ACETALS OF LACTAMS AND AMIDES.

44.* SYNTHESIS OF DERIVATIVES OF AMINOCYANOPYRIDINES FROM ENAMINO AMIDES AND ENAMINO NITRILES

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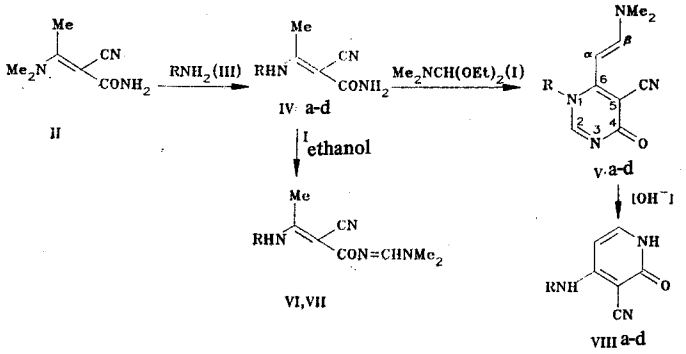
It has been established that in the reaction of a tertiary enamino amide with a primary amine a substantial influence is exerted by the basicity of the amine and the steric hindrance of its amino group. The secondary enamino amides obtained interact with the diethyl acetal of dimethylformamide to form enamino amides substituted at the amide nitrogen or 1-substituted pyramidin-4-ones, depending on the degree of steric hindrance of the NH group. Compounds of both these types, on being heated in an alkaline medium, are converted into derivatives of 4-amino-3-cyano-2-pyridone. An enamino dinitrile — α-cyano-β-dimethylaminocrotonitrile — condenses with acetals of amides and lactams to form dienic diamines which can be converted into derivatives of 3-cyano-4-dimethylaminopyridine.

It has been established previously that secondary enamino amides are cyclized by dimethylformamide acetal (I) to pyrimidin-4-one derivatives which, in an alkaline medium, recyclize to give substituted 2-pyridones [2]. In the present work we have investigated in more detail the transamination reaction of a tertiary enamino acid — α-cyano-β-dimethylaminocrotonamide (II) — with primary amines in order to then obtain pyrid-2-one derivatives. It is known that the transamination of tertiary enamines and, in particular, enamino amides with aromatic amines takes place smoothly only in acetic acid [3, 4]. More basic amines may participate in this reaction under less severe conditions. Thus, the reaction of the enamino amide (II) with β-phenylethylamine (IIIa) or with homoveratrylamine (IIIb) took place smoothly when the components were heated in ethanol for 2 h, with the formation of the secondary enamino amides (IVa, b).



IV, V, VIII a R = $C_6H_5CH_2CH_2$, b R = $(CH_3O)_2C_6H_3CH_2CH_2$, c R = C_6H_5—$CH_2CH(CH_3)$, d R = cyclohexyl; VI R = $C_6H_5CH_2CH(CH_3)$; VII R = cyclohexyl

When a compound in which the amino group is screened by an α-substituent was used in an analogous reaction, a clear hindrance to the transamination reaction was observed. Thus, the interaction of the enamine (II) with β-phenylisopropylamine required longer heating in

*For communication 43, see [1].

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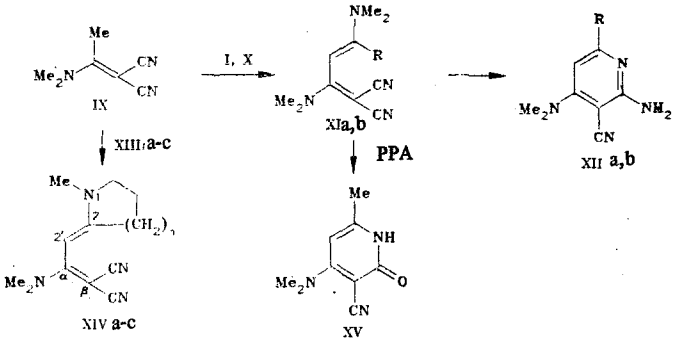
ethanol for the formation of the enamino amide (IVc), while the reaction with cyclohexylamine could not be performed under similar conditions and the production of the transamination product (IVd) required prolonged heating in DMFA. The steric environment of the amino group affected the cyclization of the secondary enamino amides (IVa-d) by the acetal (I) even more substantially. While compounds (IVa, b) cyclized smoothly even when they were heated with an ethanolic solution of the acetal (I) for 1.5 h, the enamino amide (IVc) under these conditions formed, judging from the results of mass spectroscopy, a mixture of the enamino acylamidine (VI) and the pyrimidinone (Vc),* while the cyclohexyl derivative (IVd) formed only the further substituted enamino amide (VII). To obtain the pyrimidones (Vc, d) required the compounds (IVc, d) to be heated with the acetal (I) in DMFA. The pyrimidine derivatives with N-alkyl (arylalkyl) residues smoothly recycled to give the 2-pyridones (VIIIa-d) on being heated in dilute alkali.

