INVESTIGATION OF LACTAMS

XXVII.* SYNTHESIS AND PROPERTIES OF 4-DIMETHYLAMINOMETHYLENE-3-OXOVALERO- AND -CAPROLACTAMS. TETRAHYDROPYRIDO[3,4-d]-PYRIMIDINE AND PYRIMIDO[4,5-c]AZEPINE DERIVATIVES

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3-Oxo-4-N,N-dimethylaminomethylenecapro- and valerolactams were synthesized by reaction of dimethylformamide acetal with α-oxocapro- and valerolactams, and the kinetics of the hydrolysis of the former in acid and alkaline media were investigated by polarography. 2-Substituted 9-oxo-9H,5,6,7,8-tetrahydroazepino[3,4-d]pyrimidines and 8-oxo-8H,5,6,7,8-tetrahydropyrido[3,4-d]pyrimidines were synthesized on the basis of these enamino ketones.

The transition from enamines of lactams [2, 3] to α-oxovalero- and α-oxocaprolactams (I, II) [4, 5] opens up definite prospects for the preparation of the relatively inaccessible β-substituted lactams and, from them, of various condensed heterocyclic compounds [6]. We have investigated the reaction of α-oxolactams I and II with dimethylformamide diethylacetal (III).

It is known that acetal III readily reacts with compounds having an active methylene link [7], but the reaction with aliphatic ketones (for example, with acetone) proceeds with difficulty and gives the products in low yields [8]. However, there are no data in the literature regarding the possibility of condensation of acetal III with alicyclic ketones. In a study of the properties of oxolactam II it was found that this compound readily reacts with acetal III to give 2,3-dioxo-4-N,N-dimethylaminomethylenehexahydroazepine (IV). As compared with the spectrum of α-oxocaprolactam II, the absorption band in the IR spectra of enamino ketone IV at 1720 cm^{-1} (ketone C=O) vanishes, and, in addition to absorption bands at 3060 and 3180 (NH group) and 1660 cm^{-1} (lactam CO), absorption bands at 1640 and 1550 cm^{-1}, which are characteristic for the enamino ketone fragment, appear.

Signals at 1.66 (2H, q,† 6-H), 2.51 (2H, t, 5-H), 3.08 (2H, q, 7-H), 3.10 [6H, s, $N(CH_3)_2$], 7.50 (1H, s, =CH), and 7.81 ppm (1H, t, NH) are observed in the PMR spectrum of this compound in deuterodimethyl sulfoxide.

It should be noted that on passing from the spectrum of the base (in deuterodimethyl sulfoxide) to the spectrum of the protonated form (in CF_3COOH), the singlet of the protons of the $N(CH_3)_2$ group at 3.10 ppm is converted to two singlets at 3.68 and 3.84 ppm. The signal of the CH proton, without changing its form, is shifted to weak field by $\Delta\delta = 1.16$ ppm. The indicated changes in the spectrum, together with the absence of splitting of the signal of the methylidyne proton, constitute evidence in favor of the fact that the O-protonated form (B) with two nonequivalent NCH_3 groups is realized under these conditions rather than the N-protonated form (A). Cyclic enamino ketone IV could be the starting compound in reactions with various nucleophilic reagents. In this connection it seemed of interest to study the simplest nucleophilic substitution of the dimethyl-

*See [1] for communication XXVI.

†Abbreviations: q is quintet, t is triplet, and s is singlet.

