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ACETALS OF LACTAMS AND ACID AMIDES.

53.* ENAMIDINES IN THE SYNTHESIS OF PYRIDINE AND PYRIMIDINE

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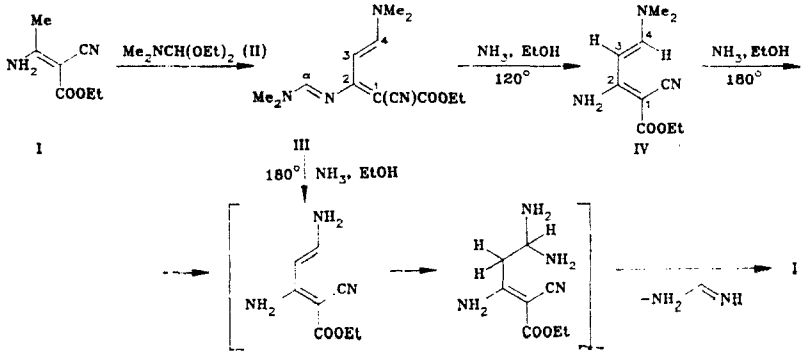
The reaction of α-cyano-β-aminocrotonic ester with DMFA diethylacetal gives 1-ethoxycarbonyl-1-cyano-2-(N-dimethylaminomethylene)-amino-4-dimethylaminobutadiene, the reaction of which with ammonium acetate and amines leads to 4-methylenepyrimidine derivatives. Condensation of α-cyano-β-aminocrotonic ester with dimethylacetamide dieethylacetal gave 2-(ethoxycarbonylcyano)methylene-4-dimethylamino-6-methylpyridine. It was found that in an alkaline medium, 1-benzyl-4-(ethoxycarbonylcyano)methylenepyrimidine recyclizes into 1-benzyl-3-cyano-4-amino-2-pyridone.

It has previously been shown that primary enamines can react with acetals of N-methyllactams to form enamidines, which are very promising starting compounds for the synthesis of various 4-pyridone derivatives [2, 3].

The aim of the present work was to study certain properties of enamidines formed in the reaction of amide acetals with ethyl ester of α-cyano-β-aminocrotonic acid (I). The reaction of the latter with DMFA diethylacetal (II) proceeds in the same way as in the case of lactam acetals [2] (at the amino and methyl groups), as a result of which dienaminoamidine-1-ethoxycarbonyl-1-cyano-2-(N-dimethylaminomethylene)amino-4-dimethylaminobutadiene (III) is formed readily and in a high yield (Table 1).

The reaction of enamidine III with ammonia in alcohol at low temperatures prodeeds very slowly, but when the temperature is increased to 120°C, transamination takes place with splitting of the amidine fragment and formation of a diene-diamine, 1-ethoxycarbonyl-1-cyano-2-amino-4-dimethylaminobutadiene (IV). It can be seen that under these conditions, the nucleophilic attack occurs at the $C_{(2)}$ atom only, without affecting the 4-position. Further increase in temperature not only led to transamination with splitting of the dimethylamino group at the 4-position, but also to rupture of the carbon-carbon bond with formation of a β-aminocrotonic ester derivative I. This unusual splitting probably proceeds by the scheme



*For Communication 52, see [1].

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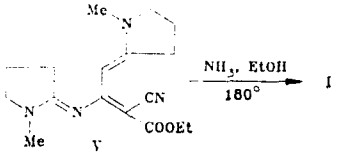
TABLE 1. Physicochemical Constants and Yield of Compounds Synthesized

