signal of the protons of the methyl group in N-acetyltetrahydroquinoline was observed experimentally (Fig. 2a) and calculated by the ACFL method (Fig. 2b).

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SYNTHESIS AND REACTIONS OF PYRROLO[2,3-c]AZEPINE DERIVATIVES*

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The construction of the pyrrolo[2,3-c]azepine system by the reaction of 2-oxo-3-hydroxy-4-cyano-2H,1,5,6,7-tetrahydroazepine with glycine ester and subsequent cyclization of the resulting N-substituted amino nitrile in an alcohol solution of sodium ethoxide was studied. The pyrrolo[2,3-c]azepine system was converted to the three-ring pyrimido[4',5':4,5]pyrrolo[2,3-c]azepine system, the alkylation of which gave N,N-dialkyl and N,N,N-trialkyl derivatives. Cyclization of 3-benzyl-4,6-dioxo-5-(N,N-dimethyl)aminoethyl-6H,3,4,7,8,9,10-hexahydropyrimido-[4',5':4,5]pyrrolo[2,3-c]azepine hydrochloride under the influence of phosphorus oxychloride gave the four-ring pyrazino[3,2,1-b,c]azepino[3,4-b]pyrrolo[3,2-d]-pyrimidine system. The structures of the compounds obtained were confirmed by their IR, UV, and PMR spectra.

In developing our research on the preparation of condensed heterocyclic compounds on the basis of lactams, in the present research we studied methods for the construction of the pyrrolo[2,3-c]azepine system and the transition from the latter to various multiring compounds using 2-oxo-3-hydroxy-4-cyano-2H-1,5,6,7-tetrahydroazepine (I) [2] as the starting compound.

The presence in I of enolized keto and CN groups created the prerequisites for the construction of a pyrrole ring with the participation of these groups as in the synthesis of furo[2,3-b]pyridines [3]. With this end in mind we investigated the reaction of hydroxy nitrile I with glycine ester. A study of this reaction showed that a substituted amino nitrile (II) is formed most smoothly when hydroxy nitrile I is heated with excess glycine ester hydrochloride in glacial acetic acid in the presence of sodium acetate. Pyrrolo[2,3-c]azepine (III) was obtained in good yield by cyclization of amino nitrile II by heating in an alcohol solution of sodium ethoxide.

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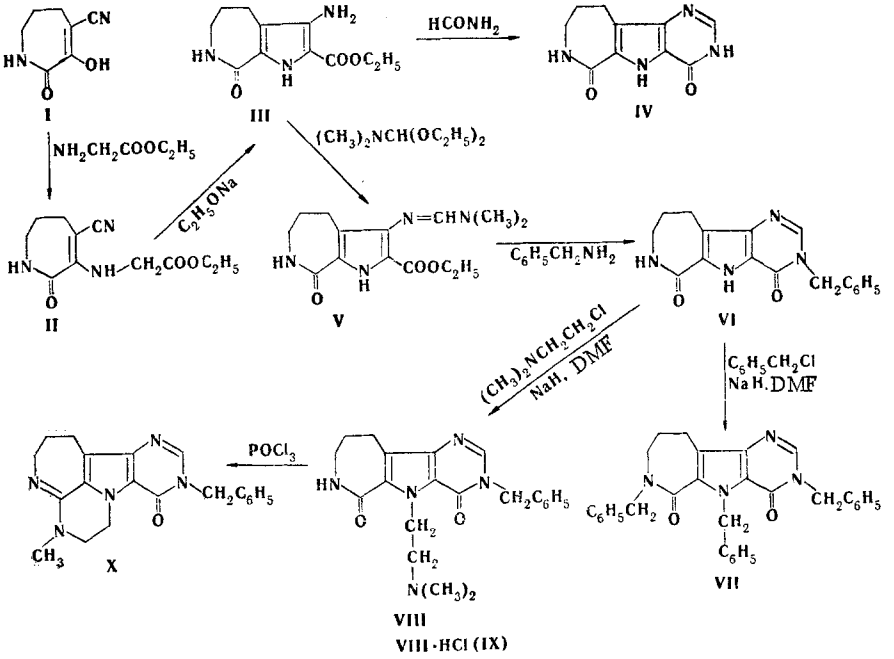
The structures of isomeric II and III were confirmed unambiguously by data from the PMR, UV, and IR spectra. In particular, the IR spectrum of II is characterized by absorption bands at 2200 (CN group), 1750 (ester CO), and 1670 cm^{-1} (amide CO) and three absorption bands at 3290-3370 cm^{-1} (NH groups). The absorption bands at 2220 and 1750 cm^{-1} vanish in the spectrum of pyrroloazepine III, while an absorption band at 1645 cm^{-1}, which is characteristic for an ester carbonyl group conjugated with a heteroaromatic system, appears. The IR spectrum of III is also characterized by the appearance of a high-frequency band at 3430 cm^{-1}, which corresponds to the stretching vibrations of the pyrrole NH group. Its PMR spectrum, which contains singlet signals of protons at 6.55 (NH_2 group) and 9.67 ppm (pyrrole NH), as well as a triplet from the proton of the NH group of the azepine ring at 7.88 ppm, also corresponds to the III structure.

