ACETALS OF LACTAMS AND ACID AMIDES.

50.* 1-CYANOMETHYLPYRROLID-2-ONE DIETHYLACETAL IN THE SYNTHESIS OF DERIVATIVES OF PYRROLO[1,2-a]PYRROLES

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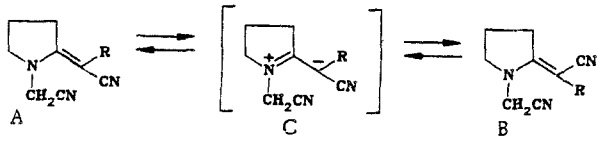
UDC 547.744'759.507:541.634:
543.422.25

We have synthesized a series of enamines — derivatives of 1-cyanomethyl-2-methylenepyrrolidine—by reaction of 1-cyanomethylpyrrolid-2-one diethylacetal with compounds having a reactive methylene link. The enamines undergo a Thorpe—Ziegler cyclization in the presence of bases with the formation of pyrrolo[1,2-a]-pyrrole derivatives. The configuration of the enamines obtained were studied using PMR spectroscopy.

It is known that acetals of N-methyllactams readily react with compounds having a reactive methylene link with the formation of the corresponding enamines [2]. Similarly, the previously synthesized 1-cyanomethylpyrrolid-2-one diethylacetal (I) [3] reacts smoothly with derivatives of cyanoacetic acid ester and malononitrile (IIa-e) giving the corresponding 1-cyanomethyl-2-(2-cyano-2-R)methylenepyrrolidines (IIIa-d) in high yield. Proton signals at 2.18 (4-CH_2), 3.09 (3-CH_2), 3.86 (5-CH_2), and 4.74 ppm (N—CH_2) are observed in the PMR spectrum of the dicyanomethylene derivative (IIIb) in $CDCl_3$. Since compound (IIIb) contains identical substituents (R = CN) at the exocyclic double bond, this data permit the proton signals from compounds having nonidentical substituents to be assigned with certainty. A double set of signals is present in the spectrum of the 2-carbethoxy derivative (IIIa) in the same solvent. These signals relate to the isomeric forms associated with the carbon—carbon double bond, and one of these forms evidently predominates (84:14) (see Table 1). By comparing the proton chemical shifts for the 3-CH_2 group with the corresponding shifts for compound (IIIb), it can be confirmed that the predominant isomer A has trans orientation for the bulky substituents (NCH_2CN and $COOC_2H_5$), while for B these are cis oriented.



The assignment of signals to the corresponding isomers of other enamines can be carried out analogously (Table 1).

It should be noted that on elevation of the temperature for recording spectra to 80°C, a gradual broadening of signals takes place for compound (IIIa) which indicates an interconversion of geometrical isomers on raising the temperature, i.e., an increase in hindered rotation with respect to the C=C bond. This phenomenon is apparent to a still greater extent for the thiocarbamide compound (IIId), for which the proton signals of the 3-CH_2 group and N—CH_2 are markedly broadened at 20°C, while on raising the temperature to 50°C the signals become narrower, i.e., an increase of the cis-trans isomerization process (A⇄B) is observed. On the other hand, a dual set of signals (in DMSO-D_6) is retained even at 80°C in the PMR spectrum of the carbamide (IIIc). Moreover no broadening of the signals is observed at all in the spectrum of this temperature. Consequently, in this case the free energy of activation for the cis⇄trans transition is sufficiently large ($\geqslant$20 kcal/mole).

It was established earlier [2, 4] that the extremely low energy barrier for cis—trans isomerization of enamines is caused to a greater degree by the difference in stability of

*For Communication 49, see [1].

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0009-3122/87/2312-1297$12.50

TABLE 1. PMR Spectral Data for Compounds (IIIa-d) and XI

Compound	Solvent	Type of isomer	PMR spectra, ppm					Ratio of isomers,* %
			3-CH_2	4-CH_2	5-CH_2	N—CH_2	NH_2	
IIIa	DMSO-D_6	A	3,20	1,94	3,68	4,93	—	90
		B	2,99	2,02	3,81	4,84	—	10
	$CDCl_3$	A	3,36	2,08	3,72	4,88	—	86
		B	3,13	2,16	3,85	4,92	—	14
IIIb	$CDCl_3$	—	3,09	2,18	3,86	4,74	—	—
IIIc	DMSO-D_6	A	3,13	1,87	3,57	4,86	6,81	60
		B	2,90	1,96	3,70	4,88	7,10	40
IIId	DMSO-D_6	—**	3,04	1,95	3,63	4,81	9,31, 8,64	—
XI	DMSO-D_6	A	3,26	1,90	3,61	4,94	3,11 $N(CH_3)_2$	70
		B	2,95	1,98	3,74	5,02	3,13 $N(CH_3)_2$	30

*The ratio of isomeric forms are given for a scan temperature of 24°C.

