ACETALS OF LACTAMS AND ACID AMIDES.

40.* SYNTHESIS AND HYDROLYTIC CLEAVAGE OF ONE-RING AND TWO-RING DERIVATIVES OF 4-PYRIMIDINONE

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UDC 547.824'854'859.7.07:542.938:
541.127.1:543.422'51

The reaction of 1-benzyl-5-cyano-6-dimethylaminomethylene-1,6-dihydro-4-pyrimidinone with acid leads to 5-benzyl-1,2,7,8-tetrahydropyrido[4,3-d]pyrimidine-1,8-dione, whereas the reaction with ammonia leads to a mixture of 3-cyano-4-benzylamino-2-pyridone and 1-amino-5-benzyl-7,8-dihydropyrido[4,3-d]-pyrimidin-8-one. Heating of the latter in aqueous ethylene glycol is accompanied by recyclization to give 4-benzylamino-5,6-dihydropyrido[2,3-d]pyrimidin-5-one. The reaction of 1-benzyl-4-dimethylaminomethylene-5-cyano-1,6-dihydro-6-pyrimidinone with ammonia leads to 1-amino-7-benzyl-7,8-dihydropyrido[4,3-d]-pyrimidin-8-one. The rate constants for cleavage of the pyrimidine ring in a number of 4-pyrimidinone derivatives were measured.

It has been previously shown that the reaction of secondary enamino amides with amide acetals leads to 1-alkyl-5-cyano-4-pyrimidinones, and it has been established that these compounds are unstable in alkaline media and, depending on their structures, either undergo hydrolytic cleavage to the starting enamino amides or undergo recyclization to substituted 2-pyridones [2, 3]. The goal of the present research was to study the possibility of the synthesis of various derivatives of pyridopyrimidine on the basis of the above-mentioned 4-pyrimidinone derivatives and to study the alkaline cleavage of the pyrimidine ring in the compounds obtained. We selected 1-benzyl-5-cyano-6-dimethylaminomethylene-1,4-dihydro-4-pyrimidinone (I) [3] as the starting compound.

In contrast to its behavior in alkaline media [3], the pyrimidine ring of I is quite stable in acids, and cyclization to pyrido[4,3-d]pyrimidine-1,8-dione (II) proceeds readily under these conditions. Opening of the pyrimidine ring in the latter compound proceeds extremely smoothly when it is heated in aqueous ethylene glycol, and 3-carbamido-4-benzylamino-2-pyridone (III) is formed. Since pyrimidinone I undergoes recyclization to pyridone IV in alkali, transformations that lead to IV, as well as to one of two (or to both simultaneously) derivatives of aminopyridopyrimidine (V or VI), could have occurred in the reaction of I with ammonia. The mass spectrum of the crude substance obtained as a result of heating I with an alcohol solution of ammonia revealed the presence of a mixture of two substances, viz., IV (M^+ 225) and a compound with M^+ 252 (V or VI). After purification, we were able to isolate a compound with M^+ 252 in pure form, the mass spectrum of which contained only two intense peaks, viz., a molecular-ion peak (40%) and the peak of a benzyl cation with m/z 91 (100%). Signals of protons at 5.32 (s, CH_2), 7.33 (m, C_6H_5), 7.99 (3-H, J_{34} = 5.8 Hz), 6.38 (d, 4-H), 8.67 (s, 6-H), and 8.7 ppm (NH) are observed in the PMR spectrum of this substance. In addition to signals of protons of this compound (V or VI), signals of protons of pyridone IV† are observed in the PMR spectrum of the crude substance.

To ascertain the structure of the substance obtained in the reaction of I with ammonia we subjected it to reaction with ethoxymethylenemalonic ester. The PMR spectrum of the com-

