ACETALS OF LACTAMS AND ACID AMIDES.

54*. NEW SYNTHESIS OF PYRIMIDO[4,5-f]PYRROLIZINES

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A synthesis of pyrimido[4,5-f]pyrrolizine derivatives has been carried out, which is based on the intramolecular cyclization of 7-functionally substituted 6-amino-pyrrolizines with the participation of substituents in the 6- and 7-positions.

We have previously [2, 3] developed a new approach to the synthesis of functionally substituted pyrrolizines based on the cyclization of 1-cyanomethyl-2-methylenepyrrolidines (I) under Thorpe-Ziegler reaction conditions. The synthesized bicyclic compounds were used for the preparation of pyrimido[4,5-e]pyrrolizine [4], i.e., the closure of the pyrimidine ring was effected with the participation of substituents at the 5 and 6-positions of the pyrrolizine system. The present work was devoted to the synthesis of an isomeric heterocyclic system, pyrimido[4,5-f]pyrrolizine by selective pyrimidine cyclization, with the participation of the functional substituents at the 6 and 7-positions of the bicyclic compound without affecting the grouping at the 5-position.

At the first stage of the investigation, we selected 1-cyano-methyl-2-(2-cyano-2-N-dimethylaminomethylenecarbamoyl)pyrrolidine (Ia) as the starting compound, which was preliminarily [3] converted into 5-cyano-6-amino-7-(N-dimethylaminomethylene)carbamoyl 1,2-dihydro-3H-pyrrolizine (IIa). As expected, further spontaneous cyclization does not occur, possibly due to the low basicity of the 6-amino group in this compound. In fact, derivatives of aminopyrrolizine having strongly electron-acceptor substituents in the positions neighboring the amino group are so slightly basic that the ΔpK values in nitromethane cannot be determined for compounds such as IIa (R = COOEt) and (IIc)(R = $CONH_2$), which we have previously synthesized [3]. The cyclization can be smoothly carried out on boiling the solution of compound IIa in glacial acetic acid. In this case an intramolecular transamination takes place (for the data that the transamination processes proceed best in acetic acid, see [5]) with the formation of 5-cyano-1,2-dihydro-3H-pyrimido[4,5-f]pyrrolizin-9-one (III). In the PMR spectra of the cyclic compound III (in DMSO-D_6) proton signals are observed at 3.13 (2H, t, 1-H_2), 2.56 (2H, m, 2-H_2), 4.27 (2H, t, 3-H_2) and 7.84 ppm (1H, s, 7H).

Another approach to the synthesis of compound III is based on the use of 5-cyano-6-amino-7-carbamoyl-1,2-dihydro-3H- pyrrolizine (IIb) [3] and DMFA diethylacetal (IV) as starting materials. It is known [6] that during the reaction of aromatic and heteroaromatic compounds containing amino- and carbamido groups in the orthoposition, with acetal IV, a closure of the pyrimidine ring takes place with the formation of the corresponding condensed pyrimidines. In the present case, the low basicity of the amino group results in that the attack of the acetal on both the aromatic and amide NH_2 groups is equally probable, and under the conditions used only the bis-N,N-dimethylaminomethylene derivative V can be isolated. In the IR spectrum of the compound obtained adsorption bands of the CO and CN groups are observed at 1640 and 2200 cm^{-1}, and there is no absorption whatsoever in the 3300...3500 cm^{-1} region.

Heating bisamidine V with 70% acetic acid is accompanied by saponification of one of the amidine fragments, followed by intramolecular transamination and formation of the tricyclic compound III.

Pyrimidopyrrolizinone III is a prospective compound for the preparation of this new heterotricyclic system. In the present work, a series of 9-amino derivatives VIa-d as well as the 9-ethoxy derivative VIe were synthesized. To do this, compound III was reacted with phosphorus oxychloride in the presence of triethylamine hydrochloride to give the oxychloride complex VII, which, without additional purification, was reacted with amines and sodium methylate.

*For communication 53, see [1].

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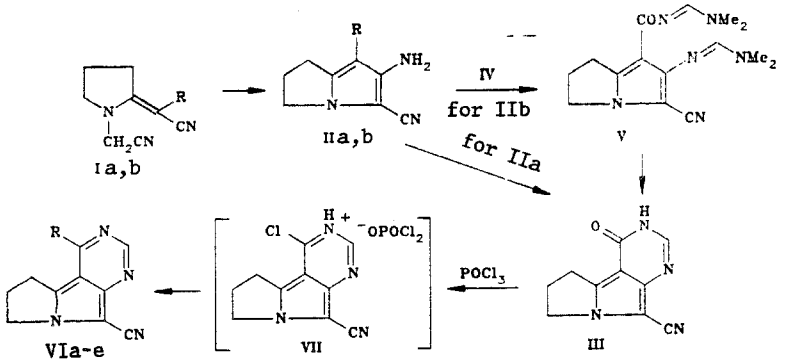

