ACETALS OF LACTAMS AND ACID AMIDES.

47.* INVESTIGATION OF THE BEHAVIOR OF SUBSTITUTED 6-(β-DIMETHYLAMINO)VINYL-4-PYRIMIDINONES IN ACIDIC MEDIA. SYNTHESIS OF 3-CYANO-4-ANILINO-5-FORMYL-2-PYRIDONE AND 3-CHLORO-4-CYANOBENZO[b][1,6]-NAPHTHYRIDINE

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The hydrolysis of 1-substituted 5-cyano-6-(β-dimethylamino)vinyl-4-pyrimidinones in acidic media was studied. It was shown that the 1-benzyl derivative is converted to a mixture of α-cyano-β-benzylamino-crotonamide and 3-cyano- and 3-carbamido-4-benzyl-amino-2-pyridones. The principal product in the hydrolysis of the 1-phenyl derivative is 3-cyano-4-anilino-5-formyl-2-pyridone. Cyclization of the latter by heating in phosphorus oxychloride leads to 3-chloro-4-cyanobenzo[b][1, 6]naphthyridine.

It has been previously established that 1-substituted 5-cyano-6-(β-dimethylamino)-vinyl-4-pyrimidinones, which are formed in the reaction of secondary enamino amides with dimethylformamide diethylacetal, are readily hydrolyzed in alkaline media with opening of the pyrimidine ring and subsequent recyclization to 2-pyridone derivatives [2, 3]. In contrast to its behavior in an alkaline medium, in acids at room temperature the pyrimidine ring is quite stable, and cyclization with the participation of the enamino and cyano groups takes place under these conditions [2, 4]. Thus pyridopyrimidine derivative II was isolated when 1-benzyl-5-cyano-6-(β-dimethylamino)vinyl-4-pyrimidinone (Ia) was treated with hydrochloric acid at 20°C [4]. When we carried out this reaction with moderate heating (60-65°C) we obtained a mixture of substances, from which we were able to isolate in individual form 3-carbamido-4-benzyl-amino-2-pyridone (III), which was identical to a sample obtained by a previously described method [4]. In the mixture we also detected, by means of mass spectrometry (the mass spectrum of the mixture was compared with the spectra of pure samples obtained by the method in [3]), 3-cyano-4-benzylamino-2-pyridone (IV) [M^+ 225 (36),† $[PhCH_2]^+$ 91 (100), and $[PhCH_2 - C_2H_2]^+$ 65 (9)] and α-cyano-β-benzylaminocrotonamide (V) [M^+ 215 (37), $[M - OH]^+$ 198 (16), $[M - OH - NCN]^+$ 171 (16), $[PhCH_2]^+$ 91 (100), and 65 (13)]. The formation of the principal product of this reaction (III) could have been due to hydrolysis of the cyano group in IV. However, it was found that cyanopyridone IV remains unchanged when it is maintained under these conditions, and it may be assumed that amide III develops via cleavage of the pyrimidine ring of intermediate pyridopyrimidine II. Enamino acid V is formed as a result of opening of the pyrimidine ring and splitting out of the enamino grouping in starting pyrimidinone Ia.

One might have expected that replacement of the benzyl substituent by a phenyl substituent in the 1 position of the pyrimidine ring would not change the fundamental scheme of hydrolysis in an acidic medium. However, two substances were isolated when a solution of 1-phenyl-5-cyano-6-(β-dimethylamino)vinyl-4-pyrimidinone (Ib) was heated in 0.1 N HCl at 60-65°C. The minor component, which was obtained in ~10% yield, was 3-carbamido-4-anilino-2-pyridone (VI). An intense molecular-ion peak (M^+) at 229 (54) is observed in its mass spectrum.

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*See [1] for Communication 46.

†Here and subsequently, the m/z values are given for the ions, and the relative intensities in percent are given in parentheses.

