ACETALS OF LACTAMS AND ACID AMIDES.

42.* CYCLIZATION OF DIENAMINO ESTERS, DIENAMINO NITRILES, AND ACYLAMIDINES TO PYRIDINE DERIVATIVES

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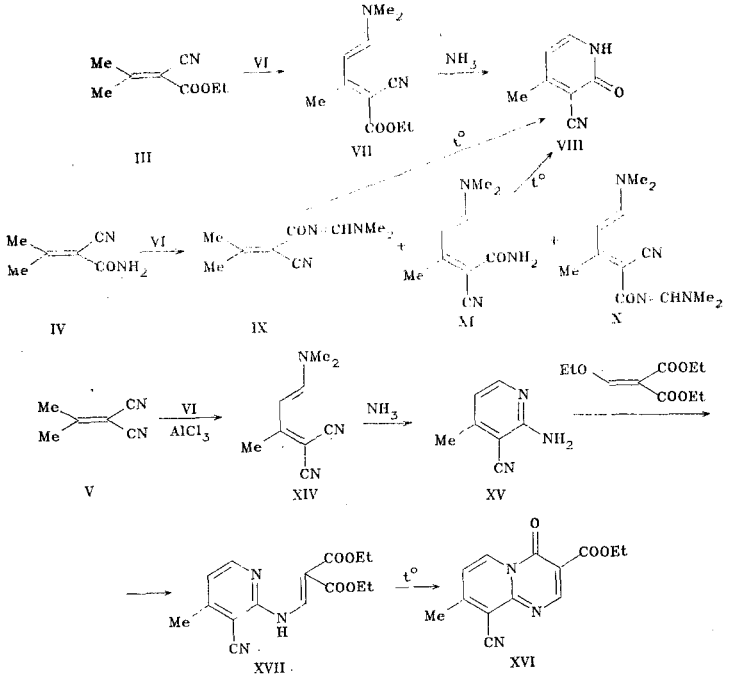
The reaction of derivatives of alkylidene(cycloalkylidene)cyanoacetic ester, -malonodinitrile, and -cyanoacetamide with dimethylformamide diethylacetal with subsequent cyclization of the resulting enamine systems gives derivatives of pyridine, 2-pyridine, and isoquinoline. 2-Amino-3-cyano-4-methylpyridine, which was synthesized by this method, was converted to a pyrido[1,2-a]pyrimidine derivative.

It has been shown [2] that cycloalkylidenemalonodinitriles (Ia,b) and cycloalkylidenecyanoacetamides (IIa, b) can be readily converted to hydrogenated derivatives of 3-amino-2-pyridine and 3-aminoisoquinoline. In a continuation of this research we have attempted to realize the synthesis of monocyclic derivatives of pyridine on the basis of 2-isopropylidene derivatives of cyanoacetic ester (III), cyanoacetamide (IV), and malonodinitrile (V).



The reaction of ester III with dimethylformamide diethylacetal (VI) proceeds smoothly to give 1-cyano-1-ethoxycarbonyl-2-methyl-4-dimethylaminobutadiene (VII),† which undergoes cyclization to 3-cyano-4-methyl-2-pyridone (VIII) when it is heated with an alcohol solution of ammonia. The reaction of amide IV with acetal VI leads to a mixture of acylamidine IX,

*See [1] for communication 41.

†The synthesis of this compound was described in [3], in which it was not characterized but was used without purification in subsequent syntheses.

