound	Method of prepn.	mp,[a] °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
VIII	A	102—104	70,3	4,2	25,6	$C_{16}H_{11}N_5$	70,4	4,0	25,6	91
IX[b]	A	170—172	—	—	—	—	—	—	—	79
X	B	159—161	61,0	3,5	35,6	$C_{10}H_7N_5$	60,9	3,6	35,5	87
XI	B	166—168	56,5	3,4	32,8	$C_{10}H_7N_5O$	56,3	3,3	32,9	76
XII	B	85—87	60,9	3,5	35,4	$C_{10}H_7N_5$	60,9	3,6	35,5	94
XIII	B	130—132	56,5	3,5	33,1	$C_{10}H_7N_5O$	56,3	3,3	32,9	90
XIV	B	164—166	66,6	4,1	24,0	$C_{16}H_{11}N_5O$	66,4	3,8	24,2	85

[a]The compounds were recrystallized: VIII and XII from methanol, IX-XI and XIII from ethanol, and XIV from methanol—benzene (1:1). [b]According to the data in [21], this compound had mp 162°C.

TABLE 2. PMR Spectra of 1-Pyrimidyl-4,5-dicarbomethoxy-1,2,3-triazoles ppm (J, Hz)

Compound	Solvent	Pyrimidine ring protons		Aromatic substituent in the pyrimidine ring		CH$_3$
		2′-H (4′-H)	5′-H	Harom	OH	
XV	$CDCl_3$	—	—[a]	8,30—8,03 m, 7,70—7,37 m 5 : 6	—	3,97 s, 3,90 s
XVI	d_6-$DMSO_5$	—	8,80 s	8,29—8,01 m, 7,71—7,26 m 7,14—6,81 m, 3 : 4 : 2	11,50 s	3,96 s, 3,93 s
XVII	$CDCl_3$	9,07 d (2)	8,47 d (2)	8,33—7,97 m, 7,67—7,33 m 2 : 3	—	4,33 s, 3,93 s
XVIII	d_6-$DMSO_5$	9,20 d (1)	8,90 d (1)	8,16 m, 7,56—7,16 m, 7,16—6,76 m, 1 : 1 : 2	11,60 s	4,00 s, 3,63 s
XIX	$CDCl_3$	9,00 d (6)	7,97 d (6)	8,53—8,10 m, 7,63—7,30m, 2 : 3	—	4,00 s, 3,97 s
XX	CF_3COOH	9,00 d (6)	7,27 d (6)	7,93 m, 7,60—7,17 m, 7,17—6,90 m, 1 : 1 : 2	12,40 s[b]	3,83 s, 3,73 s
XXI	CF_3COOH	—	8,50 s	8,13—7,17 m, 7,17—6,77m, 7 : 2	12,87 s[b]	3,83 s, 3,70 s

[a]The signal coincides with the region of absorption of phenyl protons. [b]These values are for solutions in $CDCl_3$.

sulfoxide (DMSO) or with lithium azide (obtained *in situ*) in dimethylformamide (DMF) (see Table 1).

A characteristic absorption band of an azido group is present at 2100-2200 cm^{-1} in the IR spectra of solutions of all of these compounds in chloroform.

The cycloaddition of 2- and 4-azidopyrimidines VIII-XIV was studied in the case of the reaction of azides with dimethyl acetylenedicarboxylate (DMAD), phenylacetylene, and propargyl alcohol. The formation of the corresponding substituted 1-pyrimidyltriazoles XV-XXVII (Tables 2-4) in 70-90% yields was observed in all cases. The reaction time increased significantly when the reaction was carried out in solvents (chloroform, toluene), and it was therefore carried out in an excess of the acetylenic component by heating to 140°C. As one should have expected [11-14], the 1,2,3-triazoles obtained in the reaction of 4-azidopyrimidines X-XIII with phenylacetylene and propargyl alcohol were mixtures of two isomers, viz., XXIIA-XXVIIA (1,4-disubstituted triazoles) and XXIIB-XXVIIB (1,5-disubstituted triazoles).

The ratios of the A and B isomers for XXII-XXVII were determined from the integral intensities of the signals of the protons of the triazole ring and the signals of the OH groups in the PMR spectra (see Table 3). The mixtures of isomers of XXIII, XXVI, and XXVII were separated by chromatography. In the remaining cases the assignment of the signals was made for mixtures of the A and B isomers because of significant preponderance of one of the isomers (in the case of XXIV) or because of the difficulties involved in the preparative separation of the mixtures (in the case of XXII and XXV).