Another approach to the synthesis of 4-amino-3-cyanopyridine derivatives was realized in the present work by condensing α-cyano-β-dimethylaminocrotonitrile (IX) with the acetal (I) and with the diethyl acetal of dimethylacetamide (X). The dienic diamines (XIa, b) obtained were converted on heating with an ethanolic solution of ammonia into 2-amino-3-cyano-4-dimethylaminopyridine (XIIa) and its 6-methyl derivative (XIIb). It must be mentioned that the enamino dinitrile (IX) can also be condensed with the diethyl acetals of N-methylbutyro-, -valero-, and -caprolactams (XIIIa-c) with the formation of the dienic diamines (XIVa-c). The highest reactivity in these reactions is apparently shown by the diethyl acetal of N-methylbutyrolactam (XIIIa).

In conclusion we may mention that on being heated with polyphosphoric acid the dienic diamine (XIb) cyclized to 3-cyano-4-dimethylamino-6-methyl-2-pyridone (XV).



XI, XII a R=H; XI, XII b R=Me; XIII, XIV a n=1; XIII, XIV b n=2; XIII, XIV c n=3

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer 457 instrument in paraffin oil, UV spectra on a Perkin-Elmer 575 spectrophotometer in ethanol, and PMR spectra on a XL-200 instrument with TMS as internal standard. Mass spectra were obtained on a Varian MAT-112 spectrometer with direct introduction of the sample into the ion source. The temperature of the ionization chamber was 180°C. The energy of the ionizing electrons was 70 eV. Melting points were determined on a heated stage of the Boëtius type.

α-Cyano-β-(phenethylamino)crotonamide (IVa). A mixture of 10 g (63 mmole) of the amide (II), 12 ml (94 mmole) of β-phenethylamine (IIIa) and 100 ml of absolute ethanol was boiled for 3 h and was then cooled and the precipitate that deposited was filtered off. M^+ 229.

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

The α-cyano-β-(arylethylamino)crotonamides (IVb, c) were obtained similarly.

α-Cyano-β-(cyclohexylamino)crotonamide (IVd). A mixture of 1 g (6.3 mmole) of the amide (II), 1.2 ml (9.8 mmole) of cyclohexylamine, and 10 ml of DMFA was boiled for 5 h and was

*Some of the 4-pyridones (Va, c) obtained were hydrolytically unstable, in view of which it was difficult to obtain them in the analytically pure form — their structures were shown by spectral characteristics (see the Experimental part).

TABLE 1. Physical Constants, Yields, and Analytical Characteristics of the Compounds Synthesized

Compound	mp,* °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IVa	148—150	68,4	6,8	18,5	$C_{13}H_{15}N_3O$	68,1	6,6	18,3	87
IVb	201—203	61,9	6,8	14,7	$C_{15}H_{20}N_3O_3$	62,3	6,6	14,6	85
IVc	157—159	69,3	6,8	17,6	$C_{14}H_{17}N_3O$	69,1	7,0	17,3	57
IVd	208—209	63,6	8,2	20,4	$C_{11}H_{17}N_3O$	63,8	8,2	20,3	57
VII	171—175	64,1	8,6	21,7	$C_{14}H_{22}N_4O$	64,1	8,4	21,4	47
Vb	176—178	64,4	6,5	15,8	$C_{19}H_{22}N_4O_3$	64,4	6,2	15,8	98
Vd	191—193	66,0	7,5	20,9	$C_{15}H_{20}N_4O$	66,2	7,4	20,6	84
VIIIa	217—219	70,0	5,5	17,5	$C_{14}H_{13}N_3O$	70,3	5,4	17,6	54
VIIIb	248—250	63,9	5,9	14,0	$C_{16}H_{17}N_3O_3$	64,2	5,7	14,0	99,†
VIIIc	164—166	71,3	6,0	16,3	$C_{15}H_{15}N_3O$	71,2	5,9	16,6	73†
VIIId	177—179	66,1	7,1	19,3	$C_{12}H_{15}N_3O$	66,4	6,9	19,4	88
XIb	117—119	64,6	7,8	27,7	$C_{11}H_{16}N_4$	64,7	7,8	27,5	73
XIIb	>320	61,7	6,9	31,9	$C_9H_{12}N_4$	61,4	6,8	31,8	23
XIVa	146—148	66,9	7,2	26,0	$C_{12}H_{16}N_4$	66,7	7,4	25,9	94
XIVb	103—105	68,0	7,7	24,3	$C_{13}H_{18}N_4$	67,8	7,8	24,4	59
XIVc	112—114	68,9	8,1	22,8	$C_{14}H_{20}N_4$	68,9	8,2	23,0	66
XV	310—312	60,9	6,3	23,7	$C_9H_{11}N_3O$	61,0	6,2	23,7	46

