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ACETALS OF LACTAMS AND ACID AMIDES.

XXV.* LACTIM–LACTAM TAUTOMERISM OF 6-DIALKYLAMINO-3-CYANO-2-PYRIDONE DERIVATIVES

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It is shown that the alkylation of 1-methyl-6-cyano-1,2,3,4-tetrahydro-1,8-naphthyrid-7-one under various conditions takes place at the oxygen atom of the oxo group in the 7 position. It was established by UV, IR, and mass spectroscopy that lactim–lactam tautomerism is observed in 6-dimethylamino-2-pyridone, pyrrolo[2,3-b]pyrid-6-one, 1,8-naphthyrid-7-one, and 8-oxopyrido[2,3-b]azepine derivatives. The tautomeric equilibrium constants (K_T) in various solvents were calculated. It is shown that the position of the equilibrium is shifted from the lactam to the lactim form when the polarity of the solvent decreases, when an electron-acceptor CN group is introduced, and when a 6-NR_2 group is included in the ring condensed with the pyridone ring.

Unsubstituted 2- and 4-pyridones undergo both N- and O-alkylation under various conditions. Since it has been recently established that the alkylation of dialkylamino-4-pyridones proceeds selectively at the oxygen atom [2], in the present research we investigated the problem of the direction of alkylation of similar 2-pyridone derivatives.

Alkylation of 1-methyl-6-cyano-1,2,3,4-tetrahydro-1,8-naphthyrid-7-one (I) with triethyloxonium tetrafluoroborate and methyl iodide [with dimethylformamide (DMF) (in the presence of NaH) or alcohol containing KOH as the solvent] gave II and III, the UV spectra of which in polar solvents are similar to one another but differ from the spectrum of starting I. When III is heated with hydrobromic acid, it undergoes processes involving demethylation, saponification of the cyano group, and decarboxylation, as a result of which 1-methyl-1,2,3,4-tetrahydro-1,8-naphthyrid-7-one (IV), which was also synthesized from naphthyridone I by refluxing with HBr, is formed.

It follows from these data that II and III are O-alkylation products. Ethoxy derivatives VI and VII, respectively, were synthesized from naphthyridone IV and pyridoazepine V by the method used to prepare II. Since 2-pyridone derivatives that contain (in the 6 position) a substituent with a heteroatom display lactim–lactam tautomerism [3, 4], in the

*See [1] for communication XXIV.

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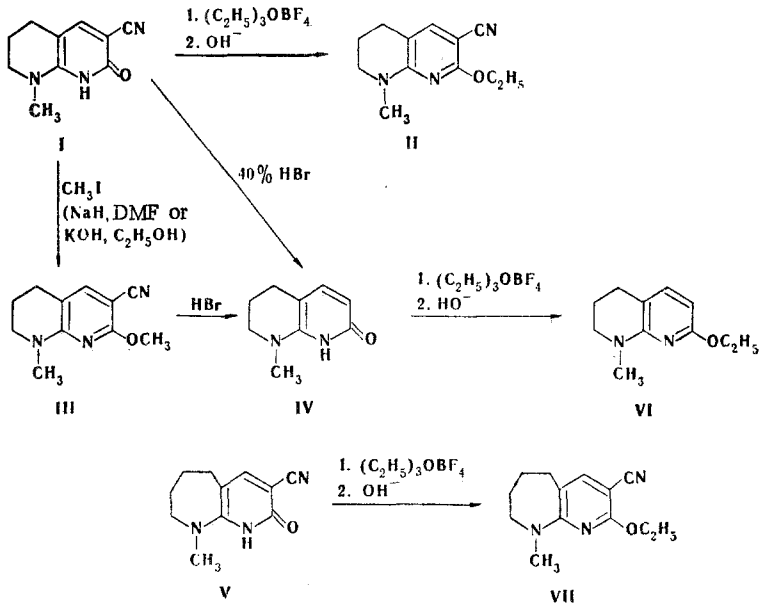

