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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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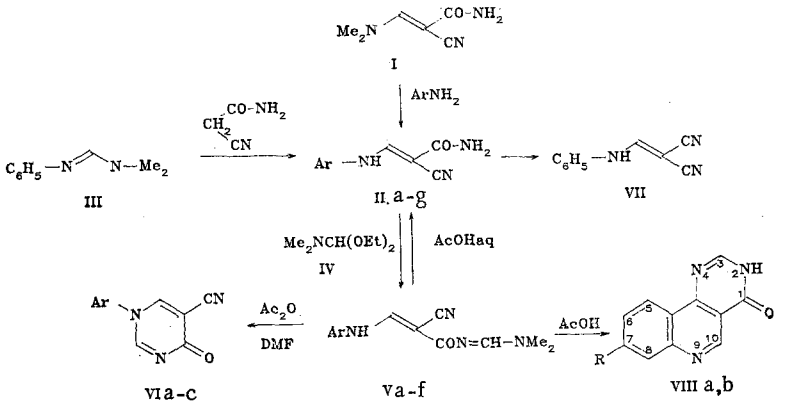
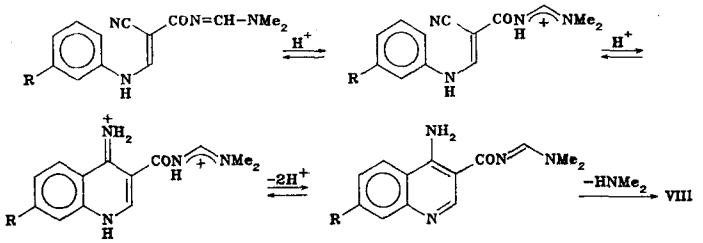
formed in aqueous acetic acid. An unexpected result was obtained when enamine Va was heated in glacial acetic acid. In this case we obtained a compound with a molecular mass of 197, according to the mass-spectral data (the M^+ peak is the most intense peak in the spectrum). We assumed that pyrimido[5,4-c]quinol-1-one (VIIIa) is formed in this case; this is confirmed by data from the PMR spectrum. A multiplet at 8.18-8.60 ppm, which was assigned to the protons of a condensed benzene ring, a singlet at 8.97 ppm (3-H), and a singlet at 10.12 ppm (10-H) are observed in the PMR spectrum if CF_3COOD. The weak-field shift of the latter signal is associated with protonation at the $N_{(9)}$ atom in CF_3COOD.



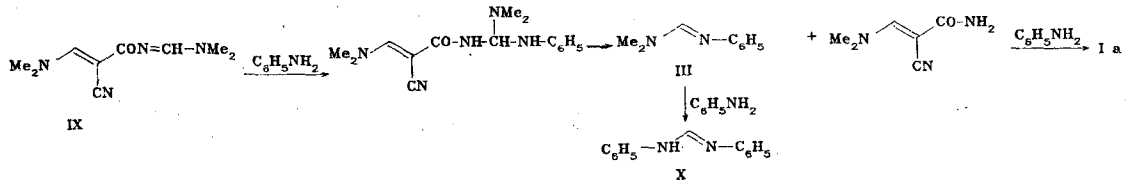
II, V, VI a Ar=Ph; b Ar=*p*-$MeOC_6H_4$, c Ar=*m*-MeC_6H_4; II, V d Ar=*p*-ClC_6H_4, e Ar=*p*-MeC_6H_4, f Ar=*m*-$MeOC_6H_4$; II g Ar=*p*-$NO_2C_6H_4$; VIII a R=H; b R=Me

Three-ring system VIIIb, which has a UV spectrum similar to the spectrum of VIIIa and a melting point that coincides with the melting point of three-ring system VIIIb obtained by a different method [4], was similarly synthesized from enaminoacylamidine Vc. Attempts to carry out the similar cyclization of IIa in glacial CH_3COOH or CF_3COOH were unsuccessful — starting enamine IIa was isolated in all of the experiments. It may be assumed that the cyclization of Va, c proceeds via the following scheme:



An extremely important step in the cyclization is protonation of the acylamidine fragment and, thereby, the creation of a powerful electron-acceptor substituent that activates the CN group — an increase in the positive charge on the carbon atom of the latter promotes cyclization.