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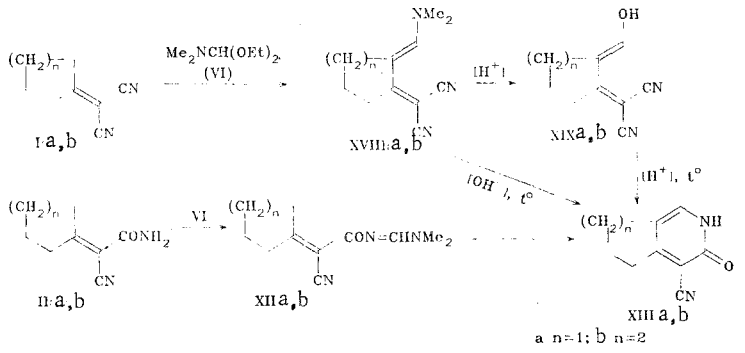
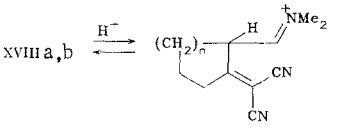
enaminoacylamidine X, and dieneamine XI. The latter is present in this mixture in small amounts, as indicated by the low intensity of the absorption bands of the NH_2 group in the IR spectrum. Molecular-ion peaks at m/z 234 (X) and 179 (IX, XI) are observed in the mass spectrum of the mixture. The principal component in this mixture is acylamidine IX, as evidenced by the next step in the cyclization, which takes place by heating in dimethylformamide (DMF) — pyridone VIII is formed in rather high yield (enaminoacylamidine X cannot undergo cyclization to pyridone VIII under these conditions).

Considering the data on the reaction of amide IV with acetal VI set forth above, we investigated the reactions of cyclic amides IIa,b with acetal VI in greater detail. We found that intermediate acylamidine XIIa, which undergoes cyclization to 4-cyano-2,3,5,6-tetrahydro-7H-2-pyridine-3-one (XIIIa) upon further heating, can be isolated in the reaction of amide IIa with acetal VI. We were unable to isolate acylamidine XIIb in the case of six-membered analog IIb — subequent cyclization evidently proceeds more rapidly than the reaction in which it is formed. This is in good agreement with previously obtained data, according to which cyclization reactions of this type proceed substantially more rapidly for six-membered compounds than for five-membered compounds [4, 5].

It has recently been established [2] that, in contrast to isopropylidenecyanoacetic ester (III), 1,1-dicyano-2-methyl-4-dimethylaminobutadiene (XIV), which was required for the synthesis of 2-amino-3-cyano-4-methylpyridine (XV), cannot be obtained from isopropylidenemalonodinitrile (V) by reaction with dimethylformamide diethylacetal (VI) under ordinary conditions.



Considering the fact that the occurrence of this reaction in an undesirable (for us) direction is due to the presence of basic substances in the reaction medium [3, 6], in the present research we used the method that we developed in [1], which consists in carrying out the condensation of V and VI in the presence of aluminum chloride. In this case the reaction proceeds extremely smoothly, and dienamine XIV was obtained in high yield. Heating of the latter with an alcohol solution of ammonia in a bomb leads to aminopyridine XV, which was the starting compound in the synthesis of 3-carbethoxy-4-oxo-8-methyl-9-cyano-4,5-dihydropyrido[1,2-a]pyrimidine (XVI) (through intermediate enamine XVII). In examining the possibility of obtaining two-ring pyridones XIIIa,b from the previously described [1] dinitriles Ia,b rather than from amides IIa,b we found that hydrolysis of the enamino grouping to give hydroxymethylene derivatives XIXa,b is observed in the case of moderate heating of cyclic dienamines XVIIIa,b [1] in 0.1 N HCl solution. It is characteristic that hydrolysis proceeds much more rapidly for six-membered compound XVIIIb than for five-membered XVIIIa, as one can judge qualitatively from the results of thin-layer chromatography (TLC). Thus the XVIIIa → XIXa process is complete after 50 h at 40°C, whereas the XVIIIb → XIXb transformation takes 6 h under these conditions. This is evidently explained by the fact that the step that determines the rate of hydrolysis is C-protonation, which is accompanied by a change in the hybridization of the ring carbon atom from sp^2 to sp^3, which is extremely energetically unfavorable for five-membered rings [4, 7, 8].



When dienamines XVIIIa,b are heated in dilute acids at higher temperatures or in dilute alkalis, they undergo smooth conversion to pyridones XIIIa,b. Differences in the rate of cyclization as a function of the size of the ring are not observed in the latter case (when alkali is used).

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Tesla BS-497 spectrometer (100 MHz) with hexamethyldisiloxane as the internal standard. The melting points were determined with a Boetius apparatus. The individuality of the compounds obtained were confirmed by TLC (Silufol UV-254).

