LACTAM ACETALS AND ACID AMIDES.

31.* SYNTHESIS, PROTONATION, AND BASICITIES OF SOME HETEROCYCLIC ENAMINO KETONES

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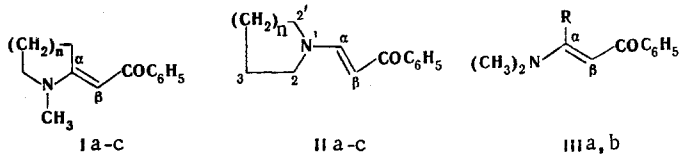
UDC 547.75/82.07

The protonation of cyclic enamino ketones of the pyrrolidine, piperidine, and hexahydroazepine series, as well as their noncyclic analogs, was studied by PMR spectroscopy. It is shown that the presence of a CH_2 or CH_3 group in the "enamine" position leads to C protonation (in CF_3COOH). In the case of enamino ketones that do not contain substituents in the "enamine" α position N- and O-protonated forms are observed in CF_3COOH. The measured pK_a values (in 10% alcohol) and the ΔpK_a values (in nitromethane) of the enamino ketones show that the compounds for which C protonation is characteristic are two to three orders of magnitude more basic than in the case of compounds that do not contain substituents in the "enamine" α position; this is explained by the different character of protonation.

It has been previously shown that the size of the saturated azaheteroring has a substantial effect on the properties of cyclic enamino ketones (Ia-c) [2-5]. In the present research we examined several possible methods for the synthesis of cyclic enamino ketones of a different type (IIa-c) and compared the physicochemical properties of the two series of compounds, as well as those of the noncyclic analogs (IIIa,b).

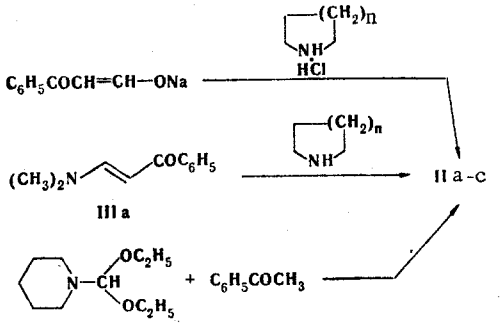


Ia-c IIa-c IIIa,b

I-II a n=1; b n=2; c n=3; III a R=H; b R=CH_3

The investigated compounds can be divided into two groups: enamino ketones that have a methyl group or a methylene link in the α position (Ia-c, IIIb), and enamino ketones that do not have a substituent in the "enamine" α position (IIa-c, IIIa).

We used three methods for the synthesis of IIa-c: a known method that consists in the reaction of benzoylacetaldehyde with secondary amines [6], the reaction of enamino ketone



*See [1] for communication 30.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 344-348, March, 1980. Original article submitted August 1, 1979.

 0009-3122/80/1603-0256$07.50

TABLE 1. Basicities of I-III

Compound	pK_a (in 10% alcohol)*	ΔpK (in nitromethane)
Ia	3,29	4,68
Ib	5,22	3,02
Ic	4,34	4,02
IIa	2,08†	6,57
IIb	2,11†	6,54
IIc	1,83‡	7,0
IIIa	1,87†	6,82
IIIb	4,44	4,05

*See [2] for the pK_a values for Ia-c.
†Calculated values.
‡Determined by spectrophotometry.

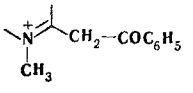
IIIa with the corresponding amines (transamination; see [7, 8]), and condensation of cyclic amide acetals with acetophenone (in the case of N-formylpiperidine diethylacetal [9]). The results (see the experimental section) show that the most promising of these methods is transamination. One should bear in mind that starting enamino ketone IIIa is easily obtained [9] and is formed in high yield by condensation of dimethylformamide acetal with acetophenone.

