ACETALS OF LACTAMS AND ACID AMIDES

XVII.* REACTION OF AMIDE AND LACTAM ACETALS WITH PRIMARY ENAMINES. SYNTHESIS OF ENAMIDINES OF THE PYRROLIDINE, PIPERIDINE, AND HEXAHYDROAZEPINE SERIES

V. G. Granik, N. B. Marchenko, E. O. Sochneva, T. F. Vlasova, A. B. Grigor'ev, M. K. Polievktov, and R. G. Glushkov

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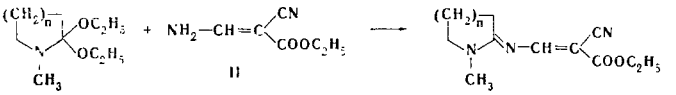
Lactam acetals and acid amides react at their NH_2 and CH_3 groups with α-cyano-β-aminocrotonic ester to give α-cyano-β-(1-methyl-2-pyrrolidinylmethylidene)-β-[N-1-methyl-2-pyrrolidinyl)imino]acrylate and its piperidine and hexahydroazepine analogs. The first step in this reaction is reaction at the amino group to give enamidines.

The synthesis of enamidines – compounds in which the amidine fragment is conjugated with the C=C bond – has previously been accomplished by reaction of acetals of acid amides and lactams with β-aminocrotonic ester [2]. In a continuation of this research we investigated the reaction of diethylacetals of N-methylbutyrolactam (Ia), N-methylvalerolactam (Ib), and N-methylcaprolactam (Ic) with considerably less basic enamines – aminomethylenecyanoacetic (II) and α-cyano-β-aminocrotonic (III) esters. The reaction of Ia-c with ester II proceeds smoothly and under relatively mild conditions to give the corresponding enamidines – 1-methyl-2-(β-cyano-β-carbethoxyvinyl)iminopyrrolidine (IVa), -piperidine (IVb), and -hexahydroazepine (IVc):

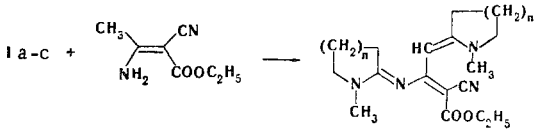


Ia-c II IVa-c

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

The PMR spectra of these compounds contain signals at 1.24-1.30 and 4.16-4.23 ppm (OC_2H_5 groups) and at 3.17-3.30 ($N-CH_3$), 3.53-3.68 (ring $N-CH_2$), 2.68-2.85 ($3-CH_2$), 1.69-2.18 (ring CH_2), and 8.32-8.52 (=C−H) ppm.

The reaction of acetals Ia-c with ester III yielded 2:1 products. An examination of the PMR spectra of these substances (Table 1) made it possible to conclude that Va-c are formed as a result of condensation of the acetals at both the NH_2 and CH_3 groups of enamine III:



Ia-c III Va-c

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

*See [1] for communication XVI.

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TABLE 1. PMR Spectra (ppm) of Va-c in d_6-DMSO

Compound	1-N(CH$_3$)$_2$ 1'-N(CH$_3$)$_2$	3- and 3'-CH$_2$	4- and 4'-CH$_2$	5- and 5'-CH$_2$	6- and 6'-CH$_2$	7- and 7'-CH$_2$	=C—H	CH$_3$(OC$_2$H$_5$)	CH$_2$(OC$_2$H$_5$)
Va	2,89 and 2,94	2,27 and 2,85	1,98	3,40	—	—	6,67	1,20	4,15
Vb	2,94 and 3,01	2,25 and 2,72	1,74		3,25	—	6,68	1,23	4,00
Vc	2,94 and 2,99	2,40 and 3,00	1,40			3,23	7,01	1,14	4,17

