ACETALS OF LACTAMS AND ACID AMIDES

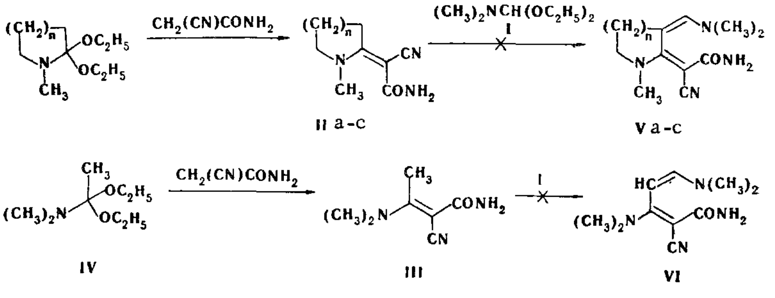
XVIII.* REACTIONS OF N,N-DIMETHYLFORMAMIDE DIETHYLACETAL WITH TERTIARY ENAMINOAMIDES AND SYNTHESIS OF 2-PYRIDONE DERIVATIVES

V. G. Granik, N. B. Marchenko,
T. F. Vlasova, and R. G. Glushkov

UDC 547.72'824.07:543.422.25.4

The reaction of dimethylformamide diethylacetal with α-cyano-β-dimethylaminoacrylamide proceeds at the NH_2 amide group to give the corresponding acylformamidine, from which 3-cyano-4-dimethylamino-2-pyridone was obtained by thermal cyclization. Pyrrolo-, pyrido-, and azepino-[3,2-c]pyridine derivatives were similarly synthesized from 1-methyl-2-(2'-cyano-2'-carbamido)-methylenepyrrolidine and the homologous six- and seven-membered enaminoamides.

It has previously been shown [1] that amide acetals are capable of undergoing condensation at the α-methyl group of tertiary enamines having strong electron-acceptor groupings in the β position. Proceeding from this, we accomplished the reaction of dimethylformamide diethylacetal (I) with 1-methyl-2-(2'-cyano-2'-carbamido)-methylenepyrrolidone (IIa), -piperidine (IIb), and -hexahydroazepine (IIc) (synthesized from the lactam acetals [2]), and also with α-cyano-β-dimethylaminocrotonamide (III) (obtained from N,N-dimethylacetamide diethylacetal (IV) and α-cyanoacetamide) in order to synthesize 2-pyridone derivatives through the corresponding dimethylaminomethylene derivatives Va-c and VI.



II a n=1; b n=2; c n=3

It was found that enaminoamides IIa-c and III react relatively readily with acetal I, and the results of elementary analysis of the products correspond to the formulas Va-c and VI. However, the IR and PMR spectral data contradict the dienediamine structures Va-c and VI. Thus only one signal of a methylidyne proton (8.37 ppm) and a singlet of a $C-CH_3$ group at 2.57 ppm (Table 1) are present in the PMR spectrum of the compound obtained from enamine III and acetal I, and the absorption bands of an NH_2 group, which corresponds to structure VI, are absent in the IR spectrum. At the same time, the spectral data provide unambiguous evidence that the amide NH_2 group of the enaminoamide rather than the α-methyl group or the methylene link participates in the reaction of acetal I with enaminoamides II and III, and acylamidines VIIa-c and VIII rather than dienediamines Va-c and VI are formed.

---

*See [1] for communication XVII.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1509-1512, November, 1976. Original article submitted December 15, 1975.

TABLE 1. Properties of Acylamidines VIIa-c, VIII

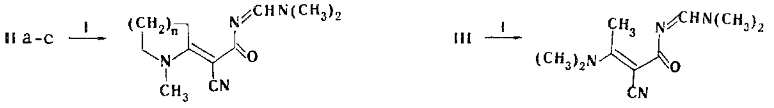
Compound	R	R′	mp, °C (solvent)	Empirical formula	Found, %			Calc., %			PMR spectra in $CHCl_3$, ppm								Yield, %
					C	H	N	C	H	N	3-CH_2	4-CH_2	5-CH_2	6-CH_2	7-CH_2	$N(CH_3)_2$ of the amidine fragment	NCH_3 of the enamine fragment	=C—H	
VIIa	$(CH_2)_2$		151—152,5 (benzene)	$C_{11}H_{16}N_4O$	60,1	7,1	25,4	60,0	7,3	25,5	3,22	1,97	3,62	—	—	3,10	3,43	8,38	100
VIIb	$(CH_2)_3$		108—110 (iso-PrOH)	$C_{12}H_{18}N_4O$	61,5	8,0	23,9	61,5	7,7	23,9	3,10	1,77		3,43	—	3,10	3,22	8,35	79
VIIc	$(CH_2)_4$		132—135 (acetone)	$C_{13}H_{20}N_4O$	62,6	8,1	22,8	62,9	8,1	22,6	3,08	1,75			3,48	3,10	3,20	8,38	86
VIII	H	CH_3	138—140 (alcohol)	$C_{10}H_{16}N_4O$	57,7	7,7	27,2	57,7	7,7	26,9	2,57 (C · CH_3)	—	—	—	—	3,15	3,20	8,37	96

