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ACETALS OF LACTAMS AND AMIDES.

42.* REACTIONS OF ENAMINO AMIDES AND ENAMINO ESTERS WITH SOME FORMYLATING AGENTS. SYNTHESIS OF DERIVATIVES OF 2-PYRIDONE AND OF PYRIMIDIN-4- AND -6-ONES

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The reactions of enamino esters and enamino amides with the diethyl acetal of dimethylformamide and with orthoformic ester have been investigated and it has been shown that the process takes place in two directions — with the formation of pyrimidone or 2-pyridone derivatives and with the replacement of an aminopropylene (or N,N-dimethylaminopropylene) fragment of the enamine by a dimethylaminomethylene (or ethoxymethylene) group. Some conditions favoring the occurrence of one or other of these processes have been determined.

In the reaction of the benzylamide of β-amino-α-cyanocrotonic acid (Ia) with the diethyl acetal of dimethylformamide (II) 1-benzyl-5-cyano-4-β-dimethylaminovinylpyridin-6-one (IIIa) is formed with good yield [2]. Continuing investigations relating to the synthesis of pyrimidine derivatives from enamino amides, we have similarly converted the β-amino-α-cyanocrotonanilide (Ib) into the 1-phenylpyrimidin-6-one (IIIb). In order to synthesize N-substituted pyrimidin-6-ones not having a β-dimethylamino group in position 4, we have made an attempt to cyclize compound (Ia) with orthoformic ester in acetic anhydride. However, instead of the expected 1-benzyl-5-cyano-4-methylpyrimidin-6-one (IVa), we isolated a compound (Va) with a molecular weight of 230 (mass spectrum). Its PMR spectrum in DMSO-D_6 contained signals at (ppm): 1.26 (t) and 4.37 (q), belonging to an OC_2H_5 group; 4.34 (d), which is characteristic for the methylene protons of a $C_6H_5CH_2NH$ group; 7.66 (m, C_6H_5); 8.00 (s, CH); and 8.20 (t, NH). These facts, and also the results of microanalysis, permitted the assumption that the compound obtained was the benzylamide of ethoxymethylenecyanoacetic acid (Va).† The structure of compound (Va) was shown by its independent synthesis from N-benzylcyanoacetamide (VIa) and $CH(OEt)_3$. By means of the analogous reaction of the N-phenylamide (Ib) with $CH(OEt)_3$ we succeeded in isolating 5-cyano-4-methyl-1-phenylpyrimidin-6-one (IVb). An investigation of the mother solutions by chromato-mass spectrometry showed the presence in them of the ethoxymethylene derivative (Vb), its mass spectrum being identical with that of the substance obtained by independent synthesis from the amide (VIb) and $CH(OEt)_3$.

The results obtained induced us to make a more detailed study of the reaction of compounds (Ia, b) with the acetal (II). An investigation by the chromato-mass-spectrometric method of the mother solution obtained after the pyrimidinone (IIIb) had been filtered off showed the presence of N-phenyl-α-cyano-β-dimethylaminoacrylamide (VIIb), the mass spectrum of which coincided with the spectrum of the authentic substance obtained by independent synthe-

*For communication 41, see [1].
†We have briefly described this reaction and others of the same type previously [3].

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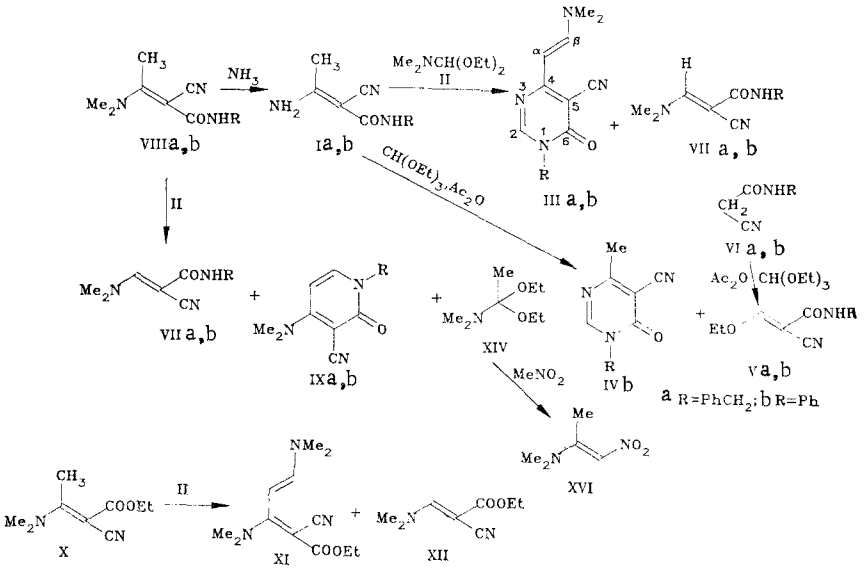
Scheme 1



