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LACTAM AND ACID AMIDE ACETALS

68.* 1-CYANOMETHYL-2-PYRROLIDONE DIETHYLACETAL IN THE SYNTHESIS OF 7,8-TRIMETHYLENEPURINE DERIVATIVES

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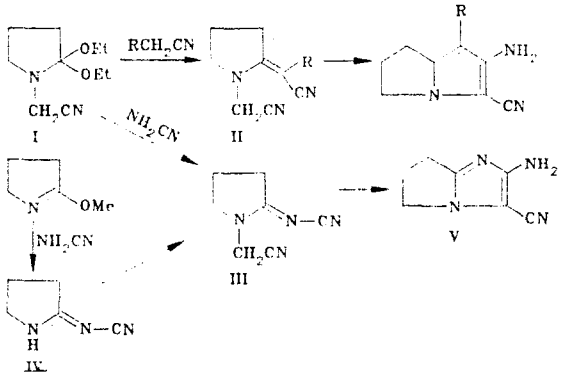
UDC 547.857'785'745.04

1-Cyanomethyl-2-cyaniminopyrrolidine was synthesized by the reaction of 1-cyanomethyl-2-pyrrolidone diethylacetal with cyanamide. The product undergoes Thorpe–Ziegler cyclization under the influence of sodium ethoxide to give 2-amino-3-cyano-5,6-dihydro-7H-pyrrolo[1,2-a]imidazole, from which 4-amino derivatives of pyrrolo[2,1-f]purine were synthesized.

This research continues studies of the intramolecular Thorpe–Ziegler cyclization of various synthones obtained from 1-cyanomethyl-2-pyrrolidone diethylacetal (I). It has been previously shown that acetal I reacts smoothly with various CH acids such as cyanoacetic esters and malonodinitrile to give enamino nitriles II, which are capable, under the influence of bases, of undergoing cyclization to 5-cyano-6-aminopyrrolizine derivatives [2]. The latter were used for the synthesis of the first representatives of two new heterocyclic systems — pyrimido[5,4-*e*]- and pyrimido[4,5-*f*]pyrrolizine derivatives [3, 4].

The present paper is devoted to the study of a similar scheme but with N-cyano amidines III, rather than enamino nitriles of the II type, as the starting compounds.



Amidines III are readily synthesized by the reaction of acetal I with cyanamide — the reaction proceeds smoothly and gives the products in virtually quantitative yields. Since the N-alkylation of cyano amidines that contain

*See [1] for Communication 67.

Center for the Chemistry of Medicinals. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119815. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 754-758, June, 1991. Original article submitted January 19, 1990.

 0009-3122/91/2706-0590$12.50

TABLE 1. Physicochemical Constants of the Synthesized Compounds

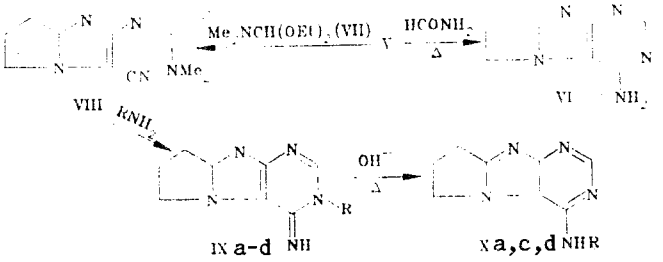
Compound	mp, °C*	Empirical formula	Yield, %	Compound	mp, °C*	Empirical formula	Yield, %
III	98...100	$C_7H_8N_4$	98	IXc	168...170	$C_{16}H_{17}N_5$	85
V	253...256	$C_7H_8N_4$	89	IXd	180...184	$C_{18}H_{21}N_5O_2$	88
VI	/300	$C_{12}H_9N_4$	97	Xa	235...238	$C_{15}H_{15}N_5$	7
VIII	135...138	$C_{10}H_{13}N_5$	91	Xc	214...217	$C_{16}H_{17}N_5$	98
IXa	165...168	$C_{15}H_{15}N_5$	58	Xd	208...210	$C_{18}H_{21}N_5O_2$	92
IXb	173...177	$C_{17}H_{19}N_5$	57				

*The compounds were crystallized: III from ethanol, V, VI, and Xd from water, VIII, IXb-d, and Xa, c from ethyl acetate, and IXa from isopropyl alcohol.

a secondary NH group is known [5], we attempted, under similar conditions (DMF, K_2CO_3, 60°C), to carry out the cyanomethylation of amidine IV, which was obtained by the reaction of O-methylbutyrolactim with cyanamide [6]. However, the reaction in this case proceeds ambiguously, and we were unable to isolate III. Nevertheless, the alkylation can be carried out by using another method for obtaining the sodium salt of amidine IV (treatment with sodium metal in toluene) with subsequent reaction with chloroacetonitrile. This method seems preparatively more convenient to us, since it does not require obtaining acetal I, which calls for the use of triethyloxonium tetrafluoroborate as the alkylating agent [7].