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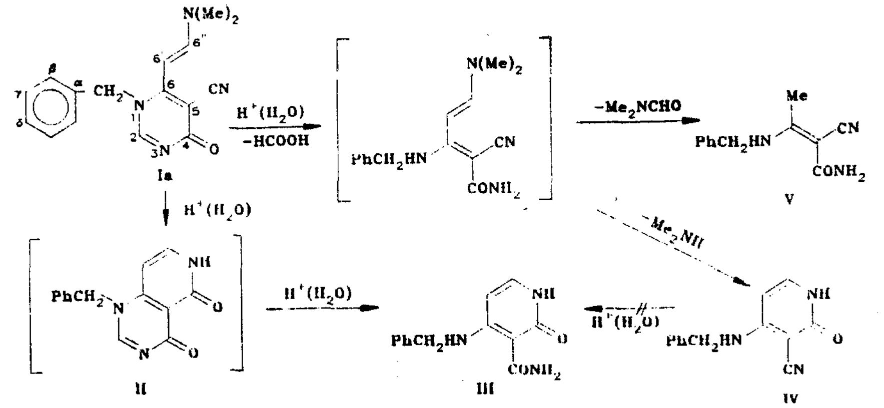
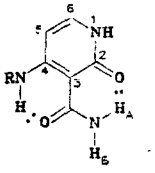
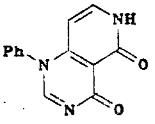


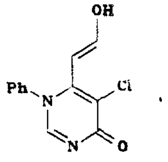
The maximally intense peak belongs to the $[M - OH]^+$ ion at 212. Subsequent elimination of a molecule of water and a molecule of CO gives peaks at 194 (25) and 184 (21), respectively. A Ph^+ peak at 77 (33) is also observed. To confirm the structure of VI we investigated its PMR spectrum simultaneously with the spectrum of known amide III (see Table 1). The spectra of pyridones III and VI are quite similar; a characteristic feature is the presence of two doublet signals of protons in the 5 and 6 positions of the pyridone rings, which are found at 6.0 and ~7.3 ppm for VI and at 5.93 and ~7.3 ppm for III. A peculiarity of the PMR spectra is the presence of signals of four labile protons; by means of the method of decoupling of the signals we were able to make reliable assignments of the signals to certain NH groups. Thus we established that the strongest-field signals are the signals of the B-H protons, which do not participate in the formation of a hydrogen bond (7.07 ppm for III and ~7.3 ppm for VI); in the spectra they are represented by doublets due to spin-spin coupling with the adjacent A-H protons ($^2J_{AB}$ = 4.5 Hz for III and 4.3 Hz for VI). The adjacent NH protons are observed at rather weak field, viz., at 9.91 ppm (VI) and 9.84 ppm (III); this makes it possible to propose that they participate in hydrogen bonding with the pyridone carbonyl group. The signals of the protons of the ring NH groups are observed in the form of either a doublet (for III, 10.99 ppm, $^3J_{NH,6-H}$ = 4 Hz) or a markedly broadened singlet (for VI, 11.21 ppm) due to spin-spin coupling with adjacent 6-H proton. Finally, the signals of the 4-RNH groups are represented in the spectra either in the form of a rather narrow singlet (for VI, 12.67 ppm) or in the form of a triplet (for III, 11.14 ppm, $^3J_{NH,CH_2}$ = 5.9 Hz). This weak-field position of the signals constitutes evidence for a strong intramolecular hydrogen bond of the chelate type. All of the data presented indicate the presence in III and VI of two rather strong intramolecular hydrogen bonds.



III,VI



VII



VIII

III $R=PhCH_2$; VI $R=P'$.

According to the results of elementary analysis, the principal substance obtained by treatment of pyrimidinone Ib with acid could have two-ring structure VII or the structure of hydroxymethylene derivative VIII.

Structure VII can be rejected starting from the data from the IR spectrum, in which an absorption band of a cyano group at 2202 cm^{-1} is observed. The PMR spectrum of IX is not in agreement with either structure VII or structure VIII. Two singlets at 9.60 ppm (1H) and 8.42 ppm (1H), two broad signals at 12.42 ppm (1H) and 10.60 ppm (1H), and a multiplet of benzene ring protons centered at 7.4 ppm (5H) are present in the spectrum. From its position, the signal at 9.6 ppm can be ascribed to an aldehyde proton, and the two broad signals can be ascribed to labile protons of NH or OH groups. It should be noted that the corresponding arylhydrazone was obtained from IX when it was heated with p-nitrophenylhydrazine; this also confirmed the presence of an aldehyde function in this compound.