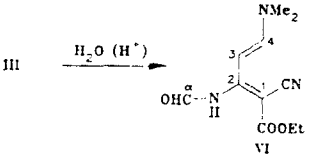
Compound	mp, °C*	Found, %			Empirical formula	Calculated, %			M·	Yield, %
		C	H	N		C	H	N		
III	156...158	59,4	7,7	21,3	$C_{13}H_{20}N_4O_2$	59,1	7,4	21,2	264	94
IV	158...162	57,2	7,4	20,4	$C_{10}H_{15}N_3O_2$	57,4	7,2	20,1	209	73
VI	166...168	55,5	6,6	17,6	$C_{11}H_{15}N_3O_3$	55,7	6,4	17,7	237	85
VIIa	186...190	56,4	4,6	22,0	$C_9H_9N_3O_2$	56,5	4,7	22,0	191	90
VIIb	198...201	68,4	5,3	14,9	$C_{16}H_{15}N_3O$	68,3	5,4	14,9	281	68
VIIc	208...211	67,7	5,0	15,7	$C_{15}H_{13}N_3O_2$	67,4	4,9	15,7	267	55
VIII	243...245	69,2	4,9	18,7	$C_{13}H_{11}N_3O$	69,3	4,9	18,7	225	60
XIa	200...203	63,2	7,0	17,0	$C_{13}H_{17}N_3O_2$	63,1	6,9	17,0	247	20

*For compounds III, XIa, the solvent was ethyl acetate, for IV – methanol, for VI, VIIa-c – 2-propanol, for VIII – acetonitrile.

It should be noted that the same pattern is also observed for enamidine V, obtained by the reaction of compound I with N-methyl-2-pyrrolidone acetal [2]. When compound V is heated with alcoholic ammonia at 180°C, the C–C bond is split, and ester I is formed:



While in the reaction with ammonia, there is an attack at $C_{(2)}$ at the first stage, a different pattern is observed in acid medium: the amidine grouping undergoes hydrolysis (attack at the $C_{(\alpha)}$ atom), as a resultof which, 1-ethoxycarbonyl-1-cyano-2-formylamino-4-dimethylaminobutadiene (VI) is formed:

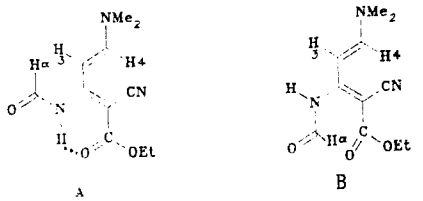


A characteristic feature of the PMR spectra of enamines III, IV and VI (Table 2) is the appreciable broadening of the 3-H proton signal, while for the α-H, and in particular 4-H-signal, the broadening is much less. With increase in the temperature of running the spectrum of the sample, the broadening of the signals decreases. The possible reason for this broadening of the signals in the spectra is the ability of the compunds studied to undergo various types of reversible conformational transformations [4-6]. To study this phenomenon, we ran PMR spectra of compounds III and VI at low temperatures in aetone-D_6. It was found that in the spectra run at −25°C, there is a double set of signals, and the ratio between the forms for compounds III and VI varies (Table 2). The maximal difference in the chemical shifts of protons in the two forms takes place for the 3-H protons (Δδ 1.24 for III and 1.23 ppm for VI), and is much smaller for the α-H protons (Δδ 0.16 for III and 0.28 ppm for VI) and for the 4-H protons (Δδ 0.09 for III and 0.07 ppm for VI). Judging from the PMR spectra, for the formylamino derivative VI, the form with an intramolecular hydrogen bond (δ_{NH} 10.98 ppm) predominates (~96%), while in the minor form, the content of which is ~4%, this hydrogen bond is absent (δ_{NH} 9.53 ppm). In the two forms a spin-spin interaction of the α-H and NH protons takes place ($^3J_{\alpha\text{-H,NH}}$ = 9.5 Hz). From the spectral data, structure A was ascribed to the predominating form of compound VI, and structure B to the minor form. For compound III, such an intramolecular hydrogen bond cannot be formed, and this is, in principle, the reason for the different content of the rotation-isomeric forms.

