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ACETALS OF LACTAMS AND ACID AMIDES.

37.* REACTIONS OF AMIDE AND LACTAM ACETALS WITH DERIVATIVES OF UREA AND URETHANE AND SYNTHESIS OF CONDENSED PYRIMIDINES

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The reactions of diethylacetals of dimethylacetamide and N-methylbutyro-, -valero-, and -caprolactams with urea, thiourea, and urethane lead to the corresponding N-carbamide- and N-ethoxycarbonylamides, on the basis of which derivatives of pyrimidine and pyrrolo- and pyrido[2,3-d]pyrimidine and pyrimido[4,5-b]azepine, as well as triazole derivatives, were synthesized.

A large amount of literature has been devoted to the chemistry of acetals and amides and lactams [2, 3]; however, their reactions with urea and urethane have remained virtually uninvestigated. Only the synthesis of N-carbamido(thiocarbamido)formamidines by the reaction of dimethylformamide diethylacetal (I) with urea and thiourea has been realized [4], and the reaction of acetal I with urethane has been mentioned [5].

The aim of the present research was to study the possibility of the preparation of N-carbamido(or N-ethoxycarbonyl)amidines on the basis of acetals of amides and lactams and the development of the synthesis of azaheterocycles (primarily condensed pyrimidines) from these amidines.

The reactions of dimethylacetamide diethylacetal (II) and lactam acetals IIIa-c with urea proceed smoothly, and the corresponding N-carbamidoamidines (IV, Va-c) are formed in high yields. A peculiarity of the amidines obtained is the fact that they crystallize with urea molecules; repeated crystallization from various solvents does not change the ratio of the amidines and the urea in the reaction product.

Signals of NCH_3 groups (2.91-3.14 ppm), ring NCH_2 groups (3.49-3.62 ppm), 3-CH_2 groups (2.58-2.91 ppm), and the remaining CH_2 groups (1.50-2.00 ppm) are observed in the PMR spectra of Va-c in D_2O and d_6-DMSO. Signals of the carbon atom of the CO group of urea at 160.19 ppm and signals of amidine Vc [170.29 and 169.42 (C=O, C=N), 53.50 and 54.47 (3CH_2 and 7-CH_2), 36.18 (NCH_3), and 28.49, 25.63, and 23.36 ppm (4,5,6-CH_2)] were present in the ^{13}C NMR spectrum of Vc.†

Peaks of molecular ions, the most favorable pathways from the fragmentation of which involve splitting out of NH_2 and $CONH_2$ fragments, are present in the mass spectra of IV and V. In addition, intense peaks with m/z 60, which are related to the urea molecule, are observed in the spectra. When amidine Va is heated in vacuo at ∿100°C (2-3 mm), one can sublime the urea and obtain a urea-free compound, in the mass spectrum of which the peak with m/z 60 is

*See [1] for Communication 36.

†Signals of an impurity (possibly a second geometrical isomer) are observed in the PMR and ^{13}C NMR spectra of Vc in d_6-DMSO.

