ACETALS OF LACTAMS AND ACID AMIDES.

30.* IONIZATION CONSTANTS OF DERIVATIVES OF 1,8-NAPHTHYRIDINE

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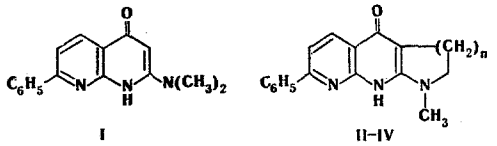
It has previously [1] been shown that the reaction of acetal amides and lactams with 6-phenyl-2-amino-3-carbethoxypyridine followed by intramolecular cyclization under conditions of acid and base catalysis yields 2-phenyl-7-dimethylamino-1,8-naphthyrid-5-one (I) and its analogs (II-IV). Since the purpose of the presented work was to compare the ionization constants of the naphthyridones obtained, I-IV, with other tricyclic (and bicyclic) compounds of similar structure, it was important to establish the site of the protonation of compounds I-IV. For this purpose in the example case of naphthyridone III we studied the



I II-IV

II n=1; III n=2; IV n=3

alkylation reaction with triethyloxonium fluoborate and ethyl iodide. It was found that the same compound forms in both cases. The mass spectrum of this compound shows an intense peak of the molecular ion with a mass number of 319. The most intense peak in the spectrum belongs to the ion with m/e 290 $[M-C_2H_5]^+$. The region of high mass numbers displays ions with m/e 276, 275, and 262, which are assigned to fragments due to the decomposition of the piperidine ring ($[M-CH_3N=CH_2]^{+\cdot}$, $[M-CH_3N=CH_2-H]^+$, $[M-CH_3-N-CH_2CH_2]^+$, respectively). The presence in the spectrum of an intense peak with m/e 274 may be attributed to the splitting off of an ethoxy group from the molecular ion. The ratio of the intensities of the ions in the spectrum is not dependent on the temperature for the admission of the sample. Therefore, compound V is 1-methyl-5-ethoxy-8-phenyl-1,2,3,4-tetrahydropyrido[2,3-b]-1,8-naphthyridine.

The same conclusion follows from the known tendency of triethyloxonium fluoborate to cause O-alkylation [2] and from a comparison of the UV spectra of the original naphthyridone III (λ_{max} 340 nm, log ε 4.30) and ethoxy derivative V (λ_{max} 376 nm, log ε 4.26) in ethanol. A similar shift of the absorption maximum to longer wavelengths has previously been observed upon O-ethylation.

A comparison of the UV spectra of ethoxy derivative V and naphthyridone III in 0.1 N HCl shows that under these conditions the spectra becomes similar: for V, λ_{max} 362 nm (log ε 4.39) and a shoulder at 376 nm (log ε 4.30); for III, λ_{max} 355 nm (log ε 4.42) and a shoulder at 370 nm (log ε 4.32). This is evidence of the O-protonation of III. This is also confirmed by the similarity of the PMR spectra of these compounds in CF_3COOH. The spectrum of cation IIIa shows signals of protons at 2.22 (3-CH_2), 2.98 (4-CH_2), 3.60 (NCH_3), 3.84 (2-CH_2), ~7.28-8.07 (Ph), 8.08 (6-H), and 9.0 ppm (7-H), and the spectrum of cation Va shows signals at 1.57 (CH_3—OEt), 7.7 (Ph), 8.13 (6-H), and 8.95 ppm (7-H). The closeness of the chemical shifts of the protons of the pyridine and piperidine rings in both compounds points out the similarity in the structure of their cations, which is possible only in the cation of the O-protonation of naphthyridone III.

Finally, structure IIIa is supported by the appearance in the IR spectrum of its hydrochloride of an absorption band at 3380 cm^{-1}, which may be assigned to an OH group.

*For report 29 see [1].

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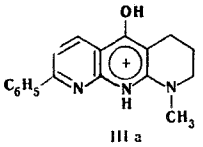
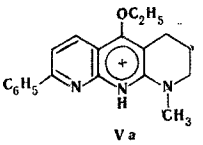
TABLE 1. Ionization Constants of Compounds I–IV and VI

Compound	pK_a, 50% ethanol, proton addition	pK_a, 70% DMFA, proton removal
I	3,85±0,05	11,01±0,05
II	4,0±0,02	10,42±0,05
III	3,86±0,06	11,56±0,06
IV	3,56±0,03	11,56±0,05
VI	4,61±0,01	12,86±0,05



III a

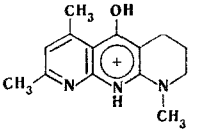


V a

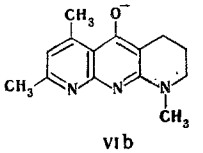
Thus, the protonation of the compounds under investigation takes place at the oxygen atom of the oxo group, making it possible to compare their ionization constants with the ionization constants of the corresponding benzene and pyrimidine analogs [6]. The corresponding data are presented in Table 1. The general laws previously discovered [6] are maintained in the present series of compounds: The most basic compound is II with a five-membered ring. In our opinion, this is due to the predominance of the influence of solvation on the basicity of these compounds over the electronic effects (for steric reasons, in the case of the five-membered ring, the positively charged nitrogen atom of the naphthyridine part of the molecule, which bears a positive charge, is most accessible to solvation by the solvent [6]). The acidity of this compound is also higher, since in the present case, the electronic and solvation effects act in the same direction [6]. The solvation effect is also very significant, since bicycle I is an appreciably stronger acid than is the six-membered analog III, while the electronic effects are similar in the case of the noncyclic and six-membered compounds.