We attempted to realize a different approach to cyanopyridones VI by the reaction of acylamidine IX [5] with aniline. However, we found that the principal product is enamino amide IIa. N,N-Dimethyl-N'-phenylformamidine (III) and N,N'-diphenylformamidine (X), which are evidently formed via the following scheme, were detected in the mother liquor after filtration of IIa by chromatographic mass spectroscopy:



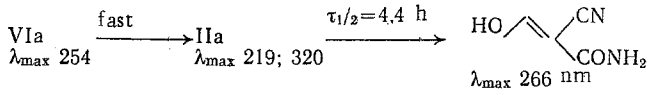
The reaction of aniline at the acylamidine group evidently proceeds more rapidly than transamination, which involves the enamine fragment, for otherwise one would have observed the formation of pyrimidinone VIa. The synthesis of pyrimidinones VI made it possible to continue research on the hydrolytic cleavage of the pyrimidine ring in these compounds with the formation of the starting enamino amides [1]. The processes were investigated by spec-

TABLE 1. Physicochemical Constants and Yields of II

Compound	mp, °C (ethanol)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIa	220—221	64,3	5,1	22,7	$C_{10}H_9N_3O$	64,2	4,8	22,5	41
IIb	220,5—221,5[a]	60,4	4,9	19,5	$C_{11}H_{11}N_3O_2$	60,8	5,1	19,4	26
IIc	189—191	65,7	5,5	20,9	$C_{11}H_{11}N_3O$	65,7	5,5	20,9	28
IId	246—247	54,1	3,7	19,1	$C_{10}H_8ClN_3O$[b]	54,2	3,6	19,0	35
IIe	231—233	65,8	5,5	21,1	$C_{11}H_{11}N_3O$	65,7	5,5	20,9	17
IIf	183—185	60,6	5,1	19,4	$C_{11}H_{11}N_3O_2$	60,8	5,1	19,4	19
IIg	284—286	51,6	3,4	24,1	$C_{10}H_8N_4O_3$	51,8	3,4	24,1	9

[a]From DMF. [b]Found: Cl 16.1%. Calculated: Cl 16.0%.

trophotometry at 23-25°C (the hydrolysis conditions and the method of investigation were described in [1]). The hydrolysis of VIa at pH 7 (0.05 M phosphate buffer solution + 10% methanol) proceeds quantitatively to give IIa; half-conversion time $\tau_{1/2} = \ln 2/K_{obs} = 77$ min. The analogous process for VIb is somewhat slower: $\tau_{1/2} = 115$ min, which is in good agreement with attack by the OH^- ion as the rate-determining step of the process (the p-MeO group in VIb hinders attack by the hydroxide ion at the 2 position of the pyrimidine ring). The hydrolysis of VIa, b in 0.1 N NaOH solution is a fast process with $\tau_{1/2} < 1$ min. If maintenance of VIa in 0.1 N NaOH solution is continued for a longer time, one observes the conversion of enamine IIa to β-hydroxymethylenecyanoacetamide (XI), the UV spectrum of which is similar to the previously described [6] spectrum of α-cyano-β-hydroxy-β-methylacrylamide [λ_{max} 265 nm (log ε 4.17)], i.e., the entire hydrolysis process at pH 13 is described by the scheme



EXPERIMENTAL

The mass spectra were recorded with an MAT-112 spectrometer with introduction of the samples at 70 eV. The UV spectra of solutions in methanol were recorded with an M-40 spectrophotometer (Karl Zeiss, Jena, East Germany). The PMR spectra of solutions in CF_3COOD were obtained with an XL-200 spectrometer with tetramethylsilane as the internal standard.

α-Cyano-β-anilinoacrylamide (IIa). A) A mixture of 2 g (14.4 mmole) of I, 1.7 ml (17 mmole) of aniline, and 25 ml of glacial acetic acid was refluxed for 1.5 h, after which it was evaporated, and the residue was washed with water. The precipitate was removed by filtration and refluxed in 30 ml of ether to give 1.1 g of IIa.

α-Cyano-β-N-arylaminoacrylamides IIb-g were similarly obtained. The physical constants, yields, and analytical characteristics are presented in Table 1.