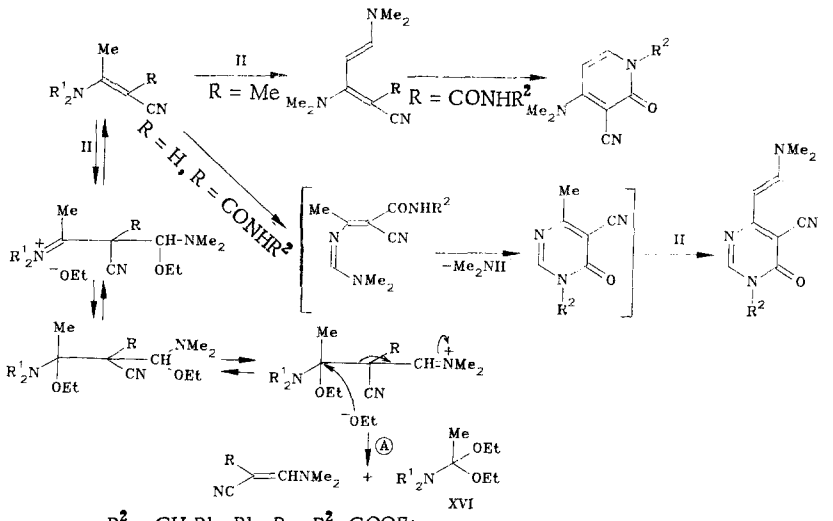
sis [from the amide (VIb) and the acetal (II)]. In the case of the reaction of the amide (Ia) and the acetal (II), the unpurified reaction product containing, according to its PMR spectra, the pyrimidinone (IIIa) and the acrylamide (VIIa) in a ratio of about 4:1.

Thus, on the interaction of the primary enamines (Ia, b) with "formylating" agents — the diethyl acetal of dimethylformamide (II) and orthoformic ester — an extremely unusual process took place accompanied by the shortening of the carbon chain by one methyl group, i.e., a "latent" acetyl group was replaced by a "latent" formamide group. In addition to this, the expected process forming a pyrimidine ring was observed. A similar reaction of aminomethylmalononitrile with the acetal (II) and with aromatic aldehydes has been reported only by Mittelbach and Junek [4], but they showed that the corresponding crotononitriles reacted differently — at the α-CH_3 group. The results that we have given show that in the case of crotonic acid derivatives the replacement of a β-amino-β-methylvinyl group by a dimethylaminomethylene group takes place. In order to understand this unusual process, it is essential to establish to what extent a primary amino group is required in the enamine, i.e., whether this reaction is characteristic only for primary enamines. With this aim, we brought the tertiary enamino amides (VIIIa, b) into reaction with the acetal (II). When a mixture of compounds (VIIIa) and the acetal (II) was heated in ethanol, a dimethylaminomethylene derivative (VIIa) was obtained, and the (mass-spectroscopic) analysis of the mother solution after compound (VIIa) had been filtered off showed the presence of 1-benzyl-3-cyano-4-dimethylamino-2-pyridone (IXa), which was identified by comparing its spectra with the mass spectrum of an authentic sample of (IXa) obtained under different conditions (see below). After the reaction of the enamino amide (VIIIb) and the acetal (II) it was possible to isolate preparatively both the enamine (VIIb) and 3-cyano-4-dimethylamino-1-phenyl-2-pyridone (IXb). The results given above apparently contradict the statement that in the reaction of ethyl α-cyano-β-dimethylamino-β-methylacrylate (X) with the acetal (II) in toluene 1-cyano-1-ethoxycarbonyl-2,4-bis(diethylamino)butadiene (XI) is formed almost quantitatively [5].