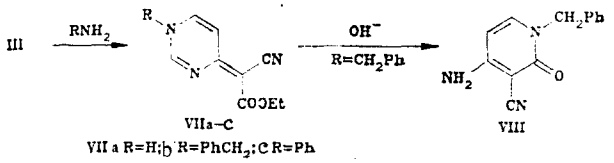
TABLE 2. PMR Spectra of Dienamine Derivatives (III, IV, VI)

Compound	Type of isomer (% content)	δ, ppm								Solvent	$T_{run.sp}$
		3-CH	4-CH	α-CH	4-$N(CH_3)_2$	α-$N(CH_3)_2$	OC_2H_5	NH_2	NH		
III	—	6,48* $^3J_{34}$=12,5 Hz	7,42 (br. d)	7,52 (br.)	2,90 and 3,10 (two br. s for 3H)	3,02 and 2,93 (two br. s for 3H)	1,18 and 4,01 (br.)	—	—	DMSO-D_6	25
	—	6,70 (br. d)	7,52 (br. d)	7,49 (br.)	3,00 (br.)	3,09; 2,88	1,22; 4,08 (br.)	—	—	Acetone-D_6	25
	A (10)	5,36 (d) $^3J_{34}$=12,6 Hz	7,73 (d)	7,41 (s)	3,13; 3,20	2,91; 3,03	1,17; 3,97	—	—	Acetone-D_6	−25
	B (90)	6,68 (d) $^3J_{34}$=12,4 Hz	7,62 (d)	7,57 (s)	3,20; 3,16	2,97; 2,93	1,22; 4,08	—	—	Acetone-D_6	−25
IV	—	5,02 (br. d) $^3J_{34}$=13,2 Hz	7,26 (d)	—	2,97 (br. s for 6H)	—	1,29 and 4,17	7,30 (br. signal)	—	$CDCl_3$	25
	—	5,01 (br. d) $^3J_{34}$=13,4 Hz	7,61 (d)	—	3,01 (br.)	—	1,23; 4,11	7,00 (br. signal)		Acetone-D_6	25
VI	—	5,46** $^3J_{34}$=12,3 Hz	7,69 (br. d)	8,42 (br.)	2,96; 3,21 (two br. s for 3H)	—	1,20 and 4,10	—	10,37 (br.)	DMSO-D_6	25
	—	5,39 (br. d)	7,76 (br. d)	8,74 (br.)	3,07 and 3,32 (two br. s for 3H)	—	1,26 and 4,17	—	11,0 (br.)	Acetone-D_6	25
	A (96)	5,27 (d) $^3J_{34}$=12,5 Hz	7,87 (d)	8,81 (d)	3,11		1,25		10,98 (d)	Acetone-D_6	−25
	B (4)	6,50 (d) $^3J_{34}$=12,5 Hz	7,80 (d)	8,53 (d)	3,39		4,16		9,53 (d) $^3J_{\alpha\text{-H, NH}}$ = =9,5 Hz		

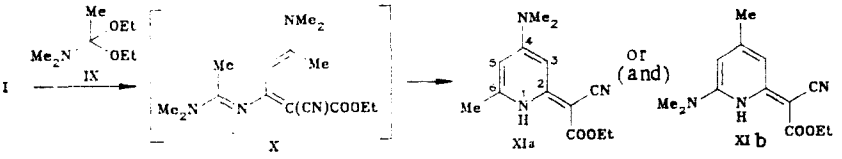
*The signal is strongly broadened, no mutliplicity is evident.
**The signal is broadened to a zero line.



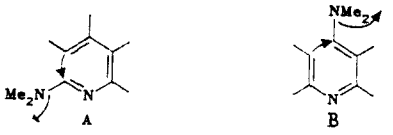
The reaction of enamidine III with ammonium acetate in acetic acid leads to 4-(ethoxycarbonylcyanomethylene)pyrimidine (VIIa) in a high yield. Taking this into account, enamidine III was reacted with benzylamine and aniline to form 1-benzyl- and 1-phenyl-4-(ethoxycarbonylcyanomethylene)pyrimidines (VII,b,c). The presence of two strong electron-accepting groupings (COOEt and CN) indicates that pyrimidines of type VIIb can be subjected to nucleophilic attack by a hydroxyl anion, similarly to the case of immobilized 4-pyrimidinones, which we have previously studied in [7]. In fact, heating of pyrimidine VIIb in an alkaline medum leads to splitting of the pyrimidine ring, followed by recyclization and formation of 1 benzyl-3-cyano-4-amino-2-pyridone (VIII) in a satisfactory yield.



