ACETALS OF LACTAMS AND ACID AMIDES.

35.* SYNTHESIS OF CONDENSED TWO- AND THREE-RING PYRIDINE SYSTEMS ON THE BASIS OF ENAMINO AMIDES

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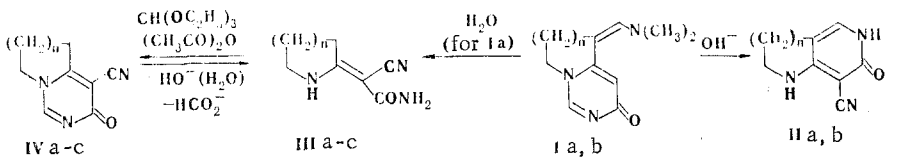
UDC 547.75'83'892.07

The synthesis of 2,3,5,6-tetrahydropyrrolo[3,2-c]pyrid-6-one was accomplished by rearrangement of 8H,1-cyano-8-dimethylaminomethylene-2,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine. Pyrrolo[3,2-c]pyrimidine, 1,6-naphthyridine, and pyrimido[4,3-b]-azepine derivatives were synthesized on the basis of enamino dinitriles. The hydrolysis of 8H,1-cyano-8-dimethylaminomethylene-2,5,6,7-tetrahydropyrrolo[1,2-c]-pyrimidine in 50% CH_3COOH leads to a pyrrolo[1,2-c]pyrido[4',3'-d]pyrimidine derivative. A similar dipyrido[4,3-d—1',2'-c]pyrimidine derivative was obtained from 1-cyano-9-dimethylaminomethylene-2,5,6,7,8,9-hexahydropyrido[1,2-c]pyrimidine under these conditions, and 3,4-dioxo-3,4,7,8,9,10-hexahydropyrido[1,2-c]pyrano[4',3'-d]-pyrimidine was synthesized by treatment with a 1 N solution of HCl.

It has been previously established [2] that the pyrimidine ring in pyrrolo-, pyrido-, and azepino[1,2-c]pyrimidine derivatives is readily cleaved by the action of nucleophilic reagents. Whereas 1-cyano-9-dimethylaminomethylene-2,5,6,7,8,9-hexahydropyrido[1,2-c]pyrimid-2-one (Ib) is converted to 1,6-naphthyridine derivative IIb when it is heated in water, not only a similar transformation but also splitting out of the dimethylaminomethylene residue in the 8 position to give enamino amide IIIa are characteristic for its five-membered analog Ia [2].

A detailed study of the factors that affect opening of the pyrimidine ring and the character of the products was required to explore the possibility of the synthesis of 7-cyano-2,3,5,6-tetrahydropyrrolo[3,2-c]pyrid-6-one (IIa) and other condensed pyridines. Polymethylenepyrimidines IVa-c, which were obtained by the method in [2] by the reaction of enamino amides IIIa-c with ethyl orthoformate in the presence of acetic anhydride, were selected for the investigation. On the basis of the scheme in [2], which we proposed for IVc → IIIc cleavage by the action of β-phenylethylamine,† we assumed that formic acid should be obtained during the reaction as a result of the action of water or the hydroxide anion.

We measured the rates of the **IVa-c → IIIa-c transformation** by means of the recently developed accurate gasometric method for the determination of formic acid [3].



IIIa n=1; b n=2; c n=3

*See [1] for Communication 34.

†The scheme was confirmed by identification of N,N'-bis-β-phenylethylformamidine among the products [2].