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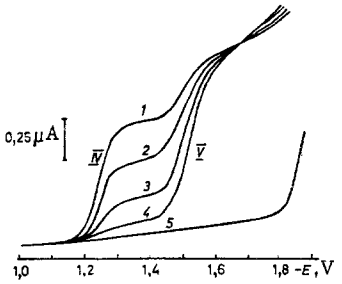


Fig. 1

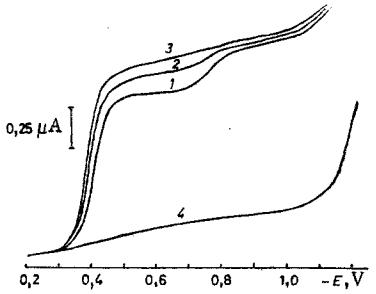
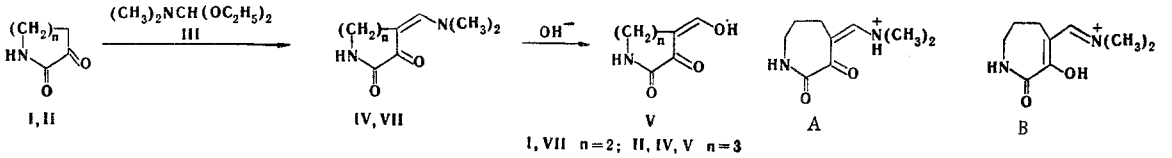


Fig. 2

Fig. 1. Dependence of the waves of reduction of enamino ketone IV and enol V in 0.093 N NaOH solution on time. Curves 1-4 were recorded 10 sec, 1 min, 3 min, and 6 min, respectively, after addition of enamino ketone IV to the solution. The rate of potential imposition was 1.25 V/sec.

Fig. 2. Polarograms of enamino ketone IV in a 0.98 M HCl base electrolyte 15 sec (1), 10 min (2), and 21 min (3) after addition of the substance to the solution. The rate of potential imposition was 1.25 V/min.

amino group – hydrolysis. To study the kinetics of the hydrolysis of enamino ketone IV we used polarography. In the first stage it was established that the hydrolysis of enamino ketone IV proceeds readily in alkaline media to give 4-hydroxymethylene-2,3-dioxohexahydroazepine (V).



A broad signal of a methylidyne proton is observed in the PMR spectrum of hydroxymethylene compound V at 8.96 ppm. When the solution (in deuterodimethyl sulfoxide) is acidified with CF_3COOH, the signal becomes a narrow singlet, i.e., exchange of the proton of OH is accelerated, and splitting (in this case broadening) of the =CH signal vanishes. These data make it possible to assign a hydroxymethylene ketone structure to V rather than the isomeric hydroxyvinyl aldehyde structure.

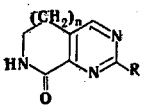
A comparison of the polarographic behavior of IV and V shows that there is one wave with $E_{1/2} = -1.36$ V on the polarogram of enamino ketone IV in neutral and alkaline nonbuffered media, whereas a wave with an $E_{1/2}$ value of -1.59 V is observed in the reduction of enol V under these conditions (Fig. 1). This difference in the $E_{1/2}$ values of the two compounds is due to the fact that enol V is a rather strong acid (pK_a 4.11) and is present in solution in alkaline and neutral media in the form of an ion, the rate of protonation of which, under these conditions, is low. At the same time, enamino ketone IV is reduced in the form of the neutral molecule under similar conditions. The considerable difference in the half-wave potentials of these compounds makes it possible to quantitatively observe the rate of hydrolysis of enamino ketone IV (Fig. 1). In HCl solutions (0.02-1.0 M) the half-wave potentials of the two compounds coincide, but in this case, in addition to the principal wave on the polarogram, a small wave at more negative potentials is also present (Fig. 2); the change in this small wave with time was adopted as a measure of the rate of hydrolysis of enamino ketone IV. In more acidic media enol V is reduced at more positive potentials than enamino ketone IV, and during hydrolysis, in addition to a decrease in the waves of reduction of IV, the appearance of a wave of reduction of hydrolysis product V is observed on the polarograms.

