ACETALS OF LACTAMS AND ACID AMIDES.

49.* REACTION OF N-METHYL-2-PYRROLIDONE AND N-METHYL-2-PIPERIDONE ACETALS WITH ENAMINO DIKETONES

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It was established that acetals of lactams react with enamino diketones to give cyclic dienediamines. The dienediamines obtained in the reaction of N-methyl-2-pyrrolidone diethylacetal with 2-aminomethylenedimedone and 2-N,N-dimethyl-aminomethylenedimedone are converted to $3-(\beta$ -methylamino)ethyl-6,6-dimethyl-5,6, 7,8-tetrahydro-5-coumarinone hydrochloride when they are heated in dilute hydrochloric acid.

In a previous study [1] we established that N,N-dimethylacetamide diethylacetal (I) is capable of reacting with enamino diketones to give derivatives of dienediamines; the scheme proposed for the process was based on the participation in this reaction of keteneacetal Ia, which exists in equilibrium with acetal I [2].



Taking into account the fact that this sort of equilibrium is also characteristic for lactam acetals [2], we studied the reaction of N-methylbutyro- and N-valerolactam diethylacetals (II, III) with aminomethylene- and N,N-dimethylaminomethylenedimedones (IV, V).

The reaction of enamine IV with lactam acetals proceeds extremely readily (warming up of the mixture is observed in the absence of a solvent), and compounds, to which, by analogy with those described in [1], dienediamine structures VI and VII were assigned, are formed in high yields.



Molecular-ion peak M⁺ at 329 (100)⁺ is observed in the mass spectrum of pyrroline derivative VI. Cleavage of the exocyclic C-N and C-C bonds gives ion peaks at 231 (34), 177 (48), and 98 (16). The subsequent fragmentation is determined by elimination of fragments of the pyrroline rings: $[231 - CH_3]^+ 216 (45)$, $[231 - NCH_3]^+ 202 (50)$, and $[231 - CH_2CH]^+$ 204 (23). On the whole, the mass-spectrometric fragmentation of piperidine derivative VII with M⁺ at 357 is similar to the fragmentation of VI.

A characteristic peculiarity of the PMR spectrum of diketone VI (Table 1) is the presence of a 2'-CH signal at 7.26 ppm, which has a constant of long-range spin-spin coupling

*See [1] for Communication 48.

'Here and subsequently, the m/z values are presented for the ion peaks (the intensities relative to the maximum ion peak in percent are given in parentheses).

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TABLE 1. Data from the PMR Spectra of the Synthesized Compounds (in $CDCl_3$)

Come				Chemical s	shift,	δ, ppr	n				Iz
pound	5-(CH ₃)2	4,6-CH₂	2'-H	NCH3	α-CH₂	β-CH₂	ү-СН₂	9'-CH2	α′-CH₂	β′- CH₂	12'B. I
VI	1,05	2,30	7,26	5-N-CH ₃ and 8-N-CH ₃ ;	3,58	3,00	-	2,66	3,61	-	2,0
VII*	1,04	2,29	7,37	5.04 and $5.085-NCH_3 and8-NCH_3;3.09$ and 3.12	3,38	1,69	2,49	2,49	3,47	1,5-1,85 (β' -CH ₂ and ν' -CH ₂)	
IX	1,06	2,33	7,75	3,21 (N-CH ₃);	3,55	2,70		-		-	1,7
X**	0,93	2,05	6,98	$\begin{array}{c} 3,61 & (N-CH_3)_2 \\ 3,61 & (N-CH_3); \\ 2,94 & (N-CH_3); \\ 2,61 & [N(CH_3)_2] \end{array}$	3,49	2,80	-	-	3,49	2,80	1,7

*The chemical shifts are given for a recording temperature of 50°C; coupling of the protons of the 2'-H and γ -CH₂ groups show up in the form of a small degree of broadening of the signal of the protons of the 2'-H group. **In d₆-DMSO at a recording temperature of 75°C. At -20°C the signals of the two pyrroline rings not only differ sharply, but one also observes even splitting of those signals due to retarded rotation relative to the 4',6' bond [this is particularly appreciable for the α, α' -H signals (3.20, 3.35, 3.53, and 3.88 ppm), is less appreciable for the β,β' -H signals, and is weakly expressed for the signals of the dimedone CH₂ groups.

with the protons of the β -CH₂ group (⁴J = 2 Hz). A 2'-H signal at 7.35 ppm is observed in the PMR spectrum of six-membered analog VII; however, the constant of spin-spin coupling of it with the protons of the methylene group of the piperidine ring is not manifested appreciably, evidently because of the greater conformational lability of the six-membered ring. A singlet at 137.2 ppm, which is converted to a doublet under conditions of recording the spectrum with partial suppression of the protons, is characteristic for the ¹³C NMR spectrum (Table 2) of VI. On the basis of this, this signal was assigned to the C_(2') atom.

Another confirmation of the structures of VI and VII was also the fact that $3-\beta$ -methylaminoethyl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocoumarin hydrochloride (VIII), the structure of which was confirmed by spectral data (see Experimental), is formed in high yield under the conditions of hydrolysis of pyrroline derivative VI with dilute hydrochloric acid.