TABLE 1. Chemical Shifts of the Protons of III, VI, IX, and X (δ, ppm)*

Compound	1-H	5-H	6-H	H_{ald}	4-RNH	A-H	B-H	CH_2
III	10,99	5,93	~7,30	—	11,14**	9,84	7,07	4,50†
VI	11,21	6,00	~7,30	—	12,67	9,91	7,3	—
IX	10,60	—	8,42	9,60	12,42	—	—	—
X	11,35	5,80	~7,30	—	9,40	—	—	—

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*In the ^1H NMR spectra the aromatic protons form a multiplet at 7.2-7.5 ppm.

†The signal of the CH_2 groups has the form of a doublet, whereas the $N_{(4')}H$ signal is a triplet [$^3J_{CH_2N(4')H}$ = 5.9 Hz].

TABLE 2. Chemical Shifts of the ^{13}C Atoms of IX and X (δ ^{13}C, ppm)

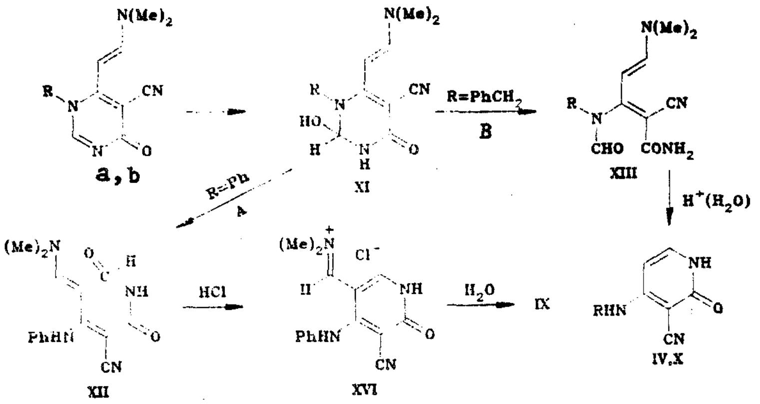
Compound	$C_{(2)}=O$	$C_{(3)}$	C≡N	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	COH	$C_{(\alpha)}$	$C_{(\beta)}$	$C_{(\gamma)}$	$C_{(\delta)}$
IX	161,4	78,0	113,9	155,6	107,4	152,6	190,7	136,1	126,0	128,4	127,1
X	161,7	80,5	116,0	158,5	94,9	138,7	—	137,9	124,0	128,9	125,5

The most valuable information regarding the structure of IX was obtained from the ^{13}C NMR spectra (Table 2). A characteristic peculiarity of the spectrum is the presence of a signal at 190.7 ppm, which is converted to a doublet under conditions of recording the spectrum with partial suppression of the protons; this made it possible to unambiguously ascribe this signal to the carbon atom of an aldehyde group. An additional confirmation of this assignment of the signal is the existence of a geminal spin–spin coupling constant (SSCC) for this signal ($^2J_{H,COC}$ = 24 Hz) in the ^{13}C NMR spectrum recorded under conditions without suppressions of the protons. A second characteristic peculiarity of the spectrum is the rather weak-field signal of the heteroaromatic carbon atom bonded directly to a hydrogen atom (CH, 152.6 ppm). In addition to the above-described signals in the spectrum of the compound obtained, one can isolate signals of a carbonyl (pyridone) carbon atom at 161.4 ppm and a carbon atom of a CN group at 113.9 ppm. The assignment of all of the signals was made by comparison of the spectrum of IX with the spectrum of a model compound, viz., 3-cyano-4-anilino-2-pyridone (X) (see Table 2). The ^{13}C NMR spectra of the investigated (IX) and model (X) compounds are quite similar; the only exception is that the 5 position of the model compound is not substituted [$C_{(5)}$ 94.9 ppm], whereas the signal of the carbon atom of this CH group was absent in the spectrum of IX; however, a signal of a quaternary heteroaromatic carbon atom at 107.4 ppm and, as we have already pointed out, a signal of an aldehyde carbon atom at 190.7 ppm were observed.

