TRANSFORMATIONS OF 2-AMINOPYRIMIDINES AND THEIR N-OXIDES UNDER DIAZOTIZATION CONDITIONS

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The diazotization of 2-aminopyrimidines and their N-oxides in solutions with various acidities was studied. It is shown that the amino group in pyrimidine N-oxides is not diazotized in strongly acidic media and that bromination in the 5 position of the pyrimidine ring is observed in concentrated hydrobromic acid. When the reaction was carried out in moderately acidic media, it was possible to synthesize the difficult-to-obtain 2-halopyrimidine N-oxides.

We have previously reported the reaction of 2-aminopyrimidines and their N-oxides with aldehydes and acylating agents [1]. In a continuation of our study of the properties of 2-aminopyrimidines and their N-oxides we investigated the behavior of these compounds under diazotization conditions in media with different acidities in order to compare the reactivities of the amino groups and to study the possibility of the synthesis of difficult-to-obtain halopyrimidine N-oxides from aminopyrimidine N-oxides [2, 3]. Reactions involving the diazotization and transformation of diazonium salts have limited application in the pyrimidine series because of the instability of the diazonium salts [4, 5]. 2-Aminopyrimidines are converted to 2-halopyrimidines in the case of diazotization in strongly acidic media [6-8], but this transformation proceeds more successfully in dilute acids with a high concentration of the halide ion, which is achieved by the addition of the corresponding salts [5, 9] or by reverse diazotization [5]. The behavior of 2-aminopyrimidine N-oxides in diazotization has not been studied, although it is known that the introduction of an N-oxide group into azines leads to the production of more stable diazonium salts [10, 11] and makes it possible to use this reaction for the synthesis of haloazines [12, 13].

A comparison of the behavior of aminopyrimidines in diazotization, which was made in the case of 2-amino-4-phenylpyrimidine (I) and its 1-oxide (II) in strongly acidic media ($[H^+] \geqslant 5.0$ M [14]; concentrated HCl, HBr, H_2SO_4, and HBF_4) and in moderately acidic media (CH_3COOH + 12% HCl) shows that they differ substantially, chiefly in strongly acid media. Thus I in concentrated H_2SO_4, HCl, or HBF_4, as well as in concentrated HCl—CH_3COOH, reacts with nitrous acid to give 2-chloro- (III) and 2-hydroxy-4-phenylpyrimidine (IV) or a mixture of these products, whereas N-oxide II is inert under these conditions. The decrease in the reactivity of the amino group in the pyrimidine N-oxide is evidently associated with the decrease in its basicity due to the introduction of an N-oxide group [13].

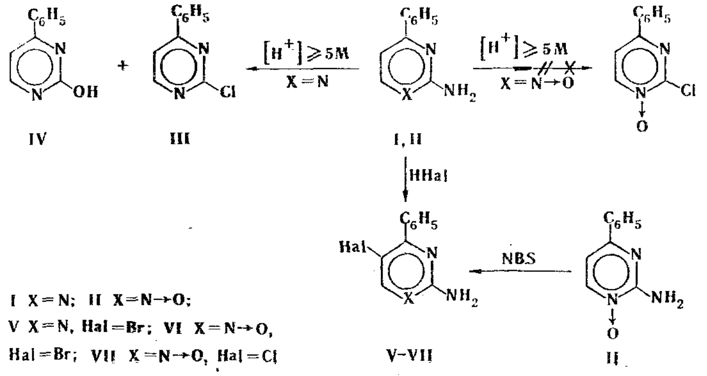

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TABLE 1. Reaction Conditions and Spectral Data for the Compounds Obtained

Starting compound	Conditions[a]	Reaction product	PMR spectrum,[b] δ, ppm (J, Hz)				UV spectrum λ_{max}, nm (log ε)	Yield, %
			5-H	6-H	H_{arom}	others		
I	A	V	—	8,40 s	7,70—7,37 m	6,83 br, NH_2	245 (4,35), 328 (3,73) (in CH_3OH)	55
	B	V						33
	F	III+IV[c]						35+20
	E	III+IV[d]						—
II	A	VI	—	8,74 s	7,83—7,28 m	3,54 br., NH_2	247 (4,22), 274 sh (3,75), 368 (4,09)	35[e]
	C	VII	—	8,64 s	7,80—7,30 m	3,59 br., NH_2	247 (4,09), 269 sh. (4,00), 370 (3,98)	23
	D	VI						10
	E	II[d]						—
	F	X+III	8,18 d (7,0)	8,88 d (7,0)	8,20—8,05 m, 7,73—7,52 m	—	288 (4,26), 326 (4,21)	46+12
XI	F	XIII	—	8,70 d (2,5)	7,48 s	8,27 d., 4-H (2,5)	261 (4,37), 333 (3,53)	55
XII	F	XIV[c]						58
XV	G	XI	—	8,73 d (2,5)	7,77—7,30 m	8,20 d, 4-H (2,5)	240 (4,27), 255 (4,29), 356 (3,81)	27
XVI	G	XII	—[f]	—	8,17—7,87 m, 7,60—7,30 m	2,40 s, CH_3	276 (3,79), 346 (4,04)	56