B) A mixture of 1 g (6.8 mmole) of III, 0.52 g (6.2 mmole) of cyanoacetamide, and 5 ml of alcohol was refluxed for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with 2 ml of ethyl acetate to give 0.45 g (36%) of IIa, which according to its melting point and IR spectrum, was identical to the compound obtained by method A.

C) A mixture of 0.65 g (4 mmole) of Va, 8 ml of glacial acetic acid, and 0.5 ml of water was refluxed for 2.5 h, after which it was evaporated, and the residue was washed with water and removed by filtration to give 0.55 g (76%) of IIa, which, according to its melting point and IR spectrum, was identical to the compound obtained by method A.

D) A 2-g (10.3 mmole) sample of N,N-dimethyl-N'-(α-cyano-β-dimethylaminoacrylyl)formamidine (IX) was refluxed in 2.9 ml of aniline for 2 h, after which it was cooled and triturated with ethyl acetate, and the precipitate was removed by filtration and washed with

TABLE 2. Physicochemical Constants and Yields of V

Compound	mp, °C (from ethanol)	Found, %			Empirical formula	Calc., %			M^+	Yield, %
		C	H	N		C	H	N		
Va	125—127	64,9	5,8	23,2	$C_{13}H_{14}N_4O$	64,5	5,8	23,1	242	72
Vb	154—156	65,6	6,4	21,9	$C_{14}H_{16}N_4O_2$	65,6	6,3	21,9	272	48
Vc	156—158	65,9	6,3	22,2	$C_{14}H_{16}N_4O$	65,6	6,3	21,9	256	42
Vd	214,5—217,5	56,3	4,6	20,2	$C_{13}H_{13}ClN_4O$[a]	56,4	4,7	20,3	276	56
Ve	170—172	65,6	6,4	21,9	$C_{14}H_{16}N_4O$	65,6	6,3	21,9	256	67
Vf	132—134	61,5	6,0	20,7	$C_{14}H_{16}N_4O_2$	61,7	5,9	20,6	272	48

[a]Found: Cl 12.9%. Calculated: Cl 12.8%.

TABLE 3. Physicochemical Constants and Yields of VI

Compound	mp, °C (from isopropyl alcohol)	Found, %			Empirical formula	Calc., %			M^+	Yield, %
		C	H	N		C	H	N		
VIa	232—234	66,9	3,4	21,3	$C_{11}H_7N_3O$	67,0	3,6	21,3	197	61
VIb	224—226	63,2	4,0	18,5	$C_{12}H_9N_3O_2$	63,4	4,0	18,5	227	72
VIc	180—181	68,1	4,3	20,2	$C_{12}H_9N_3O$	68,3	4,3	19,9	211	61

5 ml of alcohol to give 0.2 g (10%) of IIa, which, according to its melting point and IR spectrum, was identical to the compound obtained by method A.

α,α-Dicyano-β-anilinoethylene (VII). A 1-g (5.3 mmole) sample of IIa was refluxed in 10 ml of DMF until it dissolved completely, after which 0.6 ml of phosphorus oxychloride was added, and the mixture was refluxed for another 3.5 h. It was then evaporated, and the precipitate was removed by filtration and washed with water to give 0.85 g (94%) of VII with mp 253-255°C (from isopropyl alcohol) [mp 248-250°C (from methanol) [7]].

N,N-Dimethyl-N'-(α-cyano-β-N'-anilinoacrylyl)formamidine (Va). A mixture of 0.8 g (4.3 mmole) of IIa, 1.2 ml (5.6 mmole) of a 70% solution of IV, and 10 ml of alcohol was refluxed for 2 h, after which it was evaporated, and the residue was washed with ether and removed by filtration to give 0.75 g of Va.

N,N-Dimethyl-N'-α-cyano-β-N'-arylaminoacrylyl)formamidines Vb-f were similarly obtained (Table 2).

1-Phenyl-4-oxo-5-cyanopyrimidine (VIa). A) A solution of 0.6 g (2.5 mmole) of Va in 2 ml of DMF was refluxed for 6 h, after which it was evaporated, and the residue was triturated with ether to give 0.3 g of VIa.

1-Aryl-4-oxo-5-cyanopyrimidines VIb, c were similarly obtained (Table 3).