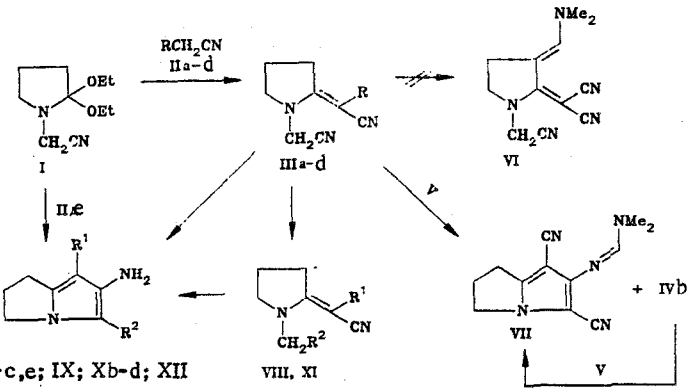
**A coalescence of signals which corresponds to an increase in rotation about the C=C bond is observed in the PMR spectrum of compound (IIId) at a scan temperature of 24°C.

transition states rather than of initial states. Since the transition state can be represented by structure C [2, 4], in which the anionic and cationic centers lie in planes mutually at right angles, it is understandable that in a series of compounds the stability of the transition state is determined by the degree of delocalization of the negative charge. From this, it follows that the transition data must be most stable for the thiocarbamoyl compound (IIId), in which the negative charge is mainly localized on the sulfur atom — energetically an extremely favorable situation. For this reason, the free energy of activation for the A⇄B process is lowest for the enamine (IIId).

A comparison of the data obtained from enamines (IIIa, c) with results published for their N-methyl analogues [5], shows that the exchange of a N-methyl group for an N-cyanomethyl substituent leads to an increase in the energy carrier for cis–trans isomerization. This increase is also easily interpreted in terms of the structure of the transition state (C). In fact, the exchange of a methyl group for cyanomethyl leads to destabilization of the transition state, since the presence of an electron-accepting N-cyanomethyl substituent (by comparison with N-methyl) makes the localization of the positive charge on the ring nitrogen atom energetically less favorable.

The enamines (IIIa-d) obtained are the starting compounds in the synthesis of pyrrolizine derivatives. The action of heat on alcoholic solutions of these compounds in the presence of sodium alkoxides leads to substituted pyrrolo[1,2-a]pyrroles (IVa-d) via a Thorpe–Ziegler cyclization. It is interesting to note that the cyclization can proceed even without the use of an alkoxide. Thus, two compounds — 5,7-dicyano-6-amino-1,2-dihydro-3H-pyrrolo-[1,2-a]pyrrole (IVb) and its dimethylaminomethylene derivative (VII) — [instead of the expected dienediamine (VI)] were separated on heating the enamine (IIIb) with dimethylformamide diethylacetal (V). (VII) was also obtained on interaction of the bi-cycle (IVb) with the acetal (V). Consequently, there is sufficient concentration of alkoxide anion present in solutions of amide acetals [6] for the indicated cyclization to proceed.

This is confirmed by the fact that only signals for the bi-cycle (IVc) are observed in the PMR spectrum on addition of a very small amount of CD_3ONa to the enamine (IIIc) solution in DMSO-D_6. The high cyclization rate makes possible direct use of cyclization in the condensation of acetal (I) with methylene components. Thus bi-cycle (IVe) immediately separated on interaction of N-benzylcyanoacetamide with acetal (I). Nevertheless, the method of obtaining pyrrolo[1,2-a]pyrroles with preparative separation of intermediate enamines is preparatively more advantageous. The considerable lowfield shift for proton signals of the 2-CH_2 group of approximately 0.4-0.5 ppm (by comparison with the corresponding signal for the 4-CH_2 group of the initial enamines) is an interesting feature of bi-cycles (IV). This shift is possibly caused by molecular steric strain associated with annelation of two five-membered rings.