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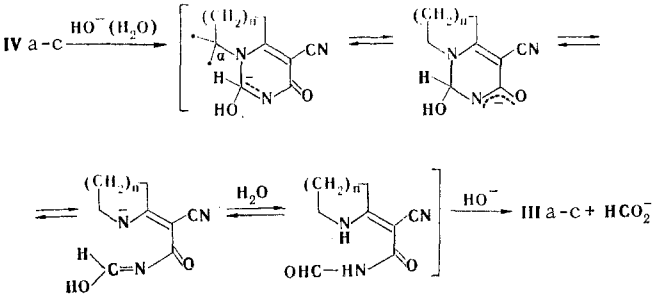
The measured rate constants and activation parameters are presented in Table 1. It is apparent that hydrolysis takes place rapidly (see [4] for data on the hydrolysis of a number of cyclic amidines); the steric requirements of the activated complex are relatively low — the entropy of activation is only −7.8 eu. From this it is logical to assume that the cyclic structure is still retained in the determining step and that the slowest step, as in the case of cyclic amidines [4], is evidently attack by the hydroxide anion at the 2 position of the pyrimidine ring. The scheme of the process can be represented as follows:



The data in Table 1 show that the rates of hydrolysis of pyrimidines condensed with five- and six-membered rings are the same, whereas the rate is somewhat decreased for the seven-membered compound, probably because of steric repulsion of the hydroxide anion by the protons of the α-methylene link of the hexahydroazepine ring.

Ring cleavage takes place smoothly only in an alkaline medium. If the buffer capacity of the solution is not sufficient to maintain a constant pH value, the process is slowed down as formic acid is formed (Table 2).

A gasometric method was also used to study the hydrolysis of two-ring system Ib [2], which has a dimethylaminomethylene group in the 9 position. We found that the amount of formic acid liberated here is less than 100%, whereas according to data from thin-layer chromatography (TLC), the Ib → IIb conversion was quantitative. In this case dimethylformamide (DMF) [determined quantitatively by means of gas–liquid chromatography (GLC)] was formed in addition to HCOOH, i.e., cleavage of the pyrimidine ring was realized not only by the action of hydroxide ion but also through the addition to the 2 position of pyrimidine (the 4 position of the two-ring system) of the dimethylamine liberated in the reaction. In fact, the Ib → IIb conversion also takes place in the reaction with amines such as benzylamine (see the Experimental section).

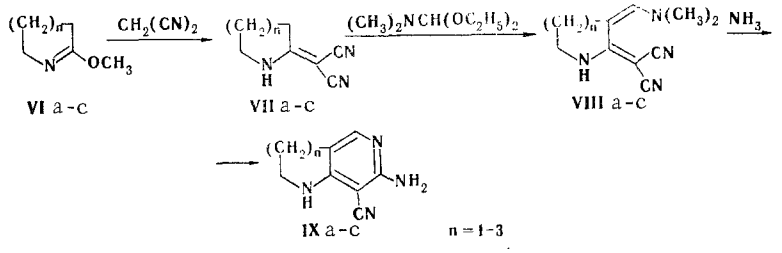
It has been previously shown [5] that the rate of opening of the pyrimidine ring increases as the pH of the solution is increased. In addition, the hydrolysis of the enamine (dimethylaminomethylene) fragment, which usually precedes ketone cleavage [6] (the Ia → IIIa process), should be slowed down as the basicity of the medium is increased, as is characteristic of enamines [7]. Hence, an increase in the pH should promote the Ia → IIa process. In fact, when two-ring system Ia is heated in water in the presence of a tenfold excess of triethylamine* or in 5% NaOH, the reaction proceeds unambiguously to give pyrrolo-2-pyridone IIa rather than with splitting out of a dimethylaminomethylene residue, as described in [2].

Thus on the basis of enamino amides IIIa,b we have developed optimal methods for the synthesis of derivatives of pyrrolo[3,2-c]pyridine IIa and 1,6-naphthyridine IIb (through a step involving the formation of condensed pyrimidines Ia, b), which do not have substituents in the 1 position of the two-ring systems. However, we found that it was impossible to obtain a similar structure with a condensed seven-membered ring by this method, since we were unable to subject two-ring system IVc to reaction with dimethylformamide diethylacetal (V) to obtain a dimethylaminomethylene derivative of the Ia,b type even at 200°C in a bomb. The construction of molecular models shows that in the case of pyrimido[3,4-a]azepine IVc the methylene link in the 10 position is considerably more shielded by the cyano group than in five- and six-membered analogs IVa,b in the 8 or 9 positions, respectively. Data for deuterium exchange of the protons in two-ring systems IVa-c also constitute evidence for this. When IVa,b are allowed to stand for a long time in CD_3COOD, the signals of the protons in the 8 and 9 positions at 3.05 and 3.08 ppm, respectively, vanish completely, whereas the intensity of the

*Traces of IIIa are detected by TLC in this case.

