RESEARCH ON NAPHTHYRIDINES.

11.* SYNTHESIS AND IONIZATION CONSTANTS OF SUBSTITUTED 10H-BENZO[b]-1,8-NAPHTHYRID-5-ONES

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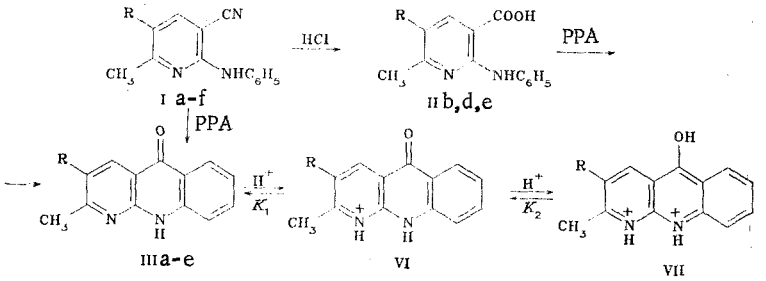
3-Substituted 2-alkyl-10H-benzo[b]-1,8-naphthyrid-5-ones were obtained by cyclization of 2-anilinonicotinic acids or the corresponding nitriles. The pK_2 values of these compounds range from −4.63 to −5.98 and correlate with the σ substituent constants.

We have previously examined the acid–base transformations of 10H-benzo[b]-1,8-naphthyrid-5-ones substituted in the benzene ring [1]. In order to study the electronic effects of substitutents in the pyridine ring of the naphthyridone system, in the present research we investigated the acid-base properties of 3-substituted 2-methyl-10H-benzo[b]-1,8-naphthyrid-5-ones (IIIa-e), as well as 2,4-dimethyl- and 2-isobutyl-10H-benzo[b]-1,8-naphthyrid-5-ones (IV, V), the synthesis of which was realized by previously described methods [3, 4] by heating the corresponding 2-anilinonicotinonitriles (I) or 2-anilinonicotinic acids (II) in polyphosphoric acid (PPA). Acids II were obtained by hydrolysis of nitriles I in the presence of concentrated hydrochloric acid.



a R=H, b R=CH_3, c R=Cl, d R=Br, e R=NH_2, f R=NO_2

Absorption maxima at 228-240 nm and 253-278 nm, as well as a broad long-wave band with two maxima at 378-394 nm and 390-424 nm, are observed in the UV spectra of the benzonaphthyridones in ethanol. The spectra of solutions of these compounds in 1-40% sulfuric acid are also similar to one another but, in contrast to the spectra of solutions in ethanol, have an additional maximum at 294-304 nm and are shifted to the long-wave region. A band at 336-352 nm, the position of the maximum of which depends on the substituents attached to the $C_{(3)}$ atom of the benzonaphthyridone system, appears in the case of solutions in 50-65% sulfuric acid. The intensity of this band increases as the acidity of the medium increases and reaches its maximum value in 90% sulfuric acid. A further increase in acid concentration does not cause substantial changes in the spectra.

We also have previously observed the same changes in the UV spectra on passing from solutions in ethanol to solutions in sulfuric scid for related 7-substitued 10H-benzo[b]-1,8-naphthyrid-5-ones [2]. From the data presented above and in analogy with [2] it should be assumed that 10H-benzo[b]-1,8-naphthyrid-5-ones (III-V) undergo successive protonation to give initially ions VI and then doubly charged ions VII when the acid concentration is increased above 50-65%. Since the pK of pyridine is considerably higher than the pK of 9-acridone [5], protonation of the $N_{(1)}$ atom should precede protonation of the carbonyl group.

*See [1] for Communication 10.

