

liquor was evaporated to dryness. The residue was triturated with water and the solid material was removed by filtration and dried.

4-(1,3-Dimethyl-4-amino-5-uracilyl)-2-oxo-3-hydroxy-1H-2,5,6,7-tetrahydroazepine Hydrobromide (XIX) and 1,3-Dimethyl-2,4,9-trioxo-9H-1,2,3,4,5,6,7,8-octahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidine (XVI). A 4.8-g (0.02 mole) sample of I was added at 20°C to a suspension of 3.1 g (0.02 mole) of 1,3-dimethyl-4-aminouracil in 30 ml of glacial AcOH, and the mixture was heated at 60°C for 1 h. It was then cooled to 20°C, and the precipitate was removed by filtration, washed with alcohol, and dried to give XIX.

Compound XIV was isolated from the acetic acid mother liquor when it was cooled to 5°C.

N-Methyl-2,4,9-trioxo-9H-1,2,3,4,5,6,7,8-octahydroazepino[3,4-b]pyrrolo[2,3-d]pyrimidines (XVII, XVIII). A suspension of 0.01 mole of 3-methyl- or 1-methyl-4-aminouracil and 0.01 mole of I in 15 ml of glacial AcOH was heated at 100°C for 8.5 h, after which it was cooled, and the precipitate was removed by filtration and suspended in 30 ml of water. The suspension was made alkaline to pH 8 with 1 N NaOH, and the precipitate was removed by filtration, washed with water, and dried to give XVII and XVIII.

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#### SYNTHESIS AND IONIZATION CONSTANTS OF

#### N-(4-CARBETHOXY-5-PYRAZOLYL)AMIDINES\*

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A number of N-(4-carbethoxy-5-pyrazolyl)amidines were synthesized by the reaction of acetals of amides and lactams with 4-carbethoxy-5-aminopyrazole, and their ionization constants in 50% alcohol were measured. It is shown that the increased basicities of the amidines obtained from the lactam acetals and dimethylacetamide acetal as compared with the basicity of N-(4-carbethoxy-5-pyrazolyl)-N',N'-dimethyl-formamidine are due to the smaller degree of steric hindrance to conjugation in the latter.

Acetals of amides and lactams readily react with aromatic and heteroaromatic amines (for example, see [2]) to give the corresponding amidines.

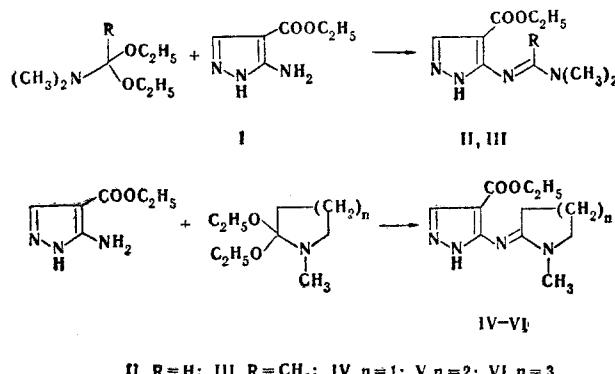
Amidines II-VI were synthesized in the present research by reaction of 4-carbethoxy-5-aminopyrazole (I) with the diethylacetals of dimethylformamide (DMF), dimethylacetamide, N-methylbutyrolactam, N-methylvalerolactam, and N-methylcaprolactam:

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TABLE 1. Ionization Constants of N-(4-Carbethoxy-5-pyrazolyl)-amidines (II-VI)

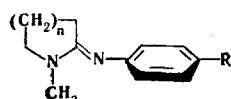
Compound	II	III	IV	V	VI
$pK_a$ (50% alcohol)	$5.57 \pm 0.04$	$6.56 \pm 0.03$	$6.51 \pm 0.03$	$6.93 \pm 0.04$	$6.46 \pm 0.03$



Attempts to cyclize these compounds to condensed 4-pyridone derivatives as in [3] were unsuccessful; this is possibly associated with the "enamino ester" character of the carbethoxy group in the 4 position of the pyrazole ring.

The problem of the dependence of the basicities of lactams [4], enamines [5], and amidines [6] on the size of the saturated azaheteroring has been studied systematically.

It follows from the data in Table 1 that the most basic of amidines IV-VI is six-membered amidine V, as previously observed in all of the above-indicated series of compounds. Formamidine II is one order of magnitude less basic than the remaining amidines. This result is unexpected, since the presence of a substituent attached to the "amidine" meso carbon atom may disrupt the "amidine" conjugation due to the creation of steric hindrance, and this lowers the basicities of these compounds. In our case, however, formamidine II has the lowest basicity. The explanation for this unusual phenomenon can be found if one turns to a recent investigation [6] of the basicities of 1-methyl-2-aryliminopyrrolidines, 1-methyl-2-aryliminopiperidines, and 1-methyl-2-aryliminohexahydroazepines, in which it is demonstrated by correlation analysis that the benzene ring in these compounds is at an angle of 50-60° relative to the C=N bond.