1-Carbethoxy-1-cyano-2-methyl-4-dimethylamino-1,4-butadiene (VII). A 12.5-ml sample of 80% diethylacetal VI was added to 10 g (0.065 mole) of ester III, and the mixture was heated at 50°C for 1 h. It was then cooled and filtered to give 7 g of VII. The physical constants, yields, and results of microanalysis are presented in Table 1.

3-Cyano-4-methyl-2-pyridone (VIII). A) A mixture of 4 g of VII and 20 ml of a 10% alcohol solution of ammonia was heated for 5 h in a bomb at 150°C, after which it was cooled and filtered to give 1.2 g of pyridone VIII. PMR spectrum (d_6-DMSO): 2.32 (3H, s, Me), 3.62 (1H, broad s, NH), 6.23 (1H, d, J = 6 Hz, 5-H), and 7.53 ppm (1H, d, J = 6 Hz, 6-H).

B) A 7.5-ml sample of an 80% solution of VI was added to 5 g of amide IV in 20 ml of dry toluene, and the mixture was refluxed for 30 min. It was then evaporated to give 5 g of a mixture of IX-XI. A solution of 1 g of this mixture was refluxed for 3 h in DMF, after which the solvent was removed by distillation *in vacuo* to give 0.5 g (67% based on IX) of pyridone VIII.

N-(Dimethylaminomethylene)cyclopentylidenecyanoacetamide (XIIa). A 6-ml sample of an 80% solution of acetal VI was added with refluxing and stirring in the course of 30 min to 5 g (0.03 mole) of amide IIa in 20 ml of dry benzene, after which the mixture was cooled and filtered to give 4.5 g of acylamidine XIIa. PMR spectrum ($CDCl_3$): 1.38-1.80 (4H, m, 3,4-CH_2), 2.62-3.07 (4H, m, 2,5-CH_2), 3.10 (6H, s, NMe_2), and 8.39 ppm (1H, s, CH).

1,1-Dicyano-2-methyl-4-dimethylamino-1,4-butadiene (XIV). A 1-g sample of $AlCl_3$ was added to a solution of 28 ml (0.25 mole) of dinitrile V in 50 ml of dry DMF, 45 ml of 80% acetal VI was added dropwise in the course of 30 min, and the mixture was refluxed for 1 h. The solvent was removed by distillation *in vacuo* to give 29 g of XIV. PMR spectrum ($CDCl_3$): 2.15 (3H, s, 2-Me), 2.93 and 3.16 (6H, d, NMe_2), 5.56 (1H, d, J = 13 Hz, 3-H), and 7.19 ppm (1H, d, J = 13 Hz, 4-H).

2-Amino-3-cyano-4-methylpyridine (XV). A mixture of 8 g (0.05 mole) of dienamine XIV and 30 ml of a 10% solution of ammonia in alcohol was heated for 3 h at 150°C in a bomb, after which the solvent was removed by distillation to give 3.3 g of aminopyridine XV. PMR spectrum ($CDCl_3$): 2.37 (3H, s, 4-Me), 5.32 (2H, broad s, NH_2), 6.47 (1H, d, J = 5 Hz, 5-H), and 7.99 ppm (1H, d, J = 5 Hz, 6-H).

2-(N-β-Diethoxycarbonylvinyl)amino-3-cyano-4-methylpyridine (XVII). A mixture of 0.8 g (6 mmole) of XV and 1 ml of ethoxymethylenemalonic ester was heated for 1 h at 150°C, after which it was cooled to 40°C and treated with alcohol. Filtration gave 1.78 g of enamine XVII. PMR spectrum ($CDCl_3$): 1.22-1.40 (6H, m, $COOCH_2CH_3$), 2.53 (3H, s, 4-Me), 4.12-4.44 (4H, m, OCH_2), 6.90 (1H, d, J = 5 Hz, 5-H), 8.28 (1H, d, J = 5 Hz, 6-H), 9.06 (1H, d, J = 12 Hz, N–CH), and 11.56 ppm (1H, d, J = 12 Hz, NH).

