mixture of mono- and dibromo ketones VII and VIII was separated by chromatography as described above. The yield of bromo derivative VII was 0.28 g (46%), while the yield of the dibromo derivative was 0.16 g (20%). With respect to their physicochemical characteristics, the compounds were identical to the compounds described in experiment A.

3-Bromoacetyl-2-phenylimidazo[2,1-a]isoquinoline and 3-Dibromoacetyl-2-phenylimidazo-[2,1-a]isoquinoline. These compounds were synthesized by method B. The yield of the monobromo ketone was 43%. The colorless needles had mp 201-203°C (dec., from alcohol). IR spectrum: 1640 cm^{-1} (C=O). Found: C 62.2; H 4.1; Br 21.6%. $C_{19}H_{13}BrN_2O$. Calculated: C 62.4; H 4.3; Br 21.9%. The yield of the dibromo ketone was 17%. The colorless needles had mp 205-207°C (dec., from butanol). IR spectrum: 1640 cm^{-1} (C=O). Found: C 51.0; H 2.7; Br 36.2%. $C_{19}H_{12}Br_2N_2O$. Calculated: C 51.3; H 2.7; Br 36.2%.

2-Methyl-3-(2-quinoxalyl)imidazo[2,1-a]isoquinoline. A solution of 0.38 g (1 mmole) of dibromo ketone VIII and 0.21 g (2 mmole) of o-phenylenediamine in 10 ml of alcohol was refluxed for 30 h, after which it was evaporated to dryness, and the residue was chromatographed with a column filled with Al_2O_3 by elution with chloroform. The first fraction was separated and worked up to give yellow needles with mp 232-233°C (from butanol). Found: C 77.1; H 4.5; N 17.9%. $C_{20}H_{14}N_4$. Calculated: C 77.4; H 4.5; N 18.2%.

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ACETALS OF LACTAMS AND ACID AMIDES.

38.* SYNTHESIS OF PYRIMIDINE AND PYRIDINE DERIVATIVES ON THE BASIS OF THE REACTION OF ENAMINO AMIDES WITH AMIDE ACETALS

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Derivatives of 1-benzyl-4-pyrimidinones and 1-benzyl-6-pyrimidinones were synthesized by the reaction of α-cyano-β-N-benzylaminocrotonamide and α-cyano-β-aminocrotonic acid N-benzylamine with dimethylformamide diethylacetal. When 1-benzyl-5-cyano-6-(β-dimethylamino)vinyl-1,6-dihydro-4-pyrimidinone is heated in an alkaline medium, it is converted to 3-cyano-4-benzylamino-2-pyridone, from which a pyrido[1,2-a]pyrimidine derivative was synthesized. When 1-benzyl-5-cyano-4-(β-dimethylamino)vinyl-1,6-dihydro-6-pyrimidinone is heated in alkaline solution, it is converted to α-cyano-β-hydroxycrotonic acid N-benzylamide.

We have previously established [2, 3] that condensed pyrimidines are formed in the reaction of cyclic enamino amides with amide acetals. In a continuation of these investiga-

*See [1] for Communication 37.

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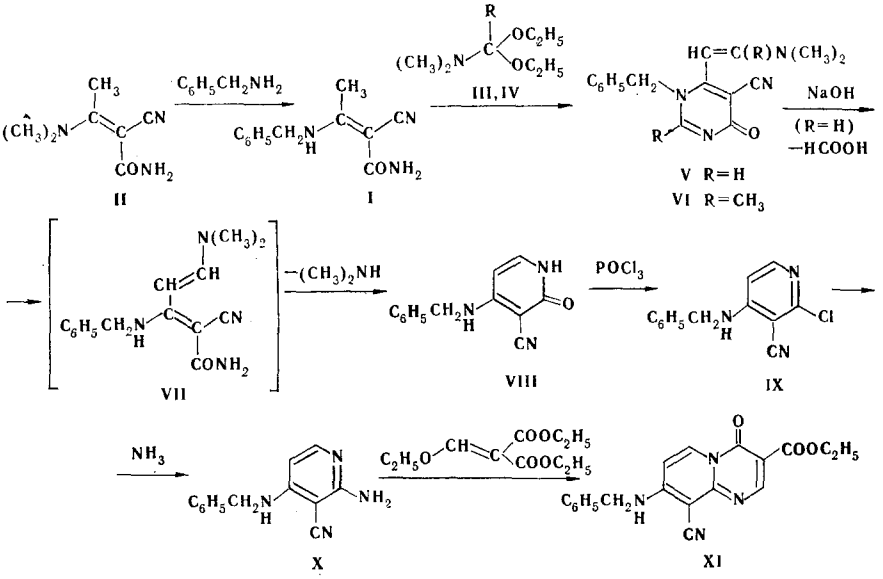
tions in the present research we studied pyrimidine cyclization reactions on the basis of some noncyclic enamino amides and a number of subsequent transformations of the 4-pyrimidinone derivatives obtained.