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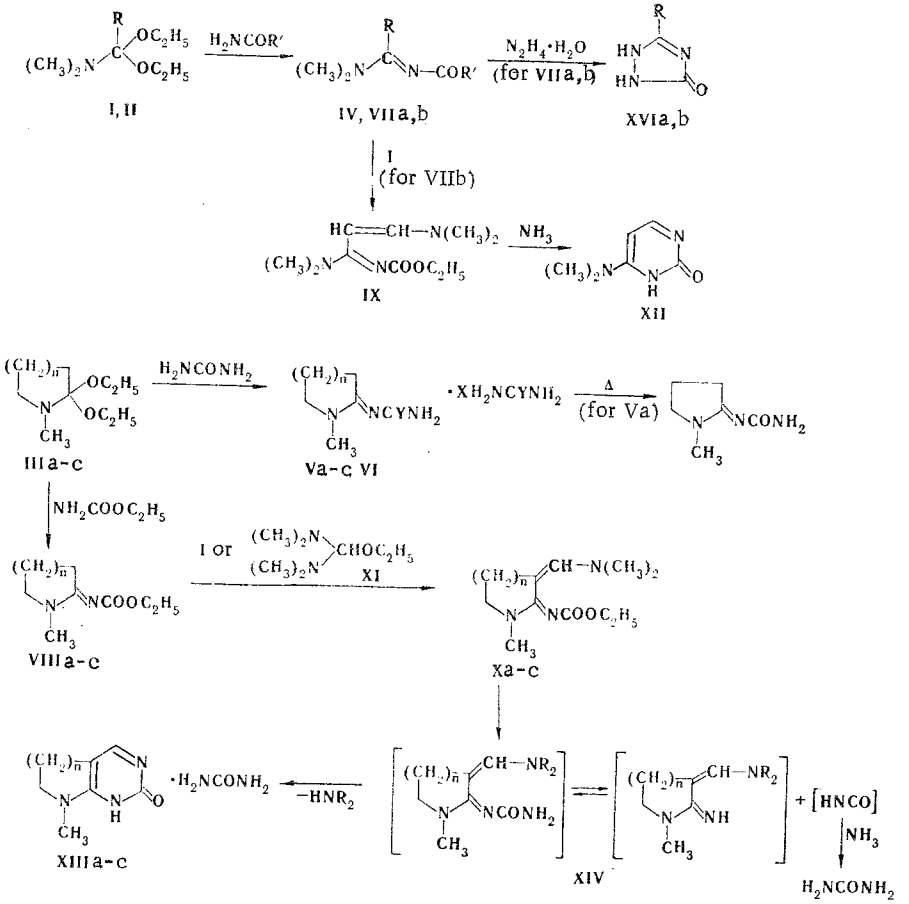
absent. A compound that contains half a molecule of thiourea per molecule of thiocarbamidoamidine VI is also formed in the reaction of N-methylcaprolactam acetal IIIc with thiourea. A molecular-ion peak (M^+) with m/z 185 and peaks corresponding to detachment of NH_2, CH_3, and SH groups, and $[M-CH_3-C_2H_4]^+$ (m/z 142), $[M-NH_2CS]^+$ (m/z 125), and $[M-NH_2CSCH_3]^+$ (m/z 110) fragments are observed in the mass spectrum of this compound. In addition, a peak with m/z 76, which corresponds to thiourea, is present in the spectrum. It should be noted that urea-free compounds cannot be isolated when amidines Vb, c are heated because of their thermal instability.

The presence of urea molecules in IV and V complicates their utilization in further synthesis. In the next stage of the research we therefore studied the possibility of the synthesis of N-ethoxycarbonylamidines from acetals II and III and urethane. The desired amidines (VII and VIIIa-c) are readily formed when the indicated components are heated. However, the condensation of these compounds with dimethylformamide acetal I depends substantially on the structures of the starting amidines. Just as in a number of other cases (for example, see [6]), noncyclic VII and six-membered amidine VIIIb successfully undergo the reaction with acetal I to give IX and Xb, whereas their five- and seven-membered analogs under these conditions do not form the corresponding enamino amidines Xa, c. In the case of amidine VIIIc we demonstrated that an aminal ether (XI) can be used in this case. However, we found that the reaction of VIIIa, c with acetal I at a high temperature (∿200°C) under pressure is more convenient — enamino amidines Xa, c were isolated in satisfactory yields.



I, VII a R=H; II, IVa, VIIb, XVIb R=CH_3; IV R′=NH_2; VIIa, b R′=OC_2H_5; V Y=O; a X=3; b, c X=1; VI Y=S, X=0,5; III, V, VIII, X, XIII, XIV a n=1; b n=2; c n=3; XIV R=H or CH_3

These compounds were subjected to pyrimidine synthesis without additional purification, and their structures were confirmed by further transformations (and by the mass spectrum in the case of Xb). A molecular-ion peak (M^+) with m/z 239 and peaks of ions formed due to detachment of OC_2H_5, C_2H_4, and OC_2H_4 groups, as well as $[M-C_2H_4CO_2]^+$ (m/z 167) and $[M-C_2H_4CO_2CH_3]^+$ (m/z 152) fragments, are observed in the spectrum of amidine Xb.

When enamino amidines IX and Xa-c are heated with ammonia, they undergo smooth conversion to 2-hydroxy-4-dimethylaminopyrimidine (XII) and derivatives of pyrrolo- and pyrido[2,3-d]pyrimidine and pyrimido[4,5-b]azepine (XIIIa-c), respectively. It is interesting to note that in this case also two-ring systems XIIIa-c crystallized with urea (in a ratio of 1:1), which is confirmed by the mass spectral data, as well as by the fact that when XIIIb is heated in vacuo one can sublime urea and obtain urea-free (according to the results of microanalysis and the mass spectra) pyridopyrimidine XIIIb. The fact that molecular compounds are formed in this case is also confirmed by crystallization of XIIIa, c from dimethylformamide (DMF), in which urea is quite soluble (otherwise, two recrystallizations from DMF would make it possible to purify two-ring systems XIIIa, c).

It seems to us that the formation of urea may be a consequence of the thermal instability of the intermediately formed carbamidoamidines (for example, of the XIV type). To a certain extent a confirmation of the possibility of this scheme is the fact that the corresponding pyridopyrimidine could not be isolated when Xb was heated with benzylamine, and the only characterized product was N,N'-dibenzylurea (XV).