The measured basicities of enamino ketones I-III led to unexpected results. It was found that IIa-c and IIIa have such low basicities that is is impossible to obtain reliable pK_a values for them in aqueous alcohol solutions when potentiometric titration is used. The ionization constants for these compounds were determined in nitromethane. Since the pK_a values in 10% alcohol for enamino ketones Ia-c and IIIb are easily determined by potentiometry, while the ionization constant for IIc was determined spectrally, we attempted to ascertain a relationship between the pK_a values (in 10% alcohol) and the ΔpK_a values (in nitromethane) by means of regression analysis. The corresponding equation is presented below (the correlation coefficient is significant at a 99% level). The data on the basicities of the investigated compounds are presented in Table 1. The pK_a values for enamino

$$pK_a = 7.7 - 0.86\Delta pK \quad (r = 0.98,\ s = 0.298,\ n = 5)$$

ketones IIa,b and IIIa in aqueous solution were calculated from the equation presented above. It is apparent from Table 1 that in the series of IIa-c compounds the ring size has a considerably smaller effect than in the series of enamino ketones Ia-c.

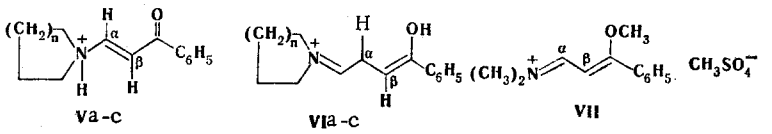
The question as to the reasons for the increase by two to three orders of magnitude in the basicities of Ia-c and IIIb as compared with the basicities of enamino ketones IIa-c and IIIa arises. In a previous study [10] of the protonation of enamino ketones of the I type it was shown that in CF_3COOH these compounds exist in the C-protonated form. In the present research we confirmed these results for all of the compounds of the first group (Ia-c, IIIb) and showed that no signals whatsoever except for the signals of immonium cations of the IV type were observed in the PMR spectra of these substances in CF_3COOH.



IV

A completely different picture is observed in the spectra of IIa-c and IIIa in CF_3COOH. Signals of two protonated forms appear distinctly in the PMR spectra of enamino ketones of this group (see the experimental section). For the predominant form the signals of the vinyl protons are noted at 5.9-6.2 ppm (β-CH doublet) and 8.6-8.8 ppm (α-CH doublet) with $J_{H_\alpha H_\beta}$ = 12 Hz. For the second (minor) form the corresponding signals are observed at 6.0-6.3 ppm (β-CH doublet, $J_{H_\alpha H_\beta}$ = 12 Hz) and 7.85-8.0 ppm (α-CH doublet, $J_{H_\alpha H_\beta}$ = 12 Hz). The absence in the spectra of these compounds in CF_3COOH of the signals of the CH_2 group indi-

cates that C protonation of enamino ketones IIa-c and IIIa does not occur under the given conditions. Since enamino ketones can also be protonated at the nitrogen atom (N protonation) or at the oxygen atom (O protonation [11, 12]), the picture observed in the PMR spectra corresponds to the joint presence of N- and O-protonated forms (types V and VI). It should be noted that this result was extremely unexpected, since up until now one could not establish the formation of N-protonated forms of enamino ketones. Proceeding from this, it was logical to assume that the predominant form (see the experimental section for the ratio of the protonated forms) is O-protonated form VI. However, a comparison of the structures of N- and O-protonated forms V and VI shows that if one takes into account only



Va-c VIa-c VII

V, VI a n=1; b n=2; c n=3

the electronic factors, the combination of the electron-acceptor effect of the ammonium group and the benzoyl residue on the chemical shift of the α proton in form V is substantially greater than that of the $>\overset{+}{N}=C$ group in cation VI, which is additionally partially compensated by the electron-donor effect of the OH group. Hence, one might have expected that the signal of the α proton in the N-protonated form should be found at weaker field than in the case of the O-protonated form, and, correspondingly, enammonium cation V predominates under the investigated conditions. To prove the correctness of this assignment of the signals we compared the PMR spectra in CF_3COOH of enamino ketones IIa-c and IIIa with the spectrum of salt VII [13], which is a model of the O-protonated form. It was found that signals of the α protons at 7.98 ppm and of the β protons at 5.98 ppm (doublets, $J_{H_\alpha H_\beta}$ = 10 Hz), as well as the signals of OMe, $\overset{+}{N}Me_2$, and the aromatic protons at 4.15, 3.90, and 7.25 ppm, respectively, are observed in the spectrum of salt VII. Thus, the spectrum of the model compound is in good agreement with the assignment of the signals of the protonated forms made above: the predominant form is the N-protonated form, and the minor form is the O-protonated form.