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TABLE 1. Parameters of the Correlation of the Logarithms of the Indicator Ratios with the H_0 and pK_2 Values of 10H-Benzo-[b]-1,8-naphthyrid-5-ones in the Sulfuric Acid–Water System

Compound	λ_{max}, nm (lg ε)[a]	$-a$[b]	$-b$[b]	$-pK_2$	r	S
IIIa	336 (4,27)	4,59	0,964	4,76±0,04	0,997	0,024
IIIb	342 (4,28)	4,29	0,928	4,63±0,05	0,998	0,016
IIIc	348 (4,13)	5,21	0,963	5,41±0,04	0,996	0,022
IIId	352 (4,23)	5,09	0,924	5,51±0,04	0,999	0,011
IIIe	344 (4,15)	5,62	0,941	5,98±0,06	0,999	0,021
IV	334 (4,24)	4,35	0,862	5,04±0,11	0,999	0,007
V	340 (4,32)	4,47	0,912	4,90±0,05	0,999	0,006

[a]In 90% sulfuric acid. [b]Parameters of the equation $\log([VII]/[VI]) = a + bH_0$.

In the case of IIIe one might assume that the amino group is protonated initially, after which the $N_{(1)}$ atom is protonated, since the pK of the first step in the ionization of 3-aminopyridine is 5.98 units [6], whereas the pK of the second step is −1.5 units [7]. An ion of the VII type, in which the NH_3^+ group acts as a substituent, is formed in 60% sulfuric acid.

It was found by spectrophotometry that a linear dependence with a slope close to unity exists between the logarithms of the indicator ratios [log ([VII]/[VI])] and the acidity of the medium expressed in terms of acidity function H_0 [8]. This made it possible to determine the pK_2 values that characterize the VI $\rightleftarrows$ VII equilibrium (Table 1), which range from −4.63 to −5.98, depending on the substituents in the 3 position of the benzonaphthyridone system, and correlate with the σ_m substituent constants [9] ($r = 0.999$, $\rho = -1.92$, $pK_2^0 = -4.75$, $S = 0.01$). The reaction constant of this series is smaller by a factor of ∿1.5 than in series of 10H-benzo[b]-1,8-naphthyrid-5-ones substituted in the benzene ring [2]. This shows that in VII ions the effect of substituents is transmitted through the protonated pyridine ring to lesser extent than through the benzene ring of the quinoline fragment.

The pK_2 values of 2,4-dimethyl-10H-benzo[b]-1,8-naphthyrid-5-one (IV) is smaller than the pK_2 value for IIIa, whereas starting from the electron-donor character of the methyl group attached to the $C_{(4)}$ atom one might have expected an increase in the basicity of IV. This disparity is possibly associated with steric hindrance to solvation of the hydroxy group in ion VII by the methyl group in the 4 position. In addition, in agreement with the small difference in the σ constants of methyl and isobutyl groups, the pK_2 value of 2-isobutyl-10H-benzo[b]1,8-naphthyrid-5-one (V) is close to the pK_2 value of IIIa.

EXPERIMENTAL

The IR spectra of solutions of the compounds in carbon tetrachloride were recorded with the UR-20 spectrometer. The UV spectra were obtained with an SF-16 spectrophotometer. The ionization constants in the sulfuric acid–water system were determined by spectrophotometry with the same apparatus at 20 ± 1°C. The analytical wavelength corresponded to the maximum at 334-352 nm. The parameters of the dependence of the logarithms of the indicator ratios on H_0 were calculated by the method of least squares. The pK_2 values were calculated from seven points at a predesignated reliability of 0.98. The characteristics of the compounds obtained for the first time are given in Table 2.

6-Isobutyl-2-chloronicotinonitrile. A mixture of 1.8 g (10 mmole) of 6-isobutyl-3-cyano-2-pyridone [10], 3 g (15 mmole) of phosphorus pentachloride, and 5 ml of phosphorus oxychloride was refluxed for 1.5 h, after which the phosphorus oxychloride was removed in vacuo, and the residue was poured into water. The precipitate was removed by filtration, shaken twice with 5% sodium hydroxide solution, washed with water, and crystallized to give 6-isobutyl-2-chloronicotinonitrile, with mp 43-45°C (ethanol), in 25% yield. Found: Cl 18.1; N 14.9%. $C_{10}H_{11}ClN_2$. Calculated: Cl 18.2; N 14.4%.