It was unexpected that the structure of the product of the reaction of acetal II with tertiary enamino diketone V depends on the ratio of reagents II and V. Pyrroline dienediamine IX is formed in the case of an equimolar ratio of II and V, just as was observed in the reaction of enamino diketone V with N-dimethylacetamide acetal II [1]. Just as in the case of VI, a split singlet of an olefin proton at 7.75 ppm ($^{4}J = 1.7 \text{ Hz}$) is present in the PMR spectrum of IX (Table 1). In the 13 C NMR spectrum (Table 2) of IX the carbon signal at 141.4 ppm corresponds to C(2') (under conditions of recording with partial suppression of the protons the singlet is converted to a doublet).

Compound X, which, judging from the spectral data, contains two pyrrolidine rings, is formed when the reaction of II and V is carried out in the presence of excess acetal II. Molecular-ion peak M^+ at 357 and peaks of ions corresponding to splitting out of methyl, methylamino, and dimethylamino groups, as well as to fragmentation of the pyrrole rings and cleavage of the molecule at the exocyclic C-C bonds at 342, 328, 313, 314, 231, 218, 216, and 204, are observed in the mass spectrum of this compound.

Just as in the case of VI and IX, the PMR spectrum of X recorded at 75°C* in d_6 -DMSO contains a singlet at 6.98 ppm that is split into a triplet (⁴J ~ 1.7 Hz). In addition to

^{*}In the PMR spectrum of X obtained at room temperature all of the signals are broadened markedly; this is evidently associated with conformational transformations.

TABLE 2	Data	1 from	the ¹³ C	NMR	Spectra	ı of t	he Synt	thesi	zed Co	punoduc	s*						
	-						Chet	nical sl	nift,	6. ppm							
punod	c ₍₁₎ , c ₍₃₎	C ₍₂₎	C(4) • C(6)	C ₍₅₎	5-(CH ₃) ₂	C _(2')	C(3')	C(4')	C _(6')	c(r')	5'-NCH3	8'-NCH3	C (9 ^r)	C _(a)	C _(B)	C (a')	C (B')
ΛI	193,2	110,3	51,6	30,0	28,4	137,2	114,6	172,2]	167,1	31,6 or	32,7 or	30,6 01	51,8 or 52,0	27,3 or 30,6	52,0 of 51,8	1,61
XIX	194,7 190,0	112,0 109,9	53,7 51,9	31,9	29,6	141,4 133,3	115,8 124,2	171,6 168,5	77,8	169,7	32,7 39,0 36,7 or 37,1	31,6 37,1 0r 36,7	27,3	56,8 53,4 or 54,7	30,801,31,1	54,7 or 53,4	31,1 or 30,8

*The spectra of VI and IX were obtained in $CDCl_3$, while that of X was recorded in d₆-DMSO. **Signals of the carbon nuclei of the N(CH₃)₂ groups: 44.2 (IX) and 40.8 ppm (X).

211,1 (14 024), 291,9 (21 440), 389,1 (17 770) 216,2 (15 224), 291,2 (20 260), 390,3 (16 304) 214 (6660), 232 (5800), 289 (16 160), 380 (17 000) 204 (8560), 288 (16 960), 391 (22 680) 219 (14 100), 289,5 (19 580), 399 (31 780)
ZEXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

TABLE 4. Characteristics of the Synthesized Compounds

Yield,	0 /0	8 2 9 7 8 8 2 9 7 8 6 6 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7
	,Ż	1,4,5,1
11c., %	Н	8,2 8,9 8,7 8,7
C	υ	69,3 70,4 58,8 69,6 70,6
Empirical	formula	C ₁₆ H ₃₇ N ₃ O2 C ₂₁ H ₃₁ N ₃ O2 C ₂₁ H ₁₉ NO ₃ ·HCI C ₁₄ H ₃₁ N ₂ O2 C ₂₁ H ₃₁ N ₃ O2 C ₂₁ H ₃₁ N ₃ O2
	z	128 9,8 11,5 9,8
6 °punc	Н	8,2 7,4 9,1 8,6
F.	c	68,9 70,7 58,8 69,2 70,4
T _{mn} , C	L.	190—191 163—165 211—213 104—106 222—224
Com-		

*The compounds were crystallized: VI, VII, and IX from ethyl acetate, VIII from acetonitrile-n-butanol (2:1), and X from toluene. signals of dimedone and pyrroline fragments (similar to the signals in the spectrum of IX) (Table 1), signals of a second pyrroline ring $(\alpha'-CH_2, \beta'-CH_2, and N-CH_3$ groups) and a singlet at 2.61 ppm (6H), which is related to a dimethylamino group, are observed.