II, III a $R=COOC_2H_5$, b $R=CN$, c $R=CONH_2$, d $R=CSNH_2$; II e $R=CONHCH_2Ph$; IV $R^2=CN$, a $R^1=COOC_2H_5$, b $R^1=CN$, c $R^1=CONH_2$, e $R^1=CONHCH_2Ph$; VIII, IX $R^1=COOC_2H_5$, $R^2=CONH_2$; X $R^2=CSNH_2$, b $R^1=CN$, c $R^1=CONH_2$, d $R^1=CSNH_2$; XI, XII $R^1=CON=CH-NMe_2$, $R^2=CN$

In the last stage of the work, an attempt was made to modify functional groups in order to obtain pyrrolo[1,2-a]pyrroles with another set of substituents in the bi-cycle. Treatment of a solution of compound (IIIa) with hydrogen chloride in formic acid leads to the carbamidomethyl compound (VIII). Bi-cycle (IX) was obtained by a Thorpe–Ziegler cyclization of this compound. However, we failed to obtain thiocarbamoyl substituted enamines — analogues of compound (VIII) — on interaction of compounds (IIIb-d) with NH_4HS solution. A spontaneous cyclization with formation of thiocarbamoylpyrrolo[1,2-a]pyrroles (Xb-d) is observed. Finally, the enaminoacylamidine (XI) was obtained on interaction of enamine (IIIc) with acetal (V). Under the usual conditions, (XI) readily cyclizes to the pyrrolizine (XII). Signals for two isomers (Table 1) are similarly observed in the PMR spectrum of enamine (XI). An increase to 80°C in the temperature for recording the spectrum of a sample (XI) leads to broadening of the corresponding signals, i.e., cis–trans isomerization with respect to the enamine double bond is observed — as was described above for enamines (III).

EXPERIMENTAL

The PMR spectra were recorded on a Varian XL-200 instrument, with TMS as internal standard. The mass spectra were obtained on a Varian-MAT-112 (Phinnigan) instrument with direct introduction of the sample into the ionic current. The temperature of the ionization chamber was 180°C, the energy of the ionizing electrons was 70 eV. The IR spectra were recorded on a Perkin-Elmer 457 instrument. Melting points were determined on a Boetius type heated stage.

1-Cyanomethyl-2-(2-cyano-2-ethoxycarbonyl)methylenepyrrolidine (IIIa). A mixture of acetal (I) (9.90 g, 50 mmole) and cyanoacetic acid (5.65 g, 50 mmole) is set aside at 5-7°C for 2 h, ether is added, and compound (IIIa) removed by filtration, M^+· 219.

1-Cyanomethyl-2-(2,2-dicyano)methylenepyrrolidine (IIIb). This is obtained from compound (I) and malonic acid dinitrile analogously to enamine (IIIa). M^+· 172.

1-Cyanomethyl-2-(2-cyano-2-carbamido)methylenepyrrolidine (IIIc). A mixture of acetal (I) (17 g, 86 mmole) and cyanoacetamide (7 g, 86 mmole) in absolute alcohol (80 ml) is

TABLE 2. IR Spectra of Synthesized Compounds, cm^{-1}

Compound	NH_2	C≡N	C=O	Compound	NH_2	C≡N	C=O
IIIa	—	2190	1700	VIII	3200, 3370	2210	Шир. 1690
IIIb	—	2210	—	IX	3250, 3310, 3360, 3480	—	1650, 1670
IIIc	3280, 3340, 3410	2190	1670				
IIId	3205, 3300, 3380	2200	—	Xb	3220—3280, 3360 3440	2200	—
IVa	3220, 3340, 3430	2190	1675				
IVb	3230, 3340, 3390	2195, 2210	—	Xc	3260, 3390	—	1680
IVc	3260, 3310, 3400, 3490	2190	1640	Xd	3290, 3460	—	—
				XI	—	2190	1640
IVe	3350, 3440	2200	1680	XII	3300, 3400	2195	1640
VII	—	2200, 2210	—				

