ACETALS OF LACTAMS AND ACID AMIDES.

33.* REACTION OF SECONDARY ENAMINO AMIDES WITH AMIDE ACETALS AND SYNTHESIS OF CONDENSED PYRIMIDINES

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Condensed pyrimidines were synthesized by the reaction of dimethylformamide and dimethylacetamide diethylacetals with secondary enamino amides. It is shown that the piperido[1,2-c]pyrimidine derivative undergoes rearrangement to a 1,6-naphthyridine derivative under mild conditions.

It is known that condensed pyrimidines are formed readily in high yields in the reaction of dimethylformamide acetal (I) with compounds that have amino and carbamido functions in the ortho position [2]. It was recently shown that the reaction of acetal I with a secondary enamino amide, viz., 2-(2'-cyano-2'-carbamido)methylenepyrrolidine (II), leads to 1-cyano-8-dimethylaminomethylene-2,5,7,8-tetrahydro-6H-pyrrolo[1,2-c]pyrimidin-2-one (III) [3].

The aim of the present research was to make a further study of the reaction for the preparation of condensed pyrimidines on the basis of secondary enamino amides as a function of the size of the saturated azaheteroring and the structure of the amide acetal used.

The reaction of O-methylvalerolactam (IV) with cyanoacetamide was used to synthesize 2-(2'-cyano-2'-carbamido)methylenepiperidine (V), which was subsequently subjected to condensation with acetal I under the conditions used to obtain two-ring system III. The product was recrystallized from water and was identified from the results of elementary analysis as the six-membered analog of III without a dimethylaminomethylene residue in the 9 position. However, the spectral data are not in agreement with this assumption: An intense molecular-ion peak ($M^{+\bullet}$) with m/e 175 and peaks corresponding to the elimination of $CH_3^{\bullet}$ (m/e 160), $CN^{\bullet}$ (m/e 149), CO (m/e 147), and C_2H_5 (m/e 146) groups from the molecular ion are observed in the mass spectrum of the compound obtained (VI). A characteristic feature of the spectrum of this compound is the presence of an intense peak with m/e 174, which indicates the advantageousness of charge stabilization in the resulting $[M - N]^+$ ion. Signals of three CH_2 groups at 1.74, 2.48, and 3.28 ppm, of one aromatic proton at 7.06 ppm, and of a proton of an NH group at 7.46 ppm are observed in the PMR spectrum of this compound (in d_6-DMSO). These data unambiguously refute the pyrido[1,2-c]pyrimidine structure for the product obtained and indicate that VI is 8-cyano-1,2,3,4,6,7-hexahydro-1,6-naphthyrid-7-one. Compound VI is a secondary reaction product. An analog of III, viz., 1-cyano-9-dimethylaminomethylene-2,5,6,7,8,9-hexahydropyrido[1,2-c]pyrimidin-2-one (VII), which is converted to naphthyridone VI when it is heated in water (during recrystallization), is formed in the first stage.

The structure of VII is confirmed by data from the PMR and mass spectra. Signals of an $N(CH_3)_2$ group at 3.55 ppm, of 6-, 7-, and 8-CH_2 groups at 4.23, 2.20, and 2.81 ppm, respectively, of an aromatic proton at 8.81 ppm, and a =C—H proton of a dimethylaminomethylene residue at 8.07 ppm are observed in the PMR spectrum (in CF_3COOH).

The most intense peak in the mass spectrum belongs to the molecular ion with m/e 230. Peaks of fragments corresponding to fragmentation of the side chain and the saturated ring are also observed: $[M - H]^+$ (299), $[M - CH_3]$ (215), $[M - C_2H_4]^+$ (202), $[M - C_2H_5]^+$ (201), and $[M - NC_3H_6]^+$ (174).

*See [1] for communication 32.

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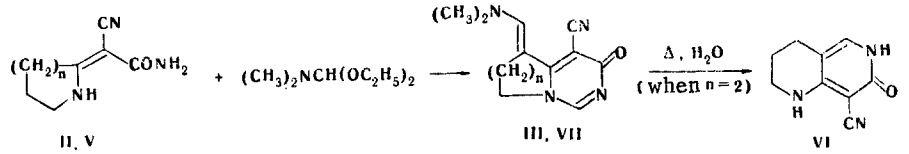
Opening of the pyrimidine ring under the influence of nucleophilic reagents has already been the subject of a detailed study [4]. Our case is characterized by two peculiarities, viz., the mildness of the conditions and the fact that the attack is directed to the 2 position of the pyrimidine ring.