present research we used UV, IR, and mass spectroscopy to investigate the tautomerism of I, IV, and V, as well as 3-cyano-6-dimethylaminopyridone (VIII) and 1-methyl-2,3-dihydro-5-cyano-6-oxopyrrolo[2,3-b]pyridine (IX).* Ethoxy derivatives II, VI, and VII were used as model compounds with a fixed lactim structure. Two absorption maxima at 320-327 and 360-365 nm are observed in the UV spectra of I, IV, V, and VIII at 300-400 nm (Fig. 1); the intensities of these maxima change as the polarity of the solvents change. Thus the first maximum is considerably more intense than the second in dioxane, whereas an intense maximum at 360-365 nm and only a small shoulder in the short-wave region of the spectrum are observed in the spectrum in the case of alcohol. The intensity of the short-wave maximum increases in dioxane–alcohol mixtures as the concentration of the nonpolar solvent increases, and the intensity of the long-wave maximum decreases correspondingly, i.e., the changes in the spectra are similar to the changes observed during a study [3, 4] of 2-pyridone derivatives. The spectra of model compounds II, VI, and VII are similar to the spectra of pyridones I, IV, V, and VIII in dioxane; the character of the spectra changes only slightly in solvents with different polarities. On the basis of the data obtained, it may be concluded that I, IV, V, and VIII are tautomeric compounds and that the position of the equilibria is shifted from the lactam to the lactim form as the polarity of the solvent decreases.

Assuming 100% absorption at 326 nm for model compounds II, VI, and VII, we calculated the percentages of the lactim forms in various solvents and the tautomeric equilibrium constants K_T = % lactam/% lactim (Table 1). Data on the lactim–lactam tautomerism of 6-amino-2-pyridone (X) [3] and 4-methyl-6-oxo-2,3-dihydropyrrolo[2,3-b]pyridine (XI) [4] are also presented in Table 1. It follows from the data presented that the inclusion of a substituent (in this case an NR_2 group) in the ring annelated with the pyridine ring (see also [6]) leads to a shift in the equilibrium to favor the lactim form (compare VIII, I, and V). A similar conclusion can also be drawn from a comparison of the K_T values for X and XI.

It also follows from the data in Table 1 that the presence of a CN group in the 3 position of the pyridone ring promotes an increase in the amount of the lactim form (I and IV). In [7] it was demonstrated by computation that the effect of the cyano group should lead to a change in the K_T value of approximately two orders of magnitude. In the case of I and IV this change is considerably smaller and ranges from 1.1 to 4, depending on the solvent. However, let us note that the literature contains data on 2,3-dihydrofuro[2,3-b]pyrid-6-one derivatives in which the introduction of a CN group in the 5 position leads to a shift in the equilibrium to favor the lactam form [8].

The IR spectra of solid I, IV, V, and VIII and $CHCl_3$ solutions of these compounds contain a bond of stretching vibrations of the CO group at 1630 cm^{-1}; the intensity of this band decreases appreciably in dioxane. A band of stretching vibrations of an OH group at 3565 cm^{-1} is observed in the spectrum of a dilute solution (0.02%) of IV in CCl_4.†

*Compound IX was not isolated in analytically pure form in [5].

†Spectra of good quality could not be obtained for I, V, and VIII because of the low solubilities of these compounds in CCl_4.

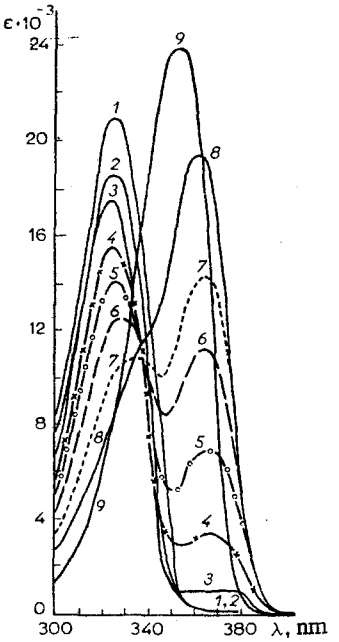

Fig. 1. UV spectra of VII and VIII in various solvents: 1) III in alcohol; 2) III in dioxane; 3) VIII in dioxane; 4) VIII in dioxane containing 10% alcohol; 5) VIII in dioxane containing 25% alcohol; 6) VIII in dioxane containing 50% alcohol; 7) VIII in dioxane containing 75% alcohol; 8) VIII in alcohol; 9) VIII in water.

