RESEARCH ON NAPHTHYRIDINES.

10.* SYNTHESIS AND IONIZATION CONSTANTS OF 10-ALKYLAMINOBENZO[b]-1,8-NAPHTHYRIDINES

A. I. Mikhalev, V. P. Chesnokov, and M. E. Konshin

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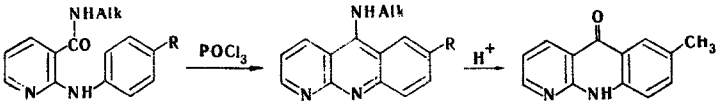
10-Alkylaminobenzo[b]-1,8-naphthyridines were synthesized by cyclization of 2-arylaminonicotinic acid alkylamides by means of phosphorus oxychloride. The pK_{a1} values of the 10-alkylaminobenzo[b]-1,8-naphthyridines, which range from 8.74 to 8.50, were determined by potentiometric titration in anhydrous ethanol.

In one of our previous papers we showed that 10-arylaminobenzo[b]-1,8-naphthyridines can be obtained by cyclization of arylamides of 2-arylaminonicotinic acids [2]. To extend this method to 10-alkylaminobenzo[b]-1,8-naphthyridines and to study the ionization constants of the latter we undertook their synthesis by cyclization of alkylamides of 2-arylaminonicotinic acids [3].



I a-h

The experiments showed that 2-anilinonicotinic acid alkylamides cannot be converted to the corresponding naphthyridines by refluxing the starting compounds in phosphorus oxychloride. At the same time, the alkylamides of 2-(p-anisidino)- and 2-(p-toluidino)nicotinic acids undergo smooth conversion to 10-alkylaminobenzo[b]-1,8-naphthyridines (Ia-h, Table 1) in 4 h. The cyclization probably proceeds through a step involving the formation of a chloroimide and an iminocarbenium ion and is an example of electrophilic aromatic substitution reactions. An increase in the electron density in the nucleophilic reaction center (the benzene ring attached to the amino group) due to the electron-donor effect of the methyl of methoxy groups ensures cyclization.

The fact that the hydrolysis of Ic leads to 8-methylbenzo[b]-1,8-naphthyrid-10-one identical to a previously obtained sample [1] constitutes evidence for the formation of 10-alkylaminobenzo[b]-1,8-naphthyridines during the cyclization.

*See [1] for communication 9.

TABLE 1. 10-Alkylaminobenzo[b]-1,8-naphthyridines (Ia-h)

Compound	R	Alk	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %	pK_{a1}
				C	H	N		C	H	N		
Ia	CH_3	C_3H_7-*n*	149—150	76,5	6,8	16,8	$C_{16}H_{17}N_3$	76,5	6,8	16,7	68	8,74±0,02
Ib	OCH_3	C_3H_7-*n*	152—153	71,9	6,4	15,7	$C_{16}H_{17}N_3O$	71,9	6,4	15,7	64	8,70±0,04
Ic	CH_3	C_4H_9-*n*	136—137	81,9	7,7	16,7	$C_{17}H_{19}N_3$	81,9	7,7	16,8	72	8,66±0,04
Id	OCH_3	C_4H_9-*n*	128—130	72,6	6,7	14,9	$C_{17}H_{19}N_3O$	72,6	6,8	14,9	70	8,60±0,04
Ie	CH_3	C_5H_{11}-*iso*	134—135	77,6	7,6	15,0	$C_{18}H_{21}N_3$	77,4	7,6	15,0	73	8,57±0,03
If	OCH_3	C_5H_{11}-*iso*	131—132	73,2	7,1	14,2	$C_{18}H_{21}N_3O$	73,2	7,1	14,2	71	8,50±0,03
Ig	CH_3	$CH_2C_6H_5$	157—158	80,3	5,7	14,1	$C_{20}H_{17}N_3$	80,2	5,7	14,0	63	
Ih	OCH_3	$CH_2C_6H_5$	160—161	76,2	5,4	13,3	$C_{20}H_{17}N_3O$	76,1	5,4	13,3	60	

