# ACETALS OF LACTAMS AND ACID AMIDES

## XIX.* SYNTHESIS OF 3-CYANO-6-DIMETHYLAMINO-2-PYRIDONE AND PYRROLO-, PYRIDO-, AND AZEPINO[2,3-b]PYRIDINE DERIVATIVES

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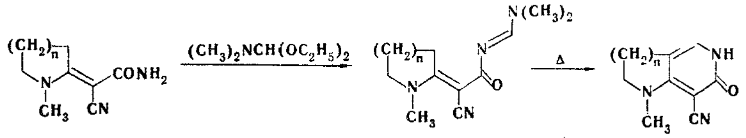
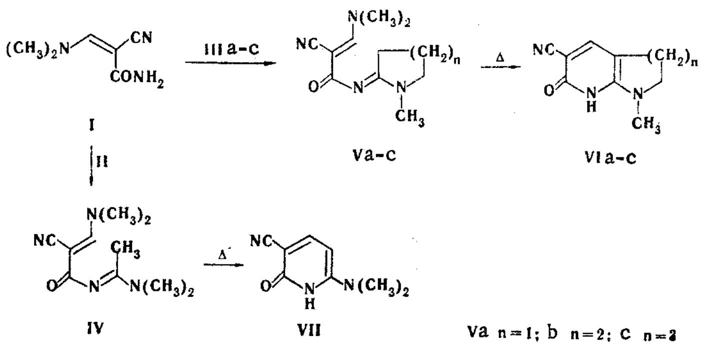
The reaction of $\alpha$-cyano-$\beta$-dimethylaminocrotonic acid amide with acetals of dimethyl acetamide and N-methylbutyro-, -valero-, and -caprolactams gave enaminoacrylamidines, cyclization of which gave 3-cyano-6-dimethylamino-2-pyridone and the corresponding pyrrolo-, pyrido-, and azepino[2,3-b]pyridine derivatives.

Dimethylformamide diethylacetal readily reacts with enaminoamides to give enaminoacylamidines, which undergo smooth cyclization to pyrrolo-, pyrido-, and azepino[3,2-c]pyridine derivatives when they are heated [1]:



As seen from the above scheme, in this case the amidine grouping is attacked at the 3-CH$_2$ link of the saturated heteroring with splitting out of dimethylamine. It seemd of interest to ascertain whether this sort of cyclization is possible when the attack occurs at an $\alpha$-CH$_2$ (CH$_3$) group in the enamine rather than in the amidine portion of the molecule and when the attacking particle is the $\alpha$-carbon atom of the enamine rather than the meso atom of the amidine fragment. With this in mind we subjected $\alpha$-cyano-$\beta$-dimethylaminoacrylamide (I) [2] to reaction with the diethylacetals of N,N-dimethylacetamide (II), and N-methylbutyro-, -valero-, and -caprolactams (IIIa-c, respectively). The IR spectra of IV and Va-c do not contain absorption bands of an NH$_2$ group but do contain absorption bands at 1580, 1650, and 2200 cm$^{-1}$, which are related to C=O, C=N, and C≡N groups. It should be noted that the signal of the dimethylamino groups in the PMR spectra (Table 1) of Va-c and one of the corresponding signals in the spectrum of amidine IV at room temperature are markedly broadened doublets that are converted to narrow singlets as the temperature is raised; this constitutes evidence for hindered rotation of these groupings.



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[*] See [1] for communication XVIII.

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TABLE 1. Enaminoacylamidines IV and Va-c

| Compound | mp, °C* | Found, % |  |  | Empirical formula | Calc., % |  |  | PMR spectrum (CDCl$_3$), ppm |  |  |  |  |  |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  | C | H | N |  | C | H | N | 1-CH$_2$ | 3-CH$_2$ | 4-CH$_2$ | 5-CH$_2$ | 6-CH$_2$ | 7-CH$_2$ | N(CH$_3$)$_2$ | =C—H |  |
| IV | 107—108 | 57,8 | 7,6 | 27,4 | $C_{10}H_{16}N_4O$ | 57,7 | 7,7 | 26,9 |  | 2,20 (C—CH$_3$) | — | — | — |  | 3,06, 3,25 (two) N(CH$_3$)$_2$ | 7,87 | 74 |
| Va | 125—126 | 59,9 | 7,1 | 25,8 | $C_{11}H_{16}N_4O$ | 60,0 | 7,3 | 25,5 | 3,24 | 3,03 | 2,04 | 3,42 | — | — | 3,24 | 7,8 | Quantitative |
| Vb | 131—131,5 | 61,6 | 7,7 | 24,0 | $C_{12}H_{18}N_4O$ | 61,5 | 7,7 | 23,5 | 3,09 | 2,79 | 1,77 |  | 3,34 | — | 3,29 | 7,7 | The same |
| Vc | 94—95 | 63,0 | 8,1 | 22,6 | $C_{13}H_{20}N_4O$ | 62,9 | 8,1 | 22,5 | 3,12 | 2,72 | 1,69 |  |  | 3,42 | 3,24 | 7,7 | „ „ |

