ACID—BASE TRANSFORMATIONS OF QUATERNARY SALTS OF PYRIDYLINDOLES

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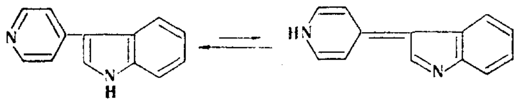
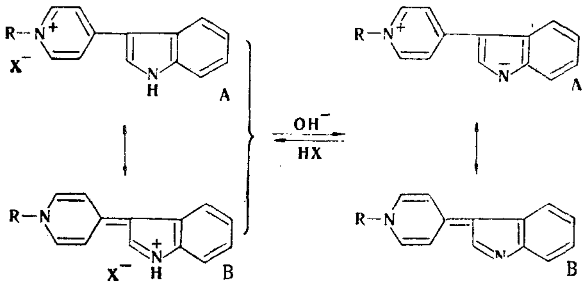
It was established that the reaction of alkali with 4-(3-indolyl)pyridinium salts gives stable anhydronium bases, which are readily alkylated at the indole nitrogen atom. The pK_a values of the anhydro bases were determined by spectrometry. The spectral data and reactivities are compared with the results of calculation by the self-consistent-field (SCF) MO LCAO method.

Conversion of the aromatic system of bonds of the benzenoid form to the quinoid (dihydropyridine) form, which is accompanied by a prototropic shift to give tautomeric forms, is characteristic for 2- and 4-substituted pyridines containing a substituent with a labile hydrogen atom [1]. The existence of this sort of tautomerism for pyridylindoles and related bisheteroaromatic systems also seemed completely acceptable, since the differences in the stabilization energies of the 6π-electron systems in pyridine (32 kcal/mole) and pyrrole (22 kcal/mole) rings are relatively small, and this difference should be even smaller in the case of indole, since the aromatic character of the benzene ring of indole does not change during these transformations:



A I B

The calculations, which we carried out within the framework of the associated variant of perturbation theory in the self-consistent-field (SCF) MO LCAO method by the procedure and with the parameters presented in [2], show that the induced π-electron currents (in units of the π-electron currents of benzene) in the benzene rings of compounds A and B differ only slightly (1.06 and 0.93), whereas in the pyrrole and pyridine rings these differences are more than doubled: 0.78 (for the pyrrole ring of A) and 0.39 (for B) and 0.95 (A) and 0.39 (B) for the pyridine rings, respectively. Indirect data on the possibility of tautomerism I are found in earlier studies [3, 4], which are devoted to other problems.



II a-f III a-b

To study the tautomerism of pyridylindoles we synthesized fixed structures of the IB type (III) by the action of alkali on quaternary salts (II) of 3-(4-pyridyl)indoles. We found that quaternization of I leads to a considerable (62 nm) bathochromic shift of the long-wave band of the π—π* transition, whereas the formation of III leads to the maximum bathochromic shift (112 nm). The calculations show that the degree of quinoid character of the system increases on passing from structures I to II and subsequently to III (Fig. 1),

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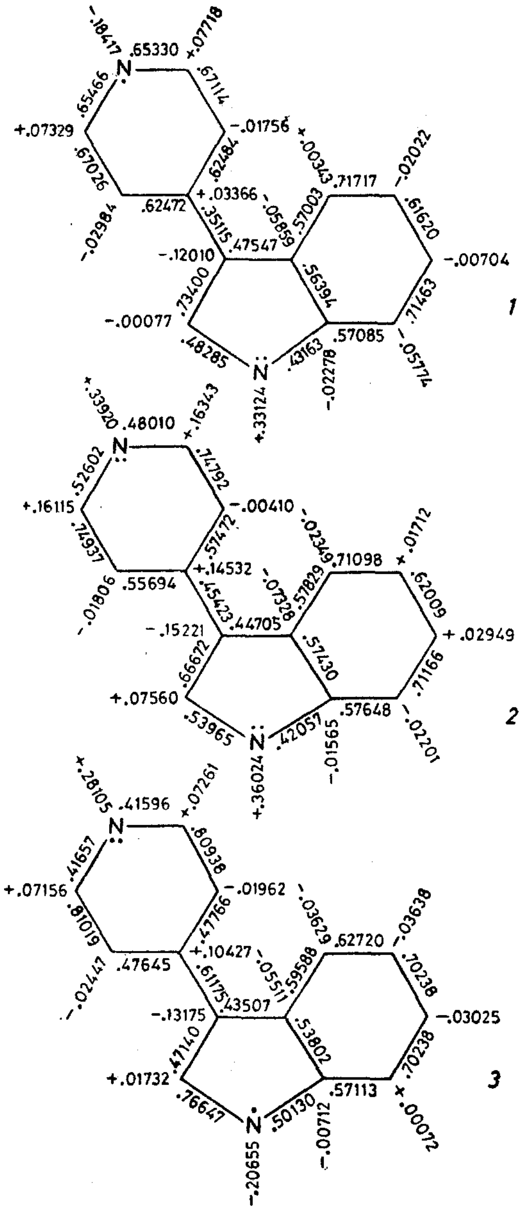