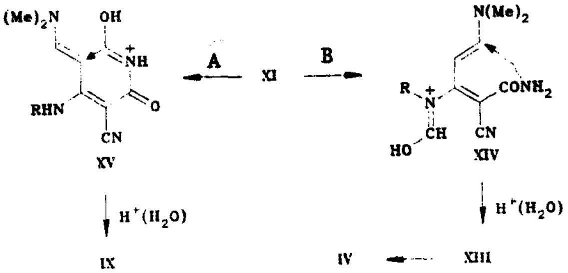
In addition to a maximally intense molecular-ion peak (M^+) at 239, the mass spectrum of aldehyde IX contains an intense $[M - H]^+$ ion peak at 238 (80). Elimination of a formyl group from M^+ gives an ion peak at 210 (47). A Ph^+ ion peak at 77 (20) is also observed in the spectrum. Thus an unusual and unexpected rearrangement with the formation of 3-cyano-4-anilino-5-formyl-2-pyridone (IX) occurs when pyrimidinone Ib is heated in an acidic medium.

It should be noted that the hydrolysis of 4-pyrimidinones under these conditions depends on the character of the substituent in the 1 position and that when a benzyl group is present in this position, as in Ia, substances with different structures (III-V, see above) are formed. This difference in the behavior of 4-pyrimidinones Ia, b could be due to a difference in the site of protonation of their enamine fragments. However, a study of the PMR spectra of Ia, b in acetic, deuteroacetic, trifluoroacetic, and deuterotrifluoroacetic acids did not reveal substantial differences in their behavior with respect to the protonating agents used.*

The fundamental difference in the cleavage of the pyrimidine ring and the subsequent recyclizations depending on the substituents may also be due to different pathways of this cleavage in connection with different degrees of stabilization of the transition states by aryl or alkyl groupings. Proceeding from this, the following scheme for the processes described above can be proposed:



According to this scheme,† ring cleavage may proceed via two pathways — with cleavage of the $N_{(1)} - C_{(2)}$bond (pathway A) or the $N_{(3)} - C_{(2)}$bond (pathway B). The realization of one or the other pathway depends on the substituent attached the $N_{(1)}$ atom. It might be assumed that the formation of two types of compounds (XIV and XV) can occur in the rate-determining step:



The presence of an N-alkyl radical stabilizes structure XIV due to a positive inductive effect, whereas, on the other hand, an aryl substituent destabilizes this structure. Probably as a consequence of this, pathway B with the formation of initially XIII and then pyridone IV is characteristic for N-benzyl derivative Ia. At the same time, the reaction for N-phenylpyrimidinone Ib is directed via pathway A with the formation of cation XV,

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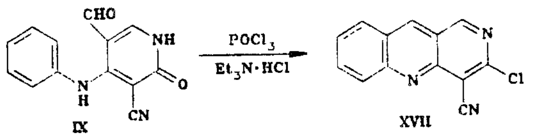
*In both cases (Ia, b) N protonation is evidently observed: the signals of the protons attached to the $C_{(6')} = C_{(6'')}$ bond of the side chain are shifted to weak field, and new signals (for example, of a CH_2 group, as would have occurred in the case of C protonation) do not appear in the spectra. ^{1}H NMR spectra (CH_3COOD): 8.28 (6''-H), 4.73 (6'-H) (Ia); 8.25 (6''-H), 4.33 (6'-H) (Ib); (CF_3COOD): 8.79 (6''-H), 5.40 (6'-H) (Ia); 8.67 (6''-H), 4.85 ppm (6'-H) (Ib).

†A pathway involving the formation of pyridopyrimidines of the II type and their cleavage to III and VI was not taken into account in the scheme. Protonation of the enamine fragment is also disregarded, since this is not essential for an examination of the synthesis of IX and the differences between hydrolytic cleavage of the ring in pyrimidinones Ia, b.

after which the imide carbon atom, which bears a partial positive charge, attacks the β position of the enamine fragment, in which the electron density is increased due to conjugation with the dimethylamino group (it is assumed that the process takes place with the participation of the unprotonated form of the enamine); cyclization with the formation of immonium cation XVI with subsequent hydrolysis to aldehyde IX occurs in this case.

