in 40 ml of acetone, after which the mixture was refluxed for 5 min and allowed to stand overnight. The resulting precipitate was removed by filtration and washed with water and acetone to give 0.7 g (83.3%) of IIIb.

2-(2-Pyridyl)-3-keto-4-thiocyanatobutyronitrile (VII). A mixture of 0.97 g (5 mmole) of 2-(2-pyridyl)-3-keto-4-chlorobutyronitrile and 0.74 g (7.5 mmole) of potassium thiocyanate in 20 ml of acetone was refluxed for 2 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with 12 ml of water and acetone to give 0.96 g (88%) of VII with mp 184 deg C (from n-propyl alcohol). IR spectrum: 2200 (CN) and 2155 cm^{-1} (SCN). Found: N 19.5; S 15.0%. $C_{10}H_7N_3OS$. Calculated: N 19.3; S 14.8%.

2-(2-Pyridyl)-3-keto-4-azidobutyronitrile (VIII). A mixture of 5.82 g (30 mmole) of 2-(2-pyridyl)-3-keto-4-chlorobutyronitrile, 2.16 g (33 mmole) of finely ground sodium azide, 25 ml of DMF, and 2 ml of water was heated at 50-60 deg C for 20 min, after which it was allowed to stand at room temperature for 12-15 h. Cold water (25 ml) was added to the reaction mixture, and the precipitate was removed by filtration and washed with water to give 5 g (83%) of a product with mp 158-159 deg C (dec., from n-propyl alcohol). IR spectrum: 2195 (CN) and 2122 cm^{-1} (N_3). Found: N 34.8%. $C_9H_7N_5O$. Calculated: N 34.8%.

2-(2-Benzimidazolyl)-3-keto-4-azidobutyronitrile (IX). A 0.72-g (11 mmole) sample of finely ground sodium azide was added to a solution of 2.34 g (10 mmole) of 2-(2-benzimidazolyl)-3-keto-4-chlorobutyronitrile in a refluxing mixture of 20 ml of DMF and 4 ml of water, after which heating was discontinued. After 2 h, 30 ml of water was added, and the resulting precipitate was removed by filtration and washed with water and alcohol to give 2.4 g (99%) of a product with mp > 320 deg C (from n-propyl alcohol). IR spectrum: 2200 (CN) and 2120 cm^{-1} (N_3). Found: N 35.2%. $C_{11}H_8N_6O$. Calculated: N 35.0%.

LITERATURE CITED

1. V. H. Schafer and K. Gewald, J. Prakt. Chem., 316, 684 (1974).
2. F. S. Babichev and Yu. M. Volovenko, Khim. Geterotsikl. Soedin., No. 7, 1005 (1975).
3. C. D. Gutsche and H.-W. Voges, J. Org. Chem., 32, No. 9, 2685 (1967).

ACETALS OF LACTAMS AND ACID AMIDES

XXII.* REACTION OF AMIDE AND LACTAM ACETALS WITH ENAMINO ESTERS. SYNTHESIS OF BENZENE, PYRIDINE, INDOLE, QUINOLINE, AND BENZAZEPINE DERIVATIVES

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UDC 547.52/59'752'821'831'892:542.951.2

It is shown that acetals of acid amides and lactams undergo condensation at the α-CH_3 (or CH_2) groups of enamino esters to give dienediamines, the cyclization of which led to benzene, pyridine, indole, quinoline, and benzazepine derivatives.

The chemical and physicochemical properties of enamines (for example, of the I type) are determined to a great extent by the electron-acceptor effect of the β substituents and the electron-donor effect of the tertiary amino group.

In the case of the reaction of enamine I with dimethylformamide diethylacetal (II), as a result of which 1-carbethoxy-1-cyano-2,4-bis(N,N-dimethylamino)butadiene (III) was isolated in 56% yield, we have shown [2]

*See [1] for communication XXI.