In neutral KCl solutions the dependence of log I_{lim} of the wave of reduction of enamino ketone IV on time has nonlinear character, and the reaction rate is relatively slow – when a 1 mM solution of IV was allowed to stand for 1.5 h in a 0.1 M KCl solution, the reductive wave decreased by ~10%. Acids and alkalis considerably accelerate the hydrolysis, since, under these conditions, the concentration of the dimethylamine formed in the reaction is low and does not affect the pH of the medium, and the dependence of log I_{lim} of the wave of reduction of IV on time acquires linear character. The rate constants for hydrolysis of enamino ketone IV in alkaline and acidic media, calculated from a first-order equation, are presented in Table 1.

TABLE 1. Rate Constants for the Hydrolysis of Enamino Ketone IV

Medium	2,1 M HCl	0,98 M HCl	0,096 M HCl	0,02 M HCl	0,009 M NaOH	0,046 M NaOH	0,093 M NaOH	0,24 M NaOH	0,96 M NaOH
$k \cdot 10^4$	2,3	6,0	13,2	9,6	2,5	14,3	28,7	73,5	310

TABLE 2. Pyrimido[4,5-c]azepine (VII) and Pyrido[3,4-d]pyrimidine (IX) Derivatives



Compound	R	n	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
VIIIb	CH_3	3	210,5—211	$C_9H_{11}N_3O$	61,2	6,4	23,8	—	61,0	6,2	23,7	—	71
VIIIc	C_6H_5	3	242—243	$C_{14}H_{13}N_3O$	70,6	5,5	17,5	—	70,3	5,4	17,6	—	70
VIId	SH	3	248—249	$C_8H_9N_3O_3S$	48,7	4,4	21,6	15,8	49,0	4,6	21,6	16,4	61
VIIIe	p-$NH_2C_6H_4SO_2NH$	3	244—245	$C_{14}H_{15}N_5O_3S \cdot H_2O$	47,4	5,0	19,9	9,1	47,9	4,8	19,9	9,1	78
VIIIf	OH	3	217—218	$C_8H_9N_3O_2$	53,2	5,0	23,4	—	53,6	5,0	23,5	—	28
IXb	NH_2	2	>300	$C_7H_8N_4O$	51,1	5,1	34,4	—	51,2	4,9	34,2	—	21,4
IXc	CH_3	2	212—213	$C_8H_9N_3O$	59,0	5,6	25,5	—	58,9	5,5	25,8	—	13

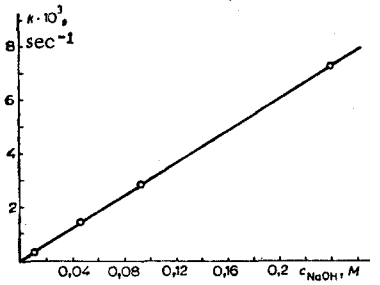
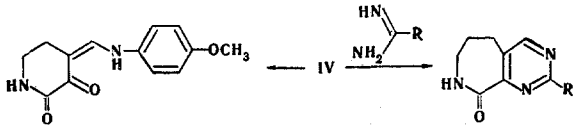


Fig. 3. Dependence of the rate constant for hydrolysis of enamino ketone IV on the hydroxide ion concentration.