TABLE 3. PMR Spectra of 1,4- and 1,5-Disubstituted Triazoles (in $CDCl_3$), ppm (J, Hz)

Compound	Isomer	Substituents in the pyrimidine ring				Substituents in the 4(5) position of triazole		Isomer ratio, A:B
		2′-H or 4′-H	5′-H	aromatic substituents (R^1 or R^2)		H	R	
				H_{arom}	OH			
XXII	A+B	H-4 8,98 d (5)	8,06 d (5)	8,62—8,42 m, 7,58—7,36 m	—	8,96 s, A; 7,83 s, B	C_6H_5 7,95—7,83 m	4 : 1
XXIII	A	H-4 8,84 d (6)	8,07 d (6)	8,38 m, 7,65—7,10 m, 7,10—6,80 m	12,75 s		A[a]	7 : 13
	B	H-4 8,82 d (6)	8,03 d (6)	Same	12,50 s	8,89 s	C_6H_5 8,07—7,87 m[a]	
						7,83 s	C_6H_5[a]	
XXIV	B	H-4 8,93 d (5)	8,09 d (5)	8,60—8,44 m, 7,89—7,42 m, 2 : 3	—	7,77 s	$HOCH_2$ 5,11 s	0 : 1
							$HOCH_2$ 5,30 s,	
XXV	A+B	H-4 8,85 d (6)	8,15 d (6)	8,15 m, 7,60—7,30 m, 7,15—6,85 m, 1 : 1 : 2	12,73 s, A; 12,75 s, B	8,70 s, A; 7,85 s, B	5,20 s	1 : 4
						8,60 s	$HOCH_2$ 5,00 s,	
XXVI	A	H-2 9,15 d (1)	8,55 d (1)	8,35—7,90 m, 7,73—7,30 m, 2 : 3	—		4,90 s	1 : 9
						7,81 s	$HOCH_2$ 4,90 s	
	B	H-2 9,24 d (1)	8,67 d (1)	Same	—	8,65 s	$HOCH_2$ 5,15 s,	
XXVII	A	H-2 9,05 d (1)	8,65 d (1)	7,95 m, 7,65—7,30 m, 7,17—6,85 m, 1 : 1 : 2	13,15 s		4,95 s	2 : 3
						8,78 s	$HOCH_2$ 5,00 s,	
	B	H-2 9,10 d (1)	8,75 d (1)	Same	12,95 s		4,90 s	

[a]The signals of the m- and p-phenyl protons of isomer A and the signal of the phenyl protons of isomer B coincide with the region of absorption of the protons of the phenyl substituent in the pyrimidine ring.

TABLE 4. Characteristics of the Substituted 1,2,3-Triazoles

Compound	Reaction time, h	mp,[a] °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
XV	3,5	193—194	63,7	4,0	16,9	$C_{22}H_{17}N_5O_4$	63,6	4,1	16,9	82
XVI	3,5	220—222	61,1	4,1	16,1	$C_{22}H_{17}N_5O_5$	61,3	4,0	16,2	77
XVII	4	171—173	56,6	4,0	20,3	$C_{16}H_{13}N_5O_4$	56,6	3,8	20,6	77
XVIII	5	218—220	53,9	3,6	19,9	$C_{16}H_{13}N_5O_5$	54,1	3,7	19,7	78
XIX	1,5	168—170	56,8	3,6	20,7	$C_{16}H_{13}N_5O_4$	56,6	3,8	20,6	89
XX	2	204—205	54,4	3,7	19,9	$C_{16}H_{13}N_5O_5$	54,1	3,7	19,7	70
XXI	3	206—208	61,2	4,1	15,9	$C_{22}H_{17}N_5O_5$	61,3	4,0	16,2	69
XXII (A + B)	3	173—177[c]	72,2	4,4	23,7	$C_{18}H_{13}N_5$	72,3	4,4	23,4	72
XXIIIA	2,5	202—204	68,7	4,4	22,1	$C_{18}H_{13}N_5O$	68,6	4,1	22,2	85
XXIV (A+B)	1	195—201[c]	61,8	4,0	27,6	$C_{13}H_{11}N_5O$	61,7	4,4	27,7	88
XXV (A+B)	1,5	152—156[c]	57,8	4,1	25,9	$C_{13}H_{11}N_5O_2$	58,0	4,1	26,0	80
XXVIA	1	172—174	61,5	4,3	27,8	$C_{13}H_{11}N_5O$	61,7	4,4	27,7	68
XXVIБ		153—154								
XXVIIA	1	198—200	58,4	4,2	26,0	$C_{13}H_{11}N_5O_2$	58,1	4,1	26,0	90
XXVIIБ		184—186								