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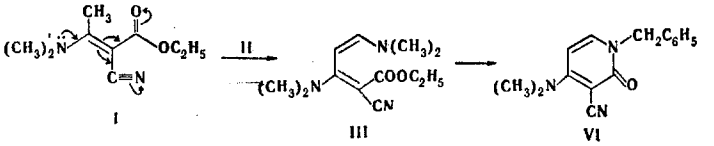
TABLE 1. Half-Wave Potentials of the Compounds Obtained (in DMF in a 0.1 M Bu_4NI Base Electrolyte)

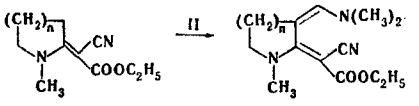
Compound	I	III	IVa	IVb	Va	Vb	IVc	XIa	XIb	XIV	XIIIa	XIIIb
$E_{1/2}$ (Ag-electrode)	1,75	1,50 2,16	1,74 --	1,78 —	1,51 2,24	1,55 2,22	1,54 2,16	1,63 2,34	1,61 2,23	2,00	2,25	2,07

*The $E_{1/2}$ values presented in Table 1 were measured from polarograms recorded in the base electrolyte solutions with the addition of the reaction mixture diluted with DMF. In this connection, the $E_{1/2}$ values should not be considered to be absolute.

that the CH_3 group in the α position of enamine I is capable of undergoing condensation; however, this reaction requires considerably more severe conditions than the reaction of amide acetals with compounds of the cyanoacetic ester type.* In connection with the fact that the properties of the starting (I) and final (III) compounds are close and their separation presents considerable difficulty, the development of a method for monitoring of the condensation process was necessary for the extension of this reaction to other enamines (IVa, b). We selected polarography for this purpose, since the half-wave potentials of the starting enamines and the dienediamines formed from them differ substantially in anhydrous dimethylformamide (DMF) (Table 1).



I III VI



IVa-c Va, b

IVa n=2; b n=3; c n=1; Va n=2; b n=3

The reaction of enamines IVa, b with acetal II was carried out until the reduction waves of the enamines disappeared completely. As a result, 1-methyl-2-(2-cyano-2-carbethoxy)methylene-3-N,N-dimethylaminomethylenepiperidine (Va) and -hexahydroazepine (Vb) were synthesized in high yields. An attempt to carry out the condensation of acetal II with pyrrolidine enamine IV under these conditions was unsuccessful – the starting compound was isolated in all cases. The structures of dienediamines Va, b were confirmed by the PMR spectroscopic data. It should be noted that all of the signals of the protons in the spectra of these compounds are doubled. This constitutes evidence for the presence of isomerism due to the C=C bonds.† The isomer ratios for Va and Vb in dimethyl sulfoxide (DMSO) are 1 : 5 and 1 : 1, respectively. The presence in the III and Va, b dienediamine structures of dimethylaminomethylene and carbethoxy groups ensures the possibility of the synthesis from them of substituted pyridines. Thus 1-benzyl-3-cyano-4,N,N-dimethylamino-2-pyridone (VI) was synthesized by reaction of III with benzylamine. Within the framework of the present research we demonstrated only the fundamental possibility of the synthesis of pyridines from dienediamines. The extension of this reaction to the other dienediamines Va, b seems expedient to us, since we have previously developed a preparatively more convenient method for the synthesis of 2-pyridones (of the VI type) [3]. It should be noted that in the case of III "transamination" with benzylamine proceeds selectively in the 4 position; this is in good agreement with the previously expressed assumption [2] regarding the steric hindrance of the $N(CH_3)_2$ group attached to the C_2 atom.

The use of dienediamines in the synthesis of cyclic systems is not restricted only to the possibility of closing of a pyridine ring. We also studied an approach that makes it possible to realize the construction of a substituted benzene ring and thus to develop a new synthesis of heterocycles of the indole, quinoline, and benzazepine series. We selected enamino ester I as the starting compound for these purposes. Dienediamines X and XIa-c were synthesized by condensation of the latter with N,N-dimethylacetamide (VII) and N-methyl-

*The considerable increase in the reaction time in the preparation of III makes it possible to synthesize it in practically quantitative yield.

†The isomerism of dienediamines Va, b will be examined in subsequent research in this series.

TABLE 2. PMR Spectra of Dienediamines X and XIa, b (chemical shifts, ppm)