TABLE 2. Synthesized Compounds

Compound	Yield, %	mp, °C (solvent)	Empirical formula	Found, %			Calculated, %			$-E_{1/2}$, V*	$\alpha = \frac{i_{lim}}{c}$
				C	H	N	C	H	N		
IVa	38	123—124,5 (C_2H_5OH)	$C_{11}H_{15}N_3O_2$	59,6	6,9	19,3	59,7	6,8	19,0	1,43	1,04
IVb	100	123—124 (ethyl acetate)	$C_{12}H_{17}N_3O_2$	61,0	7,2	18,2	61,3	7,2	17,9	1,42	1,15
IVc	98	82—83 (ethyl acetate)	$C_{13}H_{19}N_3O_2$	62,7	7,7	17,3	62,7	7,6	16,9	1,41	1,17
Va	30	184—186 (acetone)	$C_{17}H_{24}N_4O_2$	64,3	7,7	17,8	64,6	7,5	17,9	1,70 2,23	1,05 0,89
Vb	38	145—148 (ethyl acetate)	$C_{19}H_{28}N_4O_2$	66,5	7,8	16,1	66,3	8,1	16,3	1,79 2,19	1,01 0,92
Vc	81	135—138 (ethyl acetate)	$C_{21}H_{32}N_4O_2$	67,7	8,2	15,0	67,7	8,6	15,1	1,66 2,29	0,92 0,79
VIII	92	123—125 (ethyl acetate)	$C_9H_{13}N_3O_2$	55,5	6,9	21,4	55,4	6,7	21,5	1,42 2,37	
IX	55	bp 228—229° (2 mm)	$C_{12}H_{19}N_3O_2$	60,9	8,0	17,7	60,7	8,0	17,7	1,67 2,35	

*Relative to an Ag electrode.

It is not clear which process – condensation at the NH_2 group or at the CH_3 group – predominates. To follow the trend of the process we used polarography, since the starting esters II and III, enamidines IVa-c, and Va-c differ substantially (Table 2). It was found that waves similar to those that are observed for enamidines IVa-c, which in this case are model compounds for the identification of the products of reaction only at the NH_2 group of ester III, do not develop on the polarograms even when acetal Ic is added slowly to excess ester III. Waves corresponding to the formation of Vc appear on the polarograms immediately after the start of the addition of the acetal. To estimate the relative reaction rates at the NH_2 and CH_3 groups one should select the corresponding model compound and compare the rates of formation of the enamidines (reaction at the NH_2 group) and dienamines (reaction at the CH_3 group) under identical conditions. We used α-cyano-β-dimethylaminocrotonic ester VI [3] and enamine II as compounds of this type. It was found that the reaction of II and VI with dimethylformamide diethylacetal (VII) to give N,N-dimethyl-N^1-(β-cyano-β-carbethoxy)vinylformamidine (VIII) and 1-cyano-1-carbethoxy-2,4-bis(dimethylamino)butadiene (IX), respectively, can be carried out under identical conditions (in toluene at 110°). It should be noted that two signals of $N(CH_3)_2$ groups, one of which is a narrow singlet, the other of which is markedly broadened, were observed in the PMR spectrum of IX at 3 ppm; the broad signal is converted to a narrow singlet when the temperature is raised (Fig. 1). This fact indicates that free rotation of one of the dimethylamino groups is hindered. An examination of molecular models shows that the broad signal is related to the $N(CH_3)_2$ group in the β position with respect to the CN and $COOC_2H_5$ substituents. One's attention is drawn to the large difference in the chem-

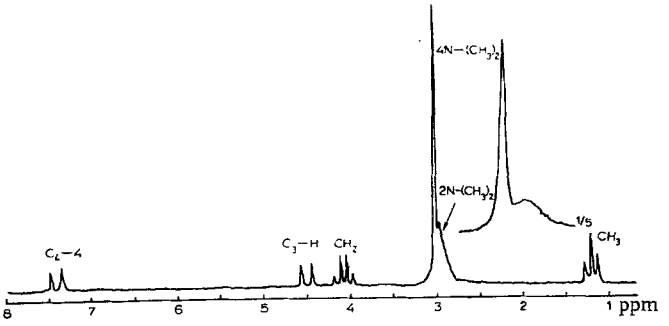
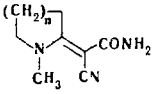


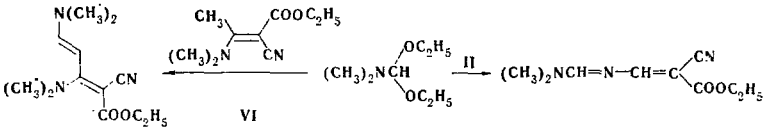
Fig. 1. PMR spectrum of 1-cyano-1-carbethoxy-2,4-bis(dimethylamino)butadiene.

