11. Ya. F. Freimanis, The Chemistry of Enamino Ketones, Enamino Imines, and Enamino Thiones [in Russian], Zinatne, Riga (1974), p. 187.
12. H. E. A. Kramer, Ann., 696, 15 (1966).
13. H. Bredereck, F. Effenberger, D. Zeufang, and K. A. Hirsch, Chem. Ber., 12, 4036 (1968).
14. R. L. Hinman, Tetrahedron, 24, 185 (1968).
15. B. A. Korolev and B. I. Stepanov, Izv. Vyssh. Uchebn. Zaved., Khim., 11, 1198 (1968).

LACTAM ACETALS AND ACID AMIDES.

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

V. G. Granik, E. M. Peresleni, T. D. Kurochkina, A. M. Zhidkova, N. B. Marchenko, R. G. Glushkov, and Yu. N. Sheinker

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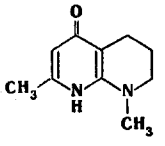
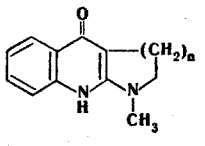
The tautomeric properties of a number of condensed 4-pyridone derivatives were investigated. The existence of lactim–lactam tautomerization in this series of compounds was established by IR and UV spectroscopy. It is shown that when α substituents are present in the 4-pyridone molecule, both intramolecular 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.

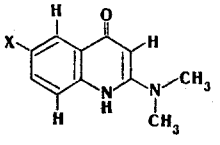
In a continuation of our study of tautomerism in a series of condensed pyridones [2-5], in the present research we investigated the tautomeric properties of 1,7-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyrid-5-one (I), derivatives of pyrrolo-, pyrido-, and azepino[2,3-b]-quinoline (IIa-c), 2-dimethylamino-4-quinolone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



I



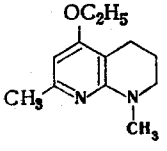
IIa-c



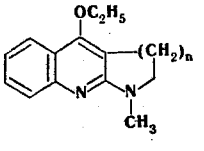
IIIa, b

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

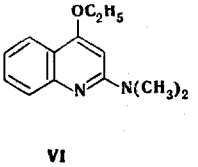
The corresponding ethoxy derivatives (IV-VI) were used as model compounds:



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.

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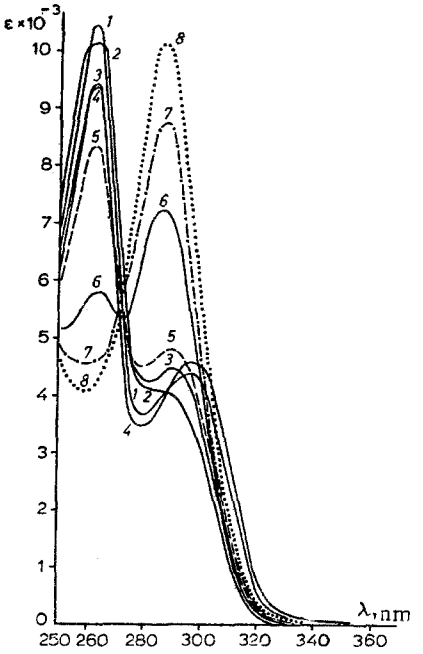


Fig. 1. UV spectra of I and IV in various solvents: 1) IV in dioxane; 2) I in dioxane; 3) I in dioxane with 10% alcohol; 4) IV in alcohol; 5) I in dioxane with 25% alcohol; 6) I in dioxane with 50% alcohol; 7) I in dioxane with 75% alcohol; 8) I in alcohol.

derivatives IV-VI appear and increase (Fig. 1). The character of the spectra of IV-VI does not depend on the polarity of the solvent. The spectra contain maxima at 263 and 297 (for IV) and at 340-360 nm (in addition to absorption at 249 and 277 nm) (for Va-c, VI). In aqueous alcohol solutions the spectra of IV-VI differ from the spectra in anhydrous solvents; for example, the spectrum of VI in 10% alcohol is identical to the spectrum in 1 N HCl. These data constitute evidence for ionization of ethoxy derivatives IV-VI in dilute (4-10 moles/liter) aqueous alcohol solutions.