The results of the spectral study explain the differences in the basicities of both investigated groups of enamino ketones (Ia-c, IIIb and IIa-c, IIIa). Under various conditions protonation of the first group leads to the thermodynamically more stable C-protonated form, which is also responsible for the increased basicities of these compounds. Steric hindrance due to steric interaction between the α-CH_3 (or CH_2 group) and the benzoyl carbonyl group promotes the C-protonated form in the series of compounds (Ia-c, IIIb). This hindrance remains in the formation of the N-protonated from, increases in the case of O protonation, but vanishes in the formation of the C-protonated form, since rotation of the benzoyl fragment relative to the Cβ—CO bond becomes possible. It should also be noted that the presence of a CH_3 group (and probably a CH_2 group) in the α position of the $>\overset{+}{N}=\overset{\alpha}{C}$ immonium fragment stabilizes the cation substantially (e.g., see [14]) and that our results are in good agreement with the previously advanced generalization [14], according to which the presence of an α-methylene group in enamines appreciably increases their tendency to undergo C protonation and consequently their basicity. The absence of an α-alkyl grouping in the compounds of the second group (IIa-c, IIIa) leads to a considerably greater shift in the equilibrium to favor the kinetically favorable forms (N- and O-) and, as a result of this, inhibition of C protonation. The fact that the N-protonated form predominates over the O-protonated form can be explained on the basis of an examination of molecular models: steric hindrance between the OH group and the α proton (or the ortho protons of the benzoyl ring) and the β proton and the N—CH_3 group (IIIa) develops in the O-protonated form (VI).

In conclusion, let us point out that the relatively small differences in the basicities between the compounds in the IIa-c series confirm our previous opinion [2] that the marked increase in the basicity of six-membered compound Ib as compared with the basicities of the five- and seven-membered analogs in the Ia-c series is due to the development of an endocyclic $C=\overset{+}{N}$ bond. In the case of enamino ketones IIa-c, in which an endocyclic double bond is not formed during protonation, the basicities of the five- and six-membered enamino ketones IIa,b are almost equal (Table 1); the small decrease in the basicity of hexahydroazepine derivative IIc is evidently due to the greater destabilization of cations Vc and

VIc, which is associated with steric interaction of the N substituent and the 2,2'-CH_2 groups of the seven-membered ring.

EXPERIMENTAL

The basicity constants in 10% alcohol and nitromethane were determined. Titration was carried out with a PNM-26 potentiometer with a G2222B glass electrode (Radiometer, Denmark). See [15] for the method used to determine the pK values. The error in the determination of the pK and ΔpK values did not exceed 0.06. The PMR spectra were recorded with C-60HL (JEOL) and XL-100 (Varian) spectrometers with tetramethylsilane as the internal standard.

1-Pyrrolidino-2-benzoylethylene (IIa). A solution of 7.1 g of enamino ketone IIIa and 5.8 g of pyrrolidine in 40 ml of absolute alcohol was refluxed for 3 h, after which the alcohol was removed by vacuum distillation to give 7.2 g (88%) of IIa with mp 119-120°C (from ethyl acetate) (mp 119-120°C [6]). PMR spectrum, δ ($CDCl_3$): 1.91 (3,3'-CH_2), 3.39 (2,2'-CH_2), 5.66 (β-CH), 8.04 (α-CH), and 7.2-8.0 (C_6H_5); (CF_3COOH): 2.23 (3,3'-CH_2), 3.79 and 4.03 (2,2'-CH_2), 5.92 and 6.04 (β-CH), 8.75 and 7.88 (α-CH), and 7.0-7.9 ppm (C_6H_5). The ratio of Va and VIa was 3:2.

1-Piperidino-2-benzoylethylene (IIb). A) Similarly, the reaction of 10 g of enamino ketone IIIa and 9.8 g of piperidine gave 11.3 g (92%) of IIb with mp 91-92°C (from ether). (mp 90-92°C [6]). PMR spectrum, δ ($CDCl_3$): 1.59 (3,3',4-CH_2), 3.29 (2,2'-CH_2), 5.89 (β-CH) 7.75 (α-CH), and 7.26-8.00 (C_6H_5); (CF_3COOH): 1.94 (3,3',4-CH_2), 3.91 and 4.19 (2,2'-CH_2), 6.08 and 6.23 (β-CH), 8.63 (the α-CH signal of the minor form of α-CH is masked by the signals of the aromatic protons), and 7.4-7.9 ppm (C_6H_5). The ratio of Vb and VIb was 85:15.