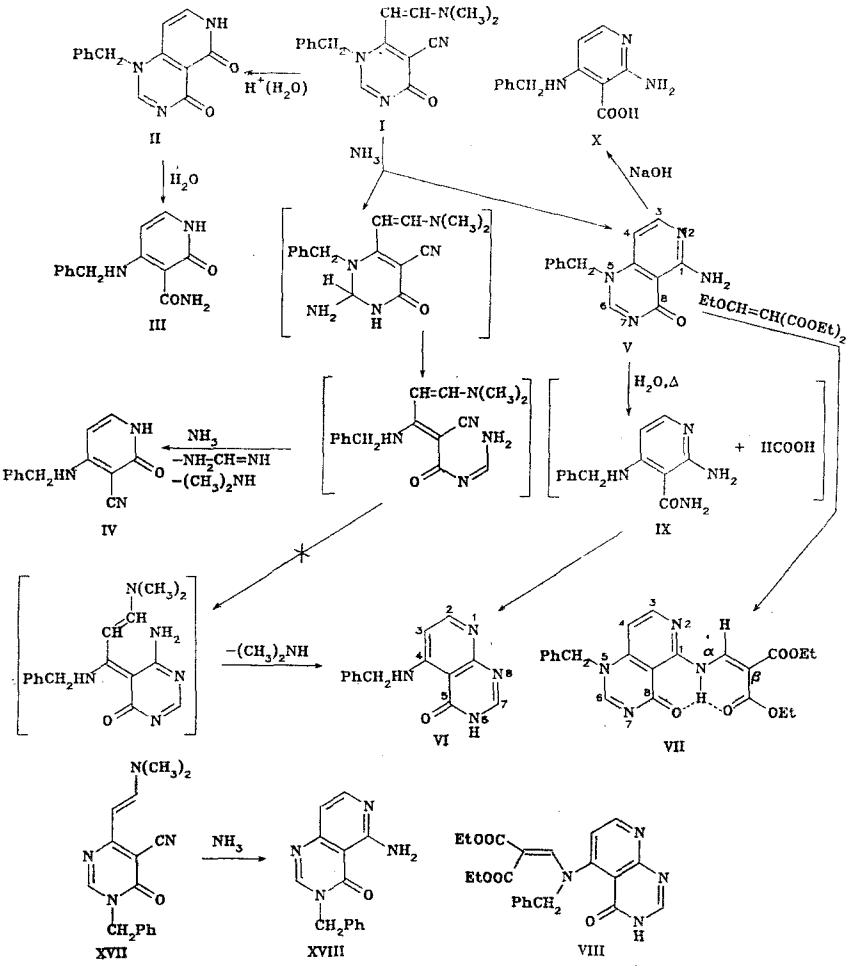
*See [1] for communication 39.

†PMR spectrum of pyridone IV: 4.49 (s, CH_2), 7.89 (t, $NHCH_2$, J_{NH,CH_2} = 6 Hz), 7.31 (m, aromatic protons and 6-H), 11.10 (s, NH), and 5.78 ppm (d, 5-H, J_{56} = 7.5 Hz).

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 532-537, April, 1984. Original article submitted April 6, 1983.

 0009-3122/84/2004-0434$08.50

pound obtained is in good agreement with structure VII (rather than VIII), and this indicates that V (rather than VI) is formed in the investigated reaction. In fact, signals of protons at 1.25 and 1.35 (t, CH_3CH_2), 4.17 and 4.31 (q, CH_3CH_2), 5.47 (s, CH_2Ph), 7.35 (m, C_6H_5), 7.08 (d, 4-H, $^3J_{34}$ = 5.9 Hz), 8.42 (d, 3-H), 8.87 (s, 6-H), 9.17 (d, C_α–H, $^3J_{H_\alpha,NH}$ = 12.8 Hz), and 13.38 ppm (NH). were observed in the PMR spectrum of VII. The signal of the α proton attached to the enamine double bond is observed in the form of a doublet at 9.17 ppm with $^3J_{H_\alpha,NH}$ = 12.8 Hz. This value of the vicinal constant indicates a trans orientation of the NH and C_α–H groups. This conformation of the side chain favors the formation of a double intramolecular hydrogen bond [4] in the VII molecule, evidence in favor of which is also provided by the weak-field shift of the signal of the proton of the NH group (13.38 ppm).



We made an attempt at the independent synthesis of VI: Two-ring system V was subjected to alkaline hydrolysis in order to obtain amino amide IX, which can be readily converted to VI by reaction with cyclizing agents such as dimethylformamide acetals, ortho esters, formamide, etc. [5]. However, in the case of heating in the presence of an alkali the process does not stop with the formation of amide IX but goes further to give amino acid X. The mass spectrum of X contains intense peaks with m/z 243 ($[M^+]$), 91 ($[PhCH_2]^+$), 106 ($[PhCH_2NH]^+$), 225 ($[M - H_2O]^+$), 199 ($[M - CO_2]^+$), and 198 ($[M - COOH]^+$). The $[M - CO_2]^+$ peak has the highest intensity.

Compound VI was obtained by heating V in aqueous ethylene glycol.