II, V

III, VII

VI

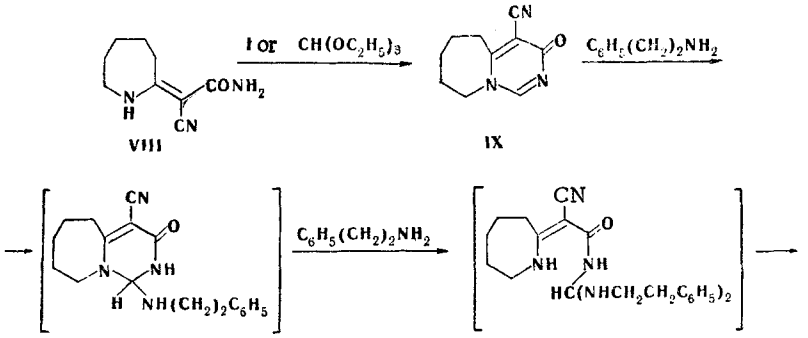
II, III n = 1; V, VII n = 2

Attempts to carry out the recyclization of III under these conditions were unsuccessful — hydrolysis of the enamine fragment in the 8 position and deformylation were observed in addition to opening of the pyrimidine ring in this case. As a result, the hydrolysis product is starting enamino amide II.

The condensation of seven-membered enamino amide VIII with dimethylformamide acetal (I) proceeds via a different mechanism. Because of steric hindrance in this reaction, the acetal does not undergo condensation in the 9 position of the pyrimido[3,4-a]azepine ring, and two-ring system IX is formed. Signals of protons at 1.68 (7, 8, 9-CH_2), 2.93 (10-CH_2), 4.17 (6-CH_2), and 8.41 ppm (4-CH) are observed in the PMR spectrum of IX (in d_6-DMSO). It should be noted that ethyl orthoformate does not react with enamino amide VIII under these conditions. However, two-ring system IX is formed when VIII is heated with $CH(OEt)_3$ in the presence of acetic anhydride.

In the case of two-ring system IX we made a more detailed analysis of the opening of the pyrimidine ring in compounds of this type under the influence of nucleophilic reagents. We selected the reaction of IX with β-phenylethylamine as a model reaction.

As a result of the reaction we isolated starting enamino amide VIII. N,N'-Bis-β-phenylethylformamidine X was detected among the reaction products from the data obtained by chromatographic mass spectrometry, and this makes it possible to represent the scheme of the cleavage process in the following way:



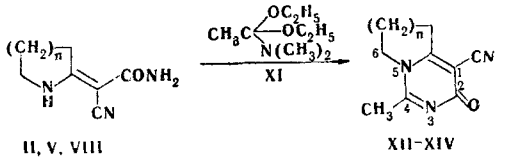
VIII

IX

$\longrightarrow$ VIII + $C_6H_5(CH_2)_2N{=}CHNH(CH_2)_2C_6H_5$

X

It is apparent from the data presented above that attack by acetal I on the CH_2 group in the 4 position of the pyrimidine ring is extremely sensitive to the steric hindrance caused by the size and conformation of the saturated ring. The steric factor should play a significant role on passing from dimethylformamide acetal (I) to a homologous acetal, viz., dimethylacetamide diethylacetal (XI). In fact, the formation of a pyrimidine ring is observed in the reaction of acetal XI with enamino amides II, V, and VIII, and condensation in the 8, 9, and 10 positions (i.e., at the CH_2 groups of the saturated rings) does not occur.