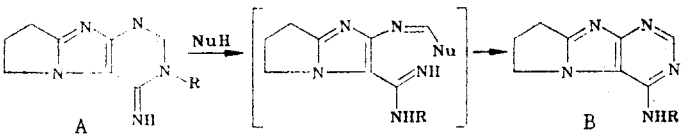
Brief heating (70°C, 5 min) of the resulting N-cyano amidine III in an alcohol solution of sodium ethoxide is accompanied by Thorpe—Ziegler cyclization to give bicyclic amino derivative V.

Thus the combination of the high reactivities of lactim ethers and lactam acetals with respect to cyanamide and the Thorpe—Ziegler reaction, which provides the simple possibility of cyclization of the N-cyano group at the active methylene link, ensures a convenient preparative approach to functionally substituted imidazoles of the V type. This, in turn, makes it possible to accomplish a new synthesis of 7,8-trimethylenepurines. Only a few studies devoted to 7,8-trimethylenepurines — pyrrolo[2,1-*f*]purines — are known [8-10]. However, these syntheses of derivatives of the indicated system are either quite complex or provide an approach only to N-substituted (in the pyrimidine ring) compounds. The new synthesis of this system, which is based on amino cyano derivative V, is also more universal and more preparative. An amino derivative (VI) of pyrrolo[2,1-*f*]purine was obtained in 97% yield in the reaction of V with formamide. The condensation of V with DMF acetal (VII) leads to amidine VIII (in 92% yield), which in transamination reactions with various amines should be converted to N-substituted pyrrolo[2,1-*f*]iminopurines IXa-d (see Table 1).



IX, X a R=$PhCH_2$; b R=$PhCH_2CH(CH_3)$; c R=$Ph(CH_2)_2$; d R=2,4-$(MeO)_2C_6H_3(CH_2)_2$

However, it follows from the structure of IX that they are typical objects of the Dimroth rearrangement, and taking into account the fact that the transamination and cyclization reactions were carried out in the presence of strong amines, the occurrence of the A → B recyclization seemed completely likely.



NuH=HOH(OH^-), EtOH(EtONa), RNH_2

TABLE 2. PMR Spectra of Pyrrolo[2,1-*f*]purine Derivatives IX and X

Compound	δ, ppm (in d_6-DMF)							
	1-R			2-CH, s	NH	5-CH_2, t	6-CH_2, m	7-CH_2, t
	CH_2	Ph (cent. of m)	OCH_3, s					
IXa	5,33 s	7,35	—	8,15	—*	2,90	2,63	4,37
IXb	1,45 d (CH_3); 5,49 m (CH); 3,25 m (CH_2)	7,25	—	8,02	5,49**	2,88	2,63	4,39
IXc	—***	7,42	—	7,82	—*	3,10	—***	4,47
IXd	4,29 t; 3,02 t	6,75	3,78; 3,77	7,73	—*	2,90	2,66	4,43
Xa	4,80 d	7,35	—	8,23	7,52 t	3,00	2,67	4,49
Xc	—***	7,28	—	8,27	7,07 t	2,99	2,66	4,42
Xd	3,71 m	6,90	3,78; 3,80	8,27	7,02 t	2,98	2,65	4,41

*The NH signal does not show up in visible form because of rapid exchange with the protons of water in the solvent and the NH protons of other molecules.

**The NH signal is overlapped with the CH signal.

***The signals of the protons are overlapped by the signal of water in the solvent.

TABLE 3. Ratios of the A and B Forms in the Unpurified Reaction Products

Mixture of compounds	Ratio, %	
	A	B
IXa Xa	57	43
IXc Xc	73	27
IXd Xd	68	32

In fact, from the reaction mixture obtained in the reaction of amidine VIII and benzylamine we isolated a mixture of two substances, which we were able to obtain in individual form by fractional crystallization. According to the PMR spectral data, one of these compounds is imino derivative IXa, while the other is Dimroth rearrangement product Xa. A characteristic difference in the PMR spectra of these compounds is the presence in the spectrum of rearrangement product Xa of a signal of an NH group (a triplet) and a doublet of a benzyl methylene grouping, while the benzyl CH_2 group shows up in the form of a singlet in the spectrum of imino derivative IXa (see Table 2).

The PMR spectra of the unpurified products of the reaction of amidine VIII with β-phenylethylamine and homoveratrylamine also reveal mixtures of IXc, d and Xc, d (the A and B forms) in the ratios indicated in Table 3. The signals of the protons of the NH groups of Xc-d (just as for Xa) show up in the form of triplets.