I, II a R=CON=CHNMe$_2$, b R=CONH$_2$; VI a R=NHCH$_2$Ph, b R=NH(CH$_2$)$_2$N(Et)$_2$, c R=—N(CH$_2$)$_5$, d, R = 4-methylpiperazino e R = OEt

EXPERIMENTAL

The PMR spectrum was recorded on a Varian XL-200 spectrometer using TMS as internal standard. The mass spectra were obtained on a Varian MAT-112 spectrometer with direct introduction of the sample, temperature of the ionization chamber of 180°C and energy of ionizing electrons of 70 eV. The IR spectra were recorded on a Perkin-Elmer spectrophotometer. The melting points were determined on a Boetius type heating stage.

The physicochemical properties of the compounds synthesized are listed in Table 1. The data of the elemental analyses of the compounds for C, H, N correspond to the calculated data.

N,N-Bisdimethylaminomethylene-5-cyano-6-amino-7-carbamido-1,2-dihydro-3H-pyrrolizine (V). A 162 g portion (1.1 mole) of acetal IV was added dropwise in the course of 1 h, at 100°C, to a solution of 79.8 g (0.42 mole) of the bicyclic compound IIb in 250 ml of DMFA. The mixture was then stirred at the same temperature for another 30 min, the reaction mixture was cooled and the precipitate that separated out was filtered to yield compound V.

5-Cyano-1,2,8,9-tetrahydro-3H-pyrimido[4,5-f]pyrrolizin-9-one (III). A. A solution of 5.8 g (24 mmoles) of IIa in 60 ml of glacial acetic acid was boiled for 3 h, cooled, and the tricyclic compound III was filtered. Yield 68%.

B. A. 3.16 g portion (10 mmoles) of bisamidine V was added to 20 ml of 70% acetic acid, the mixture was boiled with stirring for 2 h, and then cooled. The precipitate was filtered, washed with water, to yield compound III. M^+ 200. IR spectrum: br. 3080 (NH), 2200 (CN), 1675 cm^{-1} (CO).

5-Cyano-9-benzylamino-1,2-dihydro-3H-pyrimido[4,5-f]pyrrolizine (VIa). A mixture of 2 g (10 mmoles) of the tricyclic compound III, 10 ml of $POCl_3$ and 0.55 g (4 mmoles) of triethylamine hydrochloride was heated to 100°C and stirred to complete dissolution of the precipitate. The excess $POCl_3$ was then distilled off in vacuo, and the residue was washed with absolute ether. Dry dichloroethane (20 ml) was added to the oxychloride complex VII obtained, and then 5.35 g (50 mmoles) of benzylamine was added dropwise. The reaction mixture was boiled for 30 min, then evaporated in vacuo, the residue was washed with water, and compound VIa was filtered off. M^+ 289.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C*	Yield, %	Compound	Empirical formula	mp, °C*	Yield, %
III	$C_{10}H_8N_4O$	288...290	96**	VIc	$C_{15}H_{17}N_5$	192...194	82
V	$C_{15}H_{20}N_6O$	215...217	91	VId	$C_{15}H_{18}N_6$	193...195	76
VIa	$C_{17}H_{15}N_5$	255...258	54	VIe	$C_{12}H_{12}N_4O$	255...257	61
VIb	$C_{16}H_{22}N_6$	172...174	81				

*The solvent for compound III — ethanol, for V — DMFA, for VIa,e — aqueous DMFA, for VIb, — ethanol—hexane, 1:1, for VIc — acetonitrile, for VId — propanol.

**By method B.

5-Cyano-9-(2-diethylaminoethylamino)-1,2-dihydro-3H-pyrimido[4,5-f]pyrrolizine (VIb) was obtained in a similar way as compound VIa from the tricyclic compound III and diethylaminoethylamine. M^+ 298.

5-Cyano-9-piperidino-1,2-dihydro-3H-pyrimido[4,5-f]pyrrolizine (VIc) was obtained in a similar way as compound VIa from the tricyclic compound III and piperidine. After treatment with water, compound VIc was isolated by extraction with chloroform. M^+ 282.

5-Cyano-9-(4-methylpiperazino)-1,2-dihydro-3H-pyrimido[4,5-f]pyrrolizine (VId) was obtained in a similar way as compound VIa from the tricyclic compound III and N-methylpiperazine. M^+ 282.

5-Cyano-9-ethoxy-1,2-dihydro-3H-pyrimido[4,5-f]pyrrolizine (VIe) was obtained in a similar way as compound VIa from tricyclic compound III. The oxychloride complex was treated with a sodium ethylate solution in ethanol. M^+ 228.

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