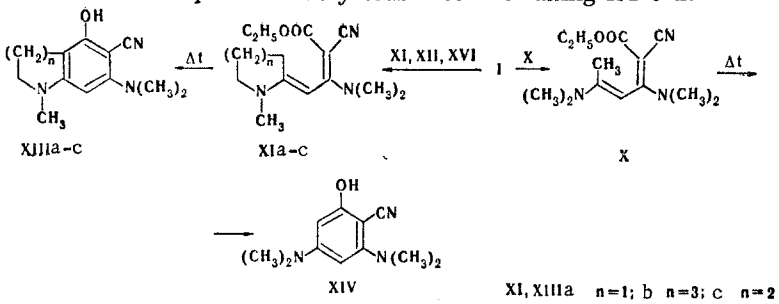
Compound	N—CH_3	$N(CH_3)_2$	3-CH_2	4-CH_2	5-CH_2	6-CH_2	7-CH_2	=C—H	CH_3 ($COOC_2H_5$)	CH_2 ($COOC_2H_5$)
X*	—	3,05 3,07	2,24 (C—CH_3)	—	—	—	—	4,56	1,26	4,12
XIa†	2,97	3,04	3,04	1,97	3,54	—	—	4,60	1,21	4,00
XIb*	3,03	3,06	2,79	1,64			3,42	4,37	1,26	4,14

*In $CDCl_3$.
†In d_6-DMSO.

TABLE 3. PMR Spectra of XIV, XIIIa, b in d_6-DMSO (chemical shifts, ppm)

Compound	N—CH_3	$N(CH_3)_2$	2-CH_2	3-CH_2	4-CH_2	5-CH_2	=C—H
XIV	2.89 and 2.98 [two $N(CH_3)_2$ groups]		—	—	—	—	5.59 and 5.78 (C_2—H and C_4—H)
XIIIa	2,76	2,89	3,40	2,88	—	—	5,52
XIIIb	2,85		3,07	1,65		2,67	5,86

butyrolactam (VIII) and N-methylcaprolactam (IX) diethylacetals. According to the polarographic data, the indicated dienediamines are formed in quantitative yields after refluxing for 8 h.



In a study of the reaction of ester I with N-methylvalerolactam diethylacetal (XII) it was observed that in addition to a compound to which structure XIc was assigned on the basis of polarographic data, another substance, which is reduced at more negative potentials, is formed simultaneously. In the course of 8 h, the wave of the latter increases to a constant height, and the reduction waves of I and XIc vanish. According to the results of elementary analysis and the IR and PMR spectra, the product is 1-methyl-5-hydroxy-6-cyano-7-N,N-dimethylamino-1,2,3,4-tetrahydroquinoline (XIIIc).* The IR spectrum of this substance contains absorption bands at 3300 (OH) and 2200 cm^{-1} (CN), and the PMR spectrum ($CDCl_3$) contains proton signals at 2.92 [$N(CH_3)_2$ and NCH_3], 1.90 (3-CH_2), 2.61 (4-CH_2), 3.28 (2-CH_2), and 5.59 ppm (C—H). Thus the condensation of acetal XII at the CH_3 group of enamino ester I under these conditions is accompanied by extremely facile cyclization to quinoline derivative XIIIc. The proposed new principle for the construction of a benzene ring can also be realized in the case of X and XIa, b. More severe cyclization conditions (200 deg C in tetralin) are necessary in this case, however. It should be noted that in this series of compounds 2-cyano-3,5-bis(N,N-dimethylamino)-phenol (XIV) is formed most easily, and the preparation of its two-ring analogs — 1-methyl-4-hydroxy-5-cyano-6-N,N-dimethylaminoindoline (XIIIa) and 1-methyl-6-hydroxy-7-cyano-8-N,N-dimethylaminobenzazepine (XIIIb) — requires more prolonged heating at 200 deg C. Thus with respect to ease of cyclization the investigated dienediamines can be arranged in the order XIc > X > XIIIb ≈ XIIIa. The structures of the compounds obtained were confirmed by spectral data (Tables 2-4).

EXPERIMENTAL

The polarographic method was the same as in our preceding paper [1]. The reactions were monitored in the following way. A 0.1-ml sample of the reaction mixture was diluted to 3 ml with DMF, and 0.1 ml of the resulting solution was placed in the polarographic cell containing 2 ml of a 0.1 M solution of Bu_4NI in DMF.

*The formation of this product is accompanied by the appearance on the polarograms of additional waves, which are also observed during the cyclization of X, XIa, b. We were unable to isolate the substance (or substances) responsible for the appearance of these polarographic waves.

