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ACETALS OF LACTAMS AND ACID AMIDES.

XVI.* NEW SYNTHESIS OF 4-PYRIDONE DERIVATIVES

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Reaction of N,N-dimethylacetamide and N-methylbutyro-,-valero-, and caprolactam diethylacetals with ethyl β-aminocrotonate gave the corresponding enamidines, through the cyclization of which 2-dimethylamino-6-methyl-4-pyridone, 1,6-dimethyl-4-oxo-2,3,4,7-tetrahydropyrrolo[2,3-b]pyridine, and 1,7-dimethyl-5-oxo-1,3,4,5,8-hexahydro-1,8-naphthyridine were synthesized.

The present research was devoted to a study of the reaction of amide and lactam acetals with ethyl β-aminocrotonate (I) and to the use of the thus obtained enamidines in the synthesis of 4-pyridone derivatives. A prerequisite for the study was the synthesis [2] of condensed 4-quinolones from lactam acetals and ethyl anthranilate. The reaction of the amide acetals with ester I is of independent interest, inasmuch as the literature does not contain data on the reactions of primary enamines with amide acetals.

The reaction of N,N-dimethylacetamide diethylacetal (II) with ester I proceeds smoothly to give N,N-dimethyl-N^1-(α-methyl-β-carbethoxyvinyl)acetamidine (III). N-Methyl-N-(α-methyl-β-carbethoxyvinyl)iminopyrrolidine (VII), -piperidine (VIII), and -hexahydroazepine (IX), respectively, were similarly synthesized from N-methylbutyro- (IV), -valero- (V), and -caprolactam (VI) diethylacetals. Signals of a carbethoxy group (1.20-1.25 and 4.02-4.08 ppm), α-CH_3 and N-CH_3 groups (1.86-2.24 and 2.86-3.01 ppm, respectively), β-C-H protons (4.84-5.14 ppm), and of 3-CH_3 (for III) or CH_2 groups (for cyclic VII-IX) are observed in the PMR spectra (Table 1) of all of the enamidines (III and VII-IX) in CD_3OD. All of the signals in the spectra are doubled (Fig. 1), and this indicates the existence of III and VII-IX in the form of mixtures of two geometrical isomers. The differences in the chemical shifts of the isomers of various groups are not identical; inasmuch as the maximum difference is observed for the chemical shifts of the α-CH_3 and C-H protons, the observed doubling of the signals is associated with cis-trans isomerism about the C=C bond.† The weak-field signal

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*See [1] for communication XV.

†The assignment to the cis or trans series was based on the mutual orientation of the CH_3 and COOEt groups.

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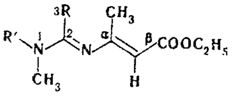
TABLE 1. PMR Spectra (in CD_3OD) of Enamidines III and VII-IX



Compound	R	R¹	Chemical shifts (δ, ppm)									
			NCH_3	$3-CH_2$ (for III — $3-CH_3$)	$4-CH_2$	$5-CH_2$	$6-CH_2$	$7-CH_2$	$\alpha-CH_3$	β-C—H	$COOC_2H_5$ group	
											CH_3	CH_2
III	CH_3	CH_3	2,95 2,99	1,86 1,99	—	—	—	—	1,86 2,19	4,87 5,09	1,20 1,25	4,02 4,06
VII	$(CH_2)_3$		2,86 2,89	1,97	2,47 2,55	3,39 3,41	—	—	1,90 2,24	5,05 5,14	1,20 1,24	4,04 4,08
VIII	$(CH_2)_4$		2,87 2,90	2,34 2,36	1,78 m		3,31 3,33	—	1,89 2,20	4,95 5,10	1,21 1,24	4,02 4,06
IX	$(CH_2)_5$		2,96 3,01	2,48	1,63 m			3,42	1,87 2,19	4,84 5,09	1,20 1,23	4,01 4,05

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*See [1] for communication XV.

TABLE 2. Deuterium-Exchange Rate Constants (K) in CD_3OD at 50°C

Compound	Time for exchange of one proton by	$K \cdot 10^5\ sec^{-1}$
VI	5,4	2,081±0,39
VII	13,4	1,44±1,36
VIII	5,0	3,77±0,46
IX	76	0,25±0,14