We assumed that a substantial role in this type of reactions may be played by the polarity of the solvent. In actual fact, it was found that when the reaction of compounds (X) and (II) was carried out in ethanol it was possible to isolated 36% of the dimethylaminomethylenecyanoacetic ester (XII), which was formed under these conditions together with the diene (XI). Taking these results into account, we performed the reaction of the crotonamide (VIIIa) and the acetal (II) in toluene — in this case, the pyridone (IXa) was obtained in good yield. Thus, by varying the polarity of the solvent used it is possible to change the course of the reactions under investigation in a desired direction.

An investigation of the mother solutions from these reactions (after the separation of the main products) by chromato-mass spectrometry showed that, in addition to the substances mentioned above, they always contained N,N-dimethylacetamide, (XIII). We assumed that in the reaction of the dimethylformamide acetal (II) with the enamino amides (Ia, b) and

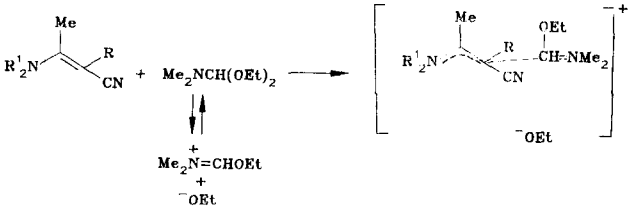
Scheme 2



$R^2 = CH_2Ph$, Ph; $R = R^2$, COOEt

(VIIIa, b) and with the enamino ester (X), the diethyl acetal of dimethylacetamide (XIV) was formed, and this was converted under the conditions of recording the mass spectra into the amide (XIII) and diethyl ether. To confirm the hypothesis of the formation of the acetal (XIV) during the reaction of the dimethylformamide acetal (II) with enamines, after the performance of the reaction between compounds (II) and (VIIIb) an excess of nitromethane was added to the reaction mixture, since it is known that this compound reacts smoothly with amide acetals [6]. Analysis of the reaction mixture by the GLC method showed the presence of β-dimethylaminonitroethylene (XV) [from CH_3NO_2 and dimethylformamide acetal (II)] and of β-dimethylamino-β-methylnitroethylene (XVI) in a ratio of 21:79, which unambiguously showed the formation of the acetal (XIV) during the reactions under study. The results obtained permit the scheme (Scheme 2) of the processes taking place to be suggested. It must be mentioned that stage A is practically irreversible, at least for the material studied in the present work. Thus, when the enamino ester (XII) was brought into reaction with the acetal (XVI) it was impossible to detect the formation of even traces of the ester (X). Scheme 2 permits the assumption that the transition state of the reaction of enamines with the acetal (II) is extremely polar, for example:

Scheme 3



which also explains the acceleraton of this process with an increase in the polarity of the solvent.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 chromato-mass spectrometer with the direct introduction of the sample into the source, and also with introduction through a chromatograph, the temperature of the ionization chamber being 180°C and the energy of the ionization electrons 70 eV. Varian Aerograph chromatograph. Conditions of chromatographic separation: column with 3% OV-101 on Chromosorb; l 180 m × 2 mm; rate of flow of He, 20 ml/min; temperature of the evaporator, 230°C; temperature of the column, 180°C; temperature of the separator, 250°C. The PMR spectra were taken on a Xα-200 instrument with TMS as internal standard and DMSO-D_6 as solvent.

TABLE 1. Physical Constants, Yields, and Analytical Characteristics

Compound	mp, °C*	Found, %			Empirical formula	Calculated, %			Yield, %, (method
		C	H	N		C	H	N	
VIIIb	138—140	68,09	6,40	18,27	$C_{13}H_{15}N_3O$	68,12	6,55	18,34	73
Ib	149—151	66,00	5,48	21,08	$C_{11}H_{11}N_3O$	65,67	5,47	20,90	86
Vb	154—156	66,81	5,70	12,95	$C_{12}H_{12}N_2O_2$	66,67	5,56	12,96	16 (B)
Va	118—120	67,79	6,06	12,21	$C_{13}H_{14}N_2O_2$	67,83	6,09	12,17	21 (A)
IVa	198—200	68,27	4,20	19,76	$C_{12}H_9N_3O$	68,25	4,27	19,91	64
VIIb	166—168	66,69	5,93	19,83	$C_{12}H_{13}N_3O$	66,98	6,05	19,53	21 (A); 89 (B)
VIIa	160—162	68,39	6,21	18,59	$C_{13}H_{15}N_3O$	68,12	6,55	18,34	64 (A); 67 (B)
IXa	145—147	70,19	5,22	17,77	$C_{14}H_{13}N_3O$	70,29	5,44	17,57	10
IIIb	214—216	67,27	5,31	20,74	$C_{15}H_{14}N_4O$	67,57	5,26	21,05	64
IIIa	169—171	68,93	5,82	20,38	$C_{16}H_{16}N_4O$	68,57	5,71	20,20	73