More nearly complete information regarding the structure of X was obtained from the ¹³C NMR spectrum. In addition to the signals that are also characteristic for IX (Table 2), signals at 54.7, 31.1, and 37.1 ppm, which can be ascribed to the α' -CH₂, β' -CH₂, and N-CH₃ groups of a second pyrroline ring (on the basis of the multiplicity of the signals under conditions of recording the spectrum with partial suppression of the protons), are present in the spectrum of X at strong field; a strong-field signal (as in the spectrum of VI at 19.1 ppm; see Table 2) is not observed. Judging from its position, intensity, and multiplicity, the signal at 40.8 ppm recorded at strong field can be assigned to the carbon atoms of the N(CH₃)₂ group. The signals of two sp²-hybridized carbon atoms (169.7 and 77.8 ppm) observed at weak field under conditions of recording the spectrum with partial suppression of the protons at weak field under conditions of recording the spectrum with partial suppression of the protons do not undergo a change in their multiplicities, i.e., they are quaternary carbon atoms.

All of these data made it possible to assign triene structure X to the compound obtained. The probable scheme of the synthesis of IX and X evidently includes the formation of intermediate α -alkoxy enamine XI, which subsequently undergoes a reaction with the liberated dimethylamine or excess acetal II.

The structure of X is also in good agreement with the presence in the ¹³C NMR spectrum of a signal at 169.7 ppm, which is related to the $C_{(7')}$ atom bonded to nitrogen atoms, as well as the signal at 77.8 ppm, which is related to the $C_{(6')}$ atom, on which the electron density is substantially increased due to the electron-donor effect of two substituted amino groups.

The compounds synthesized in this research contain a substituted dienediamine fragment similar to that observed in our previously obtained compounds XI and XII [1]. However, the presence of extremely bulky rings may have a substantial effect on the degree of conjugation of the individual fragments in these compounds. In fact, the intensity of the long-wave maximum (λ_{max} 380-400 nm) in the UV spectrum of XII is much higher than in the spectrum of piper-ideine derivative VII. Although it is expressed to a lesser extent, the same tendency is retained for XI and IX (Table 3).

The disruption of the conjugation in VI, VII, and IX is due to steric factors, including repulsion of the bulky groupings; this is clearly seen when one examines the molecular models.

In conclusion, let us note that dienediamine IX, like dieneamidino enamine VI, is converted to coumarin derivative VIII upon heating in dilute hydrochloric acid.



EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded with Varian XL-100 and Varian XL-200 spectrometers with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Varian MAT-112 spectrometer (Phinnigan) with direct introduction of the samples into the ion source; the temperature of the ionization chamber was 180°C, and the ionizing-electron energy was 70 eV. The UV spectra of solutions of the compounds in alcohol were recorded with a Perkin-Elmer-575 spectrophotometer. The melting points were determined with a heating stage of the Boetius type.

The characteristics of the synthesized compounds are presented in Table 4.

2-[2-(N-Methyl-2-pyrrolidinylene)amino-1-methyl-2-pyrrolin-3-y1]methylene-5,5-

dimethylcyclohexane-1,3-dione (VI). A 42.16-g (0.25 mole) sample of acetal II was added to 16.7 g (0.1 mole) of enamine IV (warming up to 30°C was observed), after which the reaction mixture was evaporated. The residue was washed with 50 ml of petroleum ether and triturated with 25 ml of ethyl acetate, and the precipitated VI was removed by filtration.

<u>2-[2-(N-Methyl-2-piperidinylene)amino-1-methyl-2-piperidein-3-yl]methylene-5,5-dimethyl-</u> <u>cyclohexane-1,3-dione (VII)</u>. This compound was obtained by a procedure similar to that used to prepare VI; the reaction mixture warmed up to 40°C.

 $\frac{2-(\text{N-Methyl-2-dimethylamino-2-pyrrolidin-3-yl)\text{methylene-5,5-dimethylcyclohexane-1,3-}}{\text{dione (IX).} A 5.52-g (0.283 mole) sample of V was dissolved by heating (60-80°C) in 15 ml of absolute toluene, 4.9 g (0.283 mole) of acetal II was added, heating was discontinued, and the mixture was allowed to stand for 1 h. It was then evaporated, and IX was isolated.$

<u>2-[2-(N-Methyl-2-dimethylamino-2-pyrrolin-3-yl)-1-methyl-2-pyrrolin-3-yl]methylene-5,5-</u> <u>dimethylcyclohexane-1,3-dione (X)</u>. This compound was obtained by a procedure similar to that used to prepare IX, but 9.6 g (0.566 mole) of acetal II was used.

<u>3- β -Methylaminoethyl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocoumarin Hydrochloride (VIII).</u> A 1-g sample of VI (3 mmole) or IX (3.6 mmole) was dissolved in 10 ml of 30% HCl, and the solution was then refluxed for 30 min. It was then evaporated, and the residue was treated with 1 ml of water. The precipitated coumarin VIII was removed by filtration. PMR spectrum (CDCl₃): 1.16 [6H, 7-(CH₃)₂]; 2.42 (2H, 8-CH₂), 2.73 (2H, 6-CH₂); 7.86 (1H, 4-H); 3.06 (2H, α -CH₂); 3.26 (2H, β -CH₂); 2.73 (3H, δ -CH₃); 9.54 ppm (1H, γ -NH). IR spectrum: 1670 (C=O, ketone), 1732 cm⁻¹ (C=O, ester).

LITERATURE CITED

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