The starting α-cyano-β-N-benzylaminocrotonamide (I) was synthesized by transamination of α-cyano-β-dimethylaminocrotonamide (II), which was obtained by the reaction of dimethylacetamide diethylacetal (III) with cyanoacetamide [4].

The reactions of enamino amide I with dimethylformamide diethylacetal (IV) and dimethylacetamide diethylacetal (III) proceed smoothly to give pyrimidinones V and VI. It is interesting to note that in this case, in contrast to cyclic enamino amides [5], in the reaction of I with acetal III one observes not only the formation of a pyrimidine ring but also condensation at the methyl group in the 6 position of the pyrimidine ring. In the case of five- and six-membered cyclic enamino amides this condensation takes place only when one uses dimethylformamide acetal (IV) (in the case of seven-membered compounds the formation of a pyrimidine ring is the only process, even in the reaction with acetal IV) condensation does not occur with its homolog, viz., acetal III [2, 3, 5]. In other words, steric hindrance to condensation at the CH_3 group in enamino amide I is substantially less pronounced than at the CH_2 link in cyclic enamino amides, viz., cyanocarbamidomethylenepyrrolidine, cyanocarbamidomethylenepiperidine, and hexahydroazepine.

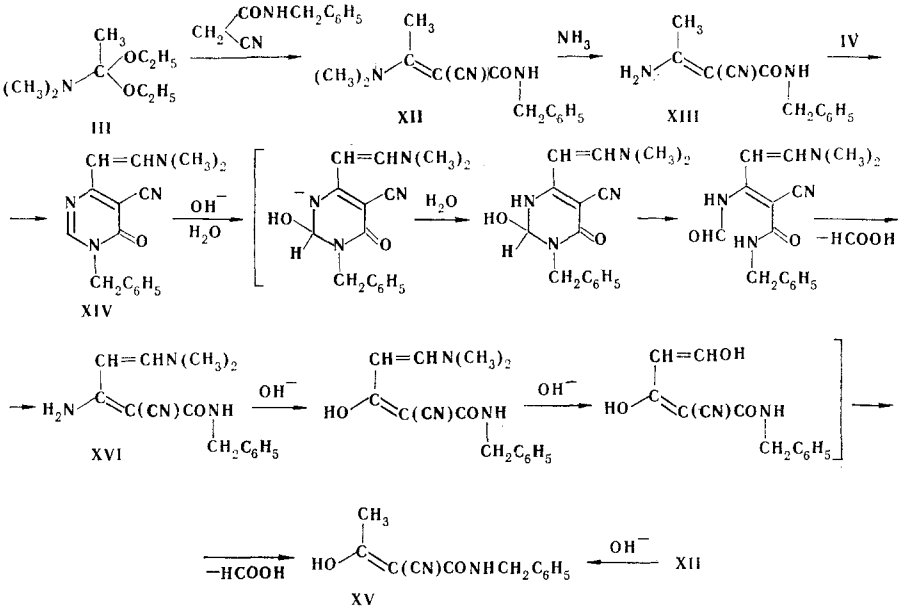
As in the case of condensed 4-pyrimidinones with similar structures [3, 5], when V is heated with alkali, one observes cleavage of the pyrimidine ring, and the intermediately formed enamino amide VII undergoes recyclization with the liberation of dimethylamine to give a 2-pyridone derivative (VIII). The recyclization proceeds extremely smoothly and is accompanied by splitting out of formic acid, which was established by means of a previously developed gasometric method [6]. Derivative VIII was then used for the synthesis of a substituted pyrido[1,2-a]pyrimidine. For this, VIII was heated with phosphorus oxychloride in the presence of dimethylaniline (the latter is necessary in the reaction, since the desired chloro derivative is not formed when it is absent), as a result of which 2-chloro-3-cyano-4-benzylaminopyridine (IX) is formed. The activity of the chlorine atom in this compound is low; however, the halogen atom can be replaced by an amino group upon reaction with alcoholic ammonia under severe conditions (in a bomb at 220°C), and the product is obtained in good yield. 3-Ethoxycarbonyl-4-oxo-8-benzylamino-9-cyanopyrido[1,2-a]pyrimidine (XI) was synthesized by heating the 2-amino-3-cyano-4-benzylaminopyridine (X) obtained in this way with ethoxymethylenemalonic ester.