The substances synthesized in the present research may be convenient intermediates for the synthesis of not only pyrimidine systems. An example of the synthesis of other heterocycles is the smooth reaction of N-carbethoxyamidines (VIIa, b) with hydrazine hydrate, as a result of which triazolones (XVIa, b) are formed.

EXPERIMENTAL

The PMR spectra were obtained with an XL-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-112 spectrometer with direct introduction of the samples into the ion source; the ionization-chamber temperature was 180°C, and the ionizing-electron energy was 70 eV.

N,N-Dimethylamino-N'-carbamidoacetamidine (IV). A solution of 8.05 g (0.05 mole) of acetal II in 5 ml of absolute ethanol was added dropwise at 60°C to 3 g (0.05 mole) of urea, and the mixture was stirred at 85°C for 3 h. It was then cooled and filtered, and the precipitate was washed with a small amount of absolute ethanol to give 2.34 g of amidine IV. Compounds Va-c and VI were similarly obtained. PMR spectrum (D_2O) of 1-methyl-2-(N-carbamidiomino)pyrrolidine Va: 3.49 (t, 5-CH_2), 2.91 (q, 3-CH_2), 2.00 (q, 4-CH_2), and 2.91 ppm (s, NCH_3). PMR spectrum of Vb (D_2O): 3.35 (broad t, 6-CH_2), 2.58 (broad t, 3-CH_2), 1.74 (m, 4,5-CH), and 2.92 ppm (s, NCH_3). PMR spectrum of Vc (d_6-DMSO): 2.72 (m, 3-CH_2), 3.64 (m, 7-CH_2), 1.5 (m, 4,5,6-CH_2), and 3.14 ppm (s, NCH_3). The reaction conditions and characteristics of the compounds are presented in Table 1.

Sublimation of Urea from Adduct Va. Adduct Va was heated at 100°C (2-3 mm) for 1 h, after which the residue was recrystallized from absolute ethanol to give urea-free 1-methyl-2-carbamidoiminopiperidine with mp 134-136°C. Found: C 51.3; H 8.1; N 30.0%. $C_6H_{11}N_3O$. Calculated: 51.1; H 7.8; N 29.8%.

N,N-Dimethylamino-N'-ethoxycarbonylacetamidine (VIIb). A solution of 14.5 g (0.09 mole) of acetal II and 7.12 g (0.08 mole) of urethane in 50 ml of absolute ethanol was refluxed for 2 h, after which the alcohol was evaporated, and the residue was distilled to give 10.9 g of amidine VIIb. Amidines VIIIa-c were similarly obtained (Table 1).

4-Dimethylamino-2-pyrimidinone (XII). A mixture of 1.26 g (0.008 mole) of amidine VIIb, 5.9 g (0.04 mole) of acetal I, and 15 ml of DMF was refluxed for 20 h, after which it was evaporated, and the residue was distilled to give 1.23 g (72%) of enamino amidine IX with bp 159-161°C (3 mm), which, without further purification, was placed in a bomb with 20 ml of an alcohol solution of ammonia (∿14%) and heated at 160°C for 11 h. The alcohol was evaporated to give 0.76 g (94%) of pyrimidinone XII as colorless crystals with mp 257-258°C (from DMF; mp 254-256°C [7]). Found: C 51.9; H 6.6; N 30.5%. $C_6H_9N_3O$. Calculated: C 51.8; H 6.5; N 30.2%. A similar method was used to obtain 1-methyl-1,2,3,4,6,7-hexahydropyrido[2,3-d]-pyrimidinone XIIIb [see Table 2; amidine Xb had bp 170-194°C (3 mm)].

1-Methyl-2,3,4,5,7,8-hexahydropyrimido[4,5-b]azepine-8-one (XIIIc). A) A mixture of 1.89 g (0.01 mole) of amidine VIIIc and 7.35 g (0.05 mole) of the acetal was heated in a bomb at 200°C for 11 h, after which it was evaporated, and the residue was distilled with selection of 2.35 g of the fraction with bp 150-160°C (3 mm), containing enamino amidine Xc, which, without further purification, was placed in a bomb with 20 ml of an alcohol solution of ammonia (∿14%) and heated at 180°C for 6 h. The alcohol was evaporated to give 0.86 g