*Compound (VIIIb) was crystallized from ethyl acetate, (Ib) from benzene, (Vb) from toluene, (Va) from hexane, (IVb), (VIIa, b) and (IIIa, b) from ethanol, and (IXb) from isopropanol.

N-Phenyl-α-cyano-β-amino-β-methylacrylamide (Ib). A solution of 2 g (14.4 mmole) of compound (VIIIb) in 50 ml of 12% ethanolic ammonia was heated at 90°C for 5 h in an autoclave and was then cooled, and 1.5 g of compound (Ib) was filtered off. Compound (Ia) has been described previously [2].

Reactions of Compounds (Ia, b) with the Acetal (II). A mixture of 0.9 g (4.5 mmole) of compound (Ib), 1.5 ml of the acetal (II), and 10 ml of absolute ethanol was boiled for 1 h 30 min, and then 0.76 g of the pyrimidinone (IIIb) was filtered off. Mass spectrum:* $M^{+\cdot}$ 266, $[M^+ - CH_3]$ 251, $[M^+ - (CH_3)_2N]$ 222, $[M^+ - CH_3 - C_6H_5]$ 174. PMR spectrum, ppm: 2.97 (s) and 3.21 (s) (NMe_2); 5.26 (d, β-H), 7.47 (m, Ph), 8.13 (9d, α-H), 8.22 (s, 2-H). The enamine (VIIb) was detected in the mother solution by mass spectrometry: $M^{+\cdot}$ 215, $[M^+ - PhNH]$ 123. Similarly, the reaction of compounds (Ia) and (II) gave the pyrimidinone (IIIa) [2] {mass spectrum (relative intensities, %): $M^{+\cdot}$ 280 (64), $[M^+ - PhCH_2]$ 182 (100), $[PhCH_2^+]$ 91 (72), $[M^+ - PhCH_2 - HCN]$ 162 (24), $[M^+ - PhCH_2 - CN - Me_2N]$ 119 (24). PMR spectrum, ppm: 2.93 (s) and 3.19 (s) (Me_2N), 4.99 (s, CH_2Ph), 5.17 (d, α-H), 7.32 (m, Ph), 8.08 (d, β-H), 8.43 (2-H)} and compound (VIIa) (detected in the mother solution by chromato-mass spectrometry) {mass spectrum: $M^{+\cdot}$ 229, $[M^+ - CH_3]$ 214, $[M^+ - OH]$ 212, $[M^+ - Me_2N]$ 185, $[M^+ - PhCH_2]$ 138, $[M^+ - HNCH_2Ph]$ 123, $[M^+ - HNCH_2Ph - HCN]$ 96, $[PhCH_2^+]$ 91, $[PhCH_2NH^+]$ 106}. PMR spectrum, ppm: 3.16 (s) and 3.24 (s) (Me_2N), 4.35 (d, α-CH_2), 7.27 (m, Ph), 7.69 (t, α-NH), 7.73 (c).

Reactions of Compounds (Ia, b) with Orthoformic Ester. A mixture of 0.9 g (4.5 mmole) of the enamine (Ib), 10 ml of $CH(OEt)_3$ and 10 ml of acetic anhydride was boiled for 16 h and cooled, and 0.25 g of the pyrimidinone (IVb) was filtered off; the mother solution was evaporated, the residue was dissolved in petroleum ether, and another 0.35 g of compound (IVb) was filtered off. Mass spectrum: 211, 210, 104, 77. PMR spectrum, ppm: 2.53 (s, Me); 7.35 (m, Ph), and 8.66 (s, CH). Compound (Vb) was detected in the mother solution by chromato-mass spectrometry. Under analogous conditions, 0.3 g of enamine (Ia) gave 0.11 g of the ethoxymethylene derivative (Va) (method A). Mass spectrum: $M^{+\cdot}$ 230, $[M^+ - CO]$ 202, $[M^+ - HCO]$ 201, $[M^+ - EtO]$ 185, $[PhCH_2NH^+]$ 106, $[PhCH_2^+]$ 91.