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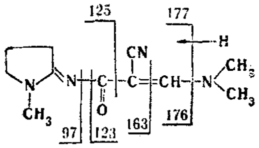
*Compounds IV and Va,b were recrystallized from ethyl acetate, and Vc was recrystallized from benzene—hexane.

TABLE 2. 3-Cyano-2-pyridone Derivatives

| Compound | mp, °C | Found, % |  |  | Empirical formula | Calc., % |  |  | PMR spectrum (CDCl$_3$), ppm |  |  |  |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  | C | H | N |  | C | H | N | 2-CH$_2$ | 3-CH$_2$ | 4-CH$_2$ | 5-CH$_2$ | —CH$_3$ | =C—H |  |
| VIb | 300 | 63,7 | 5,8 | 22,5 | $C_{10}H_{11}N_3O$ | 63,5 | 5,8 | 22,2 | 3,39 | 1,82 | 2,57 | — | 3,10 | 7,22 | 92 |
| VIc | 241—242 (2-propanol) | 64,8 | 6,3 | 20,8 | $C_{11}H_{13}N_3O$ | 65,0 | 6,4 | 20,7 | 3,51 | 1,87 |  | 3,30 | 3,25 | 7,28 | 60 |
| VII | 300 | 59,3 | 5,5 | 25,9 | $C_8H_9N_3O$ | 58,9 | 5,5 | 25,8 | — | — |  | — | 3,08 N(CH$_3$)$_2$ | 5,74-5H, 7,54-6H | 55 |

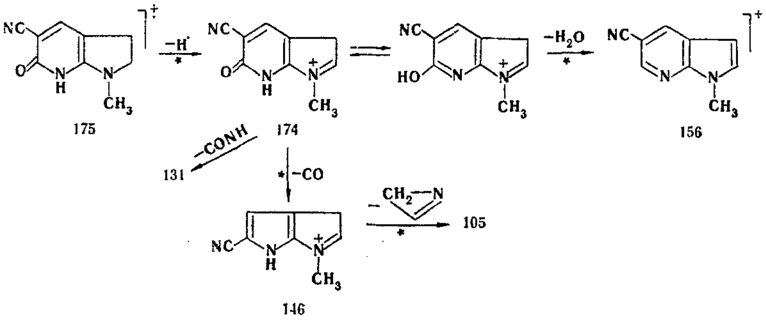
A molecular ion peak (M − 220) is observed in the mass spectrum of Va. The fragmentation is in agreement with the proposed structure and is realized via the following scheme:



The most favorable process is cleavage of the bonds in the α position relative to the carbonyl group to give fragments with m/e 125 and 123 (the most intense peak belongs to the ion with m/e 125).

From the data presented above it can be stated that the reaction of acetals of acid amides and lactams with enaminoamidines is general in character and can be used for the synthesis of various enaminoacylamidines.

We then attempted to bring about the cyclization of enaminoacylamidines IV and Va-c to 2-pyridone derivatives. It was found that the cyclization reaction is extremely sensitive to the ring size of the starting amidines. thus 1-methyl-6-cyano-7- oxo-1,2,3,4,7,8-hexahydro-1,8-naphthyridine (VIb) is formed in good yield when Vb is heated at 180°C for 7 min. A higher temperature (220°C) is required for the cyclization of IV and VII, whereas the cyclization of an enaminoacylamidine with a seven-membered ring (Vc) proceeds satisfactorily to give pyridoazepine VIc only in the presence of a catalyst (p-toluenesulfonic acid) at 200°C. Heating amidine Va under various conditions leads to pronounced resinification, and VIa could not be purified. Its structure was confirmed by the similarity between its UV spectrum and the spectra of VIb,c and VII and also by mass spectrometric data. An intense molecular ion peak (m/e 175) is observed in the mass spectrum of VIa. Elimination of a hydrogen atom, which leads to stabilization of the charge on the N atom of the five-membered ring, subsequently predominates. The resulting ion is extremely stable and has the maximum intensity. Its subsequent fragmentation is probably due to the presence of two tautomeric forms, as evidenced by the competitive elimination of $H_2O$ and CO molecules that is observed in the spectrum. The fragmentation was confirmed by the presence of the corresponding metastable transitions:



The structures of pyridines VIb,c and VII were confirmed by the PMR spectra (Table 2).

## EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM- 4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The mass spectra were recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the ion source. The ionizing-electron energy was 30 eV. The temperature of the ionization chamber was 125°C.

N,N-Dimethyl(α-cyano-β-dimethylaminoacryloyl)acetamidine (IV). A solution of 6 g of acetal II in 20 ml of toluene was added dropwise to a refluxing solution of 4.2 g of I in 20 ml of toluene, and the mixture was refluxed for 2 h. It was then cooled and filtered, and the toluene was removed from the filtrate by distillation. The residue was triturated with ether to give IV. Compounds IVa-c (Table 1) were similarly obtained.

3-Cyano-6-dimethylamino-2-pyridone (VII). A 1-g sample of IV was heated at 220°C for 10 min, after which the mixture was cooled, and ethanol was added to give VII. Compounds VIa-c were similarly obtained. See Table 2 for the analytical data and the PMR spectra of VIb,c and VII.

## LITERATURE CITED

1. V. G. Granik, N. B. Marchenko, T. F. Vlasova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 11, 1509 (1976).
2. W. Leimgrüber and M. Weigele, U.S. Patent (Cl. 260/307 H, CO7d) (1970); Chem. Abstr., 77, 140130g (1972).

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# STUDY OF THE ELECTRON INTERACTIONS OF POLYSUBSTITUTED AZOLES BY PMR AND IR SPECTROSCOPY

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The IR and PMR spectra of an extensive series of methyl derivatives of aromatic and heteroaromatic compounds were investigated. With a few exceptions, the experimental data on the chemical shifts of the protons ($\delta^{CH_3}$) and the intensity of the band of the symmetrical stretching vibration $[(A_{CH})^{1/2}]$ for five- and six-membered heterorings can be united in a single reaction series with polysubstituted toluenes within the framework of an additive scheme. The $(A_{CH})^{1/2}$ values correlate satisfactorily with the calculated (by the CNDO/2 method) total charges on the carbon and hydrogen atoms of the methyl group. In contrast to the intensities of the IR bands, linear relationships between the chemical shifts and the charges on the hydrogen atoms are observed only within the limits of particular reaction series. The lack of a unified relationship was interpreted as being the result of the effect of the ring current, the contribution of which to the $\delta^{CH_3}$ value depends on the nature of the heteroatom.

In our previous papers [1, 2] we demonstrated the applicability of the principle of additivity for the characterization of the contributions of the individual substituents and heteroatoms to the changes in the kinetic and spectroscopic parameters of the methyl group in the polysubstituted toluenes and their heteroanalogs. In the present research we made an attempt to extend the indicated approach to the IR and PMR spectroscopic characteristics of methyl derivatives of five-membered aromatic heterocycles and to ascertain the possibility of a quantum-chemical description of the trend of the change in these parameters.

## Applicability of the Additive Scheme

PMR Spectra. The chemical shifts of both aromatic protons and the protons of methyl groups bonded to the heteroaromatic ring in azoles have been studied in a number of papers (for example, see [3-19]). However, in the overwhelming majority of cases only the effect of variable substituents on the $\delta$ value as the nature and position of the heteroatomic groupings built into the ring remain fixed has been investigated. The experimental data presented in Table 1 make it possible to thoroughly analyze the entire set of data on the change in the shielding constants of the protons of the methyl group in azoles of various types.

As in [2], we used a variant of the additive scheme in which the effect of each substituent in the azole ring characterizes the $\Delta\delta_i$ increment, which reflects its contribution to the $\delta^{CH_3}$ value in the corresponding mono-substituted toluene; the contributions of the heteroatomic $-O-$, $-S-$, $-N(CH_3)-$, and $-N=$ groups are conveyed by the magnitude of the $\Delta\delta^{CH_3}$ chemical shift in the furan, thiophene, N-methylpyrrole, and pyridine rings with respect to toluene as the standard compound ($\delta^0 = 2.34$ ppm). Moreover, in conformity with the generally accepted concepts regarding the transmission capacities of the $-O-$, $-S-$, and $-NH-$ heteroatoms in five-membered rings [20], all of the azole ring positions adjacent to them are considered to be ortho-like, the 1-3(4), 2-4, and 3-5 positions are considered to be meta-like, and the 2-5 positions are considered to be para-like positions of the benzene ring.

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