Intense molecular-ion peaks with m/e 189, 164, 203, 163, and 175, respectively, are present in the mass spectra of I, IV, V, VIII, and IX.

The principal pathway of fragmentation of these compounds involves cleavage of the bonds in the saturated rings. Peaks of $(M - OH)^+$ and $(M - H_2O)^+$ ions, the intensities of which (with respect to the molecular ion) are presented in Table 2, are also present in the spectra.

Thus, according to the UV, IR, and mass spectra, the investigated compounds are tautomeric substances and exist primarily in the lactam form in polar solvents and in the lactim form in nonpolar solvents.

EXPERIMENTAL

The UV spectra of solutions of the compounds in dioxane, mixtures of dioxane with alcohol, alcohol, and a mixture of 95% water and 5% alcohol were obtained with an EPS-3 spectrophotometer. The IR spectra of mineral oil suspensions of the crystalline compounds and solutions in $CHCl_3$, dioxane, and CCl_4 were recorded with a Perkin–Elmer 457 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the source at an ionizing-electron energy of 30 eV and an ionization-chamber temperature of 125°C.

1-Methyl-6-cyano-7-ethoxy-1,2,3,4-tetrahydro-1,8-naphthyridine (II). A solution of 3.8 g of triethyloxonium tetrafluoroborate in 20 ml of CH_2Cl_2 was added dropwise to a suspension of 3.8 g (0.02 mole) of I in 30 ml of dry methylene chloride, and the mixture was maintained at room temperature for 1.5 h. It was then made alkaline to pH ~10 with aqueous potassium carbonate solution, and the precipitate was removed by filtration and washed with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2. The extract was dried with Na_2SO_4 and filtered, and the solvent was removed from the filtrate by evaporation to give 2.5 g (57.6%) of II with mp 123-124°C (from ether). Found: C 67.0; H 6.8; N 19.3%. $C_{12}H_{15}NO$. Calculated: C 67.0; H 6.9; N 19.4%.

TABLE 1. Tautomeric Equilibrium Constants (K_T = % lactam/% lactim)* for Pyridones and Condensed Pyridones (I, IV, V, VIII, X, and XI)

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	4	15	38	57	72	93
	24	5,67	1,63	0,75	0,39	0,08
IV	1	12	26	48	70	77
	99	7,35	2,84	1,08	0,43	0,3
V	17	34	43	59	70	81
	4,9	1,94	1,32	0,69	0,43	0,36
VIII	1	8	13	31	52	72
	99	11,5	6,7	2,22	0,92	0,39
X†	—	—	2	7	2,4	61
			46,6	12,5	3,14	0,64
XI†	—	—	15	29	60	88
			5,85	2,43	0,68	0,14

*The following assumptions were made in the calculations: the spectra of the compounds in mixtures of 95% H_2O and 5% alcohol (the compounds are insoluble in water) were used as the lactam models. The calculation is not a rigorous calculation, since the absorption maxima of the tautomeric compounds are shifted somewhat relative to the lactim models. Correspondingly, the extinctions of the tautomeric compounds and the models used in the calculation correspond to several different λ values: $\Delta\lambda$ shifts in dioxane and a mixture of 90% dioxane and 10% alcohol are almost zero and range from 2 to 10 nm as the amount of alcohol is increased.

†Data from [3, 4].

1-Methyl-6-cyano-7-methoxy-1,2,3,4-tetrahydro-1,8-naphthyridine (III). A) A 0.48-g sample of NaH was sprinkled into a mixture of 1.9 g (0.01 mole) of I in 40 ml of DMF in the course of 1 h, and the mixture was maintained at 30°C for 2 h. It was then treated with 3 g of CH_3I, and the mixture was heated at 40°C for 4 h. The resulting precipitate was removed by filtration, and the filtrate was evaporated. The residue was cooled, and the resulting solid was treated with water and chloroform. The chloroform extract was dried with Na_2SO_4 and evaporated to give 1.7 g (84%) of III with mp 125-126°C (from ether). Found: C 65.6; H 6.6; N 20.3%. $C_{11}H_{13}N_3O$. Calculated: C 65.0; H 6.4; N 20.7%.