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[a] Reaction conditions: A) concentrated H_2SO_4 + HBr, $NaNO_2$; B) concentrated HBr, $NaNO_2$; C) concentrated H_2SO_4 + HCl, $NaNO_2$; D) concentrated H_2SO_4 + NaBr, $NaNO_2$; E) 1) concentrated H_2SO_4, $NaNO_2$, 5 M solution of LiCl in 20% HCl; 2) concentrated HCl, $NaNO_2$; 3) 40% HBF_4, $NaNO_2$; F) 5 M solution of LiCl in 12% HCl, $NaNO_2$; G) 30% H_2O_2 + Na_2WO_4. [b] The solvent for V-VII and X-XII was d_6-DMSO, while the solvent for XIII and XIV was $CDCl_3$. [c] Identified by means of thin-layer chromatography, melting point, and the IR spectrum and by comparison with a genuine sample (III and IV [4] and XIV [3]). [d] Reaction conditions E: for I: 1) I + IV; 2) III + IV; 3) I + IV; for II: 1-3). [e] The starting compound was isolated in 35% yield. [f] The 5-H signal coincides with the H_{arom} signal.

TABLE 2. Characteristics of V-VII and X-XIII

Compound	mp,[a] °C	Found, %				Empirical formula	Calc., %				M[b]
		C	H	Hal	N		C	H	Hal	N	
V	181—183	47,5	3,16	31,6	16,7	$C_{10}H_8BrN_3$	48,0	3,22	31,9	16,8	249 (^{79}Br)
VI	210—212	44,6	2,96	30,2	15,6	$C_{10}H_8BrN_3O$	45,1	3,03	30,0	15,8	265 (^{79}Br)
VII	174—176	54,5	3,60	15,6	18,6	$C_{10}H_8ClN_3O$	54,3	3,62	15,6	19,0	221 (^{35}Cl)
X	126—130	58,2	3,21	17,5	13,2	$C_{10}H_7ClN_2O$	58,1	3,41	17,2	13,6	
XI	184—185	64,4	4,88	—	22,6	$C_{10}H_9N_3O$	64,2	4,83	—	22,4	
XI[c]	151—153	65,6	4,85	—	13,5	$C_{10}H_9N_3O \cdot C_6H_5COOH$	66,0	4,88	—	13,6	
XII	231—233	65,7	5,61	—	20,6	$C_{11}H_{11}N_3O$	65,6	5,51	—	20,9	
XIII	129—131	58,3	3,30	17,2	13,4	$C_{10}H_7ClN_2O$	58,1	3,41	17,2	13,6	

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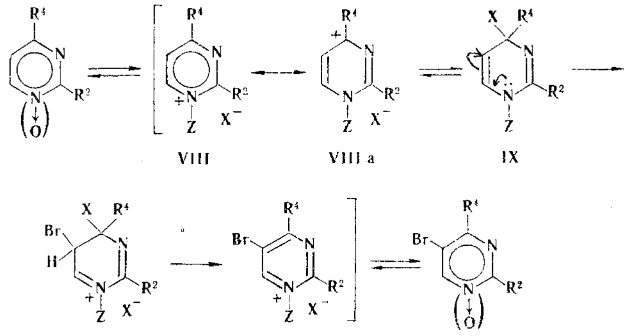
[a] The compounds were recrystallized: V, XI, and XII from alcohol, VI and VII from ethyl acetate, and X and VIII from petroleum ether. [b] By mass spectrometry. [c] Benzoate.

A different reaction pathway was observed for I and II in the case of diazotization in concentrated HBr. Under these conditions the amino group in I and II remained unchanged, and bromination to give bromine-containing aminopyrimidines was observed. On the basis of spectral and analytical data (Tables 1 and 2) these compounds were identified as 5-bromo-2-amino-4-phenylpyrimidine (V) and its 1-oxide (VI). Compound VI was identical to a sample obtained by bromination of N-oxide II with N-bromosuccinimide (NBS) in analogy with [15]. The yields of

V and VI increased substantially in the case of diazotization in concentrated H_2SO_4 + concentrated HBr. The formation of VI was observed under the conditions of diazotization of II in a mixture of concentrated H_2SO_4 and NaBr (see Table 1). Replacement of hydrobromic acid by hydrochloric acid makes it possible to obtain 5-chloro-2-amino-4-phenylpyrimidine 1-oxide (VII) from N-oxide II.