II, V, VIII

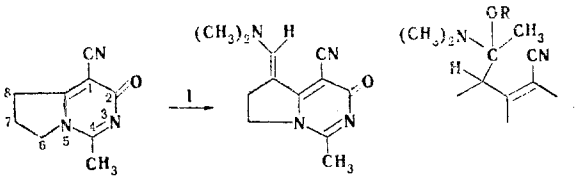
XI

XII-XIV

II, XII n = 1; V, XIII n = 2; VIII, XIV n = 3

The fragmentation of the resulting two-ring heterocycles XII-XIV proceeds via two principal pathways: first, via elimination of CO from the molecular ion, and, second, via stepwise fragmentation of the saturated ring included in the composition of the XII-XIV molecules with the formation of the following fragments: $[M - C_2H_5]^+$ with m/e 146, $[M - C_3H_5]^+$ with m/e 134, and $[M - C_3H_5 - CO]^+$ with m/e 106 for XII; $[M - C_2H_5]^+$ with m/e 160, $[M - C_3H_5]^+$ with m/e 148, $[M - C_4H_7]^+$ with m/e 134, and $[M - CO - C_3H_5]^+$ with m/e 120 for XIII; $[M - C_2H_5]^+$ with m/e 174, $[M - C_3H_5]^+$ with m/e 162, $[M - C_3H_7]^+$ with m/e 160, $[M - CO - C_3H_5]^+$ with m/e 134, $[M - C_5H_9]^+$ with m/e 134, and $[M - CO - C_5H_9]^+$ with m/e 106 for XIV. The spectra of these compounds do not contain an $[M - H]^+$ ion peak, and this also indicates a polymethylene-pyrimidine structure (rather than a naphthyridine structure, as for VI) for these compounds. The PMR spectra of XII-XIV also satisfactorily confirm the indicated structure (see the experimental section).

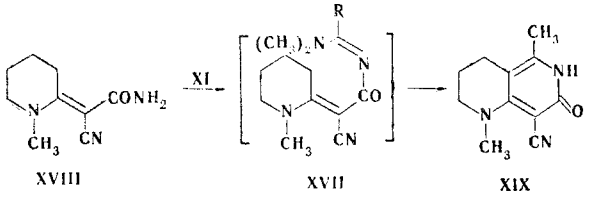
In order to demonstrate that condensation in the 8 position of XII is possible when a less bulky acetal is used, we carried out the condensation of two-ring system XII with dimethylformamide acetal (I). As a result, we synthesized 1-cyano-4-methyl-8-dimethylaminomethylene-2,5,7,8-tetrahydro-6H-pyrrolo[1,2-c]pyrimidin-2-one (XV).



XII XV XVI

Thus, because of steric interaction between the CN group of the pyrimidine ring and the CH_3 group of acetal XI in an intermediate of the XVI type, condensation of acetal XI in the 8 position of two-ring system XII does not occur.

It is interesting to note that the presence of a CH_3 group promotes the process in a condensation of another type, viz., in the formation of a pyridone ring on the basis of tertiary enamino amides and amido acetals: the rate of cyclization increases so much that the intermediate enamino acylamidine (XVII, R = CH_3) cannot be isolated, and a naphthyridone (XIX, R = CH_3) is formed immediately.

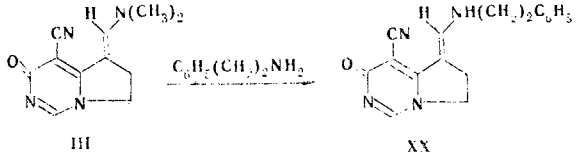


XVIII XVII XIX

XVII, XIX R = CH_3

It has been previously shown that XVII (R = H) is readily isolated in the reaction of amide XVIII with acetal I [5].

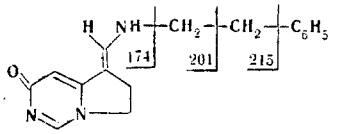
Let us note that the UV spectra of VI, XIX (R = H), and XIX (R = CH_3) are similar to one another but differ substantially from the spectra of condensed pyrimidines (see the experimental section).



III XX

In conclusion, we studied the reaction of two-ring system III with β-phenylethylamine. In this case cleavage of the pyrimidine ring is not observed, and the process proceeds via the most favorable pathway, i.e., at C_9 with transamination, and XX is formed. A molecular-ion peak ($M^{+\bullet}$) with m/e 292 is observed in the mass spectrum of XX. The fragmentation of the molecular ion takes place through the stepwise detachment of the substituent in the 8 position with the formation of the following ions $[M - Ph]^+$ with m/e 215, $[M - PhCH_2]^+$ with m/e 201, $[M - PhC_2H_4]^+$ with m/e 188, and $[M - PhC_2H_4N]^+$ with m/e 179. Elimination of the

carbonyl group from the molecular ion is observed in addition to the principal fragmentation pathway; this is characteristic for all of the compounds of this class.