The reaction evidently proceeds through amino amide IX, which immediately undergoes cyclization with the formic acid liberated in the cleavage to give pyridopyrimidine VI [2]. The structure of VI follows from the mass spectrum, in which peaks of ions with m/z 252 ($[M]^{+\cdot}$), 251 ($[M - H]^+$), 175 ($[M - C_6H_5]^+$), 147 ($[M - C_6H_5CH_2NH]^+$), 106 ($[C_6H_5CH_2NH]^+$), and 91 ($[C_6H_5CH_2]^+$) (the fragmentation indicates that, in contrast to V, the $PhCH_2NH$ fragment in VI is located in the side chain) are observed, and from the PMR spectrum, in which signals at 4.56 (s, CH_2), 7.34 (m, C_6H_5), 6.49 (d, 2-H), 8.18 (d, 3-H, $^3J_{23}$ = 6 Hz), 8.14 (s, 7-H), and 9.68 ppm (NH) are observed.

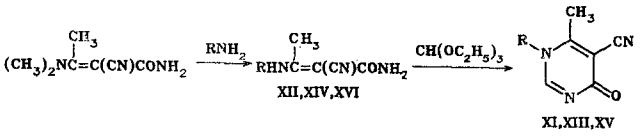
TABLE 1. Half-Conversion Times of the Compounds in Hydrolysis

Compound	$t_{1/2}=\frac{\ln 2}{K_{obs}}$		
	pH 7,00	pH 12	pH 13
I	160 h	8,5 min	50 sec
XIII	27 min	5 min	—
XV	50 min	←	≪1 min
XVII	—	—	4 h (with refluxing)

TABLE 2. Rate Constants (K) of the I → IV Process as a Function of the NaOH Concentration

NaOH concn., mole/liter	$K \cdot 10^3$ sec^{-1} at ionic strengths (NaCl), moles/liter	
	0,1	1,0
0,01	1,43; 1,29	0,91; 0,88
0,05	6,7; 6,84	5; 4,9
0,1	13,5; 13,4	8,7; 8,8
Reaction order in OH^- from the equation: $\log k_{obs} = \text{const} + \log OH^-$	1,004±0,047	1,003±0,080

One wonders why the pyrimidine ring in VI is more stable than that in two-ring system V. To shed some light on this question we synthesized N-unsubstituted pyrimidinone XI [6] from enamino amide XII and N-benzyl derivative XIII from secondary enamino amide XIV [3] via the scheme



XI, XII R=H; XIII, XIV R=CH_2Ph; XV, XVI R=Ph.

The alkaline hydrolysis of XIII leads to the starting enamino amide [2]. Measurement of the rate of hydrolysis by spectrophotometry showed that the half-conversion time for XIII at room temperature and pH 12 is ∿5 min, whereas unsubstituted XI is completely stable under these conditions. Measurement of the ionization constant of pyrimidinone XI showed that this substance is a rather strong acid (pK_a 6.29 ± 0.05 in 50% alcohol) and exists almost completely in the anionic form in an alkaline medium, which, of course, sharply reduces the rate of hydrolysis.

A comparison of the rate of hydrolysis of XIII with the rate of hydrolysis of N-phenyl derivative,* which was obtained via a similar scheme from XVI, shows (Table 1) that the half-conversion time for XIII is somewhat shorter, despite the electron-acceptor effect of the phenyl substituent (as compared with the benzyl substituent); this can be ascribed to shielding of the 2 position of the pyrimidine ring by the ortho protons of the benzene ring in phenyl derivative XV.

The hydrolysis of the pyrimidine ring was studied in greater detail in the case of I. The measurements were made by spectrophotometry and polarography. The hydrolysis of I proceeds substantially more slowly than the hydrolysis of pyrimidinone XIII, in conformity with the electron-donor effect of the dimethylaminomethylene fragment. The measurements showed that the reaction is first order in the starting substance under all the investigated conditions. To determine the order of the reaction I → IV in hydroxide ion we measured the observed first-order rate constants in solutions with a constant ionic strength at various NaOH concentrations (Table 2). The calculated value was found to be close to unity. Thus the kinetic equation of the process I → IV is first order in each of the reagents ($v = [I] \times [OH^-]$) and second order overall. The rate constants at various temperatures and the activation parameters in the hydrolysis of I in 0.1 N NaOH are presented in Table 3. The large

*The hydrolysis of XV leads to starting XVI [2].

