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.

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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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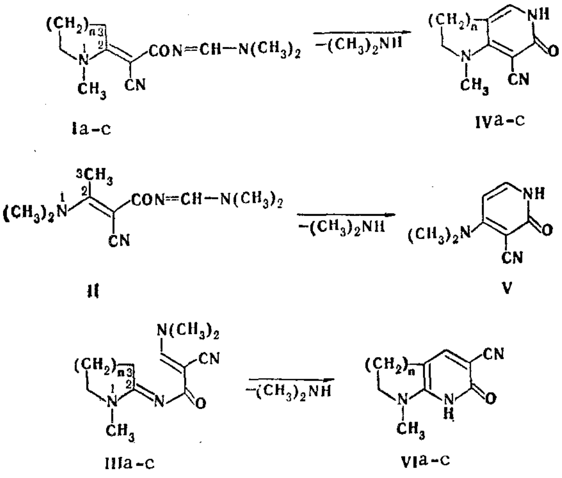
UDC 547.824'83'74'821.892:543.253

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).



I, III, IV, VI a n=1; b n=2; c n=3

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*See [1] for communication XXII.

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TABLE 1. Polarographic Characteristics of the Investigated Compounds in DMF in a 0.1 M Bu_4NClO_4 Base Electrolyte

Compound	$E_{1/2}$	$\varkappa'$
Ia	−1,92	1,40
Ib	−1,77	1,28
Ic	−1,81	1,23
II	−1,91	1,30
IIIa	−1,92 ($E''_{1/2}$−2,45)	1,69
IIIb	−1,91	2,18
IIIc	−1,92 ($E''_{1/2}$−2,45)	1,06
IVa	−1,79 ($E''_{1/2}$−2,02)	0,64
IVb	−1,76	1,29
IVc	−1,62	1,40
V	−1,64 ($E''_{1/2}$−1,84)	0,68

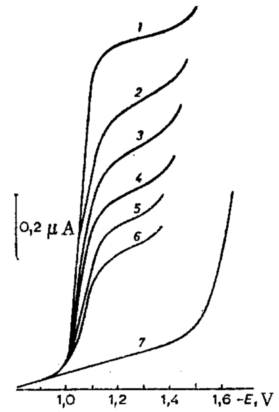

Fig. 1. Cyclization of amidine II in DMF (7.8 mm solution) at 130 deg C. Polarograms of samples of the reaction solution in an acetate buffer solution selected 1 (1), 10 (2), 20 (3), 30 (4), 40 (5), and 55 min (6) after the start of the reaction; 7) curve of the residual tone of the base electrolyte.

In the present research in order to examine the probable mechanism of the formation of pyridine rings in this unusual reaction we studied the kinetics of cyclization of Ia–c, II, and IIIb in dimethylformamide (DMF) at various temperatures. The course of the reaction was monitored by polarography. Since the $E_{1/2}$ values of the starting and final compounds in DMF were close (Table 1), for this purpose we used aqueous acetate buffer solutions (pH 4.65), inasmuch as polarographic waves of only the starting enamino acylamidines are observed in this medium over the accessible range of potentials.* The experimental data constitute evidence that all of the investigated reactions are first-order reactions.

The rate constants calculated by the method of least squares (MLS) are presented in Table 2. It is apparent from these data that the rate of cyclization decreases in the order Ib > II > Ic > IIIb > Ia.

Thus in the starting series of compounds (Ia–c, and II) the compounds with a six-membered ring undergo cyclization most easily, and the compounds with a five-membered ring undergo cyclization with the greatest

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*The dependence of the height of the wave of amidine I on the time is presented in Fig. 1 as an example (the concentration of amidine I in the reaction solution is 7.8 mm). The shift in the current of the circuit to positive potentials as the reaction proceeds is associated with the formation of dimethylamine.

TABLE 2. Rate Constants for the Cyclization of Ia-c, II, and IIIb in DMF

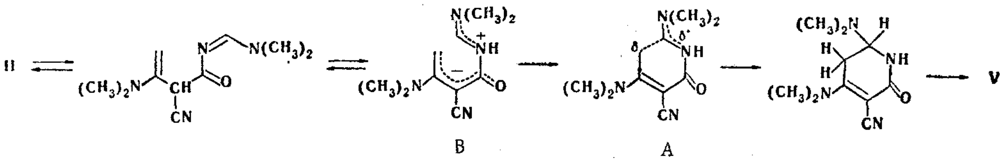
Temp., °C	150	150	150	150	150	120	130	140
Compound	Ia	Ib	Ic	II	III	II	II	II
$k \cdot 10^{-5}$, sec^{-1}	0,512± ±0,139	127±10	14,6±1,8	49,9±7,7	3,474± ±0,171	7,38±0,67	14,4±1,7	27,6±2,7

difficulty, whereas a comparison of the rate constants for cyclization of the acylamidines (Ib, IIIb) definitely indicates that attack by the meso atom of the amidine fragment on the 3 position of the enamine (Ib) is much more favorable than cyclization associated with attack by the α-carbon atom of the enamine on the 3 position of the amidine (as in the case of IIIb).

For the interpretation of the dependence of the rate of cyclization on the size of the azaheteroring it is evidently expedient to invoke the concept of I strain [4], although it is known that this concept was developed primarily in the case of cycloalkanes that have only one trigonal carbon atom (or for cases in which one sp^2-hybridized carbon atom develops during the reaction). It seems likely that although the process upon the whole is accompanied by a change in the hybridization of the $C_{(3)}$ atom from sp^3 to sp^2 in the rate-determining step of the cyclization, the opposite change in the hybridization of this carbon atom (from sp^2 to sp^3) occurs.