In connection with the arguments regarding the influence of solvation on the ionization constants of the tricyclic (and bicyclic) compounds [6], the data we obtained for 1,6,8-trimethylpyrido[2,3-b]-1,8-naphthyrid-5-one (VI) are of definite interest. This compound is somewhat more basic (in accordance with the fact that the dimethylpyridine ring has a weaker electron-acceptor effect than does the phenylpyridine ring) and has inappropriately weaker acid properties than compound III.

An examination of the structure of the protonated form of this compound (VIa) and of the anion (VIb) reveals that in the former case, the possibility of solvation of the central N atom, which bears the bulk of the positive charge, is approximately the same as that for naphthyridone III. Conversely, in anion VIb, in which the



VI a



VI b

negative charge is concentrated mainly on the most electronegative oxygen atom, solvation is hindered considerably by the presence of the bulky methyl group in position 6 of the molecule. This should cause an anomalously strong decrease in the acidity of compound VI, as is actually observed, i.e., the acidity of this naphthyridone is even lower than that of the corresponding benzene analog (pK_a 12.65) [6]. This finding is inexplicable, if only the electronic effects are considered in the interpretation of the data obtained. At the same time, in accordance with the ordinary theories, compounds I–IV are appreciably weaker bases and stronger acids than are their benzene analogs. Of course, the pyrimidine ring [6] has a significantly stronger electron-acceptor influence, and the hydroxy derivatives of pyrido[2,3-d]pyrimidine are weaker bases and stronger acids than naphthyridones I–IV.

EXPERIMENTAL

The dissociation constants were determined by potentiometric titration of 0.001 M solutions with the aid of a Radiometer PHM-26 pH-meter (Denmark) with glass (G-2222) and calomel electrodes. The pH meter was adjusted with the aid of aqueous buffer solutions. The IR spectra were obtained on a Perkin-Elmer-457 instrument, and the samples had the form of mulls in liquid petrolatum. The PMR spectra were obtained on a JNM-

4H-100 instrument, and the internal standard was TMS. The mass spectra were obtained on an MKh-1303 mass spectrometer with direct introduction into the source and an energy of the ionizing radiation equal to 50 eV.

1-Methyl-5-ethoxy-8-phenyl-1,2,3,4-tetrahydropyrido[2,3-b]-1,8-naphthyridine. A. A 1.2-g portion (4.1 mmole) of napthyridone III [1] in 20 ml of dry methylchloride was given a dropwise addition of a solution of 0.94 g (4.9 mmole) of Et_3OBF_4 in 15 ml of methylene chloride. Aqueous K_2CO_3 was added to the mixture obtained. The methylene chloride layer was separated, dried, and evaporated. The precipitate obtained was dissolved in ethyl acetate, filtered through a layer of silica gel, and washed with ethyl acetate. The ethyl acetate was distilled off. This yielded 0.7 g (54%) of compound V, mp 161-163°C (heptane). Found: C, 75.8; H, 6.28; N, 13.4%. Calculated for $C_{20}H_{21}N_3O$: C, 75.3; H, 6.58; N, 13.1%.

B. An 11.3-g portion (4.7 mmole) of 2-amino-3-carbethoxy-6-phenylpyridine [7] in 40 ml of dry toluene was given an addition of 10.55 g (5.6 mmole) of N-methylvalerolactam diethyl acetate. The mixture was boiled for 4 h and evaporated. The residue was added to a solution of BuONa, which was prepared from 2.2 g (9.4 mmole) of metallic Na in 30 ml of BuOH. The precipitating Na salt was filtered off and dried. A solution of 2 g (6.9 mmole) of the Na salt in 30 ml of dry DMFA was given an addition of 1.07 g (6.9 mmole) of ethyl iodide and stored overnight at room temperature. Then the DMFA was evaporated, and the residue was treated with water and chloroform. The chloroform layer was separated, dried, and evaporated. This yielded 1.1 g (50%) of compound V, mp 161-163°C (heptane).

1-Methyl-8-phenyl-1,2,3,4-tetrahydropyrido[2,3-b]-1,8-naphthyrid-5-one Hydrochloride. A solution of 2 g (6.9 mmole) of 1-methyl-8-phenyl-1,2,3,4-tetrahydropyridono[2,3-b]-1,8-naphthyrid-5-one in 25 ml of acetone was acidified by an ethanolic solution of HCl to pH ~2. The 1.38-g of precipitate formed (61%) were filtered off and recrystallized from a 1:1 acetone–isopropanol mixture. The melting point was 262°C. Found: Cl, 10.82%. Calculated for $C_{18}H_{18}ClN_3O$: Cl, 10.84%.

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