EXPERIMENTAL

The mass spectra were obtained with an MAT-112 chromatographic mass spectrometer at an ionization-chamber temperature of 200°C and an ionizing-electron energy of 70 eV. The PMR spectra were recorded with XL-100 and C-60 HL spectrometers with tetramethylsilane as the internal standard.

2-(2'-Cyano-2'-carbamido)methylenepiperidine (V). A mixture of 7.4 g (0.655 mole) of O-methylvalerolactim and 5 g (0.595 mole) of cyanoacetamide was heated at 120°C for 2 h, during which the solid material initially dissolved, after which a precipitate began to form immediately. The latter was treated with a small amount of isopropyl alcohol and removed by filtration to give 8.3 g (84%) of a substance with mp 177-180°C (from water). Found: C 58.2; H 6.6; N 25.8%. $C_8H_{11}N_3O$. Calculated: C 58.2; H 6.7; N 25.4%.

8-Cyano-1,2,3,4,6,7-hexahydro-1,6-naphthyrid-7-one (VI). A 0.25-g (1.08 mmole) sample of VII was refluxed in 10 ml of H_2O for 1.5 h, after which the mixture was cooled, and the precipitate was washed with alcohol and removed by filtration to give 0.15 g (79%) of a substance with mp ~300°C (from water). IV spectrum (0.1 N NaOH), λ_{max} (log ε): 290 (3.72) and 322 nm (3.81). Found: C 61.7; H 5.1; N 24.3%. $C_9H_9N_3O$. Calculated:C 61.7; H 5.1; N 24.0%.

1-Cyano-9-dimethylaminomethylene-2,5,6,7,8,9-hexahydropyrido[1,2-c]pyrimidin-2-one (VII). A solution of 8.1 g (0.055 mole) of dimethylformamide acetal (I) in 20 ml of absolute alcohol was added to 3 g (18.2 mmole) of V, and the mixture was refluxed for 4 h. It was then cooled, and the precipitate was removed by filtration to give 2.65 g (71%) of a product with mp 263-265°C (from methanol). Found: C 62.5; H 6.1; N 24.3%. $C_{12}H_{14}N_4O$. Calculated: C 62.6; H 6.1; N 24.3%. 1-Cyano-2,5,7,8,9,10-hexahydro-6H-pyrimido[3,4-a]azepin-2-one (IX) was similarly obtained.

The following compounds were similarly obtained except that the reaction was carried out by refluxing in toluene for 3 h: XII [PMR spectrum in CF_3COOH: 2.98 (CH_3), 4.61 (6-CH_2), 2.61 (7-CH_2), and 3.58 ppm (8-CH_2)], XIII [PMR spectrum in CF_3COOH: 3.01 (CH_3), 4.37 (6-CH_2), 2.17 (7-CH_2, 8-CH_2), and 3.35 (9-CH_2). UV spectrum in 0.1 N NaOH, λ_{max} (log ε): 292 nm (4.11)], XIV [PMR spectrum in CF_3COOH: 3.05 (CH_3), 4.57 (6-CH_2), 2.03 (7-CH_2, 8-CH_2, and 9-CH_2), and 3.43 pp, (10-CH_2). UV spectrum in 0.1 N NaOH, λ_{max} (log ε): 306 nm (4.28)], and XV and XIX [UV spectrum in 0.1 N NaOH, λ_{max} (log ε): 292 (3.86) and 328 nm (3.97)]. The results of elementary analysis, the melting points, and the yields are presented in Table 1.