TABLE 3. Physicochemical Properties of Synthesized Compounds

Compound	T_{mp}*, °C	Found, %				Molecular formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
IIIa	97—98	60,5	5,8	19,3	—	$C_{11}H_{13}N_3O_2$	60,3	6,0	19,2	—	68
IIIb	59—61	63,2	4,6	32,6	—	$C_9H_8N_4$	62,8	4,7	32,5	—	72
IIIc	196—198	56,7	5,3	29,5	—	$C_9H_{10}N_4O$	56,8	5,3	29,5	—	92
IIId	163—165	52,5	5,0	27,5	15,4	$C_9H_{10}N_4S$	52,4	4,9	27,2	15,5	62
IVa	246—247	60,4	6,1	19,3	—	$C_{11}H_{13}N_3O_2$	60,3	6,0	19,2	—	92
IVb	>260	62,5	4,6	32,6	—	$C_9H_8N_4$	62,8	4,7	32,5	—	94
IVc	>260	56,5	5,3	29,4	—	$C_9H_{10}N_4O$	56,8	5,3	29,5	—	85
IVe	186—188	68,3	5,8	20,2	—	$C_{16}H_{16}N_4O$	68,6	5,8	20,0	—	30
VII	184—186	63,6	5,5	31,0	—	$C_{12}H_{13}N_5$	63,4	5,8	30,8	—	88
VIII	172—173	55,7	6,2	17,6	—	$C_{11}H_{15}N_3O_2$	55,7	6,4	17,7	—	84
IX	229—230	55,3	6,3	17,8	—	$C_{11}H_{15}N_3O_2$	55,7	6,4	17,7	—	53
Xb	>260	52,3	4,8	27,1	15,4	$C_9H_{10}N_4S$	52,4	4,9	27,2	15,5	79
Xc	>260	48,4	5,3	25,2	14,2	$C_9H_{12}N_4OS$	48,2	5,4	25,0	14,3	82
Xd	263—265	44,6	5,0	23,2	27,1	$C_9H_{12}N_4S_2$	45,0	5,0	23,3	26,7	67
XI	169—170	58,9	6,3	28,4	—	$C_{12}H_{15}N_5O$	58,8	6,2	28,5	—	77
XII	217—220	58,4	6,3	28,3	—	$C_{12}H_{15}N_5O$	58,8	6,2	28,5	—	75

*Compounds (IIIa, b), (XI) are crystallized from iso-PrOH; (IIIc, d), (IVe), (VII), (VIII) from alcohol; (IVa-c) from a mixture of MeCN and DMF 1:1; (IX), (Xb-d) from aqueous DMF; (XII) from MeCN.

heated with stirring for 15 min, then cooled, and the compound (IIIc) removed by filtration, and washed with a small amount of isopropyl alcohol. M^+· 190.

1-Cyanomethyl-2-(2-cyano-2-thiocarbamido)methylenepyrrolidine (IIId). This is obtained from compound (I) and thiocyanoacetamide analogously to enamine (IIIc). M^+· 206.

1,2-Dihydro-3H-5-cyano-6-amino-7-ethoxycarbonylpyrrolo[1,2-a]pyrrole (IVa). The enamine (IIIa) (6.58 g, 30 mmole) is added with heating to a solution of sodium t-butoxide* prepared from Na (0.1 g) and t-butanol (35 ml) and the mixture boiled with stirring for 4 h. The solvent was distilled from the reaction mixture in vacuum, the residue washed with alcohol, and the compound (IVa) removed by filtration. M^+· 219.

1,2-Dihydro-3H-5,7-dicyano-6-aminopyrrolo[1,2-a]pyrrole (IVb). This was obtained from compound (IIIb) analogously to pyrrolizine (IVa). M^+· 172.

1,2-Dihydro-3H-5-cyano-6-amino-7-carbamidopyrrolo[1,2-a]pyrrole (IVc). This is obtained from compound (IIIc) analogously to compound (IVa). M^+· 190. PMR spectrum (DMSO-D_6): 2.40 (2-CH_2); 3.03 (1-CH_2); 3.88 (3-CH_2); 5.82, 6.66 ppm (NH_2).

1,2-Dihydro-3H-5-cyano-6-amino-7-(N-benzylcarbamido)pyrrolo[1,2-a]pyrrole (IVe). A mixture of acetal (I) (1g, 5 mmole) and compound (IIe) (1.58 g, 10 mmole) in absolute alcohol (15 ml) is boiled for 1 h, acetal (I) (1 g, 5 mmole) is added, and the mixture boiled for 40 min. Acetal (I) (0.2 g, 1 mmole) is added, then the mixture is boiled for another 20 min. Activated charcoal is added, and removed by filtration; the filtrate is cooled, and the precipitate filtered off, giving the bi-cycle (IVe). M^+· 280. PMR spectrum ($CDCl_3$): 2.58 (2-CH_2); 2.98 (1-CH_2); 3.96 (3-CH_2); 7.32 (Ph); 4.55 (CH_2N=); 5.07 ppm (NH).