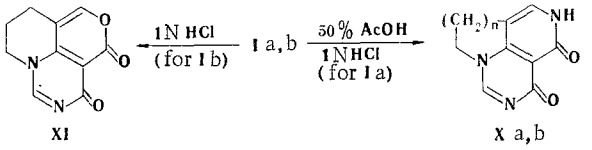
signal of the 10-CH_2 group at 3.16 ppm does not change in the case of IVc under the same conditions.

Another method was studied for the preparation of the pyrido[4,3-b]azepine structure (just as in the case of representatives of pyrrolo[3,2-c]pyridines and 1,6-naphthyridines). The reaction of O-methylbutyro-, valero-, and caprolactims VIa-c with malononitrile was used to synthesize enamino nitriles VIIa-c, from which diene diamines VIIIa-c were obtained by the action of acetal V. When diene diamines VIIIa-c were heated in a bomb with a methanol solution of ammonia, they were converted to derivatives of the desired two-ring systems IXa-c.



VI a-c VII a-c VIII a-c IX a-c n = 1-3

It is apparent from the material set forth above that the pyrimidine ring of I is completely stable in acidic solutions. This fact was used for the synthesis of heterocyclic three-ring systems on the basis of two-ring systems Ia,b. When we treated these compounds with 50% CH_3COOH we obtained three-ring systems Xa,b, evidently through saponification of the cyano group to give a carbamide group with subsequent cyclization.



XI I a,b X a,b

The reaction proceeds via a different pathway when Ib is treated with a stronger acid, viz., 1 N HCl — a three-ring derivative of 2-pyrone (XI) is formed, i.e., the CN group is saponified, evidently to a carboxy group with subsequent cyclization. It should be noted that in the case of Ia, a pyrone ring is not formed under these conditions, and the same 2-pyridone derivative (Xa) as that obtained in the case of hydrolysis in acetic acid is isolated.

EXPERIMENTAL

The IR spectra of mineral oil pastes of the compounds were obtained with a Perkin-Elmer-599 spectrometer. The UV spectra of solutions of the compounds in alcohol were obtained with EPS-3 and Perkin-Elmer-575 spectrophotometers. The PMR spectra of the compounds were recorded with an XL-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with an MKh-1303 mass spectrometer equipped with a direct inlet into the source at an ionizing-voltage energy of 50 eV.

Method for the Determination of the Rate Constants for Cleavage of the Pyrimidine Ring. A 20-ml sample of a 1.5 M phosphate buffer (if the solution had partially crystallized, it was warmed slightly and then cooled to 20°C) was placed in a reaction cell, which was a thermostatted four-necked flask equipped with a reflux condenser, thermometer, gas (N_2) bubbling tube, and a connecting tube for sample selection. After a predesignated temperature was reached, 0.15-0.30 g (the weight by difference) of the substance was introduced into the cell with continuous bubbling in of nitrogen. Samples (0.5 ml) were selected every 15-40 min by means of an accurate graduated pipette. An apparatus for microdetermination of nitrogen by the Dumas method [8] was used for the quantitative determination of CO. The sample was introduced into a reaction vessel equipped with outlet tubes for a stream of CO_2 and a dropping funnel for feeding in concentrated H_2SO_4 (the catalyst). The system in the assembly was purged with carbon dioxide (3-5 min) until the size of the bubbles passing into the graduated part of the gasometer became vanishingly small. Without interfering with the feeding in of carbon dioxide gas, 0.2-0.3 ml of sulfuric acid was added dropwise and carefully to the reac-

TABLE 1. Rate Constants and Activation Parameters (for IVc) for the IV → III Process in a 1.5 M Phosphate Buffer Solution with pH 8