TABLE 3. Rate Constants and Activation Parameters for the Hydrolysis of I^{+}

Temp., °C	$10^2 \cdot k$, sec^{-1}
25	1,35; 1,40
35	3,26; 2,8
40	4,68; 5,2

$^{+}\Delta H^{*}$ = 14.9 ± 1.7 kcal/mole; ΔS^{*} = −17 ± 6 eu.

negative entropy of activation is in agreement with the fact that attack by the hydroxide ion in the 2 position of the pyrimidine ring is the rate-determining step of the overall process. An isomer of I, viz., 1-benzyl-4-dimethylaminomethylene-5-cyano-1,6-dihydro-6-pyrimidinone (XVII) [3], which is completely stable in alkali at room temperature and is hydrolyzed (see [3] for the pathway in the hydrolysis of XVII) only by refluxing — the half-conversion time at pH 13 is 4 h (Table 1) — is considerably more stable.

Heating of pyrimidinone XVII with alcoholic ammonia led to 1-amino-7-benzyl-7,8-dihydropyrido[4,3-d]pyrimidin-8-one (XVIII). Intense peaks of a molecular ion ($[M]^{+\cdot}$) with m/z 252 (40%) and of an ion with m/z 91 (100%) are observed in the mass spectrum of XVIII. The elimination of HCO [m/z 223 (9%)] is another pathway in the fragmentation of the molecular ion. Low-intensity peaks with m/z 147 and 148, which are the result of the elimination of $PhCH_2N$ and $PhCH_2NH$ groups from the molecular ion, are also observed in the spectrum.

EXPERIMENTAL

The mass spectra were recorded 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 energy of the ionizing electrons was 70 eV. The PMR spectra (in d_6-DMSO) were recorded with a Varian XL-200 spectrometer with tetramethylsilane as the internal standard. The UV spectra of 0.04 mM solutions of the substances were recorded with an M-40 spectrophotometer (Karl Zeiss, Jena); all of the solutions contained 10% MeOH. The first-order rate constants were calculated by the method of least squares.

Polarography was carried out in a thermostated cell; a predesignated temperature was maintained with an ultrathermostat with an accuracy of ±0.1°C. The polarograms were recorded with a PAR-170 or a PAR-374 polarograph.

The melting points were determined with a heating stage of the Boetius type.

1,8-Dioxo-5-benzyl-1,2,5,8-tetrahydropyrido[3,4-d]pyrimidine (II). A 2.0-g (7.1 mmole) sample of pyrimidinone I was dissolved in 40 ml of 1 N HCl at room temperature, and the solution was allowed to stand for 24 h. It was then neutralized to pH 2-3 with 20% NaOH, after which it was allowed to stand for 1-2 h. The precipitate was removed by filtration to give 1 g of II with $M^{+\cdot}$ 253.

The physical constants, analytical characteristics, and yields of the synthesized compounds are presented in Table 4.

3-Carbamido-4-(N-benzylamino)-2-pyridone (III). A mixture of 0.8 g (3.2 mmole) of pyridopyrimidine II, 10 ml of ethylene glycol, and 0.5 ml of water was refluxed for 5 h, after which it was cooled and treated with 30 ml of water, and the precipitate was removed by filtration and washed with water to give 0.24 g of pyridone III with $M^{+\cdot}$ 243.

4-Benzylamino-5,6-dihydropyrido[2,3-d]pyrimidin-5-one (VI). This compound was similarly obtained from pyridopyrimidine V.

1-Amino-5-benzyl-5,8-dihydropyrido[4,3-d]pyrimidin-8-one (V). A mixture of 2.5 g (8.9 mmole) of pyrimidinone I and 40 ml of an alcohol solution of ammonia (~14%) was heated in a bomb at 145-150°C for 5 h, after which it was cooled, and the precipitate was removed by filtration to give 1.34 g of a dark-brown powder, which was identified as a mixture of IV and V. For purification, the mixture was washed with hot water on the filter and refluxed in 10-15 ml of DMF, and the undissolved material was removed by filtration to give 0.6 g of