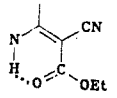
The reaction of the enamino-ester 1 with dimethylacetamide diethylacetal IX possibly proceeds nonunequivocally, with the formation of a complex mixture of compounds. From this mixture we succeeded to isolate a compound, which, judging from the data of microanalysis and IR spectral data, has the structure of either XIa or XIb. The possibility of formation of one of these compounds (or their mixture) follows from the scheme



In other words, splitting of dimethylamine in the intermeidate compound X can occur at the expense of the dimethylamino group in the amidine grouping or the enamine fragment ($C_{(4)}$-NMe_2). It has been previously found by polarography [8] that cyclizations of type A have an appreciably higher rate than cyclizations of type B:



It can be assumed from this that the product of the reaction should be pyridine XIa. Unequivocal information on the structure of the product of the reaction of compounds I and IX could be obtained by PMR spectroscopy. According to the spectral and chromatographic data, the product studied is an individual compound. In the PMR spectrum of compound XI, the signal of the NH proton is observed in a very weak field (13.0 ppm), which indicates the presence of a hydrogen bond in the compound studied, which in turn, unequivocally determines the configuration of compound XI:



The signals of cyclic =CH protons have different multiplicity: at 5.92 ppm, the signal is in the form of a strongly resolved multiplet, and the signal at 5.99 ppm is a quartet. The different multiplicity of the 3-H and 5-H signals, is due to spin-spin interaction with the NH and Ch_3 groups, and does not conform with structure XIb, in which the aromatic protons are located symmetrically both with respect to the methyl group at the 4-position, and relative to the NH fragment.

By carrying out experiments on the consecutive spin-spin decoupling of the CH_3 and N_1H group signals, we were able to determine the SSCC for 3-H ring protons (δ 5.99 ppm) and 5-H (δ 5.92 ppm): $^4J_{35}$ = 2.6, $^4J_{5\text{-H},N(1)\text{-H}}$ = 1.6, $^4J_{3\text{-H},N(_1)H}$ = 1.5, $^4J_{5\text{-H},CH_3}$ = 0.9 Hz. $^4J_{3\text{-H},CH_3}$ = 0. The PMR spectra thus show that the product formed in the condensation of the enaminoester I with dimethylacetamide acetal IX is 2-(ethoxycarbonylcyano)-methylene-4-dimethyamino-6-methylpyridine (XIa).

EXPERIMENTAL

The mass spectra were run on a Varian MAT-112 spectrometer with a direct introduction of the sample to the source, at 70 eV. The temperature of ionization chamber was 180°C. The IR spectra were obtained in mineral oil on a Perkin-Elmer 457 spectrophotometer, and the UV spectra in ethanol on a M-40 spectrophotometer (Carl Zeiss, Jena GDR). The PMR spectra were recorded on Varian XL-100 and Varian XL-200 spectrometers, using TMS as internal standard.

1-Ethoxycarbonyl-1-cyano-2-(N-dimethylaminomethylene)amino-4-dimethylaminobutadiene (III). A mixture of 1.54 g (10 mmoles) of compound I and 4.4 g (30 mmoles) of compound II is boiled in 7 ml of toluene for 2 h. The precipitate is filtered and 2.5 g of compound III are obtained.

1-Ethoxycarbonyl-1-cyano-2-amino-4-dimethylaminobutadiene (IV). A mixture of 1 g (4 mmoles) of compound III and 20 ml of alcoholic ammonia (14%) is heated in an autoclave at 120°C for 1 h, and then evaporated to yield 0.6 g of compound IV.