Fig. 1. Molecular diagrams: 1) 4-(3-indolyl)pyridine; 2) 4-(3-indolyl)pyridinium cation; 3) 4-(3-indolenylidene)pyridine.

which explains these spectral peculiarities. The calculated energies of the lower singlet—singlet transitions for I-III are in good agreement with the experimental data (Table 1).

It follows from the experimental data that tautomeric equilibrium I is shifted markedly to favor IA, whereas a significant contribution of the boundary structures is characteristic for II and III.

The presence of one absorption band (of $\pi-\pi^*$ transitions), the intensity of which decreases as the pH of the medium increases, is characteristic for the absorption spectra of solutions of 3-(4-pyridyl)indole methiodide at various pH values (Fig. 2). The intensity of the absorption band of anhydro base III increases simultaneously as the alkalinity increases, and the solution gradually turns yellow; the absorption spectra are characterized by a distinctly expressed isosbestic point, and this indicates binary character of the system and makes it possible to determine the II$\rightleftarrows$III equilibrium constants:

$$K_a=\frac{[H^+][C_{III}]}{[C_{II}]} \qquad (1)$$

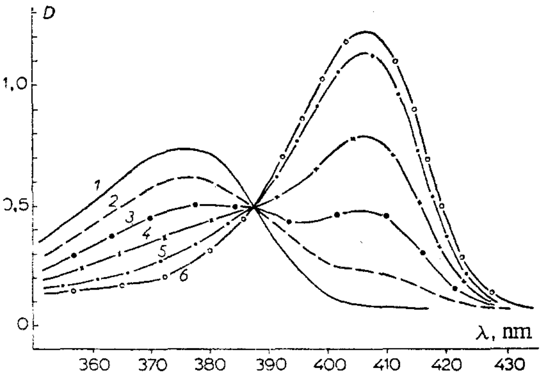


Fig. 2

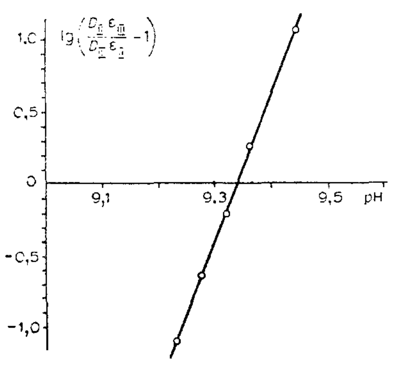


Fig. 3

Fig. 2. UV spectra of 4-(3-indolyl)pyridine methiodide at various pH values: 1) pH 7.0; 2) pH 9.26; 3) pH 9.36; 4) pH 9.52; 5) pH 9.68; 6) pH 13.0.

Fig. 3. Determination of the pK_a values of III.

Expressing the concentration in terms of the optical densities and extinctions and transforming Eq. (1) we obtain

$$pH = pK_a - \lg\left(\frac{D_{II} \cdot \varepsilon_{III}}{D_{III} \cdot \varepsilon_{II}} - 1\right), \qquad (2)$$

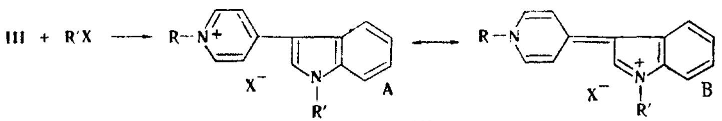
where D_{II} is the optical density of 1-alkyl-4-(3-indolyl)pyridinium iodide in the starting concentration, D_{III} is the optical density of the anhydro base at a certain pH, and ε_{II} and ε_{III} are the extinction coefficients of the solution of the quaternary salt and its anhydronium base.

A straight line in coordinates of pH and log $\left(\frac{D_{II}\varepsilon_{III}}{D_{III}\varepsilon_{II}} - 1\right)$ is then obtained (Fig. 3), and the segment cut out by the line on the axis of abscissas corresponds to $pK_a = 9.33$. The pK_a value found may serve as a characteristic feature of the anhydro bases of pyridylindoles and, consequently, as a numerical measure of their stabilities.