TABLE 4. Characteristics of the Synthesized Compounds

Compound	mp, °C (solvent)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
II	162—164	66,3	4,6	16,4	$C_{14}H_{11}N_3O_2$	66,4	4,4	16,6	56
III	253—254	64,2	5,5	17,5	$C_{13}H_{13}N_3O_2$	64,2	5,4	17,3	31
V	323—325	66,6	4,7	22,2	$C_{14}H_{12}N_4O$	66,7	4,8	22,2	35
VI	264—266	66,7	4,8	22,4	$C_{14}H_{12}N_4O$	66,7	4,8	22,2	75
VII	206—208	62,6	4,8	13,5	$C_{22}H_{22}N_4O_5$	62,6	5,2	13,3	48
X	229—230	64,5	5,5	17,6	$C_{13}H_{13}N_3O_2$	64,2	5,4	17,3	85
XII	173—174	48,0	5,5	34,1	$C_5H_7N_3O$	48,0	5,6	33,6	97
XIII	166—167	69,1	4,9	18,8	$C_{13}H_{11}N_3O$	69,3	4,9	18,7	67
XV	262—264	68,2	4,1	20,2	$C_{12}H_9N_3O$	68,3	4,3	19,9	70
XVI	195—196	65,5	5,7	21,0	$C_{11}H_{11}N_3O$	65,7	5,5	20,9	68
XVIII	191—192	66,4	4,8	22,2	$C_{14}H_{12}N_4O$	66,7	4,8	22,2	28

*The following solvents were used for crystallization: ethanol (II, XII, XV), DMF (III, V, X), DMF—ethanol (1:1) (VI, XIII, XVIII), and methanol (VII, XVI).

V with mp 316-319°C. Cooling of the filtrate gave another 0.19 g of V, with mp 317-320°C, for a total of 0.79 g of V.

3-Benzyl-7-diethoxycarbonylvinylamino-3,6-dihydropyrido[4,3-d]pyrimidin-6-one (VII). A mixture of 1.01 g (4 mmole) of pyridopyrimidine V, 1.08 g (5 mmole) of ethoxymethylenemalonic ester, and 15 ml of DMF was refluxed for 4 h, after which it was evaporated, and the residue was triturated in ethyl acetate to give 0.81 g of VII with $M^{+\cdot}$ 422.

2-Amino-3-carboxy-4-(N-benzylamino)pyridine (X). A 0.5-g (2 mmole) sample of pyridopyrimidine V was refluxed in 10 ml of 1 N NaOH for 5 h, after which the solution was filtered, and the filtrate was neutralized to pH 7 with 1 N HCl. The precipitate was removed by filtration to give 0.41 g of pyridine X with $M^{+\cdot}$ 243.

1-Cyano-2-aminocrotonamide (XII). A mixture of 1.5 g (9.8 mmole) of 1-cyano-2-(N,N-dimethylamino)crotonamide and 30 ml of an alcohol solution of ammonia was heated in a bomb at 100°C for 6 h, after which it was evaporated *in vacuo* to give 1.19 g of amide XII with $M^{+\cdot}$ 125.

1-Benzyl-5-cyano-6-methyl-4-pyrimidinone (XIII). A mixture of 1.63 g (7.6 mmole) of amide XIV, 15 ml of ethyl orthoformate, and 15 ml of acetic anhydride was refluxed for 3 h, after which it was evaporated *in vacuo*, a small amount of absolute alcohol was added to the residue, and the precipitate was removed by filtration to give 1.15 g of pyrimidinone XIII with $M^{+\cdot}$ 225. UV spectrum (0.05 M phosphate buffer), λ_{max} (log ε): 243 (4.41) and 283 nm (3.95).

1-Phenyl-4-oxo-5-cyano-6-methylpyrimidine (XV). A mixture of 2 g (10 mmole) of amide XVI, 40 ml of ethyl orthoformate, and a catalytic amount of p-toluenesulfonic acid was refluxed for 14 h with simultaneous removal of the resulting alcohol by distillation, after which it was evaporated *in vacuo*. A small amount of absolute alcohol was added to the residue, and the mixture was filtered to give 1.47 g of pyrimidinone XV with $M^{+\cdot}$ 211. UV spectrum (0.05 M of phosphate buffer), λ_{max} (log ε): 245 (4.41) and 290 nm (4.04).

1-Cyano-2-(N-phenylamino)crotonamide (XVI). A mixture of 4.59 g (0.03 mole) of 1-cyano-2-(N,N-dimethylamino)crotonamide, 3.35 g (0.036 mole) of aniline, and 35 ml of glacial acetic acid was refluxed for 4 h, after which it was allowed to stand overnight. The precipitate was removed by filtration, washed with water until the washwater had pH 6-7, and washed with ether to remove acetate to give 4.13 g of amide XVI with M^{+} 201.