1-Ethoxycarbonyl-1-cyano-2-formylamino-4-dimethylaminobutadiene (VI). A solution of 1 g (4 mmoles) of compound III and 10 ml of 1 N HCl is stirred at room temperature for 30 min, the precipitate is filtered, washed with water, and dried. Yield 0.76 g of compound VI.

4-(Ethoxycarbonylcyano)methylenepyrimidine (VIIa). A mixture of 1.5 g (6 mmoles) of compound III with 0.44 g (6 mmoles) of ammonium acetate is boiled in 15 ml of glacial acetic acid for 2 h. The precipitate is filtered, washed with water to yield 0.1 g of compound VIIa. The mother liquor is evaporated, the precipitate formed is filtered, and washed with water to yield another 0.87 g of compound VIIa.

1-Benzyl-4-(ethoxycarbonylcyano)methylenepyrimidine (VIIb). A mixture of 1 g (4 mmoles) of compound III with 0.43 g (4 mmoles) of benzylamine is boiled in 10 ml of DMFA for 1 h. The mixture is evaporated, the residue is ground in ether, and 0.75 g of compound VIIb are filtered. PMR spectrum (acetone-D_6): 1.24 (t, CH_3CH_2), 4.16 (q, CH_2CH_3), 7.46 (C_6H_5), 5.30 ($CH_2C_6H_5$) 7.86 (d.d, 6-H, $^3J_{56}$ = 7.9, $^4J_{26}$ = 2.2 Hz), 8.00 (d. d, 5-H, $^5J_{25}$ = 1.0 Hz), 8.52 ppm (q, 2-H).

1-Phenyl-4-(ethoxycarbonylcyano)methylenepyrimidine (VIIc). A mixture of 1 g (4 mmoles) of compound III with 0.53 g (5.7 mmoles) of aniline is boiled in 10 ml of glacial acetic acid for 2 h. The precipitate is filtered, boiled in 20 ml of ether, and 0.4 g of compound VIIc is filtered off. The mother liquor is evaporated, the residue is ground in ethyl acetate, the precipitate is filtered and boiled in 15 ml of ether, and another 0.2 g of compound VIIc is filtered. PMR spectrum (DMSO-D_6): 1.24 (t, CH_3CH_2), 4.15 (q, CH_2CH_3), 7.45...7.75 (m, C_6H_5), 7.97 (d. d, 5-H), 8.17 (d. d, 6H, $^3J_{56}$ = 7.8 Hz), 8.80 ppm (q, 2-H, $^4J_{26}$ = 2.1, $^5J_{25}$ = 0.9 Hz).

1-Benzyl-3-cyano-4-amino-2-pyridone (VIII). A 1.8 g portion (6 mmoles) of compound VIIb is boiled in 20 ml of 2 N NaOH for 2 h. The precipitate is filtered, washed with water to yield 0.85 g of compound VIII. UV spectrum, λ_{max} (log ε): 226 (4.59), 287 nm (4.02).

2-(ethoxycarbonylcyano)methylene-4-dimethylamino-6-methylpyridine (XIa). A mixture of 1.54 (10 mmoles) of compound I with 8.1 g (50 mmoles) of compound IX is boiled in 15 ml of toluene for 2 h. The solution is evaporated, the residue is ground in a small amount of petroleum ether and 0.5 g of compound XIa is filtered off. IR spectrum: 3100 (NH), 2190 (C ≡ N), 1625 (C=O), 1590 cm^{-1} (C=C). PMR spectrum ($CDCl_3$): 1.32 (t, CH_3CH_2) 4.19 (q, CH_2CH_3), 2.35 (s, CH_3), 3.07 [s, $N(CH_3)_2$], 5.92 (m, 5-H), 5.99 (q, 3H), 13.0 ppm (NH).

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