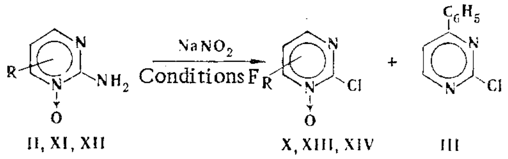
Bromination in the 5 position of the pyrimidine ring under the examined conditions is evidently an electrophilic substitution reaction associated with the possibility of liberation of bromine in the redox reaction of hydrobromic acid and sodium nitrite [5], since I and II are not brominated when sodium nitrite is absent. The literature contains information regarding bromination in the 5 position of the pyrimidine ring of 2-aminopyrimidines under conditions of diazotization of the latter in concentrated HBr + $NaNO_2$ when free bromine is also added to the reaction medium [7]. Either protonation of the aminopyrimidines of reaction of them with the nitrosating particle at the ring nitrogen atom or at the oxygen atom of the N→O group, respectively, to give intermediates VIII evidently occurs under the conditions that we found (H_2SO_4 + HBr + $NaNO_2$). In these compounds, in addition to a decrease in the basicity of the amino group as compared with starting I and II, one may assume, in analogy with [15, 16], disruption of the aromatic character of the pyrimidine ring, which leads to the formation of intermediates IX. The enamine fragment in the latter is activated with respect to electrophilic substitution, as shown in the following scheme:



Z = H, OH, NO or ONO

The behavior of I and II in moderately acidic media differed from the behavior in strongly acidic media. The diazotization of I and II in a mixture of acetic acid and dilute hydrochloric acid with added lithium chloride, in analogy with [9], led to the production of the expected 2-chloropyrimidines, respectively, III, and 2-chloro-4-phenylpyrimidine 1-oxide (X). In addition to these compounds, 2-hydroxypyrimidine IV was isolated from the reaction mixture in the case of pyrimidine I, while III was isolated in the case of N-oxide II. Compound III is evidently formed as a result of deoxygenation of N-oxide X. We did not detect 2-hydroxypyrimidine IV and its N-oxide in the reaction mixture in the diazotization of N-oxide II. This is possibly a consequence of the high stability of the resulting diazonium salt in conformity with the literature data on the effect of an N-oxide group on the stabilization of diazonium salts in other azines [10].

2-Chloro-5-phenyl- (XIII) and 2-chloro-6-methyl-4-phenylpyrimidine 1-oxide (XIV), respectively, were obtained in good yields in the diazotization of 2-amino-5-phenyl- (XI) and 2-amino-6-methyl-4-phenylpyrimidine 1-oxide (XII) in moderately acidic media.



II, X R=4-C_6H_5; XI, XIII R=5-C_6H_5; XII, XIV R=6-CH_3, 4-C_6H_5; conditions F (see the experimental section)

Thus the diazotization of 2-aminopyrimidine 1-oxides in moderately acidic media was found to be a convenient method for the synthesis of 2-chloropyrimidine 1-oxides, which up until now have been difficult-to-obtain substances in view of the complications encountered in the oxidation of the corresponding chloropyrimidines [2].

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds (c 0.25%) were recorded with UR-20 and Specord spectrometers. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A 56/60 spectrometer with hexamethyldisiloxane as the internal standard. The yields, melting points, results of elementary analysis, and spectral data for the newly synthesized compounds are presented in Tables 1 and 2. The known III, IV, and XIV were identified by comparison with genuine samples with respect to thin-layer chromatography (TLC) and their melting points and IR spectra.

Diazotization in Strongly Acidic Media. Conditions A. A 6-mmole sample of the substituted pyrimidine was dissolved in 10 ml of concentrated H_2SO_4, and 2 ml of concentrated HBr was added carefully with cooling and stirring. A cooled solution of 20 mmole of $NaNO_2$ and another 6 ml of HBr were then added successively and slowly dropwise at 5°C to the reaction mixture, and the resulting mixture was stirred at 0°C for 1 h with subsequent raising of the temperature to room temperature. Urea (~0.5 g) was added to the reaction mixture, and the resulting mixture was cooled to 0°C. Chloroform was added, and the mixture was neutralized with 20% potassium carbonate solution. The organic layer was washed with water, dried with magnesium sulfate, and evaporated, and the residue was separated with a column filled with silica gel by elution with chloroform and chloroform–acetone (9:1, 7:3). The characteristics of the 5-bromopyrimidines obtained are given in Tables 1 and 2.

Conditions B. A saturated solution of 20 mmole of $NaNO_2$ was added dropwise at 5°C to a solution of 6 mmole of the substituted pyrimidine in 10 ml of concentrated HBr. The reaction mixture was then worked up as in method A.