1-Amino-7-benzyl-7,8-dihydropyrido[4,3-d]pyrimidin-8-one (XVIII). A mixture of 1 g (3.6 mmole) of pyrimidinone XVII and 20 ml of an alcohol solution of ammonia (~14%) was heated in a bomb at 150°C for 8 h, after which it was cooled to give 0.25 g of XVIII.

LITERATURE CITED

1. V. G. Granik, N. I. Smetskaya, N. A. Mukhina, N. V. Persianova, and V. G. Klimenko, Khim. Geterotsikl. Soedin., No. 9, 1279 (1983).

2. V. G. Granik, A. M. Zhidkova, and R. A. Dubinskii, Khim. Geterotsikl. Soedin., No. 4, 518 (1982).
3. V. G. Granik, and S. I. Kaimanakova, Khim. Geterotsikl. Soedin., No. 6, 816 (1983).
4. A. I. Kol'tsov and G. M. Kheifets, Usp. Khim., 40, 1646 (1971).
5. W. Stanovnik and M. Tišler, Synthesis, No. 2, 120 (1974).
6. M. Mittelbach and H. Junek, Z. Naturforsch., B, 34, 1580 (1979).

ACETALS OF LACTAMS AND ACID AMIDES.

41.* ENAMINO AMIDES IN THE SYNTHESIS OF PYRIMIDINE DERIVATIVES

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UDC 547.831.6'298'836.7'854.2.07: 542.951.2:543.422'51

The reaction of α-cyano-β-dimethylaminomethyleneacrylamide with arylamines was used to synthesize α-cyano-β-arylaminoacrylamides, which react readily with dimethylformamide diethylacetal to give the corresponding N-dimethylaminomethylene derivatives. The latter undergo cyclization to 1-aryl-5-cyano-4-pyrimidinones when they are heated in dimethylformamide or acetic anhydride and to pyrimido-[5,4-c]quinolone derivatives when they are heated in glacial acetic acid.

The aim of the present research was to investigate pyrimidine cyclization on the basis of β-arylamino-α-cyanoacrylamides (IIa-g). The starting enamino amides IIa-g were obtained by transamination of tertiary enamino amide I [2] with aromatic amines. In a study of this reaction it was established that it cannot be carried out by heating the components in various organic solvents and that it proceeds best in acetic acid; however, the isolation of the desired products is complicated in this case due to the simultaneous formation of acetanilide derivatives under the reaction conditions. Although the yields of enamino amides IIa-g are low (Table 1), this method is, nevertheless, a preparative method owing to the accessibility of the starting compounds and the simplicity with which it is carried out. In the case of the preparation of IIa we attempted to use another method of synthesis based on the condensation of N,N-dimethyl-N'-phenylformamidine (III) with cyanoacetamide. However, the yield of enamine IIa in this case (36%) does not exceed its yield (41%) in the first method. The synthesized N-aryleneamines IIa-f react readily with dimethylformamide diethylacetal (IV) to give N,N-dimethyl-N'-(α-cyano-β-arylamino)acrylylformamidines (Va-f). It is interesting to note that in this case, in contrast to the reactions of cyclic enamino amides [3] and α-cyano-β-arylamino-β-methylacrylamides [1], further cyclization to pyrimidine derivatives does not occur in the reaction with the acetal, and the process stops at the step involving the production of acylamidines Va-f. This probably indicates a substantial decrease in the basicity of the nitrogen atoms of enamines of the V type as compared with enamines with a methyl group or a methylene link in the β position relative to the acylamidine grouping (in the latter case we are dealing with cyclic enamines in which an aryl substituent attached to the nitrogen atom is absent [3]). In the case of Va-c it was established that cyclization proceeds extremely smoothly when solutions in dimethylformamide (DMF) are heated — the cyclization proceeds with splitting out of dimethylamine to give 1-aryl-5-cyano-4-pyrimidinones (VIa-c). We also attempted to obtain Va (or VIa immediately) by heating amide IIa with the Vilsmeier reagent. However, α-cyano-β-anilinoacrylonitrile (VII) is formed in high yield in this case, i.e., dehydration of the amido group proceeds much faster than condensation at the NH_2 group. The possibility of the cyclization of Va by other methods was investigated in greater detail. Pyrimidinone VIa is formed when Va is heated in acetic anhydride, whereas the starting enamino amide IIa is

*See [1] for communication 40.

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0009-3122/84/2004-0439$08.50