The observed changes in the spectra and a comparison of the spectral characteristics for the investigated (I-III) and model (IV-VI) compounds indicate the existence of lactim–lactam tautomerism in the investigated series of 4-pyridone derivatives (I-III); the percentage of the lactim form is comparable to the percentage of the lactam form and increases as the polarity of the solvent decreases.

We were able to make a quantitative estimate of the position of tautomeric equilibrium for I. The data presented in Table 1 for the remaining investigated substances are approximate because of overlapping of the absorption maxima of the lactam and lactim forms. Nevertheless, it may be asserted that these errors are not so great as to change the overall pattern of the tautomerism observed for these compounds.

Bands of stretching vibrations of a CO group at 1627-1640 cm^{-1}, of double bonds at 1518-1610 cm^{-1}, and of NH groups at 2700-3270 cm^{-1} are observed in the IR spectra of I-III in the crystalline state (we were unable to obtain the IR spectra of solutions of the compounds because of their low solubilities). The spectra of model compounds IV-VI contain absorption bands of stretching vibrations of C=C and C=N bonds at 1500-1630 cm^{-1}, whereas absorption is absent in the high-frequency region. Although it is difficult to rigorously interpret the data from the IR spectra (since the difference between ν_{CO} in the spectra of the investigated compounds and $\nu_{C=C}$ and $\nu_{C=C}$ in the spectra of the model compounds are small), a systematic comparison of the spectra of the tautomeric and corresponding model substances shows that I-III exist in the lactam form in the crystalline state.

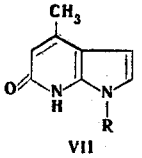
TABLE 1. Percentages of the Lactim Forms for Condensed 4-Pyridones (I, IIa-c, and IIIa)

Compound	Solvent					
	alcohol	25% dioxane and 75% alcohol	50% dioxane and 50% alcohol	75% dioxane and 25% alcohol	90% dioxane and 10% alcohol	dioxane
I	12	20	38	75	90	97
IIa	—	—	27	45	70	89
IIb	3	—	15	17	27	49
IIc	—	—	9	13	26	31
IIIa	—	—	7	17	40	67

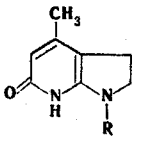
The fact that the investigated compounds in solutions were found to be tautomeric is not unexpected. It has been pointed out repeatedly in the literature [2] that a shift in the lactim–lactam equilibrium to favor the lactim form is observed when substituents that have an I effect are introduced in the α position of 2- and 4-pyridones. It has been assumed that in these cases the I effect of the substituent is responsible for a greater degree of "acidification" of the pyridone N–H group as compared with the pyridol OH group. In addition, it is known that transition to less polar solvents [2] or to the gas phase [6] also substantially shifts the tautomeric equilibrium to favor the lactim form. The effects of these factors (the effect of the substituent and the effect of the solvent) are comparable in magnitude, and when one examines the effect of structural changes in the molecules of tautomeric compounds on the position of the equilibrium, one should take into account to an equal extent both the intramolecular effects and the effects of the relative stabilization of the tautomeric forms due to interaction with the solvent.

In dioxane this stabilization is realized by the creation of an H bond due to the pairs of electrons on the oxygen atom of the solvent and the OH or NH group in the lactim and lactam forms, respectively. It follows from a comparison of structures I and IIb that the creation of this hydrogen bond for the lactim tautomer in I is hindered only by the presence of the protons of the 4-CH_2 group of the piperidine ring, whereas in IIb steric hindrance for the lactim form also arises due to the proton of the benzene ring in the 6 position of the molecule. This fact is probably one of the reasons for the decrease in the percentage of the lactim tautomer for IIb as compared with I.

In addition, the effect of the benzene ring in IIb on the shift of the tautomeric equilibrium to favor an increase in the lactam form may also be explained by electronic effects [7]. The question of the contribution of the different effects during the study of the lactim-lactam equilibrium remains open to discussion. From this point of view, the data that pertain to the hydroxy derivatives of azaindoles and azaindolines are demonstrative [8]. In a number of these compounds (VII and VIII, respectively) replacement of the hydrogen