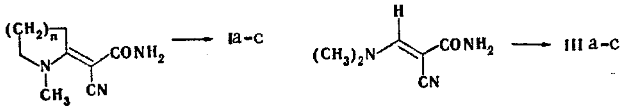
The proposed mechanism of the reactions should also explain why the free energy of activation for the cyclization of I (or II) to IV (or V) is lower than that for the general analogous process III → VI (the rate constant for the cyclization of Ib is greater by a factor of more than 30 than in the case of IIIb (Table 2). The $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values were calculated for the cyclization of acylamidine II from the Eyring equation and were found to be, respectively, 21.6 ± 0.42 kcal/mole and −23.53 ± 1.02 kcal/mole deg.

One's attention is directed to the high entropy of activation; this indicates a high degree of orderliness of the transition state as compared with the starting state. This provides a basis for the assumption that the structure of the activated comples (A) is more similar to that of the final state than to that of the starting state. In this connection, one can conceive of the following pathway for the achievement of the transition state and the formation from it of 2-pyridones for the cyclization of Ia-c (in the case of II):



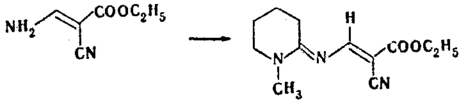
It follows from the scheme above that the B → A conversion is accompanied by rehybridization of the $C_{(3)}$ atom from sp^2 to sp^3; as we have indicated above, this promotes acceleration of the reaction in the case of six-membered rings and slowing down of the reaction in the case of five- and seven-membered rings [4]. If it is assumed that the III → VI cyclization proceeds via a similar mechanism, the positive charge will be localized on the dimethylamino group in the activated complex for this reaction. Hence the energy of the transition state in this process will be higher than in the case of cyclization of II, in which the positive charge in activated complex A is effectively delocalized over the amidine system; this is also manifested in the considerably higher rate of formation of pyridone IVb as compared with VIb. It should be noted that we have also previously observed substantial facilitation of cyclization at the heteroring $C_{(3)}$ atom in the case of six-membered rings during the synthesis of condensed 4-pyridones [5] or in the case of closing of a benzene ring [1] and that this is a general feature in cyclizations of this type.

The data presented in Table 1 constitute an additional confirmation of the conclusions in [6] regarding the dependence of the $E_{1/2}$ values on the size of the saturated heteroring. Since the enamine C = C bond in both series of compounds (Ia-c and IIIa-c) undergoes reduction, a dependence of $E_{1/2}$ on the ring size should be observed only for Ia-c [6], in which the ring $C_{(2)}$ atom is involved in the formation of an anion radical; this is actually observed experimentally. As seen from Table 1, as in the case of enamino ketones, enamino amides, and enamino esters [6], of the enamino acyl amidines Ia-c, six-membered Ib undergoes reduction most readily. On the other hand, the $E_{1/2}$ values of the first reduction wave of amidines IIIa-c, in which the enamine fragment is not included in the ring, do not depend on the size of the saturated ring.



n=1, $E_{1/2}=-2{,}11$ V ; n=2, $E_{1/2}=-1{,}92$ V ; n=3, $E_{1/2}=-1{,}92$ V
$E_{1/2}=-2{,}00$ V

It is interesting to note that even at a considerable distance from the reaction center the conversion of the amide NH_2 group to an amidine group [5]



$E_{1/2}=-2{,}01$ V, $E'_{1/2}=-1{,}42$ V, $E''_{1/2}=-2{,}25$ V

leads to an appreciable facilitation of the reduction of the indicated compounds. An even greater effect is observed in those cases in which the conversion of the amino group to an amidine group occurs directly at the reaction center.

Thus polarography is both a convenient analytical method for the study of reactions involving the conversion of an amino group to an amidine group and a useful method for the solution of various structural problems in the examined class of compounds.

EXPERIMENTAL

Polarography was carried out in a thermostatted cell at 25 ± 0.1 deg C. A dropping electrode with characteristics m = 0.75 mg/sec and t = 0.26 sec was used for the work with aqueous DMF solutions; the anode was a saturated calomel electrode. The dropping mercury electrode in the work in anhydrous DMF had the following characteristics: m = 0.73 mg/sec and t = 0.3 sec; the anode was a silver spiral submerged in the test solution (the $E_{1/2}$ values in Table 1 and in the text are presented relative to this electrode). The polarograms were recorded with a Radiometer PO-4 polarograph.

The cyclization kinetics were studied in a thermostatted vessel at the temperatures indicated in Table 2. A 4-ml sample of DMF was poured into this vessel, and, after the working temperature had been reached, 0.5 ml of the solution of the investigated substance in DMF was added with magnetic stirring. The concentration of the substance was 10 mM in all cases. Samples of the solution were selected from the reaction mixture at definite time intervals as a function of the rate of the process. After cooling, 0.2 ml of this solution was transferred to the polarographic cell, to which 3 ml of 0.1 M acetate buffer solution had been previously added. The polarograms were recorded immediately after removal of the dissolved oxygen with a stream of nitrogen. The rate constants were calculated by the method of least squares from the dependence of log i_{lim} on time.

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