The unexpected formation of formylpyridine IX opens up significant possibilities from the point of view of the synthesis of heterocyclic compounds on the basis of it. In particular, it was established that cyclization with the formation of 3-chloro-4-cyanobenzo[b][1,6]naphthyridine (XVII) takes place when a solution of IX in phosphorus oxychloride is heated in the presence of triethylamine hydrochloride. Signals at 9.83 ppm (1-H) and 9.68 ppm (10-H) are the most characteristic signals in the ^1H NMR spectrum of XVII. The signal at 9.68 ppm is broadened somewhat due to coupling with the proton in the 6 position (8.40 ppm). In the mass spectrum of three-ring compound XVII the maximally intense peak belongs to the molecular ion (M^+) at 239, which contains one chlorine atom. The primary act of fragmentation is the elimination of halogen with the formation of a fragment peak at 204 (19). Ions at 177 (20) and 150 (9) are formed by the successive detachment of two molecules of HCN. The peak at 153 (which does not contain Cl) probably beongs to the $[M - (NC{-}C{=}CCl + H)]^+$ fragment (12).



EXPERIMENTAL

The mass spectra were record with a Varian MAT-112 spectrometer with direct introduction of the samples into the ion source; the temperature of the ionization chamber was 180°C, and the ionizing-electron energy was 70 eV. The ^1H NMR spectra were recorded with a Varian XL-200 spectrometer, and the ^{13}C NMR spectra were obtained with a Varian XL-100 spectrometer; the solvent was d_6-DMSO, and the internal standard was tetramethylsilane (TMS). The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer.

1-Benzyl-5-cyano-6-(β-dimethylamino)vinyl-4-pyrimidinone (Ia). This compound was previously synthesized in [3]. ^1H NMR spectrum (in $CDCl_3$): 4.46 (6'-H, d, $^3J_{6'6''}$ = 12.8 Hz), 8.05 (d, 6''-H), 8.09 (2-H), 5.11 (s, CH_2), and 2.84 (s) and 3.01 ppm (s) (Me_2N). ^{13}C NMR spectrum (in $CDCl_3$): 154.3* $[C_{(2)}]$, 167.5 (C=0), 82.9 $[C_{(5)}]$, 118.8 (CN), 156.6 $[C_{(6)}]$, 82.8 $[C_{(6')}]$, 152.2* $[C_{(6'')}]$, ~39 $[CH_3)_2N]$,† 53.1 (CH_2), 135.4 $[C_{(\alpha)}]$, 126.3 $[C_{(\beta)}]$, 128.6 $[C_{(\delta)}]$, and 127.6 ppm $[C_{(\delta)}]$.

1-Phenyl-5-cyano-6-(β-dimethylamino)vinyl-4-pyrimidinone (Ib). This compound was previously synthesized in [5]. ^1H NMR spectrum: 4.05 (d, 6'-H, $^3J_{6'6''}$ = 13 Hz), 7.87 (d, 6''-H), 8.40 (2-H), and 3.06 and 2.56 ppm (Me_2N). ^{13}C NMR spectrum: 152.7* $[C_{(2)}]$, 167.5 (C=O), 82.2 $[C_{(5)}]$, 118.7 (CN), 160.0 $[C_{(6)}]$, 83.7 $[C_{(6')}]$, 151.5* $C_{(6'')}]$, 138.0 $[C_{(\alpha)}]$, 127.5 $[C_{(\beta)}]$, 129.7 $[C_{(\gamma)}]$, 129.7 $[C_{(\delta)}]$, and 39 ppm $[(CH_3)_2N]$.†