2-Anilino-5-bromo-6-methylnicotinonitrile (Id). A mixture of 2.2 g (10 mmole) of 5-bromo-6-methyl-2-chloronicotinonitrile [11] and 0.93 g (10 mmole) of aniline was heated at 150-180°C for 4-5 h, after which it was treated with hot water, and the residue was dissolved in benzene and chromatographed with a column packed with aluminum oxide. The benzene was removed by distillation, and the residue was crystallized from ethanol.

Compound Ic was similarly obtained from 6-methyl-2,5-dichloronicotinonitrile [12], and 2-anilino-6-methyl-5-nitronicotinonitrile (If) was similarly obtained from 6-methyl-5-nitro-2-chloronicotinonitrile [12].

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Hal	N		C	H	Hal	N	
Ic	129—131			14,1	17,3	$C_{13}H_{10}ClN_3$			14,6	17,2	31
Id	143—144			27,8	14,6	$C_{13}H_{10}BrN_3$			27,7	14,6	56
Ie	130—131	69,7	5,1		25,4	$C_{13}H_{12}N_4$	69,6	5,4		25,0	67
If	180—182	61,5	4,3		22,5	$C_{13}H_{10}N_4O_2$	61,4	4,0		22,0	58
IId	248—250			26,5	9,3	$C_{13}H_{11}BrN_2O_2$			26,0	9,1	47
IIe	224—226				17,8	$C_{13}H_{13}N_3O_2$				17,3	59
IIIb[a]	319—321	74,7	5,6		12,1	$C_{14}H_{12}N_2O$	75,0	5,4		12,5	38
IIIc	296 (dec)			14,4	11,9	$C_{13}H_9ClN_2O$			14,5	11,5	36
IIId	325—327			27,5	9,3	$C_{13}H_9BrN_2O$			27,6	9,7	34
IIIe	300—302				19,1	$C_{13}H_{11}N_3O$				18,7	30
V	231—233	75,7	6,0		11,0	$C_{16}H_{16}N_2O$	76,2	6,4		11,1	36

[a]Compound IIIc was obtained by cyclization of nitrile Ic, and IIIb, d, e were obtained by cyclization of acids IIb, d, e.

5-Amino-2-anilino-6-methylnicotinonitrile (Ie). A suspension of 3 g (16 mmole) of 2-anilino-6-methyl-5-nitronicotinonitrile in 15 ml of ether was treated with a solution of 50 g of stannous chloride in 50 ml of concentrated HCl at such a rate that the ether had evaporated at the end of the reaction. The precipitate was removed by filtration and dissolved in water, and the solution was made alkaline to pH 14 with sodium hydroxide solution. The solution was extracted with benzene, the benzene was removed by distillation, and the residue was crystallized from ethanol.

5-Substituted 2-Anilino-6-methylnicotinic Acids (IId, e). A 10-mmole sample of nitrile Id, e was refluxed in 20 ml of concentrated HCl for 20-40 h, after which the mixture was cooled and treated with sodium carbonate solution to pH 5. The resulting precipitate was removed by filtration and crystallized. 2-Anilino-5,6-dimethylnicotinic acid (IIb), which was indentified from a mixed-melting-point determination with a previously obtained sample [3], was similarly obtained from nitrile Ib [3].

6-Isobutyl-2-chloronicotinamide. A 1.95-g (10 mmole) sample of 6-isobutyl-2-chloronicotinonitrile was heated at 100-110°C for 2 h in 10 ml of concentrated H_2SO_4, after which the mixture was cooled and poured into a mixture of water and ice. The mixture was made alkaline with ammonia to give 6-isobutyl-2-chloronicotinamide, with mp 114-116°C (ethanol), in 65% yield. Found: Cl 16.1; N 13.0%. $C_{10}H_{13}ClN_2O$. Calculated: Cl 16.7; N 13.2%.

6-Isobutyl-2-chloronicotinic Acid. A mixture of 2.12 g (10 mmole) of 6-isobutyl-2-chloronicotinamide and 20 ml of 2 N sodium hydroxide solution was refluxed for 3 h, after which it was cooled and acidified with dilute sulfuric acid to give 6-isobutyl-2-chloronicotinic acid, with mp 75-77°C (water), in 76% yield. Found: Cl 16.6; N 6.8%. $C_{10}H_{12}ClNO_2$. Calculated: Cl 16.6; N 6.6%.