The anhydro bases that we obtained are more stable than the anhydro bases of β- and γ-carbolines but are less stable than the anhydro bases of the α-carboline series [5].

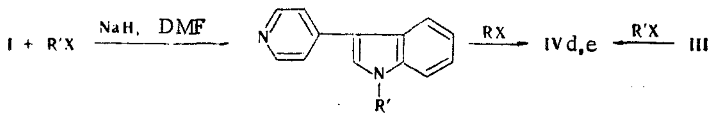
Anhydro bases III form salts in acidic media, during which the indole nitrogen atom is protonated, as evidenced by the absence of splitting of the signal of the CH_3 group at 4.3 ppm in the PMR spectrum of III in trifluoroacetic acid (a doublet should have been observed in the case of protonation of the pyridine nitrogen atom).

Anhydro bases III also react similarly with alkylating agents (alkyl iodides and dimethyl sulfate) to give 4-(1-alkyl-3-indolyl)pyridinium salts (IV):



IV a-e

We confirmed the direction of quaternization of anhydro bases III by alternative synthesis:



Despite the Iyer–Robinson rule [6], we obtained the starting anhydro bases III rather than the expected 1-alkyl-3-(4-pyridyl)indoles when salts IV were treated with alkali. This result can be explained if it is assumed that the positive charge in salts IV is localized on the nitrogen heteroatom of indole rather than pyridine (structure IVB). In fact, the results of the calculation show that the highest positive charge (+0.36024) in the 3-(4-pyridyl)indole cation is localized on the indole nitrogen atom (see Fig. 1); in starting base I the charge of the indole nitrogen atom is somewhat lower (+0.33124), and considerable negative charge (−0.26131) is localized on the same atom in anhydronium base III.

TABLE 1. Energies of the Lower Singlet π–π^* Transitions

Molecule	Calc., eV	Exptl., eV
4-(3-Indolyl)pyridine	4,231	3,961
4-(3-Indolyl)pyridinium cation	3,024	3,306
4-(3-Indolenylidene)-1,4-dihydropyridine	2,888	3,009[a]

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a) The experimental data for 1-methyl-4-(3-indolenylidene)-1,4-dihydropyridine are presented.

TABLE 2. 3-(4-Pyridyl)indole Derivatives

Compound	R	R′	X	mp, °C (ethanol	R_f	Found, %				Empirical formula	Calc., %				Yield, %
						C	H	Hal	N		C	H	Hal	N	
IIb	CH_3	H	Cl	222—223	0,40	68,4	5,5	14,1	11,7	$C_{14}H_{13}ClN_2$	68,7	5,3	14,5	11,4	96
IIc	CH_3	H	Br	228—229	0,41	58,4	4,1	27,9	9,7	$C_{14}H_{13}BrN_2$	58,1	4,5	27,7	9,7	92
IId	CH_3	H	ClO_4	232—233	0,37	54,7	4,4	11,2	8,9	$C_{14}H_{13}ClN_2O_4$	54,5	4,2	11,5	9,1	97
IIe	C_2H_5	H	I	249—250	0,35	51,2	4,5	36,1	8,2	$C_{15}H_{15}IN_2$	51,4	4,3	36,3	8,0	95
IIf	C_3H_7	H	I	185—186	0,32	52,8	4,9	35,0	7,5	$C_{16}H_{17}IN_2$	52,7	4,7	34,9	7,6	93
IIIa	CH_3	—	—	218—219	0,68	81,2	5,5	—	13,6	$C_{14}H_{12}N_2$	80,8	5,8	—	13,5	95
IIIb	C_2H_5	—	—	100—102	0,66	81,2	6,2	—	12,8	$C_{15}H_{14}N_2$	81,1	6,3	—	12,6	91
IVa	CH_3	CH_3	I	277—278	0,40	51,5	4,2	36,4	7,8	$C_{15}H_{15}IN_2$	51,4	4,3	36,3	8,0	92
IVb	CH_3	C_2H_5	I	123—125	0,41	53,0	4,8	34,5	7,6	$C_{16}H_{17}IN_2$	52,7	4,7	34,9	7,6	97
IVc[a]	CH_3	CH_3	CH_3SO_4	142—143	0,30	57.7	5,1	—	8,5	$C_{16}H_{18}N_2O_4S$	57,5	5,4	—	8,4	90
IVd^{8}	CH_3	$CH_2CH{=}CH_2$	I	210—212	0,32	54,1	4,6	33,9	7,2	$C_{17}H_{17}IN_2$	54,3	4,5	33,8	7,4	94
IVd^{8}	C_2H_5	CH_3	I	229—231	0,39	52,8	4,9	34,8	7,5	$C_{16}H_{17}IN_2$	52,7	4,7	34,9	7,6	93

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a) Found: S 9.7%. Calculated: S 9.6%.