3-Carbamido-4-(N-benzylamino)-2-pyridone (III). A 1 g (3.6 mmole) sample of pyrimidinone Ia was heated in 20 ml of 1 N HCl at 60°C for 5 h, after which the resulting precipitate was removed by filtration and washed with water to give 0.03 g of a crude substance, the principal constituent of which, according to the mass spectroscopic data, was IV with M^+ 225. IR spectrum: 3280, 3140 (NH), 2200 (C≡N), 1640, 1620 cm^{-1} (C=O). The aqueous mother liquor was made alkaline to pH 9-10 with 40% NaOH, and the resulting

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*The direct SSCC $^1J_{^{13}C,H}$ were taken into account for the $C_{(2)}$ and $C_{(6'')}$ atoms in the assignment of the signals: δ 154.3 ppm, $J_{2-^{13}C,H}$ = 206 Hz (2-C); δ 152.2 ppm, $^1J_{6''-^{13}C,H}$ = 166 Hz $[C_{(6'')}]$. The assignment of the signals in the spectrum of Ib was also accomplished similarly.

†The signal of the carbon atom is broadened markedly.

precipitate was removed by filtration and washed with water to give 0.13 g of a crude substance with molecular-ion peaks M_1^+ 215 (V) and M_2^+ 243 (III). Allowing the aqueous mother liquor to stand at 20°C for 12 h precipitated 0.21 g (24%) of III with M^+ 243 (35) and $[M - OH]^+$ 226 (100) and peaks at 197 (75), 169 (65), 91 (90), 65 (25); the product had mp 253-254°C (from DMF; 253-254°C [4]). Found: C 64.3; H 5.6; N 17.8%. $C_{13}H_{13}N_3O_2$. Calculated: C 64.2; H 5.4; N 17.3%.

3-Cyano-4-(N-phenylamino)-5-formyl-2-pyridone (IX). A 5-g (20 mmole) sample of pyrimidinone Ib was dissolved in 100 ml of 1 N HCl, and the solution was heated at 65°C for 5 h. The precipitate was removed by filtration and washed with water to give 3 g (67%) of IX with mp 280°C [dec., from DMF—water (2:1)] and M^+ 239. IR spectrum: 3260, 3180 (NH), 2200 (C≡N), 1690, 1650, 1630 cm^{-1} (C=O). Found 65.3; H 3.6; N 17.5%. $C_{13}H_9N_3O_2$. Calculated: C 65.3; H 3.8; N 17.6%.

The p-nitrophenylhydrazone was obtained in 58% yield by heating IX with p-nitrophenylhydrazine in alcohol; the product had M^+ 374 and mp 314-316°C (from DMF). Found: N 22.1%. $C_{19}H_{14}N_6O_3$. Calculated: N 22.5%. The aqueous mother liquor after isolation of IX was made alkaline to pH 9-10 with 40% NaOH, and the resulting precipitate was removed by filtration and washed with water to give 0.36 g (8.4%) of VI with mp 280-283°C [DMF—MeOH (2:1)] and M^+ 229. IR spectrum: 3300, 3110 (NH), 1650, 1600 cm^{-1} (C=O). Found: C 63.1; H 4.8; N 18.4%. $C_{12}H_{11}N_3O_2$. Calculated: 62.9; H 4.8; N 18.3%.

3-Chloro-4-cyanobenzo[b][1,6]napthyridine (XVII). A mixture of 1 g (4 mmole) of IX with 0.4 g (2.9 mmole) of triethylamine hydrochloride was refluxed in 12 ml of $POCl_3$ for 1 h, after which the resulting yellow precipitate was removed by filtration and washed with methanol and water to give 0.5 g of XVII with M^+ 239. The mother liquor was poured into 150 ml of water with ice, and the resulting precipitate was removed by filtration and washed with water to give another 0.4 g of XVII for an overall yield of 90%; the product had mp 300°C (dec., from DMF). IR spectrum: 2220 (C≡N), 1630, 1610 cm^{-1} (C=N). ^{1}H NMR spectrum: 8.17 and 7.85 (7-H, 8-H), 8.31 and 8.40 (6-H, 9-H), 9.68 (10-H), and 9.83 ppm (1-H). Found: C 65.5; H 2.0; Cl 14.8; N 17.2%. $C_{13}H_6ClN_3$. Calculated: C 65.1; H 2.5; Cl 14.8; N 17.5%.

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