TABLE 4. Synthesized Compounds

Compound	Found, %			Empirical formula	Calc., %			IR spectrum, cm^{-1}	UV spectrum	
	C	H	N		C	H	N		λ,nm	lg ε
Va	63,8	8,1	15,9	$C_{14}H_{21}N_3O_2$	63,9	8,0	16,0	2180 (CN), 1675 ($COOC_2H_5$)	288, 327, 362	3,99, 4,02, 4,01
Vb	65,2	8,5	15,2	$C_{15}H_{23}N_3O_2$	65,0	8,3	15,2	2180 (CN), 1670 ($COOC_2H_5$)	322, 364	4,17, 4,11
VI	71,3	6,3	16,6	$C_{15}H_{15}N_3O$	71,2	6,0	16,6	2200 (CN), 1640 (CO)	305	4,21
X	62,0	8,1	17,0	$C_{13}H_{21}N_3O_2$	62,2	8,4	16,7	2180 (CN), 1670 ($COOC_2H_5$)	220, 324, 362	4,17, 4,28, 4,38
XIa	63,7	8,0	16,0	$C_{14}H_{21}N_3O_2$	63,9	8,0	16,0	2180 (CN), 1660 ($COOC_2H_5$)	226, 320, 358	4,10, 4,33, 4,36
XIb	66,2	8,8	14,5	$C_{16}H_{25}N_3O_2$	66,0	8,6	14,4	2180 (CN), 1665 ($COOC_2H_5$)	220, 326, 367	4,20, 4,26, 4,39
XIIIc	67,6	7,6	18,5	$C_{13}H_{17}N_3O$	67,6	7,4	18,2	3300 (OH), 2200 (CN)	236*, 260, 300	4,17, 4,37, 4,34
XIV	64,3	7,5	20,6	$C_{11}H_{15}N_3O$	64,4	7,3	20,5	3200 (OH), 2200 (CN)	230*, 258, 294	4,17, 4,40, 4,39
XIIIa	66,6	6,8	19,5	$C_{12}H_{15}N_3O$	66,4	6,9	19,4	3180 (OH), 2180 (CN)	260, 298, 310*	4,41, 4,15, 4,09
XIIIb	69,0	7,8	17,2	$C_{14}H_{19}N_3O$	69,0	7,8	17,1	3300 (OH), 2180 (CN)	236, 260, 300	4,11, 4,18, 4,09

*Shoulder.

The oxygen was removed with a stream of nitrogen, and the polarogram was recorded. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The UV spectra of alcohol solutions were obtained with an EPS-3 spectrophotometer.

1-Methyl-2-(2-carbethoxy-2-cyano)methylene-3-N,N-dimethylaminomethylenepiperidine (Va) and 1-Methyl-2-(2-carbethoxy-2-cyano)methylene-3-N,N-dimethylaminomethylenehexahydroazepine (Vb). A 3.05-g sample of acetal II was added to a refluxing solution of 3.03 g of enamine IVa in 30 ml of dry toluene, and the mixture was refluxed for 20 h (2 ml of II was added after 8 h and 16 h). The solvent was then removed by vacuum distillation, and the residue was triturated with hexane to give Va, with mp 130-131 deg C (from ethyl acetate), in 97% yield. PMR spectrum, δ (in d_6-DMSO): 3.04 ($N-CH_3$), 3.15 [$N(CH_3)_2$], 7.19 and 7.39 (=C–H), 1.21 and 1.24 ($CH_3-COOC_2H_5$), 3.97 and 4.18 ($CH_2-COOC_2H_5$), 1.83 (5-CH_2), 2.53 (4-CH_2), 3.32 ppm (6-CH_2). A similar procedure was used to obtain Vb, with mp 114-115 deg C, in 84% yield. PMR spectrum, δ (in d_6-DMSO): 2.77 and 3.07 [$N(CH_3)_2$], 2.90 and 2.92 ($N-CH_3$), 6.63 and 6.71 (=CH), 1.19 ($CH_3-COOC_2H_5$), 3.99 and 4.01 ($CH_2-COOC_2H_5$), 1.59 (5,6-CH_2), 2.28 and 2.40 (4-CH_2), 3.30 ppm (7-CH_2).

1-Benzyl-3-cyano-4-N,N-dimethylamino-2-pyridone (VI). A 3.21-g sample of benzylamine and a catalytic amount of p-toluenesulfonic acid were added to 2.37 g of III, and the mixture was refluxed for 2.5 h. It was then cooled and treated with ethanol, and the precipitated VI was removed by filtration. The mother liquor was evaporated, and the residue was triturated with hexane to give an additional amount of VI. The product, with mp 173-174 deg, was obtained in 77% overall yield. PMR spectrum: ($CDCl_3$): 3.23 [$N(CH_3)_2$], 5.07 ($N-CH_2C_6H_5$), 5.76 (5-CH), 7.4 (6-H), 7.27 ppm (C_6H_5).