VII



VIII

atom attached to the nitrogen atom of the five-membered ring by an n-butyl group (R = C_4H_9) leads to a substantial shift of the tautomeric equilibrium to favor the lactim form. This fact cannot be explained by a change in the electronic effect of the substituent. One might have attempted to interpret these data as a manifestation of destabilization of the lactam form due to steric repulsion of the N_7–H and N_1–C_4H_9 groups. However, the distinct dependence of the amount of the lactim form on the character of the solvent makes it possible to assume that another effect, viz., deterioration in the conditions for solvation of the lactam form in VIIb and VIIIb as compared with VIIa and VIIIa (under identical conditions for the solvation of the lactim forms of these compounds), plays a substantial role in the indicated shift in the tautomeric equilibrium. From the same point of view it may be assumed that the chlorine atoms in 2,6-dichloro-4-pyridone (which exists in the hydroxy form [2]) exert their effect on the position of tautomeric equilibrium not only due to electronic effects but also due to deterioration in the conditions of solvation of the lactam form (for comparison, let us point out that in the case of 3,5-dichloro-4-pyridone the equilibrium is shifted virtually completely to favor the oxo form [2]).

In the same respect, one may attempt to compare the behavior of IIb with its two-ring analog IIIa, in which a condensed piperidine ring is absent. A comparison of these compounds is legitimate, since the electronic characteristics of the dimethylamino group and N-methyl group included in the six-membered ring are usually close to one another. The conditions for solvation of the lactim form by dioxane are better in two-ring system IIIa than in three-ring system IIb (because of the absence in the former of protons of the ring CH_2 group in the 6 position), and, in conformity with this, the amount of the lactim form in dioxane is appreciably higher (Table 1).* The transition from 6-hydroxy-2-pyridone to 6-methoxy-2-pyridone, i.e., to a compound that has a bulkier substituent in the 6 position of the molecule, also leads to a considerable increase in the percentage of the pyridol tautomer [12].

One cannot exclude the possibility that an increase in steric hindrance to solvation of the lactim tautomer also makes its contribution to our observed shift of the tautomeric equilibrium as the size of the condensed ring changes from a five-membered system to a six-membered system and then to a seven-membered system (the percentage of the hydroxy tautomer decreases in this case; see Table 1).

We have already mentioned that the real amounts of the lactim tautomers in pyridone–pyridol tautomeric equilibrium can usually be observed when the 6 position of the pyridone ring contains substituents of the Hal, NR_2, and OR type, which bear unshared electron pairs, and when solvents that are capable of forming H bonds due to the unshared pairs of electrons of their own heteroatoms (ether and dioxane) are used [2]. One should also point out yet another possible effect, that hinders solvation of the lactam form by means of $>N-H\cdots O<$, bonds, that is associated with repulsion of the electron pairs of the solvent and the substituent in the α position.

In even less polar solvents (heptane and cyclohexane) that are incapable of forming hydrogen bonds, stabilization of the lactam forms is realized by intermolecular association (dimerization) of the lactam tautomer, and this factor begins to lose its effect only in very dilute solutions ($c \approx 10^{-7}$ M), and the hydroxy form becomes the predominant species [9].

Thus, when α substituents are introduced in the molecules of tautomeric derivatives of the heterocyclic series (of the pyridone and other types), one should take into account not only the intramolecular effects but also the effect of the substituents on solvation of one or another form and consequently on the position of the tautomeric equilibrium.

EXPERIMENTAL

The UV spectra of solutions in dioxane, mixtures of dioxane with alcohol, alcohol, and a mixture of 95% H_2O and 5% alcohol were obtained with an EPS-3 spectrophotometer. The IR spectra of mineral oil pastes of the crystalline compounds were recorded with a Perkin–Elmer 457 spectrophotometer. The investigated compounds were synthesized in [10-12].

LITERATURE CITED

1. V. G. Granik, S. S. Kiselev, N. P. Solov'eva, I. V. Persianova, M. K. Polievktov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 3, 344 (1980).
2. J. M. Elguero, C. Marzin, A. R. Katritzky, and P. Lindo, Tautomerism of Heterocycles. Advances in Heterocyclic Chemistry, Supplement 1, Academic Press, New York–San Francisco–London (1976).
3. L. N. Yakhontov (Jakhontov), D. M. Krasnokut-skaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, Tetrahedron, No. 10, 3325 (1966).
4. E. M. Peresleni, M. Ya. Uritskaya, V. A. Loginova, Yu. N. Sheinker, and L. N. Yakhontov, Dokl. Akad. Nauk SSSR, 183, 1102 (1968).
5. V. G. Granik, E. M. Peresleni, O. Ya. Belyaeva, T. D. Zotova, O. S. Anisimova, R. G. Glushkov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 6, 793 (1978).
6. P. Beak, F. Fry, J. Lee, and F. Steele, J. Am. Chem. Soc., 98, 171 (1976).
7. Yu. N. Sheinker, Sb. Tr. Vses. Nauchno-Issled. Khim.-Farm. Inst., 2, 219 (1971).
8. L. N. Yakhontov, D. M. Krasnokut-skaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, Dokl. Akad. Nauk SSSR, 172, 118 (1967).
9. P. Beak, J. B. Covington, and S. G. Smith, J. Am. Chem. Soc., 98, 8284 (1976).