*Compounds (IVa, c) were crystallized from ethanol; (IVb) and (XIIb) from DMFA; (IVd), (VII), and (VIIId) from isopropanol; (Vb) from methanol; (Vd), (XIb), and (XIVa and c) from ethyl acetate; (VIIIa and c) from water; (VIIIb) from DMFA—water (7:3); (XIVb) from heptane; and (XV) from DMFA—water (1:1).
†On the starting material (Vc).

then evaporated and the residue was triturated in ether, after which 1.2 g of compound (IVd) was filtered off. M^+ 207.

5-Cyano-6-(β-dimethylaminovinyl)-1-phenethylpyrimidin-4-one (Va). A mixture of 12 g (44 mmole) of he amide (IVa), 120 ml of the acetal (I), and 90 ml of absolute ethanol was boiled for 2.5 h and was then cooled and the precipitate that deposited was filtered off. Yield 88%. $M^{+\cdot}$ 294. UV spectrum, λ_{max}, nm (log ε): 208 (4.23); 245 (4.10); 295 (4.19); 378 (4.36). PMR spectrum (DMFA-d_6), ppm: 3.04 (t, Ph-CH_2); 3.12 (s, NMe_2); 4.30 (t, CH_2N); 4.92 (d, α-H); 7.28 (m, Ph); 7.96 (d, β-H); 8.05 (s, 2-H).

5-Cyano-6-(β-dimethylaminovinyl) -1-homoveratrylpyrimidin-4-one (Vb) was obtained similarly. $M^{+\cdot}$ 354. UV spectrum, λ_{max}, nm (log ε): 208 (4.47); 235 (4.22); 290 (4.24); 378 (4.35).

1-Cyclohexyl-5-Cyano-6-(β-dimethylaminovinyl)pyrimidin-4-one (Vd). A mixture of 1 g (4.8 mmole) of the amide (IVd), 10 ml of the acetal (I), and 10 ml of DMFA was boiled for 5 h and evaporated, and the residue was triturated with ether, after which 1.1 g of compound (Vd) was filtered off. $M^{+\cdot}$ 272.

The pyrimidinone (Vc) was obtained similarly. Yield 71%. $M^{+\cdot}$ 308. UV spectrum, λ_{max}, nm (log ε): 208 (4.20); 245 (4.08); 295 (4.11); 378 (4.28). PMR spectrum (DMFA-d_6): 1.58 (d, CH_3); 3.02 (s, NMe_2); 2.18 (d, $PhCH_2$); 4.68 (d, α-H); 5.01 (q, NCH); 7.24 (s, Ph); 7.45 (d, β-H); 8.52 (s, 2-H).

α-Cyano-β-cyclohexamino-N-dimethylaminomethylenecrotonamide (VII). A mixture of 1 g (4.8 mmole) of compound (IVd), 6.2 ml of 70% dimethylformamide diethyl acetal (I), and 15 ml of absolute ethanol was boiled for 2.5 h and evaporated, and the residue was triturated with ether, after which 0.6 g of compound (VII) was filtered off. $M^{+\cdot}$ 262.

3-Cyano-4-phenylisopropylaminopyridin-2-one (VIIIc). A mixture of 1 g (4.1 mmole) of compound (IVc), 6 ml of 70% dimethylformamide diethyl acetal (I) and 10 ml of absolute ethanol was boiled for 5 h. Then it was evaporated and the residue was washed with petroleum ether, the ether was decanted off, and the 0.1 g of oil left was treated with 10 ml of a 4% solution of NaOH and the mixture was boiled for 2 h, cooled, and neutralized with 10% HCl, after which 0.5 g of compound (VIIIc) was filtered off. M^+ 253.