If it is assumed that in the case of N-pyrazolylamidines III-IV the steric hindrance due to the presence of the  $\text{CH}_2$  group of the saturated heteroring (or the  $\text{CH}_3$  group in III) also leads to rotation of the N-pyrazolyl residue, whereas in the case of formamidine II this rotation is absent (or is realized to a lesser degree), the observed results are easily interpreted. In fact, the electron-acceptor effect of the N-(4-carbethoxy-5-pyrazolyl) substituent is then manifested to a full extent only in the case of amidine II: This also lowers the basicity of this compound. The construction of molecular models completely confirms this assumption. The UV spectra are also in complete agreement with the concepts stated above: Only the spectrum of amidine II contains an expressed long-wave maximum at 287 nm ( $\epsilon 11200$ ). In the case of III-VI the spectra contain shoulders with  $\epsilon 720-860$  at 260 nm; this constitutes evidence for disruption of the conjugation in these amidines.

#### EXPERIMENTAL

The ionization constants of amidines II-VI were measured by the method in [6]. The UV spectra of alcohol solutions of the compounds ( $\sim 10^{-4}$  mole/liter) were recorded with an EPS-3

TABLE 2. Synthesized II-VI

Compound	mp, °C (crystallization solvent)	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	N	Cl		C	H	N	Cl	
II	95-97 (acetone)	51,5	6,9	27,1	-	C <sub>9</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	51,4	6,7	26,7	-	91
III	100-102 (ethyl acetate)	53,4	7,2	25,3	-	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	53,6	7,1	25,0	-	89
IV	168-169 (acetone)	56,1	6,9	23,5	-	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	55,9	6,8	23,7	-	-
V	132-133 (ethyl acetate)	58,4	7,3	22,5	-	C <sub>12</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	57,6	7,2	22,4	-	80
VI	90-92 (ethyl acetate-hexane)	59,3	7,6	21,4	-	C <sub>13</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub>	59,1	7,6	21,2	-	-
II · HCl	169 (2-propanol)	43,4	6,1	22,9	12,5	C <sub>9</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> · HCl	43,8	6,1	22,7	12,4	-
III · HCl	181 (2-propanol)	-	-	21,4	14,2	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> · HCl	-	-	21,5	14,0	-
IV · HCl	(acetone-2-propanol)	-	-	20,8	12,9	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> · HCl	-	-	20,6	13,0	91
V · HCl	198 (ethyl acetate)	50,2	6,6	19,5	12,5	C <sub>12</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> · HCl	50,3	6,6	19,6	12,4	-
VI · HCl	228 (alcohol)	-	-	18,9	11,8	C <sub>13</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> · HCl	-	-	18,6	11,8	85

spectrophotometer (layer thickness 1 cm).

**N-4-Carbethoxy-5-pyrazolyl-N',N'-dimethylformamidine (II).** A mixture of 5 g (32.3 mmole) of 4-carbethoxy-5-aminopyrazole (I), 5.22 g (35.5 mmole) of dimethylformamide acetal, and 25 ml of dry benzene was refluxed for 2 h, after which the benzene was removed by distillation to give amidine II. Amidines III and V were similarly synthesized. The yields and the results of elementary analysis are presented in Table 2.

**1-Methyl-2-[N-(4-carbethoxy-5-pyrazolyl)]iminohexahydroazepine (VI).** A mixture of 5 g (32.3 mmole) of aminopyrazole I, 7.15 g (35.5 mmole) of N-methylcaprolactam acetal, and 25 ml of dry benzene was refluxed for 4 h, after which the benzene was removed by distillation, and the residue was dissolved in ether. The ether solution was acidified with an alcohol solution of HCl and worked up to give 9.75 g (85%) of the hydrochloride of amidine VI. The hydrochlorides of amidines II-V were similarly obtained (Table 2).

The hydrochloride of amidine VI was dissolved in a small amount of water, and the solution was made alkaline to pH 7 with 40% K<sub>2</sub>CO<sub>3</sub> solution and extracted with chloroform. The extract was separated and dried with Na<sub>2</sub>SO<sub>4</sub>, and the chloroform was removed by distillation. The residue was crystallized from ethyl acetate-hexane (1:1) to give amidine VI. Amidine IV was similarly synthesized (see Table 2).

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