Reaction of 2-(2'-Cyano-2'-carbamido)methylenehexahydroazepine (VIII) with ethyl orthoformate. A mixture of 2 g (11.2 mmole) or VIII, 17.8 g (0.12 mole) of ethyl orthoformate, and 37.2 g (0.37 mole) of acetic anhydride was refluxed for 3.5 h, after which it was allowed to stand overnight. It was then evaporated to dryness *in vacuo*, and the residue was treated with isopropyl alcohol and removed by filtration to give 1.3 g (61%) of IX with mp 192-194°C. This product was identical to a sample of the compound synthesized from the known VIII and acetal I (Table 1).

1-Cyano-8-β-phenylethylaminomethylene-2,5,7,8-tetrahydro-6H-pyrrolo[1,2-c]pyrimidin-2-one (XX). A mixture of 2.35 g (15.6 mmole) of II and 3.75 g (0.031 mole) of phenylethylamine was heated at 150°C for 4 h, after which it was allowed to stand overnight. It was then washed with acetone, and the precipitate was removed by filtration to give 1.5 g (33%) of a product with mp 265-268°C. Found: C 70.0; H 5.4; N 19.2. $C_{17}H_{16}N_4O$. Calculated: C 69.9; H 5.5; N 19.2%.

Reaction of Two-Ring System IX with β-Phenylethylamine. A mixture of 1.3 g (7.25 mmole) of IX and 1.76 g (14.5 mmole) of phenylethylamine was refluxed for 3 h, after which the alcohol was removed by distillation, and the residue was treated with a small amount of ethyl acetate, and the precipitate was removed by filtration to give 0.53 g (41%) of a product with

TABLE 1. Condensed Pyrimidines IX, XII-XV, and XIX

Compound	mp., °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IX	192—194 [a]	63,1	5,6	22,7	$C_{10}H_{11}N_3O$	63,5	5,8	22,2	77
XII	225—227 [b]	61,8	5,3	24,2	$C_9H_9N_3O$	61,7	5,1	24,0	66
XIII	235—238 [b]	63,6	5,6	22,5	$C_{10}H_{11}N_3O$	63,5	5,8	22,2	67
XIV	202—205 [b]	65,2	6,5	20,9	$C_{11}H_{13}N_3O$	65,0	6,4	20,7	88
XV	242—245 [c]	62,4	6,4	24,1	$C_{12}H_{14}N_4O$	62,6	6,1	24,4	96
XIX	330[c]	65,1	6,13	20,8	$C_{11}H_{13}N_3O$	65,0	6,4	20,7	30

[a]From water. [b]From methanol. [c]From DMF.

mp 136-138°C (from alcohol). Found: C 60.6; H 7.0; N 23.9%. $C_9H_{13}N_3O$. Calculated: C 60.4; H 7.3; N 23.5%.

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HETEROCYCLIC DERIVATIVES OF PURINES.

3.* SYNTHESIS AND MASS SPECTROMETRIC STUDY OF IMIDAZO[1,2-]PURINE

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and A. K. Sheinkman

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A mixture containing 65% 1-methyl-2-phenyl-5,7-dichloro- and 35% 1-methyl-2-phenyl-3,5,7-trichloroimidazo[1,2-f]purine (the percentages of the components were established by means of chromatographic mass-spectrometric analysis) was obtained by refluxing 1,8-dimethyl-2-phenylimidazo[1,2-f]xanthine in $POCl_3$ in the presence of excess PCl_5. Reduction of this mixture with concentrated HCl in the presence of red phosphorus leads to 1-methyl-2-phenylimidazo[1,2-f]purine, while heating with piperidine gives a mixture consisting of 55% 1-methyl-2-phenyl-6-piperidino-8-chloroimidazo[1,2-f]purine and 45% 1-methyl-2-phenyl-3,8-dichloro-6-piperidinoimidazo[1,2-f]purine. The IR, PMR, and mass spectra of the compounds obtained are discussed.

In a preceding communication [1] we demonstrated that imidazo[1,2-f]xanthine derivatives readily undergo electrophilic substitution. The behavior of imidazo[1,2-f]purine derivatives with respect to nucleophilic and electrophilic substitution reactions is of definite interest. The literature contains data on the synthesis of derivatives of imidazo[1,2-a]purine [2], imidazo[2,1-b]purine [3], and imidazo[2,1-i]purine [4, 5], whereas no information on the synthesis of imidazo[1,2-f]purine is available.

*See [1] for communication 2.

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