Conditions C. A saturated solution of 20 mmole of $NaNO_2$ was added dropwise at 5°C to a solution of 5 mmole of II in a mixture of 10 ml of concentrated H_2SO_4 and 2 ml of concentrated HCl, after which 6 ml of concentrated HCl was added, and the mixture was stirred at 0°C for 1 h. The mixture was then worked up and separated as in method A to give VII (Tables 1 and 2).

Conditions D. A 6-ml sample of 70% CH_3COOH saturated with NaBr was added to a solution of 5 mmole of II in 10 ml of concentrated H_2SO_4, after which a saturated solution of 20 mmole of $NaNO_2$ was added dropwise at 5°C, and the mixture was stirred at 0°C for 1 h. It was then diluted with chloroform and neutralized with 20% K_2CO_3 solution. The organic layer was dried and evaporated, and the residue was recrystallized from alcohol to give 0.15 g (10%) of VI.

Conditions E. A solution of 20 mmole of $NaNO_2$ was added slowly dropwise at 0°C to a solution or suspension of 5 mmole of pyrimidine I or II in 10–15 ml of the acid, and the mixture was stirred at 0°C for 1–3 h. It was then diluted with chloroform and neutralized with 20% K_2CO_3 solution. The organic layer was dried and evaporated. The following acids were used: concentrated H_2SO_4, concentrated HCl, 40% HBF_4, and concentrated HCl + glacial CH_3COOH (1:1). The results are given in Table 1.

When the reaction was carried out in concentrated H_2SO_4, a 5 M solution of LiCl in 12% HCl solution was added dropwise after the addition of the $NaNO_2$ solution, and the reaction mixture was stirred at 0°C for 3 h. It was then worked up as indicated above.

Diazotization in Moderately Acidic Media. Conditions F. A 25-ml sample of a 5 M solution of LiCl in 12% HCl was added to a solution of 6 mmole of the substituted 2-aminopyrimidine in the minimum amount of acetic acid, after which the mixture was cooled to –15°C, and 40 mmole of solid $NaNO_2$ was added in the course of 30 min. The reaction mixture was stirred at 0°C for 1 h, after which it was maintained at 20°C for 24 h. It was then cooled to 0°C, 150 ml of chloroform was added, and the mixture was neutralized with 20% potassium carbonate solution. The organic layer was dried with magnesium sulfate and evaporated, and the residue was separated with a column filled with silica gel by elution with chloroform and chloroform–acetone (9:1, 7:3) (Tables 1 and 2).

2-Amino-5-phenylpyrimidine 1-oxide (XI) and 2-amino-6-methyl-4-phenylpyrimidine 1-oxide (XII) were obtained by a method similar to that in [1] by oxidation of, respectively, 2-amino-5-phenylpyrimidine (XV) and 2-amino-6-methyl-4-phenylpyrimidine (XVI) with a mixture of 30% of H_2O_2 and Na_2WO_4. N-Oxides XI and XII were isolated from the reaction mixtures in the form of the benzoates, as in [1]. The data are presented in Tables 1 and 2.

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RECYCLIZATION OF 2,2-DISUBSTITUTED 4(3H)-OXO- AND 4-CHLORO-1,2-DIHYDROPYRIMIDINES TO 4-AMINOPYRIDINE DERIVATIVES

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The intramolecular cationotropic rearrangement of salts of two-ring 2,2-disubstituted 4-chloro-1,2-dihydropyrimidines to 4-aminopyridine derivatives was observed. Recyclization to 4-aminopyridines can take place in the reaction of two-ring 2,2-disubstituted 4(3H)-oxo-1,2-dihydropyrimidines with phosphorus oxychloride without isolation of the intermediate chloro derivatives. A probable mechanism that makes it possible to assert that the observed recyclization is a variant of the intramolecular cationotropic rearrangement that is characteristic for 2,2-dialkyl-substituted 1,2-dihydropyrimidines with functional substituents (for example, oxo or chloro) in the 4 position of the ring is discussed.

It is known that 2,2-disubstituted 4(3H)-oxo-1,2-dihydropyrimidines I under the influence of polyphosphoric acid (PPA) at 135°C undergo cationotropic rearrangement to give 2-pyridone derivatives in good yields and 4-oxo- and 4-aminopyridine derivatives in very small amounts [1].

We assumed that 2,2-disubstituted 4-chloro-1,2-dihydropyrimidines are also capable of undergoing similar transformations. In fact, instead of the usual chloro derivatives of 1,2-dihydropyrimidine, 4-aminopyridine derivatives II with known structures [2, 3] are formed in 38-85% yields in the reaction of I with an eightfold to tenfold excess of phosphorus oxychloride (by refluxing in toluene for 10-24 h).

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