1-Cyano-1-carbethoxy-2,4-bis(N,N-dimethylamino)-4-methylbutadiene (X). A 4-g sample of acetal VII was added to a refluxing solution of 3.4 g of I in 30 ml of dry xylene, and the mixture was refluxed for 8 h. The xylene was then removed by vacuum distillation, and the residue was triturated with hexane to give X, with mp 135-136 deg C (from ethyl acetate), in 56% yield. A similar procedure was used to obtain the following compounds: XIa, with mp 108.5-109 deg C (from ether), in 79% yield; XIb, with mp 100-102 deg C (from ether), in 89% yield; XIc, with mp 156-157 deg C (from iso-C_3H_2OH), in 50% yield (based on I).

2-Cyano-3,5-bis(N,N-dimethylamino)benzene (XIV). A solution of X in 10 ml of tetralin was refluxed for 1 h, after which it was cooled and filtered to give substituted benzene XIV, with mp 203-204 deg C (from benzene), in 70% yield. The following compounds were similarly obtained by refluxing in tetralin for 2 h and

isolation of the products by the addition of petroleum ether: XIIIa, with mp 199-200.5 deg C (from benzene), in 49% yield; XIIIb, with mp 131.5-132.5 deg C (from hexane), in 35% yield.

LITERATURE CITED

1. V. G. Granik, A. B. Grigor'ev, and M. K. Polievktov, Khim. Geterotsikl. Soedin., No. 10, 1352 (1977).
2. V. G. Granik, N. B. Marchenko, E. O. Sochneva, T. F. Vlasova, A. B. Grigor'ev, M. K. Polievktov, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 11, 1505 (1976).
3. V. G. Granik, N. B. Marchenko, T. F. Vlasova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 11, 1509 (1976).

ACETALS OF LACTAMS AND ACID AMIDES

XXIII.* KINETICS OF CYCLIZATION OF N,N-DIMETHYL-N'-(α-CYANO-β-DIMETHYLAMINO)CROTONYLFORMAMIDINE AND ITS FIVE-, SIX-, AND SEVEN-MEMBERED ANALOGS AND N-METHYL-2-[N-(α-CYANO-β-DIMETHYLAMINO)-ACRYLOYLIMINO]PIPERIDINE TO 2-PYRIDONE DERIVATIVES

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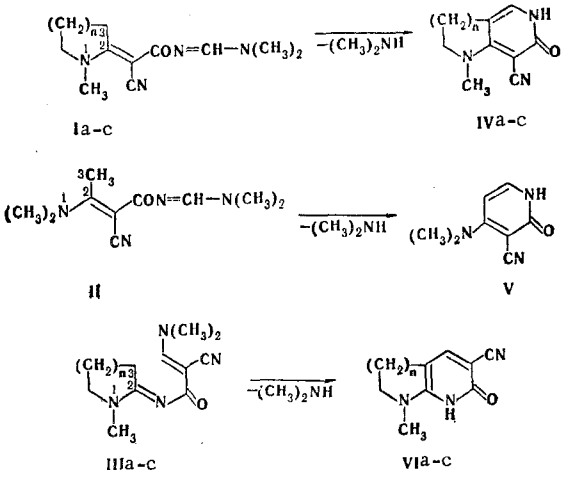
UDC 547.824'83'74'821.892:543.253

The rate constants for cyclization of N,N-dimethyl-N'-(α-cyano-β-dimethylamino)-crotonylformamidine and its five-, six-, and seven-membered analogs and N-methyl-2-[N-(α-cyano-β-dimethylamino)acryloylimino]piperidine to derivatives of 2-pyridone, pyrrolo-, and pyrido-, and azepino[3,2-c]pyridine and 1,8-naphthyridine were measured in dimethylformamide (DMF) at 120-150 deg C. It is assumed that a new C—C bond with a change in the hybridization of the $C_{(3)}$ atom from sp^2 to sp^3 develops in the rate-determining step.

During a study of the chemistry of acetals and acid amides and lactams it was shown [2, 3] that these compounds react smoothly with enamino amides to give amidines (Ia-c, II, and IIIa-c), which on heating undergo cyclization to derivatives of pyrrolo-, pyrido-, and azepino[3,2-c]pyridine (IVa-c), 3-cyano-4-dimethylamino-2-pyridone (V), and of pyrrolo-, pyrido-, and azepino[2,3-b]pyridine (VIa-c).



*See [1] for communication XXII.

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