Indexes	IVa	IVb	IVc		
	80°	80°	70°	80°	90°
$K \cdot 10^3$, min^{-1}	5,58±0,11	5,58±0,09	1,21±0,47	3,53±0,13	9,63±0,56
$\Delta H^{\neq}$ kcal/mole	—	—		24,9±1,2	
$\Delta S^{\neq}$ cal/mole·deg	—	—		−7,8±3,3	

TABLE 2. Degree of Conversion of IVb to IIIb as a Function of the Buffer Concentration

Molar concn. of the phosphate buffer	Yield of IIIb in percent prior to spontaneous cessation of the reaction
0,2	12
1,0	24
1,5	100

tion vessel from the dropping funnel. The liberated carbon monoxide was collected in an azotometer filled with 50% KOH. Bubbling in of carbon dioxide gas was terminated after the size of the gas bubbles passing into the graduated part of the azotometer became vanishingly small. The rate constants were calculated by means of a first-order equation.

1H,6-Oxo-7-cyano-2,3,5,6-tetrahydropyrrolo[3,2-c]pyridine (IIa). A 1.0-g (4.6 mmole) sample of Ia was refluxed in 30 ml of 5% aqueous alkali for 1 h, after which the mixture was evaporated, and 10 ml of H_2O was added to the residue. The mixture was filtered to give 0.6 g (80%) of two-ring system IIa with mp >300°C (from DMF). Found: C 59.6; H 4.5; N 26.2%. $C_8H_7N_3O$. Calculated: C 59.6;

8-Cyano-1,2,3,4,6,7-hexahydro-1,6-naphthyrid-7-one (IIb). A 1.15-g (5 mmole) sample of two-ring system Ib and 1.60 g (15 mmole) of benzylamine were refluxed in 30 ml of DMF for 5 h, after which the mixture was evaporated, and the residue was triturated with acetone. The mixture was filtered to give 0.5 g (57%) of IIb with mp >300°C (from DMF) [2]. UV spectrum (in 0.1 N NaOH), λ_{max} (log ε): 224 (4.47), 290 (4.13), and 320 nm (4.13).

2H,1-Cyano-2-oxo-5,6,7,8-tetrahydropyrrolo[2,1-c]pyrimidine (IVa). A mixture of 6.0 g (4 mmole) of enamide IIIa in 60 ml of ethyl orthoformate and 110 ml of acetic anhydride was stirred at 150°C for 1 h, after which it was evaporated, and the residue was triturated in ethyl acetate. The mixture was filtered to give 3.2 g (50%) of Va with mp 176-178°C (from 2-propanol). IR spectrum: 1615 (C=N), 1640 (C=O), and 2220 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 200 (4.14), 243 (3.76), and 284 nm (3.95). PMR spectrum (CD_3COOD): 1.97 (7-H), 3.05 (8-H), 4.07 (6-H), and 8.35 ppm (4-H). Found: C 59.6; H 4.5; N 26.0%. $C_8H_7N_3O$. Calculated: C 59.6; H 4.4; N 26.1%.

Similarly, from 20 g (1.21 mole) of enamide IIIb, 150 ml of ethyl orthoformate, and 300 ml of acetic anhydride we obtained 15.0 g (71%) of IVb with mp 197-198°C (from methanol). IR spectrum: 1610 (C=N), 1630 (C=O), and 2220 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 205 (4.20), 246 (4.05), and 290 nm (3.81). PMR spectrum (in CD_3COOD): 2.03 (7, 8-H), 3.08 (9-H),

4.16 (6-H), and 8.47 ppm (4-H). Found: C 61.6; H 5.4; N 24.1%. $C_9H_9N_3O$. Calculated: C 61.7; H 5.1; N 24.0%.