It is apparent from the data presented here and previously obtained data [3, 5] that all of the pyrimidine derivatives for which a high tendency to undergo ring cleavage in an alkaline medium was observed have a hydroxy group in the 4 position, a substituent attached to the N_1 atom, and, correspondingly, a p-quinoid orientation of the double bonds. In order to ascertain how necessary precisely this structure is for attack of the hydroxide anion at the 2 position of the pyrimidine ring, in the present research we made an attempt to obtain a

compound that is an isomer of VIIa, viz., the correspondingly substituted 1-benzyl-6-pyrimidinone, which has an o-quinoid orientation of the ring double bonds. It should be noted that the directed synthesis of compounds of this type is also of independent interest, since it is extremely difficult to obtain them by the usual pyrimidine synthesis. The preparation of the desired product was accomplished via the following scheme: condensation of acetal III with N-benzylcyanoacetamide gave tertiary enamine XII, which readily undergoes transamination upon heating with alcoholic ammonia at 80°C. In the reaction of primary enamino amide XIII obtained in this way with excess acetal IV, in addition to the formation of a pyrimidine ring, one observes condensation at the methyl group in the 4 position to give 1-benzyl-4-(β-N,N-dimethylamino)vinyl-5-cyano-1,6-dihydro-6-pyrimidinone (XIV). It seems to us that the proposed method is general and suitable for the synthesis of various 1-substituted 1,6-dihydro-6-pyrimidinones.

As in the case of pyrimidinone V, in the hydrolysis of XIV one observes opening of the pyrimidine ring however, in this case hydrolysis is not accompanied by cyclization, but a number of processes associated with hydrolysis of the enamine fragments occur. The only product isolated was α-cyano-β-hydrocrotonic acid N-benzylamide (XV). The fundamental scheme of the hydrolysis is presented below.*



According to this scheme, in addition to cleavage of the pyrimidine ring, one observes splitting out of a dimethylaminomethylene fagment, as was previously observed in the alkaline hydrolysis of enamino ketones [7].

Compound XV was also obtained by alternative synthesis, viz., by hydrolysis of enamino amide XII.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds (except for I and XI, for which KBr pellets were used) were recorded with a Perkin–Elmer 457 spectrometer. The UV spectra of solutions in alcohol were recorded with a Perkin–Elmer 575 spectrophotometer. The mass spectra were obtained with a Varian MAT-112 spectrometer with direct introduction of the samples into the ion source; the ionization-chamber temperature was 180°C, and the ionizing-electron energy was 70 eV. The melting points were determined with a heating stage of the Boetius type.

α-Cyano-β-N-benzylaminocrotonamide (I). A mixture of 1.53 g (0.01 mole) of amide II, 2.14 g (0.02 mole) of benzylamine, and 20 ml of absolute ethanol was refluxed for 2 h, after

*The sequence of the steps in the scheme is indicated arbitrarily. At present there are no data that make it possible to form a judgment as to which of them — opening of the pyrimidine ring or hydrolysis and splitting out of the dimethylaminomethylene link — occurs earlier. A detailed analysis of the hydrolysis of XIV will be published later.