3-Cyano-4-(phenethylamino)pyridin-2-one (VIIIa). A mixture of 13.5 g (45.9 mmole) of the pyrimidinone (Va) and 140 ml of a 4% solution of NaOH was boiled for 2 h, cooled, and neutralized with 10% HCl solution, after which 9 g of compound (VIIIa) was filtered off. $M^{+\cdot}$ 239.

The pyridin-2-ones (VIIIb, d, f) were obtained similarly.

1,1-Dicyano-2,4-bis(dimethylamino)penta-1,3-diene (XIb). A mixture of 1 g (7.4 mmole) of the enamine (IX), 5 ml of the acetal (X), and 10 ml of dry xylene was boiled for 7 h and evaporated, and the residue was triturated with ether, after which 1.1 g of compound (XIb) was filtered off. $M^{+\cdot}$ 204. PMR spectrum (DMSO), ppm: 2.10 (s, CH_3); 3.01 (s, 4-NMe_2); 3.35 (s, 2-NMe_2); 4.43 (s, CH=).

Prepared similarly were the dienic diamine (XIa), which has been described previously [5], and the dicyanodiene (XIVa). $M^{+\cdot}$ 216. PMR spectrum, ppm (DMSO): 1.60 (m, 4-CH_2); 2.89 (s, NCH_3); 3.05 (s, NME_2); 3.30 (t, 3-CH_2); 3.48 (t, 5-CH_2); 4.44 (s, CH=).

2-(β, β-Dicyano-α-dimethylaminovinylmethylene)-1-methylpyridine (XIVb). A mixture of 0.6 g (4.4 mmole) of the enamine (IX) in 2.5 ml of the acetal of N-methylvalerolactam (XIIIb) in 6 ml of dry xylene was boiled for 7 h and evaporated; the residue was boiled with 3 ml of heptane, the heptane was decanted off, and the final residue was triturated with ether to give 0.6 g of compound (XIVb). $M^{+\cdot}$ 230. PMR spectrum ($CDCl_3$), ppm: 1.69 (m, 4-CH_2); 1.88 (m, 5-CH_2); 2.68 (t, 3-CH_2); 2.90 (s, NCH_3); 3.03 (s, NMe_2); 3.27 (t, 6-CH_2); 4.42 (s, CH=).

The enamine (XIVc) was obtained similarly from the enamine (IX) and the acetal of N-methylcaprolactam (XIIIc). $M^{+\cdot}$ 244. PMR spectrum (DMSO), ppm: 1.58 (m, 4,5,6-CH_2); 2.71 (t, 3-CH_2); 2.96 (s, NCH_3); 3.06 (s, NMe_2); 3.34 (t, 7-CH_2); 4.25 (m, CH=).

2-Amino-3-cyano-4-dimethylamino-6-methylpyridine (XIIb). A mixture of 1 g (4.9 mmole) of the dicyanodiene (XIb) and 25 ml of alcoholic ammonia was heated in a stainless steel bomb at 130-140°C for 6 h and was then evaporated and the residue was triturated with ethyl acetate, after which 0.2 g of the pyridine (XIIb) was filtered off. $M^{+\cdot}$ 176. IR spectrum, cm^{-1}: 3400, 3300, 3150 (NH_2); 2200 (C≡N).

The 2-aminopyridine (XIIa) described previously [6] was obtained similarly from the dienic diamine (XIa). UV spectrum, λ_{max}, nm (log ε): 235 (4.55), 320 (3.91).

3-Cyano-4-dimethylamino-6-methyl-2-pyridone (XV). A mixture of 5 g of phosphorus pentoxide and 5 ml of phosphoric acid was heated at 100°C and stirred for 30 min, and it was then brought to 20°C and 1 g (4.9 mmole) of compound (XIb) was added and the mixture was heated at 100°C with stirring for 3 h. After this, it was cooled, 15 ml of water was added, and the mixture was neutralized with 10% NaOH solution. The precipitate that deposited was filtered off and washed with water to give 0.4 g of the pyridone (XV). M^{+} 177. IR spectrum, cm^{-1}: 2200 (C≡N); 1610 (C=O).

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