TABLE 3. Characteristics of the Compounds Obtained

Compound	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
III	105—106*	$C_{10}H_{18}N_2O_2$	60,0	9,1	13,6	—	60,6	9,1	14,1	—	60
X	168—169 (acetone—iso-PrOH)	$C_4H_{11}ClN_2$	39,7	8,9	—	28,6	39,2	9,0	—	29,0	
IX	142—145*	$C_{13}H_{22}N_2O_2$	65,8	9,4	12,0	—	65,6	9,2	11,8	—	63
VIII	128—129*	$C_{12}H_{20}N_2O_2$	64,2	8,8	12,5	—	64,3	8,9	12,5	—	92
VII	107—109*	$C_{11}H_{18}N_2O_2$	62,5	8,6	13,1	—	62,9	8,6	13,3	—	35
XII	243—245 (iso-PrOH)	$C_8H_{12}N_2O \cdot HCl$	50,6	6,7	14,9	19,0	50,9	6,9	14,9	18,8	24
XI	156—157 (ethyl acetate)	$C_{10}H_{14}N_2O$	67,1	8,2	15,5	—	67,4	7,9	15,7	—	80
XIII	186—188 (ethyl acetate)	$C_9H_{12}N_2O$	65,8	7,6	17,1	—	65,9	7,3	17,1	—	24

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*This is the boiling point at 1 mm.

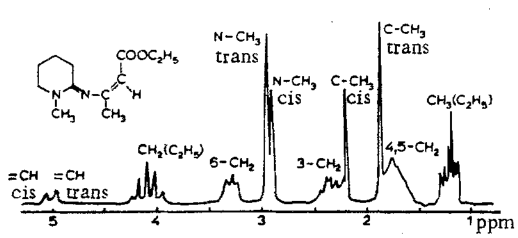
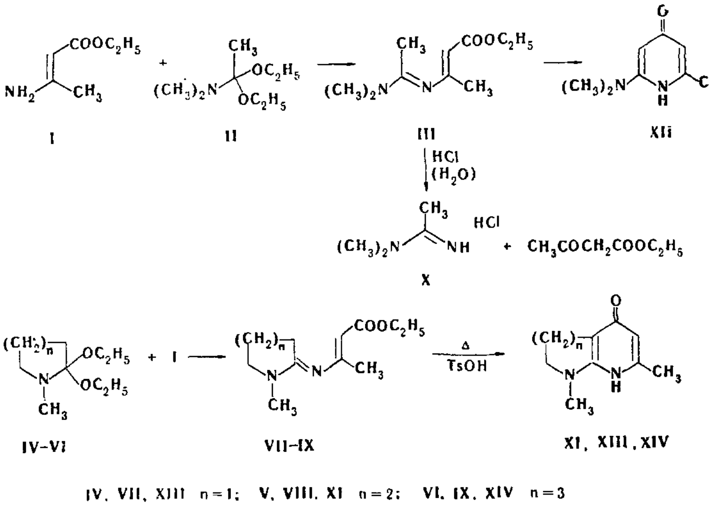


Fig. 1. PMR spectrum of N-methyl-N¹-(α-methyl-β-carbethoxyvinyl)iminopiperidine (VIII) in CD_3OD.

of the C-CH_3 group was assigned to the cis isomer, in which this sort of shift of the signal is due to the effect of the magnetic anisotropy of the carbethoxy group. The ratios of the cis and trans isomers (at 20° in CD_3OD) for enamidines III and VII-IX are, respectively, 10 : 8, 10 : 9, 7 : 10, and 9 : 10; these ratios change only slightly when the mixtures are heated for a few hours.

In an attempt to obtain the hydrochloride of enamidine III we isolated N,N-dimethylacetamidine hydrochloride (X), the structure of which was confirmed by its PMR spectrum [singlet of a 2-CH_3 group at 2.34 and two singlets of an $N(CH_3)_2$ group at 3.16 and 3.24 ppm]. Thus, as in the case of enamines, the C–N bond is cleaved during the hydrolysis of the enamidines.

The protons of the 3-CH_3 of 3-CH_2 groups in III and VII-IX differ considerably with respect to their labilities, depending on the ring size. According to the PMR spectroscopic data (Table 2), the observed regularities are in agreement with the data for 2-arylimino derivatives of lactams [3], i.e., the rate of deuteration as a function of the ring size decreases in the order 6 > 5 > 7, and noncyclic III is found between the six- and five-membered enamidines.



The results of thermal cyclization of these compounds are in good agreement with the deuterium-exchange rates. Intramolecular cyclization proceeds more rapidly under the selected conditions in the case of VIII to give 1,7-dimethyl-5-oxo-1,2,3,4,5,8-hexahydro-1,8-naphthyridine (XI). When the reflux time was prolonged, we were able to subject enamidines III and VII to cyclization and synthesize, respectively, 2-dimethylamino-6-methyl-4-pyridone (XII) and 1,6-dimethyl-4-oxo-2,3,4,7-tetrahydropyrrolo[2,3-b]pyridine (XIII). However, pronounced resinification was observed during attempts to cyclize IX, and we were unable to isolate final product XIV. Thus the deuterium-exchange data can be used as a preliminary estimate of the abilities of enamidines of the III and VII-IX type to undergo cyclization to 4-pyridone derivatives.