The presence of carbethoxy and amino groups in the 2 and 3 positions in pyrroloazepine III made it possible to realize its cyclization with formamide and to synthesize three-ring compound IV. The 3-benzyl derivative of IV was obtained via the following scheme: The reaction of pyrroloazepine III with dimethylformamide diethylacetal yielded amidine V, which underwent cyclization to monobenzyl derivative VI when it was heated with benzylamine. A study of the alkylation of VI showed that a 3,5,7-tribenzyl derivative (VII) is formed by the action on it in dimethylformamide (DMF) in the presence of sodium hydride of excess alkylating agent (for example, benzyl chloride). The more acidic pyrrole NH group can be alkylated selectively to give VIII by alkylation of VI under the same conditions with an equimolar amount of dimethylaminoethyl chloride. The presence in VIII of a basic group is confirmed by its ability to form a hydrochloride (IX). During a study of the properties of IX we established that it undergoes cyclization with the participation of the dimethylamino group and the carbonyl group of the azepine ring under the influence of phosphorus oxychloride to give a four-ring system (X).



The structures of IV-X were confirmed by the results of elementary analysis and the spectral characteristics.

EXPERIMENTAL

The UV spectra of solutions of IV in 0.1 N NaOH and of II, III, V, VII, and X in alcohol were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil pastes of the compounds were obtained with Perkin–Elmer 457 and UR-10 spectrometers. The PMR spectra of solutions of II and X in $CDCl_3$, of III, V, VII, and IX in d_7-DMF, and of IV in NaOD were recorded with a JMN-4H-100 spectrometer with tetramethylsilane as the internal standard. The melting points of the substances were determined with an MP-1 apparatus (Yamato Scientific Co., Ltd.). The purity of the substances was monitored by chromatography on Silufol UV-254 plates.

2-Oxo-3-carbethoxymethylamino-4-cyano-2H-1,5,6,7-tetrahydroazepine (II). A 9.8-g (120 mmole) sample of anhydrous sodium acetate was added at 60°C to a mixture of 6 g (40 mmole) of hydroxy nitrile I, 12 g (88 mmole) of glycine ethyl ester hydrochloride, and 60 ml of glacial acetic acid, and the mixture was heated at 100°C for 2 h. It was then cooled, and the precipitated sodium chloride was removed by filtration. The mother liquor was evaporated *in vacuo*, and the residue was dissolved in water. The solution was made alkaline to pH 7 with 2 N sodium hydroxide solution and cooled, and II was removed by filtration (Table 1). PMR spectrum: 1.27 (3H, t, CH_3), 1.94 (2H, quintet, 6-CH_2), 2.27 (2H, t, 5-CH_2), 3.26 (2H, quartet, 7-CH_2), 4.21 (4H, m, OCH_2 and N—CH_2), 5.52 (1H, broad t, NH), and 7.36 ppm (1H, broad t, 1-NH).

2-Carbethoxy-3-amino-8-oxo-8H-4,5,6,7-tetrahydropyrrolo[2,3-c]azepine (III). A 5.6-g (23.6 mmole) sample of II was added to a solution of sodium ethoxide (from 0.31 g of sodium and 40 ml of absolute alcohol), and the mixture was maintained at 20°C for 30 min and then heated at 60°C for 40 min. It was then cooled, and the precipitate was removed by filtration, washed with water, and dried to give III (Table 1). The mother liquor was evaporated *in vacuo*, and the residue was triturated with water, removed by filtration, and dried to give an additional amount of III. Extraction of the wash waters with chloroform gave another additional amount of III. PMR spectrum: 1.31 (3H, t, CH_3), 1.98 (2H, m, 5-CH_2), 2.64 (2H, t, 4-CH_2), 3.32 (2H, q, 6-CH_2), 4.26 (2H, q, OCH_2), 6.55 (2H, s, NH_2), 7.88 (1H, t, azepine NH), and 9.67 ppm (1H, s, pyrrole NH).