TABLE 2. Properties of 2-Pyridones IXa-c, X

Compound	R	R′	Cyclization temp., °C	mp, °C (solvent)	Empirical formula	Found, %			Calc., %			PMR spectra in CF_3COOH, ppm						Yield, %
						C	H	N	C	H	N	2 CH_2	3-CH_2	4-CH_2	5-CH_2	N-CH_3	=CH	
IXa	$(CH_2)_2$		235—240	315 (DMF)	$C_9H_9N_3O$	61,8	5,3	24,4	61,7	5,1	24.0	4,23	3,20	—	—	3,10	7,32	55
IXb	$(CH_2)_3$		130—150	294—298 (DMF)	$C_{16}H_{11}N_3O$	63,4	5,8	22,3	63,5	5,8	22,2	3,72	2,15	2,78	—	3,72	7,40	100
IXc	$(CH_2)_4$		175—195	230—232 (DMF)	$C_{11}H_{13}N_3O$	64,6	6,4	21,0	65,0	6,4	20,7	3,85	2,12		2,93	3,60	7,48	100
X	H	CH_3	200	262—264 (DMF)	$C_8H_9N_3O$	59,0	5,7	26,2	58,9	5,5	25,8	—	—	—	—	3,53 (NMe_2)	6,65 (6-H, J 8,0 Hz)* 7,73 (7-H, J 8,0 Hz)	88

---

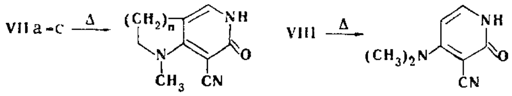
* For the 5- and 6-CH doublet of the pyridine ring.



VII a-c

VII a n=1; b n=2; c n=3

Considering the fact that amidines are capable of undergoing condensation with compounds having an active methylene group [3] (the N-acyl group favors this condensation to an even greater extent), we attempted to realize cyclization of the compounds obtained in this research to 2-pyridone derivatives. It was found that heating acylamidines VIIa-c and VIII leads to 1-methyl-6-oxo-7-cyano-2,3-dihydropyrrolo- (IXa), 1-methyl-7-oxo-8-cyano-1,2,3,4-tetrahydropyrido- (IXb), and 1-methyl-8-oxo-9-cyano-2,3,4,5-tetrahydro-1H-azepino[3,-2-c]pyridines (IXc), and 2-oxo-3-cyano-4-dimethylaminopyridine (X):



IX a-c

X

IX a n=1; b n=2; c n=3

The structures of the 2-pyridone derivatives were confirmed by the PMR spectral data (Table 2).

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral-oil pastes of the compound were obtained with a Perkin–Elmer 457 recording spectrometer.

α-Cyano-β-dimethylaminocrotonamide (III). A 16.1-g (0.1 mole) sample of acetal IV and 20 ml of absolute alcohol were added to 8.4 g (0.1 mole) of cyanoacetamide, and the mixture was refluxed for 30 min. It was then cooled, and the resulting precipitate was removed by filtration and dried to give 11 g (72%) of enaminoamide III with mp 194-196° (from methanol). Found: C 55.0; H 7.4; N 27.2%. $C_7H_{11}N_3O$. Calculated: C 54.9; H 7.2; N 27.5%.

1-Methyl-2-/2'-cyano-2'-(N-dimethylaminomethylene)carbamido/methylenepiperidine (VIIb). A mixture of 3.3 g (18 mmole) of enamine IIb, 4 g (28 mmole) of I, and 20 ml of anhydrous toluene was refluxed for 2 h, after which it was cooled, and unchanged enamine IIb was removed by filtration. The filtrate was evaporated, and the residue was triturated with ether. The resulting solid was removed by filtration and dried to give 3.4 g (79%) of acylamidine VIIb. Acylamidines VIIa,c and VIII were similarly obtained. The yields, physical characteristics, and results of elementary analysis of these compounds are presented in Table 1.

1-Methyl-7-oxo-8-cyano-1,2,3,4-tetrahydropyrido[3,2-c]pyridine (IXb). A 2.7-g (12 mmole) sample of acylamidine VIIb was heated at 130-150° for 20 min, during which dimethylamine was evolved. The mixture was worked up to give 2.2 g (quantitative yield) of pyridopyridine IXb. Pyridine derivatives IXa,c and X were similarly obtained. The yields, physical characteristics, and results of elementary analysis of these compounds are presented in Table 2.

LITERATURE CITED

1. 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).
2. I. P. Kostyuchenko, V. G. Granik, A. M. Zhidkova, R. G. Glushkov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 9, 1212 (1972).
3. R. Hull, B. I. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, J. Chem. Soc., 357 (1946).