The structures of the 4-pyridine derivatives X-XII were confirmed by their PMR spectra (see the experimental section).

EXPERIMENTAL

The PMR spectra were obtained with a JNM 4H-100 spectrometer with tetramethylsilane as the internal standard.

N,N-Dimethyl-N^1-(α-methyl-β-carbethoxyvinyl)acetamidine (III). A mixture of 5 g (0.031 mole) of acetal II and 3.33 g (0.025 mole) of ester I was refluxed for 3 h, after which the liberated alcohol was evaporated, and the residue was distilled. Amidine hydrochloride X was isolated in an attempt to obtain the hydrochloride of III.

N-Methyl-N^1-(α-methyl-β-carbethoxyvinyl)iminohexahydroazepine (IX). A mixture of 8.22 g (0.041 mole) of acetal VI and 5 g (0.039 mole) of ester I was refluxed for 3 h, after which the alcohol was evaporated, and the residue was distilled.

N-Methyl-N^1-(α-methyl-β-carbethoxyvinyl)iminopiperidine (VIII). A mixture of 10.53 g (56.5 mmole) of acetal V and 7.29 g (56.5 mmole) of ester I was refluxed for 3 h, after which the alcohol was evaporated, and the residue was fractionated.

N-Methyl-N^1-(α-methyl-β-carbethoxyvinyl)iminopyrrolidine (VII). A mixture of 6.1 g (61.6 mmole) of acetal IV and 7.95 g (61.7 mmole) of ester I was refluxed for 3 h, after which the alcohol was evaporated, and the residue was fractionated.

2-Dimethylamino-6-methyl-4-pyridone (XII) Hydrochloride. A 10.3-g sample of III was heated in the presence of catalytic amounts of p-toluenesulfonic acid at 220° for 1.5 h with removal of the alcohol by distillation. The mixture was then dissolved in acetone, an alcohol solution of HCl was added, and the mixture was filtered. PMR spectrum (δ, ppm): 2.50 (6-CH_3), 3.22 [$N(CH_3)_2$], 6.14 (3-CH), and 6.30 (5-CH) (CD_3OD).

1,7-Dimethyl-5-oxo-1,2,3,4,5,8-hexahydro-1,8-naphthyridine (XI). A 27.58-g (0.123 mole) sample of VIII was heated in the presence of p-toluenesulfonic acid at 220° for 30 min with removal of the alcohol by distillation. The mixture was then triturated with hexane and filtered. PMR spectrum (δ, ppm): 2.43 (7-CH_3), 3.23 (NCH_3), 6.31 (6-CH), 2.75 (4-CH_2), 3.57 (2-CH_2), and 2.04 (3-CH_2) (CF_3COOH).

1,6-Dimethyl-4-oxo-2,3,4,7-tetrahydropyrrolo[2,3-b]pyridine (XIII). A 4.6-g sample of VII was heated in the presence of catalytic amounts of p-toluenesulfonic acid at 200° for 1 h with removal of the alcohol by distillation. The mixture was then triturated with anhydrous ether and filtered. PMR spectrum (δ, ppm): 2.24 (6-CH_3), 2.91 (NCH_3), 5.81 (5-CH), 2.82 (3-CH_2), and 3.52 (2-CH_2) (CD_3OD).

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STEREOCHEMISTRY OF 2,7-DISUBSTITUTED AND 1,2,7-TRISUBSTITUTED 4-ALKYLDECAHYDRO-4-QUINOLOLS

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The configurations of the 2 and 4 centers in 1,2,7-trimethyl-, 2,7-dimethyl-, and 1,2-dimethyl-7-tert-butyl-4-alkyldecahydro-4-quinolols were assigned on the basis of a comparison of the $^{I}[M-CH_3]^+/^{I}[M]^+$ and $^{I}[M]^+$ peak intensity ratios (the $[M-CH_3]^+$ and $[M-C_2H_5]^+$ ions are due to elimination of 2-CH_3 and 4-C_2H_5 groups, respectively) in the mass spectra of the stereoisomers.

A mass spectrometric method was previously used [1,2] for the determination of the configurations of the 2 and 4 centers in molecules of 1,2-disubstituted 4-alkyldecahydro-4-quinolols with trans fusion of the rings. In the present paper we present mass spectrometric data that make it possible to assign the configurations of the same centers in more complex 1,2,7-trisubstituted Ia-c, IIa-c, Va,c, and VIa,c and 2,7-disubstituted 4-alkyldecahydro-4-quinolols IIIa and IVa. The synthesis of the compounds under consideration will be

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