*The situation is different in protogenic solvents, and the predominance of the lactam form can be explained by stabilization of the molecules by means of bonds of the $>C=O\cdots H-O-R$ type.

10. A. M. Zhidkova, V. G. Granik, R. G. Glushkov, T. F. Vlasova, O. S. Anisimova, T. A. Gus'kova, and G. N. Pershin, Khim. Geterotsikl. Soedin., No. 5, 670 (1974).
11. I. B. Marchenko, V. G. Granik, R. G. Glushkov, E. M. Peresleni, A. I. Polezhaeva, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 11, 49 (1976).
12. V. G. Granik, A. M. Zhidkova, S. S. Kiselev, R. G. Glushkov, A. I. Polezhaeva, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 7, 66 (1978).

KINETICS OF THE N OXIDATION OF SOME COMPOUNDS OF THE PYRIDINE SERIES WITH PERBENZOIC ACID IN CHLOROFORM AND AQUEOUS DIOXANE

R. E. Lokhov

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A comparative study of the kinetics of the N oxidation of 19 derivatives of the pyridine series with perbenzoic acid in chloroform and aqueous dioxane at 20, 25, 30, and 35°C was made. The rate constants, the parameters of the Arrhenius equation, and the activation energies of the N oxidation of the indicated monoazines were determined. The scale of the reactivities of the derivatives of the pyridine series was calculated within the framework of the Pearson hard-soft acid–base concept.

It is known [1-3] that the methods for the preparation of N-oxides of aromatic nitrogen-containing heterocycles by oxidation of the latter with peracids have important practical value. Despite this, the mechanism of N oxidation has not been adequately studied. The timeliness of research of this sort is due among other things to the possibility of investigation of the interaction of the ring nitrogen atom of the monoazine with the electron-deficient δ^+(OH) group of the peracid. The importance of data on such interactions becomes evident if one takes into account the fact that most electrophilic and nucleophilic reactions in series of nitrogen-containing heterocycles proceed with initial coordination at the hetero nitrogen atom both as a kinetically independent electropositive particle and as an electropositive part of an ion pair [4].

Extensive use has recently been made of hydroperoxide oxidation in the azine series [5]; however, this method is less acceptable for the study of the indicated problems by virtue of the fact that the ease of hydroperoxide oxidation is not determined by the affinity of the nucleophile for the hydroperoxide but rather by the affinity for the metal (the catalyst). It is not surprising that the reaction is also complicated by the possibility of the formation of a complex between the catalyst and the functional group.

The formal kinetics of the N oxidation with perbenzoic acid was studied for the first time [6, 7] only in the case of alkyl- and chloropyridines at a single temperature in aqueous dioxane.

Somewhat later [8] the activation energy (E) of the N oxidation of pyridine was determined (the rate constants were determined at 0, 13, and 25°C). On the basis of a limited amount of kinetic data Dondoni and co-workers [7] concluded that there is a correlation between the rate of N oxidation and the basicity of the heterocycle. However, this assumption seems insufficiently substantiated even from the point of view of the experimental data presented. For example, although the basicity of 4-methylpyridine (pK_a 6.02) is considerably higher than that of 3-methylpyridine (pK_a 5.68), the rate constants for their oxidation virtually coincide ($7.25 \cdot 10^3$ and $7.20 \cdot 10^3$ liters/mole-sec, respectively), whereas the rate constant for 2-methylpyridine (pK_a 5.94) is higher by a factor of 1.2 ($8.40 \cdot 10^3$ liters/mole-sec). The highly basic isomeric aminopyridines do not undergo N oxidation at all [1]. Other examples of the anomalous behavior of some monoazines in preparative N oxidation are

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 0009-3122/80/1603-0264$07.50