B) A mixture of 6.1 g of N-formylpiperidine diethylacetal [9] and 3.9 g of acetophenone was heated at 120°C for 3 h, after which it was evaporated in vacuo to give 5.6 g (80%) of enamino ketone IIb with mp 91-92°C (from ether). According to the results of a mixed-melting-point determination, the IR spectra, and the results of thin-layer chromatography (TLC), the product was identical to the product obtained by method A.

1-Hexahydroazepino-2-benzoylethylene (IIc). A) A solution of 10 g of the Na salt of benzoylacetaldehyde and 8 g of hexamethyleneimine hydrochloride in 60 ml of absolute alcohol was refluxed for 1 h, after which it was filtered, and the alcohol was removed by vacuum distillation. The residue was treated with water and chloroform, and workup of the chloroform extract gave 7 g (53%) of IIc with mp 54-55°C (from petroleum ether), PMR spectrum, δ ($CDCl_3$): 1.6 (3,3',4,4'-CH_2), 3.40 (2,2'-CH_2), 5.71 (α-CH), 7.81 (β-CH), and 7.2-7.9 (C_6H_5); (CF_3COOH): 1.77 (4,4'-CH_2), 2.00 (3,3'-CH_2), 4.92 (2,2'-CH_2), 6.00 and 6.17 (β-CH), 8.65 and 7.85 (α-CH), and 7.4-7.9 ppm (C_6H_5). The ratio of Vc and VIc was 3:1. Found: C 78.5; H 8.5; N 5.9%. $C_{15}H_{19}NO$. Calculated: C 78.6; H 8.3; N 6.1%.

B) A solution of 10 g of IIIa and 11.1 g of hexamethyleneimine in 60 ml of absolute alcohol was refluxed for 5 h, after which the alcohol was removed in vacuo to give 12.8 g (98%) of IIc with mp 54-55°C. The reaction products obtained by methods A and B were identical with respect to the results of mixed-melting-point determinations, the IR spectra, and chromatographic mobilities.

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LACTAM ACETALS AND ACID AMIDES.

32.* LACTIM–LACTAM TAUTOMERIZATION OF CONDENSED 4-PYRIDONES

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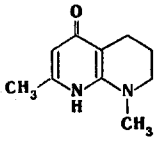
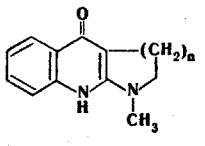
UDC 541.623:547.834.2

The tautomeric properties of a number of condensed 4-pyridone derivatives were investigated. The existence of lactim–lactam tautomerization in this series of compounds was established by IR and UV spectroscopy. It is shown that when α substituents are present in the 4-pyridone molecule, both intramolecular electronic effects and the effect of substituents on solvation of one or another tautomeric form and, consequently, on the position of the equilibrium should be taken into account.

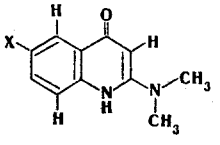
In a continuation of our study of tautomerism in a series of condensed pyridones [2-5], in the present research we investigated the tautomeric properties of 1,7-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyrid-5-one (I), derivatives of pyrrolo-, pyrido-, and azepino[2,3-b]-quinoline (IIa-c), 2-dimethylamino-4-quinolone (IIIa), and its 6-chloro derivative (IIIb), which were previously synthesized from amide and lactam acetals.



I



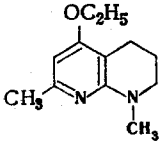
IIa-c



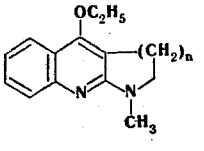
IIIa, b

IIa n=1; b n=2; c n=3; IIIa X=H; b X=Cl

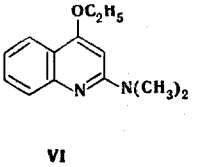
The corresponding ethoxy derivatives (IV-VI) were used as model compounds:



IV



Va-c



VI

Va n=1; b n=2; c n=3

The UV spectra of the investigated compounds are characterized by long-wave absorption maxima in water and in alcohol at 290 (for I), 318-322 (for IIa-c), and 306 nm (for IIIa). The character of the spectra changes appreciably as the polarity of the solvent decreases, during which the absorption maxima corresponding to those that are observed for model ethoxy

*See [1] for communication 31.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 349-353, March, 1980. Original article submitted September 19, 1979.

 0009-3122/80/1603-0260$07.50