TABLE 1. Synthesized Compounds

Compound	mp,[a] °C (solvent)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
I	183—184	67,1	6,1	19,5	$C_{12}H_{13}N_3O$	67,0	6,1	19,5	87
V	210—211	68,8	5,9	20,0	$C_{16}H_{16}N_4O$	68,6	5,7	20,0	84
VI	181—183	70,0	6,5	18,0	$C_{18}H_{20}N_4O$	70,1	6,5	18,2	42
VIII	266—268	69,2	5,0	18,8	$C_{13}H_{11}N_3O$	69,3	4,9	18,7	89
IX[b]	135—136	64,3	4,5	17,1	$C_{13}H_{10}ClN_3$	64,1	4,1	17,3	87
X	179—181	69,5	5,3	25,2	$C_{13}H_{12}N_4$	69,6	5,4	25,0	77
XI	297—299	65,8	4,9	15,9	$C_{19}H_{16}N_4O_3$	65,5	4,6	16,1	35
XII	111—112	69,1	7,1	17,4	$C_{14}H_{17}N_3O$	69,1	7,0	17,3	85
XIII	123—125	67,1	6,0	19,5	$C_{12}H_{13}N_3O$	67,0	6,1	19,5	91
XIV	169—171	68,9	5,8	20,4	$C_{16}H_{16}N_4O$	68,6	5,7	20,0	84
XV	116—118	66,7	5,8	13,0	$C_{12}H_{12}N_2O_2$	66,7	5,6	13,0	45

[a]The compounds were crystallized: I and XI from DMF, V and X from methanol, VI from ethyl acetate—DMF (10:1), VIII from aqueous DMF, IX and XIII-XV from ethanol, and XII from ethyl acetate. [b]Found: Cl 14.5%. Calculated: Cl 14.6%.

which it was cooled, and the resulting precipitate was removed by filtration and washed with a small amount of absolute alcohol to give 1.86 g of amide I with $M^{+\cdot}$ 215. IR spectrum: 2200 (C≡N); 1655 (C=O); 1610 (C=C); 3100, 3200, 3380 cm^{-1} (NH, NH_2). The physical constants, analytical characteristics, and yields of the synthesized compounds are presented in Table 1.

1-Benzyl-4-oxo-5-cyano-6-(β-N,N-dimethylaminovinyl)-1,4-dihydropyrimidine (V). A mixture of 10 g (0.047 mole) of amide I, 27.6 g (0.19 mole) of acetal IV, and 50 ml of absolute alcohol was refluxed for 4 h, after which it was allowed to stand overnight. The resulting precipitate was removed by filtration and washed with a small amount of absolute alcohol to give 11 g of pyrimidinone V with $M^{+\cdot}$ 280. IR spectrum: 2218 (C≡N); 1640, 1590 cm^{-1} (C=O, C=N). UV spectrum (in alcohol), λ_{max} (log ε): 212 (4.16), 238 (4.19), 290 (4.23), and 378 nm (4.37).

1-Benzyl-2-methyl-4-oxo-5-cyano-6-(β-N,N-dimethylaminomethyl)-vinyl-1,4-dihydropyrimidine (VI). A mixture of 1.07 g (5 mmole) of amide I, 24.g (0.015 mole) of acetal III, and 15 ml of absolute ethanol was refluxed for 2 h, after which it was evaporated in vacuo, and the residue was triturated with ethyl acetate. The mixture was then filtered to give 0.65 g of pyrimidinone VI with $M^{+\cdot}$ 308.

3-Cyano-4-N-benzylamino-1,2-dihydro-2-pyridone (VIII). A 0.64-g (0.3 mmole) sample of pyrimidinone V was refluxed in 15 ml of 1 N NaOH for 1 h, after which the mixture was cooled and neutralized to pH 7 with concentrated HCl. The precipitate was removed by filtration and washed with water to give 0.46 g of pyridone VIII.

2-Chloro-3-cyano-4-N-benzylaminopyridine (IX). A mixture of 1.12 g (5 mmole) of pyridone VIII, 15 ml of phosphorus oxychloride, and 0.5 ml of dimethylaniline was refluxed for 1 h, after which the $POCl_3$ was removed by distillation in vacuo, 5 g of crushed ice was added to the residue, and the mixture was refluxed for 30 min. It was then neutralized with 10% NaOH solution, and the precipitate was removed by filtration and washed with water to give 1.06 g (87%) of pyridine IX with $M^{+\cdot}$.