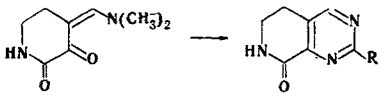
As seen in Fig. 3, the dependence of the rate constants in alkaline media on the alkali concentration has linear character when $k_{OH} = 3 \cdot 10^{-2}$ liter · mole^{-1} · sec^{-1}. However, it follows from the data in Table 1 that in acid medic acceleration of hydrolysis as the hydronium ion concentration increases is observed only up to a certain limit, after which the reaction rate again decreases, i.e., as in the hydrolysis of enamines [9], in the case of enamino ketone IV the dependence of the hydrolysis rate constant on the H_3O^+ concentration is bell-shaped. An interpretation of this phenomenon was presented in [9]. The data from a comparison of the rate constants for hydrolysis of IV in acidic and alkaline media made it possible to assume that in this case (in contrast to the simplest enamines) there is no need to use an acid catalyst to carry out the reaction with nucleophilic reagents. To verify this assumption we carried out the transamination of enamino ketone IV with p-anisidine, both in the presence of TsOH and in the absence of a catalyst. In both cases we obtained 3-oxo-4-(p-methoxyphenyl)aminomethylenecaprolactam (VI) in high yield, and the catalyst did not affect the trend of the process. These results, as well as data on the hydrolysis of enamino ketone IV in alkaline and acidic media, constitute evidence for considerable activation of the enamine α position of IV by both keto and lactam groupings. This circumstance opens up considerable prospects for the use of enamino ketone IV for the preparation of various heterocyclic compounds, particularly condensed pyrimidines. Thus 2-substituted 9-oxo-5,6,7,8-tetrahydro-9H-pyrimido[4,5-c]azepines (VIIa-e) are formed in the reaction of IV with guanidine, amidines, and thiourea (in the presence of sodium ethoxide).



VI VII

VII a R = NH_2; b R = CH_3; c R = C_6H_5; d R = SH; e R = $NH_2C_6H_4SO_2NH$; f R = OH

It should be noted that reaction of enamino ketone IV with urea could not be carried out and that 2-oxo derivative VIf was obtained by diazotization of the NH_2 group in VIIa. The reaction of acetal III with lactam I leads to the extremely hygroscopic enamino ketone VIII, which, without isolation, was subjected to reaction with thiourea, guanidine, and acetamidine. This method was used to synthesize 2-substituted 8-oxo-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidines (IXa-c).



VIII IX

IX a R = SH, b R = NH_2, c R = CH_3

The physical characteristics of VII and IX are presented in Table 2.

EXPERIMENTAL

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

Polarography was carried out in a thermostatted cell at 25 ± 0.1° on a dropping mercury electrode (m = 0.82 mg/sec, t = 0.4 sec). A saturated calomel electrode served as the anode. The polarograms were recorded with a Radiometer PO-4 polarograph. In the study of the kinetics of hydrolysis, the appropriate solution of the base electrolyte was poured into the cell, the curve was recorded, and a freshly prepared aqueous solution of enamino ketone IV was added to the same solution; after brief (~10 sec) stirring with a stream of nitrogen, the curve was recorded. The subsequent polarograms were recorded at various time intervals as a function of the reaction rate in the investigated medium. The time required to reach the limiting currents of enamino ketone IV from the start of recording of the polarogram was taken into account in the construction of the dependence of log i_{lim} on time.

4-(N,N-Dimethyl)aminomethylene-2,3-dioxotetrahydroazepine (IV). An 8.82-g (0.06 mole) sample of dimethylformamide acetal was added dropwise to a solution of 5.1 g (0.04 mole) of α-oxocaprolactam in 72 ml of dry benzene, and the mixture was heated at 70-75° for 2 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with benzene, and dried to give 5.9 g (81%) of enamino ketone IV with mp 175-176° (from isopropyl alcohol). Found: C 58.9; H 7.6; N 15.3%. $C_9H_{14}N_2O_2$. Calculated: C 59.3; H 7.1; N 14.9%.

4-Hydroxymethylene-2,3-dioxotetrahydroazepine (V). A 7.28-g (0.04 mole) sample of IV was dissolved in 30 ml of 2 M NaOH, and the mixture was stirred to 0° for 2 h, after which 2 N HCl solution was added up to pH ~2, and the mixture was maintained at 0° for 1 h. The resulting precipitate was removed by filtration, washed with cold water, and dried to give 4.34 g (70%) of azepines V with mp 144.5-145° (from ethyl acetate). Found: C 54.1; H 9.0; N 5.8%. $C_7H_9NO_3$. Calculated: C 54.2; H 9.0; N 5.8%.