B) A 1-g (4.1 mmole) sample of Va was refluxed in 10 ml of acetic anhydride for 5 h, after which the mixture was evaporated, and the precipitate was removed by filtration and washed with 3 ml of ethanol to give 0.5 g (61%) of a compound, which, according to its melting point and IR spectrum, was identical to VIa.

Pyrimido[5,4-c]quinol-1-one (VIIIa). A 1-g (4 mmole) sample of Va was refluxed in 8 ml of glacial acetic acid for 2.5 h, after which the mixture was cooled, and the precipitate was removed by filtration and washed with water to give 0.8 g (98%) of VIIIa with mp 360-362°C (from DMF). UV spectrum, λ_{max} (log ε): 277 (4.38), 340 shoulder (3.78), 353 (3.88), and 370 nm shoulder (3.72). Found: C 67.3; H 3.5; N 21.6%. M^+ 197. $C_{11}H_7N_3O$. Calculated: C 67.1; H 3.6; N 21.3%.

7-Methylpyrimido[5,4-c]quinol-1-one (VIIIb). This compound, with mp 360-363°C (from DMF) (mp 360-363°C [4]), was similarly obtained in 61% yield. UV spectrum, λ_{max} (log ε): 278 (4.41), 340 shoulder (3.92), 352 (3.96), and 376 nm shoulder (3.75).

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SYNTHESIS OF GLYCOSYLPYRIMIDINES ON THE BASIS OF GLYCOSYLUREA

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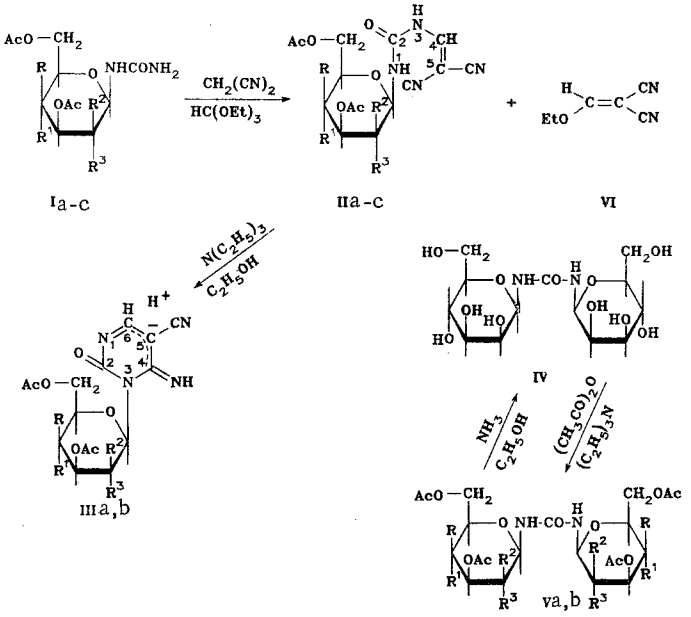
Acetylated derivatives of glycosylpyrimidines were synthesized on the basis of acetylated glycosylureas, malononitrile, and ethyl orthoformate. The spectral characteristics of the compounds obtained were studied.

We have previously developed a new method for the preparation of arabinosylpyrimidines by construction of the heterocyclic part of the molecule on the basis of arabinosyl derivatives of urea [1].

In the present research we used acetylated derivatives of 1-D-glucopyranosyl-, 1-D-mannopyranosyl-, and 1-D-galactopyranosylurea (Ia-c) as starting compounds. 1-(2',3',4',5'-Tetra-O-acetyl-β-D-glucopyranosyl)-, 1-(2',3',4',5'-tetra-O-acetyl-β-D-mannopyranosyl)-, and 1-(2',3',4',5'-tetra-O-acetyl-β-D-galactopyranosyl)ureidomethylenemalononitriles (IIa-c) were obtained by the reaction of Ia-c with malonitrile and ethyl orthoformate. In addition to nitriles IIa-c, ethoxymethylenemalononitrile (VI) is formed as an impurity. Attempts to subject unacetylated derivatives of glycosylureas to the described reaction were unsuccess-



Ia, IIa, IIIa R=R²=H, R¹=R³=OAc; Ib, IIb, IIIb R=R³=H, R¹=R²=OAc; Ic, IIc R¹=R²=H, R=R³=OAc; Va R=R³=H, R¹=R²=OAc; Vb R¹=R²=H, R=R³=OAc

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