It should be noted that the rearrangement is accelerated in the presence of alkaline agents (EtONa, NaOH); whereas the recyclization proceeds rather slowly (IXa → Xa, ~20 h) when sodium ethoxide is used, considerably less time (~2 h) is required when 0.25 N NaOH solution is used.

It is interesting that a Dimroth rearrangement product is not formed in the reaction of amidine VIII with β-phenylisopropylamine; this probably indicates hindrance to attack at the 2 position of the pyrimidine ring associated with steric hindrance due to the presence of an α-methyl fragment in the substituent attached to the ring nitrogen atom.

EXPERIMENTAL

The mass spectra were recorded with a Varian MAT-112 spectrometer (direct introduction of the samples) at 70 eV at an ionization-chamber temperature of 180°C. The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin—Elmer-457 spectrometer. The PMR spectra were recorded with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard.

The results of elementary analysis of the synthesized compounds were in agreement with the calculated values.

1-Cyanomethyl-2-(N-cyanimino)pyrrolidine (III). A. A 0.7-g (17 mmole) sample of cyanamide was added in portions with stirring to 3.35 g (17 mmole) of I in 25 ml of methanol (exothermic reaction), and the reaction mixture was stirred at 20-25°C for 1 h. It was then evaporated to give 2.45 g of III.

B. Sodium metal [0.46 g (20 mmole)] was added to 50 ml of refluxing toluene, after which 2.18 g (20 mmole) of N-cyano amidine IV was added, the mixture was refluxed with vigorous stirring for 20 min, 2 ml of alcohol was added, and the mixture was refluxed for 15 min. Some of the solvent was then removed from the reaction mixture by distillation up to a vapor temperature of 110°C, and the mixture was then cooled to 0°C. Chloroacetonitrile [1.66 g (22 mmole)] was added at 0-5°C, and the mixture was maintained at this temperature for 1 h. The temperature was then raised to 20°C, and the mixture was stirred for 2 h. It was then filtered and evaporated in vacuo, and the residue was crystallized from alcohol to give the product, with $M^{+\cdot}$ 148, in 44% yield.

2-Amino-3-cyano-5,6-dihydro-7H-pyrrolo[1,2-*a*]imidazole (V). A solution of sodium ethoxide (0.2 g of Na in 10 ml of alcohol) was added with stirring to a solution of 6 g (41 mmole) of III in 40 ml of absolute alcohol, after which the mixture was heated at 70°C for 5 min. The precipitate was removed by filtration, washed with water, and dried to give 5.4 g of bicyclic compound V with $M^{+\cdot}$ 148. IR spectrum: 1560, 1645 (=C, C=N); 2190 (C≡N); 3320, 3400 cm^{-1} (NH_2). PMR spectrum (d_6-DMSO): 5.85 (br s, NH_2), 3.85 (t, 5-CH_2), 2.68 (t, 7-CH_2), 2.50 ppm (m, 6-CH_2).

9-Amino-6,7-dihydro-6,7-5H-pyrrolo[2,1-*f*]purine (VI). A mixture of 1 g (7 mmole) of III and 2.5 ml of formamide was refluxed for 50 min, after which it was cooled and treated with 10 ml of water, and the resulting precipitate was removed by filtration to give 1.15 g of purine VI with $M^{+\cdot}$ 175. IR spectrum: 1670, 1625 (=C, C=N); 3340 cm^{-1} (NH_2). PMR spectrum (d_6-DMSO): 8.11 (s, CH), 4.31 (t, 7-CH_2), 2.57 (m, 6-CH_2), 2.94 (t, 5-CH_2), 6.81 ppm (br s, NH_2).

2-(N-Dimethylaminomethylene)-3-amino-3-cyano-5,6-dihydro-7H-pyrrolo[1,2-*a*]imidazole (VIII). A mixture of 4 g (28 mmole) of III and 28 g of acetal VII in 60 ml of DMF was refluxed for 14 h, after which it was evaporated in vacuo, and the residue was triturated with ether to give 4.97 g of VIII. PMR spectrum (d_6-DMSO): 8.33 (s, =CH), 3.96 (t, 4-CH_2), 2.94 (s, NMe_2), 2.75 (t, 6-CH_2), 2.47 ppm (m, 5-CH_2).

1-Benzyl-6,7-dihydro-5H-9-iminopyrrolo[2,1-*f*]purine (IXa) and 9-Benzylamino-6,7-dihydro-5H-pyrrolo[2,1-*f*]purine (Xa). A mixture of 2 g (10 mmole) of amidine VIII and 2.1 g (20 mmole) of benzylamine in 20 ml of DMF was refluxed for 6 h in the presence of catalytic amounts of p-toluenesulfonic acid, after which it was evaporated in vacuo, and the residue was triturated with ether to give 2.4 g of a crude substance. Recrystallization from ethyl acetate gave 0.2 g of Xa with $M^{+\cdot}$ 265. The precipitate in the mother liquor was removed by filtration to give 1.56 g of purine IXa.