[a]The compounds were recrystallized: XV-XXI, XXIIIA, XXV (A + B), XXVIIA, and XXVIIB from ethanol—DMF, XXII (A + B) and XXIV (A + B), XXVIA, and XXVIB from ethanol. [b]The overall yield of A + B is given for XXII-XXVII. [c]The A:B isomer ratios for XXII, XXIV, and XXV were, respectively, ∿1:0, ∿0:1, and 1:3.

In the spectra of these isomers of XXII-XXVII the signals of the protons of the triazole ring (H_{tr}) differed by 0.8-1.0 ppm, whereas the signals of the o-hydroxy groups differed by up to 0.25 ppm. The differences in the chemical shifts of the remaining signals were slight (within the range of 0.1 ppm). It is known that the H_{tr} signal for 1,4-disubstituted triazoles (the A isomer) is found at weaker field than in the case of 1,5-disubstituted triazoles (the B isomer) [14, 15]. Splitting of the signal of the protons of the phenyl substituent in the triazole, which is characteristic for 1,4-disubstituted triazoles, whereas this signal shows up as a singlet in the case of 1,5-disubstituted triazoles [14-16], serves as an additional confirmation of the structures in the case of XXIIA and XXIIB.

It is apparent from Table 3 that primarily 1,5-disubstituted triazoles XXIVB-XXVIIB are formed from 4-azidopyrimidines in the case of propargyl alcohol. This is possibly associated with the spatial orientation of the propargyl alcohol molecules with respect to the nitrogen atom of the pyrimidine ring. The introduction of an o-hydroxyphenyl group in the pyrimidine ring in place of a phenyl group increases the amounts of the A isomers (compare XXIV and XXV and XXVI and XXVII, respectively); this is probably due to a change in the basicity of the nitrogen atom of the pyrimidine ring under the influence of the o-hydroxyphenyl group.

The ratios of the A and B isomers for XXII and XXIII were, respectively, 4:1 and 7:13 (Table 3), and the literature data on the compositions of isomeric mixtures in the case of phenylacetylene [11-14] do not shed any light on this problem.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with Varian A 56/60 (60 MHz), Brucker HX-90 (90 MHz), and WP-80 (80 MHz) spectrometers. The course of the reactions and the individuality of the products were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates. The starting chloropyrimidines (I [17]; II, IV, VI [18]; III [19]; V [20]) were previously described. Compound VII was obtained in 93% yield by the method in [18] and had mp 101-102°C (benzene—petroleum ether). Found: C 67.9; H 4.1; N 9.6%. $C_{16}H_{11}ClN_2O$. Calculated: C 68.0; H 3.9; N 9.9%.

Synthesis of Azidopyrimidines. A) A solution of 1 mmole of substituted 2-chloropyrimidine and 1.3 mmole of NaN_3 in 40 ml of dry DMSO was heated at 90°C for 6 h, after which it was poured into water, and the precipitate was removed by filtration, washed with water, dried, and recrystallized. The characteristics of the compounds obtained are presented in Table 1.

B) A solution of 5 mmole of substituted 4-chloropyrimidine, 10 mmole of NaN_3, and 10 mmole of anhydrous LiCl in 100 ml of dry DMF was stirred at room temperature for 2 days, after which it was poured into water, and the resulting precipitate was removed by filtration, washed with water, and dried. Data on the azides obtained are presented in Table 1.

Reaction of 2- and 4-Azidopyrimidines with Acetylenic Compounds. A 0.5-g sample of the substituted azidopyrimidine was heated in 3 ml of the corresponding acetylene derivative at 140°C for several hours until the starting azide vanished. The precipitate that formed when the reaction mixture was cooled by filtration and washed with ethanol.

In the case of XXVI and XXVII the mixtures of A and B isomers were separated on plates with silica gel by elution with chloroform. In the case of XXIII only the A isomer was isolated. Data on the substituted 1,2,3-triazoles obtained are presented in Table 4; data from the PMR spectra are presented in Tables 2 and 3.

The IR spectra of XV-XXI contain an absorption band of an ester C=O bond at 1730-1760 cm^{-1}.

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