Independent Synthesis of Ethozymethyl-N-benzylcyanoacetamide (Va) and the Corresponding N-Phenyl Compounds (Vb) (Method B). A mixture of 1 g (6.3 mmole) of compound (VIb), 15 ml of $CH(OEt)_3$, and 15 ml of acetic anhydride was boiled for 21 h and evaporated, and the residue was triturated with ether, to give 0.4 g of compound (Vb). Substance (Va) was obtained similarly.

N-Phenyl-α-cyano-β-dimethylaminocrotonamide (VIIIb). A mixture of 6.4 g (40 mmole) of the acetal (XIV) and 5.3 g (33 mmole) of N-phenylcyanoacetamide in 25 ml of absolute ethanol was boiled for 1 h and evaporated, giving 6.7 g of the amide (VIIIb). The amide (VIIIa) has been described previously [2].

*Here and below, the values of m/z for the peaks are given.

Reactions of the Amides (VIIIa, b) with the Diethyl Acetal of Dimethylformamide (II). A mixture of 1 g (4.4 mmole) of compound (VIIIb), 1 ml of the acetal (II), and 10 ml of absolute ethanol was boiled for 7 h and cooled, after which 0.2 g of compound (VIIb) was filtered off (method A), and then the mother solution was evaporated and the residue was triturated first with ether and then with isopropanol, and 0.1 g of the pyridone (IXb) was filtered off. Mass spectrum: $M^{+\cdot}$ 239, $[M^+ - H]$ 238, $[M^+ - Me]$ 224, $[Ph^+]$ 77. PMR spectrum, ppm: 3.27 (s, Me_2N), 6.12 (d, 5-H), 7.41 (m, Ph), 7.58 (d, 6-H).

Similarly, 1 g of compound (VIIIa) gave 0.6 g of the enamine (VIIa), while the pyridone (IXa) was detected by mass spectrometry; mass spectrum: $M^{+\cdot}$ 253, $[M^+ - H]$ 252, $[M^+ - Ph]$ 176, $[M^+ - PhCH_2]$ 162, $[M^+ - Ph - HCN]$ 149, $[PhCH_2^+]$ 91.

Independent Synthesis of the Enamines (VIIa, b) (Method B). A mixture of 0.5 g (3 mmole) of compound (VIb), 0.9 ml of the acetal (II), and 10 ml of absolute ethanol was boiled for 4 h and cooled, and 0.6 g of the enamine (VIIb) was filtered off. The enamine (VIIa) was obtained similarly.

Reaction of Ethyl α-Cyano-β-dimethylaminoacrylate (X) with the Acetal (II). A solution of 0.3 g (1.65 mmole) of the ester (X) and 0.7 ml of the acetal (II) in 3 ml of absolute ethanol was boiled for 5 h, the ethanol was distilled off, and the residue was triturated first with hexane and then with water, giving 0.1 g of the enamino ester (XII), mp 79-81°C [7]. The dienediamine (XI) [5] was detected mass-spectrometrically in the mother solution.

1-Benzyl-3-cyano-4-dimethylamino-2-pyridone (IXa). A solution of 0.5 g (2 mmole) of the enamino amide (VIIIa) and 1 ml of the acetal (II) in 15 ml of absolute toluene was boiled for 11 h, the mixture was cooled, and 0.4 g of the pyridone (IXa) was filtered off (method B); mp 172-174°C [5].

Detection of Dimethylacetamide Diethyl Acetal (XIV) in the Products of the Reaction of the Imine (VIIIb) with the Acetal (II). A mixture of 1 g (4.4 mole) of compound (VIIIb), 1 ml of the acetal (II), and 10 ml of anhydrous ethanol was boiled for 7 h and was cooled, and then 1.5 ml of nitromethane was added and boiling was resumed for another 1.5 h. The mixture was shown by GLC to contain 1-dimethylamino-2-nitroethylene [from the acetal (II) and $MeNO_2$] and 2-dimethylamino-1-nitroprop-1-ene (XVI) in a ratio of 21:79.

The physical constants, yields, and analytical characteristics of the compounds synthesized are given in Table 1.

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