TABLE 3. Half-Wave Potentials of Enamines Xa-c of the General Formula



Compound	n	$-E_{1/2}$, V	$\varkappa = \frac{i_{lim}}{c}$
Xa	1	1,90	1,58
Xb	2	1,80	1,14
Xc	3	1,82	1,11

ical shifts of the protons in the 3 and 4 positions of the molecule ($\Delta\delta$ 2.9 ppm). The pronounced weak-field shift of the C_4=H signal is due to conjugation with the CN and $COOC_2H_5$ groups through the diene system, and the position of the C_3–H signal corresponds to the electron-donor effect of the $N(CH_3)_2$ group on the "enamine" β position. The $J_{3,4}$ spin–spin coupling constant of 12.4 Hz is in agreement with the trans orientation of these protons; this also follows from an examination of the molecular models.



IX VII VIII

The reaction rates of acetal VII were compared with the rates of esters II and VI by means of polarography. It was found that the reaction of VII and II proceeds extremely rapidly (in toluene at 110°), and only the waves of enamidine VIII are observed 1 min after the start of the reaction. On the other hand, the reaction of acetal VII with enamine VI under the same conditions proceeds quite slowly, and a decrease (with time) in the wave of starting VI ($E_{1/2}$ = 1.87 V) and an increase in the wave with $E_{1/2}$ = 1.67 V, related to reaction product IX, are recorded on the polarogram; the reaction is only 15% complete after 3.5 h. Nevertheless, the reaction of acetal VII with enamine VI provides evidence for the possibility of condensation of amide acetals at the methyl (or methylene) group in the α position of enamines. On the other hand, the acceleration of this process as a result of conversion of the amino group to an amidine group indicates substantially less electron-donor activity of the latter. The same conclusion can also be drawn on the basis of a comparison of the half-wave potentials of IVa-c and enamines Xa-c (Table 3) if it is assumed that electron transfer in both cases to the carbon atom in the β position with respect to the electron-acceptor groups (CN and $COOC_2H_5$) is realized, as in the reduction of activated enamines on a dropping mercury electrode [4].

EXPERIMENTAL

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

The polarograms were recorded in a polarographic cell thermostatted at 25 ± 0.1°. A silver coil submerged in the solution served as the anode. The characteristics of the dropping mercury electrode with forced detachment of the drops were as follows: t = 0.3 sec and m = 0.73 mg/sec. The polarograms were recorded with a PO-4 polarograph (Radiometer, Denmark). A 0.1 M solution of Bu_4NClO_4 in DMF served as the base electrolyte. The DMF was dried over fused KOH and vacuum fractionated.

1-Methyl-2-(β-cyano-β-carbethoxyvinyl)iminohexahydroazepine (IVc). A mixture of 5 g (25 mmole) of acetal Ic and 2.66 g (22 mmole) of ester II in 20 ml of anhydrous toluene was refluxed for 2 h, after which the toluene was removed by distillation. The residue began to crystallize on cooling and was worked up to give enamidine IVc in 98% yield. Enamidines IVa, b, and IX, bis products Va-c, and X were similarly synthesized. The yields, physical characteristics, and results of elementary analysis of these compounds are presented in Table 2.

Reaction of Acetal VII with Esters II and VI. A weighed 0.1-g sample of ester II or VI was dissolved by refluxing in 40 ml of absolute toluene, and 0.2 ml of acetal VIII was added to the refluxing solution. Samples (0.2 ml) of the reaction mixture were placed in a polarographic cell with 2 ml of the base electrolyte solution, and the polarograms were recorded after removal of the dissolved oxygen with a stream of nitrogen.

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4. A. B. Grigor'ev, Master's Dissertation, Moscow (1974).