2-Dicyanomethyleno-1,2,3,4,5,6-hexahydropyridine (VIIb). A mixture of 11.4 g (0.1 mole) of O-methylvalerolactim (VIb) and 6.6 g (0.1 mole) of malononitrile in 30 ml of absolute alcohol was maintained at 20°C for 1 h, after which the precipitate was removed by filtration to give 11.6 g (79%) of enamine IXb with mp 145-146°C (from alcohol). Found: C 65.4; H 6.0; N 28.3%. $C_8H_9N_3$. Calculated: C 65.3; H 6.1; N 28.6%. Similarly, from 22.0 ml of O-methylcaprolactim VIc and 9.9 g of malononitrile we obtained 22.0 g (91%) of VIIc with mp 161-162°C (from alcohol). Found: C 67.4; H 6.8; N 26.4%. $C_9H_{11}N_3$. Calculated: C 67.1; H 6.8; N 26.1%. Similarly, from 20.0 ml of O-methylbutyrolactim VIa and 9.9 g of malononitrile we obtained 19.0 g (98%) of VIIa with mp 167.5-168.5°C (from alcohol). Found: C 63.1; H 5.1; N 31.7%. $C_7H_7N_3$. Calculated: C 63.1; H 5.3; N 31.6%.

2-Dicyanomethyleno-3-(N,N-dimethylaminomethyleno)pyrrolidine (VIIIa). A mixture of 3.1 g of enamine VIIa and 5 ml of dimethylformamide acetal in 20 ml of dry DMF was refluxed for 4 h, after which it was evaporated, and the residue was triturated in ethyl acetate. The mixture was filtered to give 3.2 g (73%) of VIIIa with mp 212-213°C (from alcohol). Found: C 63.9; H 6.5; N 30.0%. $C_{10}H_{12}N_4$. Calculated: C 63.8; H 6.4; N 29.8%. Similarly, from VIIb we obtained VIIIb, with mp 185-186°C (from alcohol), in 81% yield. Found: C 65.4; H 7.1; N 27.7%. $C_{11}H_{14}N_4$. Calculated: C 65.3; H 7.0; N 27.7%. Similarly, from VIIc we obtained VIIIc, with mp 155-156° (from alcohol), in 32.4% yield. Found: C 66.6; H 7.5; N 26.2%. $C_{12}H_{16}N_4$. Calculated: C 66.7; H 7.4; N 25.9%.

1H,6-Amino-7-cyano-2,3-dihydropyrrolo[3,2-c]pyridine (IXa). A mixture of 3.0 g (15.9 mmole) of enamino nitrile VIIIa in 45 ml of methanol saturated with NH_3 was heated in a bomb at 150°C for 5 h, after which it was evaporated, and the precipitate was removed by filtration to give 1.0 g (47%) of two-ring system IXa. Found: C 60.0; H 5.2; N 34.9%. $C_8H_8N_4$. Calculated: C 60.0; H 5.0; N 35.0%. Similarly, from enamino nitrile VIIIb we obtained two-ring system IXb, with mp 225-226°C (from water), in 97% yield. Found: C 62.1; H 5.8; N 32.1%. $C_9H_{10}N_4$. Calculated: C 62.1; H 5.7; N 32.2%. Similarly, from enamino nitrile VIIIc we obtained two-ring system IXc, with mp 195-196°C (from methanol), in 40% yield. Found: C 63.8; H 6.3; N 29.7%. $C_{10}H_{12}N_4$. Calculated: C 63.8; H 6.4; N 29.8%.

1,8-Dioxo-4,5-dimethylene-1,2,5,8-hexahydropyrido[4,3-d]pyrimidine (Xa). A) A 1.0-g (4.6 mmole) sample of two-ring system Ia was stirred at 50°C in 50% AcOH for 4 h, after which it was cooled and filtered to give 0.75 g (85%) of Xa with mp 300°C (from DMF). IR spectrum: 1615 and 1660 cm^{-1} (C=N, C=O). Mass spectrum: $M^{+\bullet}$ 189. Found: C 57.8; H 3.6; N 22.4%. $C_9H_7N_3O_2$. Calculated: C 57.2; H 3.7; N 22.2%.