2-Anilino-6-isobutylnicotinic Acid. A solution of 2.13 g (10 mmole) of 6-isobutyl-2-chloronicotinic acid and 0.93 g (10 mmole) of aniline in 50 ml of 50% acetic acid was refluxed for 10 h, after which it was cooled, made slightly acidic with sodium carbonate, and filtered to give 2-anilino-6-isobutylnicotinic acid, with mp 161-163°C, in 64% yield. Found: C 70.7; H 7.2; N 10.3%. $C_{16}H_{18}N_2O_2$. Calculated: C 71.1; H 6.7; N 10.4%.

3-Substituted 2-Methyl-10H-benzo[b]-1,8-naphthyrid-5-ones (IIIa-e). A) A 10-mmole sample of nitrile Ia [3] or Ic was added to 10 g of polyphosphoric acid (PPA), and the mixture was heated at 150°C for 14-15 h. It was then cooled, diluted with water, made alkaline with 10% ammonium hydroxide, and filtered to give IIIa [3] or IIIc, respectively.

B) A 10-mmole sample of the corresponding acid II was heated in 10 g of PPA at 160°C for 5 h, after which it was cooled, diluted with water, and neutralized with 10% ammonium hydroxide. The resulting precipitate was crystallized from butanol. 2-Isobutyl-10H-benzo[b]-1,8-naphthrid-5-one (V) was similarly obtained from 6-isobutyl-2-anilinonicotinic acid.

Compound IV was obtained by the method in [3], and its composition and structure were confirmed by the results of elementary analysis and by comparison of its melting point with the melting point of a previously obtained sample.

Absorption bands at 1615 (CO) and at 3150 and 3210 cm^{-1} (NH) were observed in the IR spectra of IIIa-e, IV, and V.

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SYNTHESIS AND LACTIM-LACTAM TAUTOMERISM OF 1,2-DIHYDROFURO[2,3-b]QUINOL-4-ONE DERIVATIVES

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The reaction of O-ethylbutyrolactonium tetrafluoroborate with derivatives of ethyl anthranilate was used to synthesize tetrafluoroborates of cyclic imido esters, which were cyclized to furo[2,3-b]quinol-4-one derivatives by heating in a solution of sodium ethoxide. A number of N- and O-alkyl derivatives were obtained by alkylation of these compounds. The tautomerism of 6-chloro- and 7-chloro-2,3-dihydrofuro[2,3-b]quinol-4-ones that are unsubstituted in the benzene ring was studied, and a dependence of the position of the tautomeric equilibrium on the solvent and the substituent in the benzene ring was established.

It has been previously shown [1] that imido ester salt Ia, obtained by the reaction of O-ethylbutyrolactonium tetrafluoroborate (II) with ethyl anthranilate (III), undergoes cyclization to 2,3-dihydrofuro[2,3-b]quinol-4-one (IVa) on treatment with sodium ethoxide. Salts Ib, c similarly undergo cyclization under the same conditions to furo[2,3-b]quinol-4-one derivatives (IVb, c). It was recently established [2] that substituted pyrrolino[2,3-b]quinol-4-ones are tautomeric compounds. One might have expected that replacement of the nitrogen atom in the five-membered ring by oxygen, as in the case of diazabicyclic systems [3], would promote a shift of the equilibrium to favor the lactim form. It therefore seemed of interest to study the corresponding analogs of pyrroloquinoline, viz., furo[2,3-b]quinolones (IVa-c).

For the investigation of tautomerism in this series of compounds it was necessary to synthesize their O- and N-alkyl derivatives, which could serve as models for the study of the tautomerism of IVa-c. The synthesis of such model compounds was realized by alkylation of the Na salts (V) of the furo[2,3-b]quinoline derivatives that are formed as intermediates in the cyclization of tetrafluoroborates Ia-c.

It should be noted that both N- and O-alkyl derivatives can be isolated from the resulting mixtures in the alkylation of salts V only in some cases (for example, for derivatives VIb and VIIa and the VId and VIIc isomeric pair). One isomer was isolated in the remaining cases, although it may be assumed from the mass-spectral data that both isomeric

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