EXPERIMENTAL

The PMR spectra of 10% solutions of the compounds in trifluoroacetic acid were recorded with a Varian T-60 spectrometer. The UV spectra of $2 \cdot 10^{-5}$ M solutions of the compounds in ethanol were recorded with a Specord spectrophotometer. For the determination of the pK_a values, we prepared $2 \cdot 10^{-4}$ M solutions of the quaternary salts in water; these solutions were diluted to the working concentration of $2 \cdot 10^{-5}$ M with borate buffer immediately prior to the recording of the spectra. Chromatography in a loose layer of activity II Al_2O_3 was accomplished by elution with methanol. The chromatograms were developed with iodine vapors or in UV light. 3-(4-Pyridyl)indole was obtained by the method in [7].

4-(3-Indolyl)pyridine Methiodide (IIa). A mixture of 4 g (0.02 mole) of 4-(3-indolyl)-pyridine, 2.8 g (0.02 mole) of methyl iodide, and 25 ml of methanol was refluxed for 2 h, after which it was cooled, and the precipitated crystals were removed by filtration and recrystallized from ethanol to give 6.6 g (98%) of a product with mp 264-265°C and R_f 0.36. Found: C 50.3; H 3.9; I 38.0; N 8.5%. $C_{14}H_{13}IN_2$. Calculated: C 50.0; H 3.9; I 37.8; N 8.3%.

1-Methyl-4-(3-indolenylidene)-1,4-dihydropyridine (IIIa). A solution of 1.7 g (5 mmole) of 4-(3-indolyl)pyridine methiodide in an aqueous alcohol solution of alkali (15 g of KOH in 15 ml of water and 75 ml of ethanol) was refluxed in a stream of nitrogen for 4 h, after which it was cooled and poured into 200 ml of water, and the precipitate was removed by filtration, washed repeatedly with water, and recrystallized from ethanol containing a small amount of water to give 0.95 g (95%) of a product with mp 218-219°C and R_f 0.68. Found: C 81.2; H 5.5; N 13.6%. $C_{14}H_{12}N_2$. Calculated: C 80.8; H 5.8; N 13.5%. 1-Ethyl-4-(3-indolenylidene)-1,4-dihydropyridine (IIIb) was similarly obtained (Table 2).

1-Methyl-4-(3-indolyl)pyridinium Chloride (IIb). A stream of dry HCl was passed into a solution of 2 g (0.01 mole) of 1-methyl-4-(3-indolenylidene)-1,4-dihydropyridine in 30 ml of chloroform, and the resulting precipitate was removed by filtration and recrystallized from ethanol to give 2.4 g (98%) of a product with mp 222-223°C and R_f 0.40. Found: C 68.4; H 5.5; Cl 14.1; N 11.7%. $C_{14}H_{13}ClN_2$. Calculated: C 68.7; H 5.3; Cl 14.5; N 11.5%.

1-Methyl-4-(1-methyl-3-indolyl)pyridinium Iodide (IVa). A mixture of 2 g (0.01 mole) of 1-methyl-4-(3-indolenylidene)-1,4-dihydropyridine, 1.4 g (0.01 mole) of methyl iodide, and 15 ml of ethanol was refluxed for 15 min, after which the precipitate was removed by filtration and recrystallized from ethanol to give 3.2 g (92%) of a product with mp 277-278°C and R_f 0.40. Found: C 51.7; H 4.1; I 36.7; N 7.9%. $C_{15}H_{15}IN_2$. Calculated: C 51.4; H 4.3; I 36.3; N 8.0%.

The other pyridylindole quaternary salts, the principal characteristics of which are presented in Table 2, were similarly obtained.

Demethylation of 1-Methyl-4-(1-methyl-3-indolyl)pyridinium Methosulfate. A solution of 1.2 g (0.005 mole) of 1-methyl-4-(1-methyl-3-indolyl)pyridinium methosulfate in an aqueous alcohol solution of alkali (10 g of KOH in 15 ml of water and 75 ml of alcohol) was refluxed in a stream of nitrogen for 1 h, after which the mixture was poured into 200 ml of water, and the precipitate was removed by filtration and recrystallized from alcohol containing a small amount of water to give 0.9 g (90%) of 1-methyl-4-(3-indolenylidene)-1,4-dihydropyridine. No melting-point depression was observed for a mixture of this product with an authentic sample.

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