3-Oxo-4-(p-methoxyphenyl)aminomethylenecaprolactam (VI). A 1.84-g sample of p-anisidine was added to a solution of 1.82 g of IV, and the mixture was refluxed for 5 h. It was then cooled, and VI was removed by filtration to give a product with mp 233-233.5° (from DMF) in 95% yield. Found: C 65.0; H 6.5; N 10.8%. $C_{14}H_{16}N_2O_3$. Calculated: C 64.6; H 6.2; N 10.8%. When TsOH was used as the catalyst, VI was obtained in 95% yield.

2-Amino-9-oxo-9H-5,6,7,8-tetrahydroazepino[3, 4-d]pyrimidine (VIIa). A 2.5-g (0.0137 mole) sample of IV was added to a solution of 2 g (0.0134 mole) of guanidine carbonate in 40 ml of absolute methanol, and the mixture was refluxed for 4 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with water and ether to give 2.1 g (86%) of pyrimidine VIIa with mp 273.5-274° (from water). Found: C 53.6; H 5.6; N 31.1%. $C_8H_{10}N_4O$. Calculated: C 53.9; H 5.6; N 31.5%. Compounds VIIb-f (Table 2) were similarly obtained.

2-Mercapto-8-oxo-8H-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (IXa). A 14-g sample of acetal III was added to a solution of 3.4 g of lactam VIII in 20 ml of absolute alcohol, and the mixture was refluxed for 8 h. The alcohol was removed by distillation, 20 ml of alcohol, 2.5 g of thiourea, and a solution of sodium methoxide (from 0.75 g of Na in 15 ml of alcohol) were added, and the mixture was refluxed for 4 h and allowed to stand overnight. The precipitated IXa was removed by filtration and crystallized from water to give the hemihydrate of IXa, with mp 221-222° in 28% yield. Found: N 22.2; S 16.3%. $C_7H_7N_3OS \cdot 0.5\ H_2O$. Calculated: N 22.1; S 16.8%. Compounds IXb, c (see Table 2) were similarly obtained.

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6H-ANTHRA[1,9,8-c,d,e,f]-2,7-NAPHTHYRIDINE DERIVATIVES

II.* NITRATION OF ANTHRANAPHTHYRIDINE-1,6,11-TRIONES

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5,7-Dinitro derivatives are formed in the nitration of 2H,10H-anthra[1,9,8-c,d,e,f]-2,7-naphthyridine-1,6,11-trione and its N,N'-dimethyl derivatives. 5,7-Dichloro- and 5,7-dibromoanthranaphthyridine-1,6,11-triones were obtained by reaction of 1,8-diamino-4,5-dihaloanthraquinones with diethyl malonate. Disubstituted anthranaphthyridine triones react with amines to give the corresponding 5,7-diaryl(alkyl)aminoanthranaphthyridine 1,6,11-triones.

We have previously synthesized 2H,10H-anthra[1,9,8-c,d,e,f]-2,7-naphthyridine-1,6,11-trione (Ia) and its N,N'-dimethyl derivative (Ib) [1]. In a study of the nitration of these compounds it was observed that a difficult-to-separate mixture of the starting compound and the mono- and dinitro derivatives is formed when one equivalent of nitric acid in sulfuric acid is used. When two equivalents of nitric acid are used, dinitro derivatives (IIa, IIb) are formed smoothly. It might have been expected that, like anthraquinone [2] and anthrapyridone [3], nitration leads to substitution of the free α positions of the anthrone ring. To verify the structure of dinitro derivative IIa, it was converted by exchange reaction with p-toluidine to the di-p-tolylamino derivative (IIIa), which in turn was obtained by arylamination of 5,7-dichloroanthranaphthyridinetrione (IVa).

Compound IVa was obtained by condensation of 1,8-diamino-4,5-dichloroanthraquinone (Va) with diethyl malonate in the presence of potassium acetate. Compound Va was synthesized by nitration of 1,8-dichloroanthraquinone and subsequent reduction.

*See [1] for communication I.
†Deceased.

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