4,6-Dioxo-6H-3,4,7,8,9,10-hexahydropyrimido[4',4':4,5]pyrrolo[2,3-c]azepine (IV). A mixture of 2 g (13 mmole) of pyrroloazepine III and 25 ml of formamide was heated at 210°C for 1.5 h, after which it was cooled, and the precipitated IV was removed by filtration (Table 1). Evaporation of the mother liquor and treatment of the residue with acetone gave an additional amount of IV. PMR spectrum: 1.85 (2H, m, 9-CH_2), 2.69 (2H, t, 10-CH_2), 3.20 (2H, t, 8-CH_2), and 8.05 ppm (1H, s, 2-CH═).

2-Carbethoxy-3-(N,N-dimethyl)aminomethyleneamino-8-oxo-8H-4,5,6,7-tetrahydropyrrolo[2,3-c]azepine (V). A mixture of 1.2 g (5 mmole) of pyrroloazepine III, 0.6 g (8 mmole) of dimethylformamide diethylacetal, and 20 ml of toluene was refluxed for 6.5 h, during which 0.6 g of the acetal was added every 1.5 h. The mixture was cooled, and V was removed by filtration. Evaporation of the mother liquor and treatment of the residue with ether gave an additional amount of V (Table 1). PMR spectrum: 1.24 (3H, t, CH_3), 1.91 (2H, m, 5-CH_2), 2.64 (2H, m, 4-CH_2), 3.06 [6H, s, $N(CH_3)_2$], 3.26 (2H, m, 6-CH_2), 4.17 (2H, q, OCH_2), and 7.84 ppm (1H, s, CH═).

3-Benzyl-4,6-dioxo-6H-3,4,7,8,9,10-hexahydropyrimido[4',5':4,5]pyrrolo[2,3-c]azepine (VI). A 13-g (44.5 mmole) sample of V was heated in 30 ml of benzylamine at 120°C for 1 h, after which the mixture was cooled, and the precipitate was removed by filtration and washed with ether to give VI (Table 1). An additional amount of VI was obtained from the mother liquor.

3,5,7-Tribenzyl-4,6-dioxo-6H-3,4,7,8,9,10-hexahydropyrimido[4',5':4,5]pyrrolo[2,3-c]-azepine (VII). A 0.2-g (7.5 mmole) sample of sodium hydride was added to a suspension of 0.5 g (1.5 mmole) of VI in 20 ml of DMF, and the mixture was maintained at 20°C for 30 min. A 1-g (7.5 mmole) sample of benzyl chloride was added, and the mixture was maintained at 20°C for 20 min and then heated at 60°C for 4 h. It was then cooled, and the precipitated sodium chloride was removed by filtration. The mother liquor was evaporated *in vacuo*, and the residue was triturated with ether. The solid material was removed by filtration and dried to give VII (Table 1). PMR spectrum: 1.90 (2H, quintet, 9-CH_2), 2.88 (2H, m, 10-CH_2), 3.13 (2H, t, 8-CH_2), 4.72 (2H, s, benzyl CH_2), 5.33 (2H, s, benzyl CH_2), 6.20 (2H, s, benzyl CH_2), 7.0-7.5 (15H, m, aromatic CH═), and 8.41 ppm (1H, s, 2-CH═).

3-Benzyl-4,6-dioxo-5-(N,N-dimethyl)aminoethyl-6H-3,4,7,8,9,10-hexahydropyrimido[4',5':4,5]pyrrolo[2,3-c]azepine (VIII). A 0.9-g (37.5 mmole) sample of sodium hydride was added in portions to a suspension of 9.3 g (30.2 mmole) of VI in 300 ml of dimethylformamide, and the mixture was maintained at 20°C for 1.5 h. A 4-g (37.5 mmole) sample of 1-chloro-2-(N,N-dimethylamino)ethane was added, and the mixture was maintained at 20°C for 40 min and then heated at 65°C for 3 h. It was then cooled, and the precipitated sodium chloride was removed by filtration. The mother liquor was evaporated *in vacuo*, and the residue was triturated with ether, removed by filtration, and dried to give VIII (Table 1).