TABLE 1. Reaction Conditions and Characteristics of the Synthesized Compounds

Compound	Reaction time, h	mp, °C (solvent), bp, °C (mm)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IV	3	168 (isopropanol)	42,8	8,1	34,3	$C_5H_{11}N_3O \cdot {}^1/_3NH_2CONH_2$	42,5	8,3	34,4	31
Va	1	110—113 (ethanol)	33,8	7,1	39,5	$C_6H_{11}N_3O \cdot 3NH_2CONH_2$	33,6	7,2	39,3	75
Vb	0,5	114—115 (2-propanol)	44,8	8,0	32,5	$C_7H_{13}N_3O \cdot NH_2CONH_2$	44,7	7,9	32,6	68
Vc	2	83—86 (ethyl acetate)	47,2	8,5	30,6	$C_8H_{15}N_3O \cdot NH_2CONH_2$	47,2	8,3	30,6	90
VI	2	124—126 (ethanol)	45,6	7,5	25,6	$C_8H_{15}N_3S \cdot {}^1/_2NH_2CSNH_2$*	45,7	7,6	25,1	86
VIIb	2	123—125 (3)	53,1	8,8	17,9	$C_7H_{14}N_2O_2$	53,2	8,9	17,7	86
VIIIa	2	140—141 (3)	56,3	8,3	16,5	$C_8H_{14}N_2O_2$	56,5	8,2	16,5	85
VIIIb	1	152—153 (3)	58,6	8,6	15,2	$C_9H_{16}N_2O_2$	58,7	8,7	15,2	63
VIIIc	2	151—152 (2)	60,6	9,0	14,0	$C_{10}H_{18}N_2O_2$	60,6	9,1	14,1	67
XIIIa	5	276—278 (DMF)	46,0	6,5	32,7	$C_7H_9N_3O \cdot NH_2CONH_2$	45,5	6,2	33,2	15
XIIIb	6	264—265 (ethanol)	48,4	6,5	31,5	$C_8H_{11}N_3O \cdot NH_2CONH_2$	48,0	6,7	31,1	26
XIIIc	6	192—194 (DMF)	50,6	7,4	29,3	$C_9H_{13}N_3O \cdot NH_2CONH_2$	50,2	7,1	29,3	36

*Found: S 21.9%. Calculated: S 21.5%.

(36%) of azepinone XIIIc. A similar procedure gave 1-methyl-2,3,5,6-tetrahydropyrrolo[2,3-d]-pyrimidin-6-one (XIIIa) [amidine Xa had bp 180-197°C (3 mm)]. The physical constants and analytical characteristics are presented in Table 1.

B) A mixture of 1 g (0.05 mole) of amidine VIIIc, 3.0 g (0.02 mole) of aminal XI, and 10 ml of DMF was refluxed for 8 h, after which it was evaporated, and the residue was distilled with selection of the fraction with bp 145-162°C (3 mm), containing enamino amidine Xc, which, without further purification, was placed in a bomb with 20 ml of an alcohol solution of ammonia (≈14%) and heated at 180°C for 10 h. The alcohol was evaporated to give 0.49 g (41%) of a reaction product that was identical to the compound obtained by method A.

Sublimation of Urea from Adduct XIIIb. Compound XIIIb was heated at 180-185°C (2-3 mm) for 2 h to give urea-free 1-methyl-7-oxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine with mp 258-261°C (from DMF). Found: C 58-0; H 6.0; N 25.5%. $C_8H_{11}N_3O$. Calculated: C 58.2; H 6.7; N 25.5%.

N,N'-Dibenzylurea (XV). A mixture of 0.86 g (3.6 mmole) of enamino amidine Xb and 1.3 g (4 mmole) of benzylamine was heated at 150-160°C for 6 h, after which the reaction mass was washed several times with water (10-ml portions) and treated with 10 ml of absolute ethanol. The precipitate was removed by filtration and washed with ethanol to give 0.2 g (23%) of colorless crystals of XV with mp 171-172°C (from 2-propanol; mp 170°C [8]). Found: C 75.4; H 7.2; N 11.6%. $C_{15}H_{16}N_2O$. Calculated: C 75.0; H 6.7; N 11.7%.

3-H-1,2-Dihydro-1,2,4-triazol-3-one (XVIa). A mixture of 1.44 g (0.01 mole) of amidine VIIa, 0.5 g (0.01 mole) of hydrazine hydrate, and 15 ml of absolute methanol was refluxed for 2 h, after which the alcohol was removed by evaporation, and the precipitate was removed by filtration to give 0.2 g (25%) colorless crystals of triazolone XVIa with mp 239-240°C (from ethanol; mp 237°C [9]). Found: C 27.8; H 3.1%. $C_2H_3N_3O$. Calculated: C 28.2; H 3.5%. A similar procedure was used to obtain triazolone XVIb with mp 250°C (from ethanol; mp 248 °C [10]). Found: C 36.5; H 5.5%. $C_3H_5N_3O$. Calculated: C 36.4; H 5.1%.

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