B) A mixture of 0.4 g of KOH in 4 ml of water and 9.1 g of CH_3I was added to a mixture of 0.9 g (0.005 mole) of I in 40 ml of ethanol, and the mixture was refluxed for 2 h. The alcohol was removed by distillation, and the residue was treated with water and chloroform. The chloroform extract was dried with Na_2SO_4 and filtered, and the filtrate was evaporated. The resulting solid was crystallized from isopropyl alcohol, the mother liquor was evaporated, and the residue was crystallized from hexane to give a substance with mp 125°C, which was identical to III.

1-Methyl-1,2,3,4-tetrahydro-7-naphthyridone (IV). A) A mixture of 1 g (0.005 mole) of I and 5 ml of 40% HBr was refluxed for 5 h, after which it was cooled and made alkaline to pH ~10 with ammonia. It was then filtered, and the filtrate was extracted with chloroform. The extract was dried with Na_2SO_4 and filtered, and the solvent was removed from the filtrate by distillation. Ether was added to the residue, and the resulting precipitate (0.13 g of I) was removed by filtration. The ether mother liquors were evaporated to give 0.7 g (87.5%) of IV with mp 135-137°C (from ethyl acetate). Found: C 65.8; H 7.2; N 17.2%. $C_9H_{12}N_2O$. Calculated: C 65.9; H 7.3; N 17.1%.

B) A mixture of 1.3 g (0.0064 mole) of III and 7 ml of 40% HBr was refluxed for 8 h, after which it was cooled, made alkaline to pH ~10 with ammonia, and filtered. The filtrate was extracted with chloroform. The pH of the aqueous solution was brought up to seven, and it was again extracted with $CHCl_3$. The combined extracts were dried with Na_2SO_4 and filtered, and the filtrate was evaporated. Ether was added to the residue, and the mixture was worked up to give 0.43 g of IV. The ether mother liquors were evaporated to give 0.42 g of IV. The overall yield was 0.85 g (80%).

TABLE 2. Intensities (in percent with respect to the molecular ion) of $(M - OH)^+$, $(M - H_2O)^+$, and $(M - H - H_2O)$ Ions (m/e) in the Mass Spectra of I, IV, V, and IX

Ion	Compound			
	I	IV	V	IX
$(M-OH)^+$	172 (6,4)	147 (2,2)	186 (6,5)	158 (2,1)
$(M-H_2O)^+$	171 (4,7)	146 (1)	185 (5,6)	157 (2,1)
$(M-H-H_2O)^+$	—	144 (1,7)	—	156 (4,9)

1-Methyl-7-ethoxy-1,2,3,4-tetrahydropyrido[2,3-b]pyridine (VI). A solution of 6.7 g (0.035 mole) of $(C_2H_5)_3OBF_4$ in 20 ml of CH_2Cl_2 was added to a solution of 4.9 g (0.03 mole) of IV in 20 ml of dry CH_2Cl_2, and the mixture was maintained at room temperature for 2 h. It was then made alkaline to pH 8-9 with aqueous potassium carbonate solution, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the extract was dried with Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was fractionated. Collection of the fraction with bp 115-116°C (4 mm) gave 2 g (34%) of VI. Found: C 68.9; H 8.5; N 15.0%. $C_{11}H_{16}N_2O$. Calculated: C 68.8; H 8.3; N 14.6%.

1-Methyl-7-cyano-8-ethoxy-2,3,4,5-tetrahydro-1H-pyrido[2,3-b]azepine (VII). A solution of 3.5 g (0.0185 mole) of $(C_2H_5)_3OBF_4$ in 20 ml of CH_2Cl_2 was added to a solution of 3.6 g (0.018 mole) of V in 40 ml of CH_2Cl_2, and the mixture was maintained at room temperature for 2 h. It was then made alkaline to pH ~10 and filtered, and the aqueous layer was extracted with CH_2Cl_2. The extract was dried with Na_2SO_4 and filtered, and the filtrate was evaporated to give 0.75 g (18%) of VII with mp 72-74°C (from petroleum ether). Found: C 67.7; H 7.8; N 18.2%. $C_{13}H_{17}N_3O$. Calculated: C 67.5; H 7.4; N 18.2%.

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