Reaction of 1-Cyanomethyl-2-(2,2-dicyano)methylenepyrrolidine (IIIb) with Dimethylformamide Diethylacetal (V). Compound (V) (0.78 g, 6 mmole) is added to a solution of enamine (IIIb) (1.72 g, 10 mmole) in dry benzene (30 ml). The mixture is boiled for 30 min, then another 0.78 g (6 mmole) of compound (V) added. The mixture is boiled for another 30 min, then cooled, and the precipitate (IVb) removed by filtration (yield 44%). (IVb) is identical with the compound obtained by cyclization of enamine (IIIb) with sodium t-butoxide. The benzene mother liquor is evaporated in vacuum, and the residue triturated with ethyl acetate, and compound (VII) removed by filtration (yield 25%). M^+· 227. PMR spectrum ($CDCl_3$): 2.56 (2-CH_2); 3.02 (1-CH_2); 3.05, 3.06 ($N(CH_3)_2$); 4.06 (3-CH_2); 7.97 ppm (CH=N).

1,2-Dihydro-3H-5,7-dicyano-6-(N,N-dimethylaminomethylene)aminopyrrolo[1,2-a]pyrrole (VII). Compound (V) (0.78 g, 6 mmole) is added to a solution of compound (IVb) (1.72 g, 10 mmole) in DMF (20 ml) at 90°C, the mixture is heated for 30 min, another 0.78 g (6 mmole) of compound (V) is added, then the mixture is heated for another 30 min. The solvent is distilled from the reaction mixture in vacuo, the residue triturated with isopropyl alcohol,

*The use of $NaOC_2H_5$ in absolute ethanol leads to an analogous result.

and the compound (VII) removed by filtration. M^+· 227. The physical and spectral characteristics are identical to the data for sample (VII) obtained in the preceding experiment.

1-Carbamidomethyl-2-(2-cyano-2-ethoxycarbonyl)methylenepyrrolidine (VIII). Dry HCl is passed through a solution of enamine (IIIa) (5.6 g, 23.7 mmole) in 99.7% formic acid (50 ml) at 0°C for 2 h. The solvent is evaporated from the reaction mixture in vacuum, the residue triturated with isopropyl alcohol, and (VIII) removed by filtration. M^+· 237.

1,2-Dihydro-3H-5-carbamido-6-amino-7-ethoxycarbonylpyrrolo[1,2-a]pyrrole (IX). Compound (VIII) (6.64 g, 28 mmole) is added to a solution of sodium ethoxide, prepared from Na (1 g) and absolute alcohol (100 ml). The mixture is stirred for 1 h at 20°C, then boiled for 10 min, and cooled. The precipitate is removed by filtration, washed with alcohol, and the pyrrolopyrrole (IX) is obtained. M^+· 237.

1,2-Dihydro-3H-5-thiocarbamido-6-amino-7-cyanopyrrolo[1,2-a]pyrrole (Xb). A 10% solution of NH_4HS (28 ml, 50 mmole) is added to a suspension of enamine (IIIb) (1.1 g, 5 mmole) in 50 % aqueous alcohol (40 ml). The mixture is stirred at 20°C for 6 h, the precipitate removed by filtration, washed with water and compound (Xb) is obtained. M^+· 206.

1,2-Dihydro-3H-5-thiocarbamido-6- amino-7-carbamidopyrrolo[1,2-a]pyrrole (Xc). This is obtained from compound (IIIc) analogously to compound (Xb). M^+· 224.

1,2-Dihydro-3H-5,7-dithiocarbamido-6-aminopyrrolo[1,2-a]pyrrole (Xd). This is obtained from compound (IIId) analogously to compound (Xb). M^+· 240.

1-Cyanomethyl-2-[2-cyano-2-(N,N-dimethylaminomethylene)carbamido]methylene pyrrolidine (XI). The acetal (V) (4.4 g, 30 mmole) is added to a suspension of enamine (IIIc) (7.6 g, 40mmole) in dry benzene (100 ml), the mixture boiled with stirring for 1 h; then another 2.2 g (15 mmole) of acetal (V) is added, and boiling continued for 30 min. Then another 2.2 g (15 mmole) of acetal is added, the mixture boiled for 20 min, cooled, and compound (XI) removed by filtration. M^+· 245.

1,2-Dihydro-3H-5-cyano-6-amino-7-(N,N-dimethylaminomethylene)carbamidopyrrolo[1,2-a]-pyrrole (XII). Compound (XI) (2.45 g, 10 mmole) is added to a solution of sodium ethoxide, prepared from Na (0.1 g) and absolute ethanol (25 ml), the mixture boiled for 10 min, cooled, and compound (XII) removed by filtration. M^+· 245.

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