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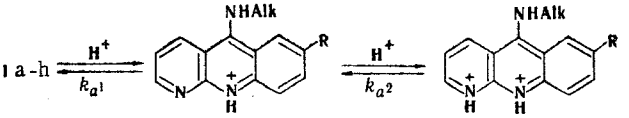
Benzonaphthyridines Ia-h are yellow crystalline substances, the IR spectra of which contain ν_{NH} bands at 3400 cm^{-1}; however, in contrast to the spectra of the starting amides, their spectra do not contain a band of stretching vibrations of a carbonyl group. They display basic properties — they are soluble in dilute mineral acids. The acid–base transformations of Ia-h should be expressed by the scheme



Due to conjugation of the N_5 atom with the unshared electron pair of the alkylamino group in the 10 position, the electron density on the N_5 atom is considerably higher than on the N_4 atom. As a consequence of this, the first proton should add to the N_5 atom. This idea regarding the site of protonation of Ia-h is confirmed by the fact that the basicity of 9-aminoacridine is higher by one or more orders of magnitude than the basicities of 2-, 3-, and 4-aminoacridines [4], i.e., the amino group in the γ position of the pyridine ring has the strongest effect on the basicity. It is also in agreement with the conclusion regarding the protonation of substituted 1,5-naphthyridine [5] made on the basis of a comparison of the pK values of these compounds found by an experimental method and calculated from correlation equations.

The pK_{a1} values of Ia-f (Table 1), which range from 8.74 to 8.50 units, are lower by almost unity than the pK_a value of 9-butylaminoacridine [6]; this is associated with the electron-acceptor properties of the nitrogen atom of the adjacent pyridine ring. According to approximate data, the pK_{a2} values are less than two and were not determined because of the limited solubilities of Ia-f.

10-Alkylaminobenzo[b]-1,8-naphthyridines have antimicrobic activity. The minimal concentrations of Ia-h that give rise to destruction of an Escherichia coli culture range from 1:2000 and 1:8000, as compared with 1:2000-1:4000 in the case of staphylococcus aureus.

EXPERIMENTAL

The IR spectra of solutions of the compounds in carbon tetrachloride were obtained with a UR-20 spectrometer. The ionization constants of the 10-alkylaminobenzo[b]-1,8-naphthyridines were determined by potentiometric titration of 0.01 M solutions of Ia-f in anhydrous ethanol with a 0.1 N ethanol solution of perchloric acid by means of a pH-340 potentiometer with glass and silver chloride electrodes. The calculation was made from seven points corresponding to 10-90% neutralization in accordance with [7].

10-Alkylaminobenzo[b]-1,8-naphthyridines (Ia-h). A 5-ml (0.05 mole) sample of phosphorus oxychloride was added to 0.01 mole of the appropriate 2-arylaminonicotinic acid alkylamide, and the mixture was heated at 105-110°C for 4 h, after which it was cooled and poured into cold water. The aqueous mixture was neutralized with 10% sodium hydroxide solution, and the liberated bases (Ia-h) were removed by filtration and crystallized from ethanol.

Hydrolysis of 8-Methyl-10-butylaminobenzo[b]-1,8-naphthyridine. A solution of 0.7 g (0.003 mole of Ic in 10 ml of concentrated hydrochloric acid was refluxed on a sand bath for 10 h, after which it was cooled and neutralized with 10% ammonium hydroxide. The resulting precipitate was removed by filtration and crystallized from ethanol to give 0.31 g (58%) of 8-methylbenzo[b]-1,8-naphthyrid-10-one with mp 270-271°C. No melting-point depression was observed for a mixture of this product with a sample [1] obtained by cyclization of 2-(p-toluidino)nicotinic acid.

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