1-(β-Phenyl-α-methyl)ethyl-6,7-dihydro-5H-9-iminopyrrolo[2,1-*f*]purine (IXb). This compound was obtained in the same way as IXa from amidine VIII and β-phenylisopropylamine.

1-(β-Phenyl)ethyl-6,7-dihydro-5H-9-iminopyrrolo[2,1-*f*]purine (IXc). This compound was obtained in the same way as IXa from amidine VIII and β-phenylethylamine.

1-Homoveratryl-6,7-dihydro-5H-9-iminopyrrolo[2,1-*f*]purine (IXd). This compound was obtained in the same way as IXa from amidine VIII and homoveratrylamine.

9-(β-Phenyl)ethylamino-6,7-dihydro-5H-pyrrolo[2,1-*f*]purine (Xb). A mixture of 2.4 g (12 mmole) of purine IXc and 20 ml of 0.25 N NaOH was refluxed for 2.5 h, after which the precipitate was removed by filtration, washed with water, and dried to give 2.4 g of Xc.

9-Homoveratrylamino-6,7-dihydro-5H-pyrrolo[2,1-*f*]purine (Xd). This compound was obtained in the same way as Xc from imino purine IXd.

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SYNTHESIS OF NEW CONDENSED ANALOGS OF ISOINDOLINIUM SALTS*

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UDC 547.677:542.947

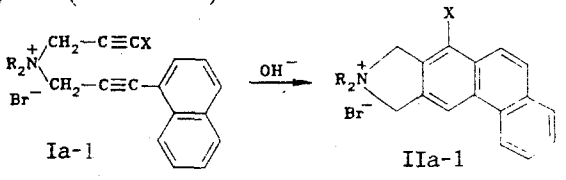
Quaternary ammonium salts that contain a 3-(α-naphthyl)propargyl group in addition to a group of the propargyl type undergo intramolecular cyclization of the diene-synthesis type under base-catalysis conditions to give condensed isoindolinium analogs.

Among the practically important nitrogen-containing heterocyclic compounds not much data relative to compounds of the isoindolinium series and their condensed analogs containing a phenanthrene ring are available.

It has been reported [2] that an accessible method for obtaining condensed dihydroisoindolinium salts was developed on the basis of the cyclization of ammonium salts containing a 3-(α-naphthyl)propargyl group in addition to a group of the allyl type.

In the present research, to synthesize potentially biologically active nitrogen-containing heterocycles with a phenanthrene ring we studied the cyclization of dialkylpropargyl[3-(α-naphthyl)propargyl]- (Ia-f) and dialkylbis[3-(α-naphthyl)propargyl]ammonium (Ig-l) salts.

It was established that salts Ia-l in the presence of an aqueous solution of 0.2 mole of alkali per mole of the salt, in contrast to the allyl analogs [2], undergo cyclization at room temperature rapidly with spontaneous heat evolution to give 2,2-dialkylnaphth[*f*]isoindolinium (IIa-e) and 2,2-dialkyl-4-(α-naphthyl)naphth[*f*]isoindolinium (IIg-l) bromides in almost quantitative yields (see Table 1).



I, IIa-f X=H, g-l X=α-naphthyl; a, R=CH_3, b,h R=C_2H_5, c,i R=C_3H_7; d,j R_2= =$(CH_2)_4$, e,k R_2=$(CH_2)_2O(CH_2)_2$

In [3], despite the data in [4], it was shown that dialkylbis(3-phenylpropargyl)ammonium salts undergo cyclization both in the presence and absence of a base when aqueous or aqueous alcohol solutions of them are heated. Salts Ig-l undergo almost quantitative cyclization under similar conditions.

The IR spectra of cyclic salts IIa-l do not contain the absorption bands of a disubstituted C≡C bond at 2230-2235 cm^{-1} that are characteristic for starting salts Ia-l and of a monosubstituted C≡C bond at 2120-2130 cm^{-1} that are characteristic for salts Ia-f; characteristic absorption bands of a 1,2,3,4-substituted aromatic ring at 810 cm^{-1}, of 1,2,4,5- and 1,2,3,4,5-substituted aromatic rings at 860-900 cm^{-1}, of a 1,2,3-substituted aromatic ring at 780-785 cm^{-1}, and of a 1,2-substituted aromatic ring at 730-770 cm^{-1} are observed.

*Communication 209 from the series "Research on amines and ammonium compounds." See [1] for Communication 208.

Institute of Organic Chemistry, Academy of Sciences of the Armenian SSR, Yerevan 375094. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 759-762, June, 1991. Original article submitted May 28, 1990.

 0009-3122/91/2706-0594$12.50