3-Carbethoxy-4-oxo-8-methyl-9-cyano-4,5-dihydropyrido[1,2-a]pyrimidine (XVI). A mixture of 0.6 g (2 mmole) of enamine XVII and 10 ml of Dowtherm was heated at 250°C for 1.5 h, after which it was cooled rapidly and poured into cold hexane. The mixture was filtered to give 0.45 g of XVI. PMR spectrum ($CDCl_3$): 1.36 (3H, t, $COOCH_2CH_3$), 2.76 (3H, s, 8-Me), 4.27-4.48 (2H, q, OCH_2), 7.17 (1H, d, J = 7 Hz, 6-H), 9.02 (1H, s, 2-H), and 9.17 ppm (1H, d, J = 7 Hz, 7-H).

1-Dicyanomethylene-2-hydroxymethylenecyclopentane (XIXa) and 1-Dicyanomethylene-2-hydroxymethylenecyclohexane (XIXb). A mixture of 2 g of dieneamine XVIIIa and 20 ml of a 0.1 N HCl solution was heated at 40°C for 50 h, after which it was filtered to give 1.2 g of hydroxymethylene derivative XIXa. PMR spectrum (CF_3COOD): 1.72-2.03 (2H, m, 4-CH_2), 2.5-2.66 (2H, t, 3-CH_2), 2.72-2.86 (2H, t, 5-CH_2), and 7.42 ppm (1H, s, CH). A similar reaction gave 1.2 g of XIXb. PMR spectrum (CF_3COOD): 1.48 (4H, broad s, 4- and 5-CH_2), 2.34 (2H, broad s, 3-CH_2), 2.64 (2H, broad s, 6-CH_2), and 7.42 ppm (1H, s, CH).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
VII	96—97,5[a]	63,8	7,7	13,4	$C_{11}H_{16}N_2O_2$	63,4	7,7	13,5	60
VIII	236—238[a]	62,3	4,7	20,7	$C_7H_6N_2O$	62,7	4,5	20,9	46 (A), 67 (B)
XIIa	127—129[a]	64,7	7,4	20,9	$C_{11}H_{15}N_3O$	64,4	7,4	20,5	75
XIV	151—154[a]	67,2	6,6	26,4	$C_9H_{11}N_3$	67,1	6,9	26,1	73
XV	150—151[b]	63,5	5,6	31,7	$C_7H_7N_3$	63,1	5,3	31,6	50
XVI	215—217[c]	60,5	4,3	16,5	$C_{13}H_{11}N_3O_3$	60,7	4,3	16,3	90
XVII	126—128[a]	59,7	5,8	14,0	$C_{15}H_{17}N_3O_7$	59,4	5,7	13,9	98
XIXa	290—292[a]	67,6	5,2	17,6	$C_9H_8N_2O$	67,5	5,0	17,5	81
XIXb	220—223[d]	69,2	5,9	16,4	$C_{10}H_{10}N_2O$	68,9	5,8	16,1	80

[a]From ethanol. [b]Sublimation. [c]From alcohol. [d]From hexane with benzene.

4-Cyano-2,3,5,6-tetrahydro-7H-2-pyrindin-3-one (XIIIa) and 4-Cyano-2,3,5,6,7,8-hexahydro-3-isoquinoline (XIIIb). A) A mixture of 1 g of XIXa and 10 ml of a 0.1 N HCl solution was heated at 80°C for 10 h, after which it was made alkaline to pH 7-8 with NaOH to give 0.4 g of pyrindinone XIIIa. A similar reaction of XIXb gave 0.53 g of isoquinoline XIIIb.

B) A mixture of 1 g of dienamine XVIIIa and 10 ml of a 0.1 N NaOH solution was heated at 40°C for 25 h, after which it was acidified to pH 7 to give XIIIa in 38% yield. Compound XIIIb was similarly obtained in 90% yield.

C) A mixture of 2 g of XIIa and 20 ml of DMF was refluxed for 5 h, after which it was cooled, and the precipitate was removed by filtration and washed with alcohol to give 0.88 g (55%) of XIIIa. The substances obtained by methods A-C were identical to previously synthesized samples [1] with respect to their physical constants, the results of TLC, and their spectra.

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