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C (solvent)	IR spectrum, cm^{-1}		λ_{max}, nm (lg ε)	Found, %			Empirical formula	Calc., %			Yield, %
		C=O	NH, NH_2		C	H	N		C	H	N	
II	102—104[a]	1750, 1670	3370, 3325, 3290[b]	225 (3.62), 305 (3.95)	56.1	6.4	17.6	$C_{11}H_{15}N_3O_3$	55.7	6.4	17.7	60
III	165—167[a]	1670, 1645	3430, 3335, 3290, 3200	233 (4.10), 282 (4.27)	55.8	6.4	17.9	$C_{11}H_{15}N_3O_3$	55.7	6.4	17.7	75
IV	>300[c]	1690, 1650	3600, 3340, 3290, 3190	246 (4.25), 286 (4.13)	54.9	4.9	25.7	$C_{10}H_{10}N_4O_2$	55.0	4.6	25.7	98
V	169—172[d]	1700, 1650	3460, 3275, 3160	223 (4.18), 266 (4.41)	57.5	7.0	19.5	$C_{14}H_{20}N_4O_3$	57.5	6.9	19.2	90
VI	>300[e]	1675, 1645	3275, 3185, 3060	—	65.9	5.2	18.4	$C_{17}H_{16}N_4O_2$	66.2	5.2	18.2	72
VII	98—101[f]			253 (4.50), shoulder 285 (4.17)	76.2	5.8	11.5	$C_{31}H_{28}N_4O_2$	75.9	5.8	11.3	63
VIII	158—162[g]	1670, 1635	3265, 3180	—	66.5	6.8	18.5	$C_{21}H_{25}N_5O_2$	66.5	6.6	18.5	95
IX	250—252[f]	1675, 1625	3400, 3250, 3130	—	—	—	16.8	$C_{21}H_{26}N_5O_2Cl$[h]	—	—	16.9	90
X	207—209[g]	1665	—	260 (4.34), 299 (4.13)	68.8	6.1	20.0	$C_{20}H_{21}N_5O$	69.1	6.1	20.2	42

[a]From water. [b]$\nu_{C\equiv N}$ 2200 cm^{-1}. [c]From formamide. [d]From ethyl acetate. [e]From DMF. [f]From EtOH. [g]From iso-PrOH. [h]Found: Cl 8.5%. Calculated: Cl 8.2%.

3-Benzyl-4,6-dioxo-5-(N,N-dimethyl)aminoethyl-6H-3,4,7,8,9,10-hexahydropyrimido[4',5':4,5]pyrrolo[2,3-c]azepine (IX). A 10.8 g sample of VIII was dissolved in 60 ml of chloroform, an alcohol solution of HCl was added to bring the mixture to pH 5, and the hydrochloride (IX) of VIII was removed by filtration (Table 1). Removal of the chloroform by distillation and treatment of the residue with isopropyl alcohol gave an additional amount of IX. PMR spectrum: 2.03 (2H, m, 9-CH_2), 2.90 (2H, m, 10-CH_2), 3.01 [6H, s, $N(CH_3)_2$], 3.29 (2H, m, 8-CH_2), 3.68 (2H, t, CH_2N), 5.12 (2H, t, pyrrole CH_2N), 5.33 (2H, s, benzyl CH_2), 7.39 (6H, m, aromatic CH=), and 8.24 ppm (1H, s, 2-CH).

3-Methyl-10-benzyl-11-oxo-1,2,3,5,6,7,10,11-octahydropyrazino[3,2,1-b,c]azepino[3,4-b]-pyrrolo[3,2-d]pyrimidine (X). A 1-g sample of hydrochloride IX was refluxed in 10 ml of phosphorus oxychloride for 4 h, after which the solution was evaporated *in vacuo*, and the residue was dissolved in ice water. The solution was treated with charcoal and filtered, and the filtrate was made alkaline to pH 9 with ammonium hydroxide and extracted with chloroform. The extract was dried and evaporated *in vacuo*, and the residue was triturated with ether to give X (Table 1). PMR spectrum: 2.02 (2H, m, 6-CH_2), 3.02 (2H, t, 7-CH_2), 3.04 (3H, s, 3-NCH_3), 3.47 (2H, m, 2-CH_2), 3.72 (2H, t, 5-CH_2), 4.66 (2H, m, 1-CH_2), 5.14 (2H, s, benzyl CH_2), 7.27 (5H, s, aromatic CH=), and 7.86 ppm (1H, s, 9-CH=).

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