B) A 2.16-g (10 mmole) sample of Ia was maintained at 20°C in 50 ml of 1 N HCl for 24 h, after which the precipitate was removed by filtration to give 1.5 g (79%) of Xa with mp > 300°C (from DMF). Mass spectrum: $M^{+\bullet}$ 189. Under conditions similar to method A, from 1.0 g (4.3 mmole) of double ring Ib, we obtained 0.7 g (80%) of Xb, mp 300°C (from DMF). Mass spectrum: $M^{+\bullet}$ 203. Found: C 56.2; H 4.5; N 19.8; H_2O 5.6%. $C_{10}H_9N_3O_2 \cdot 2/3\,H_2O$. Calculated: C 55.8; H 4.8; N 19.9; H_2O 5.6%.

1,8-Dioxo-4,5-dimethylene-5,8-dihydropyrano[4,3-d]pyrimidine (XI). A 1.0-g (4.3 mmole) sample of the two-ring system was allowed to stand in 30 ml of 1 N HCl for 4 h, after which the mixture was evaporated and filtered to give 0.35 g (40%) of XI with mp 300°C (from DMF). Mass spectrum: $M^{+\bullet}$ 204. Found: C 58.6; H 4.3; N 13.8%. $C_{10}H_8N_2O_3$. Calculated: C 58.8; H 3.9; N 13.7%.

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EPR SPECTROSCOPY AND POLAROGRAPHY OF NITROAZOLES.

3.* NITROPYRAZOLES

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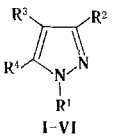
The results of an EPR investigation are presented with polarographs of electrochemical excitation of nitropyrazoles in acetonitrile. It is shown that 3- and 4-nitropyrazoles are excited in two single-electron stages with formation of dianion radicals. Upon excitation, N-alkylnitropyrazoles form stable anion radicals. 1-Nitro- and 1,4-dinitropyrazoles are excited upon splitting off of the NO_2 anion. Excitation potentials of the nitropyrazoles and hyperfine interaction constants for the corresponding ion radicals are given.

Pyrazole derivatives have found extensive application as medicinal preparations (antipyrine, pyramidon, and analgin) [2]. The nitro derivatives of heterocycles have the most clearly expressed biological activity [3]. There is no doubt that the mechanism of their action includes a step involving one-electron transfer [4]. The study of the behavior of nitropyrazoles in redox processes and the structure of their free radicals and the distribution of spin density in them is therefore extremely timely.



I-VI

I $R^1=R^3=R^4=H$, $R^2=NO_2$; II $R^1=R^2=R^4=H$, $R^3=NO_2$; III $R^1=CH_3$, $R^2=R^4=H$, $R^3=NO_2$; IV $R^1=C_2H_5$, $R^2=R^4=H$, $R^3=NO_2$; V $R^1=NO_2$, $R^2=R^3=R^4=H$; VI $R^1=R^3=NO_2$, $R^2=R^4=H$

In a continuation of our research on nitroazoles [1, 5] we studied the electrochemical reduction of C- and N-nitropyrazoles I-VI in acetonitrile by EPR spectroscopy and polarography.

Nitrogen-unsubstituted 3(5)-nitro- and 4-nitropyrazoles are reduced in two one-electron steps in acetonitrile. The first wave in the polarogram corresponds to irreversible one-electron transfer, while the second wave corresponds to reversible one-electron transfer. Although the solutions remain colorless during electrolysis, at the potentials of the second half waves we were able to record EPR signals, the character and hyperfine structure (hfs) of which correspond to interaction of the unpaired electron with all of the magnetic nuclei of the molecule, in addition to one proton (Table 1 and Fig. 1). As we have previously shown [5], these EPR signals are related to dianion radicals of the corresponding nitropyrazoles, which are probably formed via Scheme 1 (top, following page).

It is apparent from Scheme 1 that cleavage of the primary anion radical at the polar covalent N–H bond with the ejection of atomic hydrogen occurs during transfer of the first electron to the nitropyrazole molecule with an unsubstituted nitrogen atom. The half-wave potentials and the parameters of the EPR signals of the ion radicals of nitropyrazoles I-VI are

*See [1] for Communication 2.

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