2-Amino-3-cyano-4-N-benzylaminopyridine (X). A mixture of 1.5 g (6 mmole) of pyridine IX and 20 ml of an alcohol solution of ammonia (~14%) was heated in a bomb at 220°C for 9 h, after which the alcohol was evaporated, and the precipitate was washed on the filter with a small amount of absolute alcohol to give 1.05 g of pyridine X.

3-Ethoxycarbonyl-4-oxo-8-N-benzylamino-9-cyanopyrido[1,2-a]pyrimidine (XI). A mixture of 0.48 g (2.1 mmole) of aminopyridine X, 0.46 g (2.1 mmole) of ethoxymethylenemalonic ester, and 15 ml of DMF was refluxed for 6 h, after which it was evaporated in vacuo, the residue was triturated with a small amount of ether, and the mixture was filtered to give 0.26 g of XI with $M^{+\cdot}$ 348.

α-Cyano-β-N,N-dimethylaminocrotonic Acid N-Benzylamide (XII). A mixture of 6 g (0.035 mole) of cyanoacetic acid N-benzylamide, 6 g (0.037 mole) of acetal III, and 30 ml of absolute ethanol was refluxed for 2 h, after which it was evaporated. A small amount of ethyl acetate was added to the residue, and the mixture was filtered to give 7.08 g of amide XII with $M^{+\cdot}$ 243.

α-Cyano-β-aminocrotonic Acid N-Benzylamide (XIII). A mixture of 1.15 g (4.7 mmole) of amide XII and 20 ml of an alcohol solution of ammonia (∿14%) was heated in a bomb at 80°C for 6 h, after which it was evaporated to give 0.93 g of amide XIII.

1-Benzyl-4-(β-N,N-dimethylamino)vinyl-5-cyano-1,6-dihydro-6-pyrimidinone (XIV). A mixture of 1 g (4.7 mmole) of amide XIII, 2.8 g (18.8 mmole) of acetal IV, and 20 ml of absolute ethanol was refluxed for 4 h, after which it was evaporated, and the residue was triturated with a small amount of alcohol to give 1.09 g of pyrimidinone XIV. IR spectrum: 2210 (C≡N) 1600, 1620 cm^{-1} (C=O, C=N). UV spectrum (in alcohol), λ_{max} (log ε): 214 (4.20), 287 (4.37), and 376 nm (4.31).

α-Chano-β-hydroxycrotonic Acid N-Benzylamide (XV). A) A 0.2-g (0.71 mmole) sample of pyrimidinone XIV was refluxed from 3 h in 20 ml of 1 N NaOH, after which the solution was cooled and neutralized to pH 4-5 with concentrated HCl. The precipitate was removed by filtration to give 0.07 g of amide XV. IR spectrum: 2220 (C≡N), 3340 (OH), and 1600 cm^{-1} (C=O).

B) A mixture of 0.5 g (2 mmole) of amide XII and 20 ml of 1 N NaOH was refluxed for 1 h, after which it was cooled and neutralized to pH 4-5 with concentrated HCl to give 0.23 g of a product with a melting point and IR spectrum identical to those for amide XV.

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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF 1,5-DIKETONE HYDRAZONES. 2.* OXIDATIVE CYCLIZATION OF δ-BICYCLANONE BIS(PHENYLHYDRAZONES) AS A METHOD FOR THE SYNTHESIS OF SUBSTITUTED 2-PHENYL-4R-$\Delta^{1(8a)}$-OCTAHYDROCINNOLINE-3-SPIROCYCLOHEXANES

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The oxidation of δ-bicyclanone bis(phenylhydrazones) with oxygen or ferric chloride leads to the formation of 2-phenyl-4R-$\Delta^{1(8a)}$-octahydrocinnoline-3-spiro-1'-cyclohexan-2'-one phenylhydrazones. The structures of these compounds were proved by the ^{13}C NMR, IR, and mass spectra, as well as by transformations in acidic media to the corresponding keto derivatives and tetrahydrocarbazole derivatives.

Little study has been devoted to the reaction of 1,5-diketone hydrazones. We have previously shown that the phenylhydrazones of semicyclic and alicyclic 1,5-diketones undergo Fischer cyclization to give, respectively, pyridocarbazoles [1] and indoloacridines [2].

*See [1] for Communication 1.

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