270°C (dec., from benzene). IR spectrum: 3400 cm^{-1} (indole ring NH). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 208 (35.4), 227 (38.4), 256 (16.9), 279 (17.3), 303 (11.6), 327 HM (9.2). Found: C 84.1; H 4.5; N 11.0%. $C_{18}H_{12}N_2$. Calculated: C 84.4; H 4.7; N 10.9%.

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ANHYDRO BASES OF 3-PYRIDYLINDOLES

T. V. Stupnikova, B. P. Zemskii,
Yu. B. Vysotskii, R. S. Sagitullin,
and Kh. Ya. Lopatinskaya

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The reactions of quaternary salts of 3-pyridyl- and benzopyridylindoles with alkali proceed via two pathways, viz., deprotonation, the products of which are anhydro bases, and dealkylation of the pyridine ring, as a consequence of which the corresponding nonquaternized bases are formed. The reactions are interpreted from a quantum-chemical point of view.

It is known [1, 2] that quaternary pyridinium salts in alkaline media add a hydroxide ion to give covalent hydration products that exist in equilibrium with the open prototropic form. In a number of cases the latter may undergo ring closure to give a new cyclic system as, for example, in the recyclization of quaternary salts of α-picoline to aniline [3], nicotyrine to indole [4], and 2-(3-pyridyl)indole to carbazole [5]. It is usually assumed that these rearrangements proceed through the formation of the corresponding anhydro bases [3], and this is also responsible for the recent increased interest in the study of this interesting class of organic compounds.

Pyridylindoles are of interest because the presence of an indole NH group in the molecule makes deprotonation to give anhydro bases through the action of alkali on their quaternary salts more likely. Thus, for example, it has been shown [6] that a stable anhydro base, viz., 1-methyl-4-(3-indolenylidene)-1,4-dihydropyridine, is formed under these conditions, and its electronic structure, UV spectra, and basicity constant have been studied. In the present research we investigated the UV spectra and the prototropic transformations of the quaternary salts of benzopyridylindoles in relationship to their structures.

Colored anhydro bases are formed in the reaction of quaternary salts of substituted 2-phenyl-3-(4-pyridyl)indoles (I) with an alcohol solution of alkali. Anhydro bases were obtained under similar conditions from the isomeric 2-phenyl-3-(2-pyridyl)indole methiodide and from the quaternary salts of 3-(2-quinolyl)-, 3-(1-isoquinolyl)-, 3-(benzo[f]-quinolyl)-, and 3-(9-acridinyl)indoles (III-VI). The color of the anhydro bases of benzopyridylindoles is deeper than that of the anhydro bases of pyridylindoles and deepens in the series presented from red to violet, apparently because of an increase in the conjugation chain.

In addition to attack by the nucleophile on the NH group of the indole fragment, which leads to anhydro bases (VII-X), one also observes competitive N-dealkylation, which increases in the order I, III, and VI. In the latter example dealkylation becomes the principal process, whereas anhydro base X is formed in low yield under comparable conditions.

To explain this fact we performed a quantum-chemical calculation of the cations of III, IV, and VI by the Pariser–Parr–Pople (PPP) method with the parametrization proposed in [7]; it was assumed that these compounds are nonplanar, and the dihedral angle (θ) was calculated from the van der Waals radii of the sterically hindered groups and was found to be 68° for the cis conformers of the cations of III and IV and 71° for the

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Donetsk State University, Donetsk 340055. M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 959-964, July, 1980. Original article submitted July 12, 1979.

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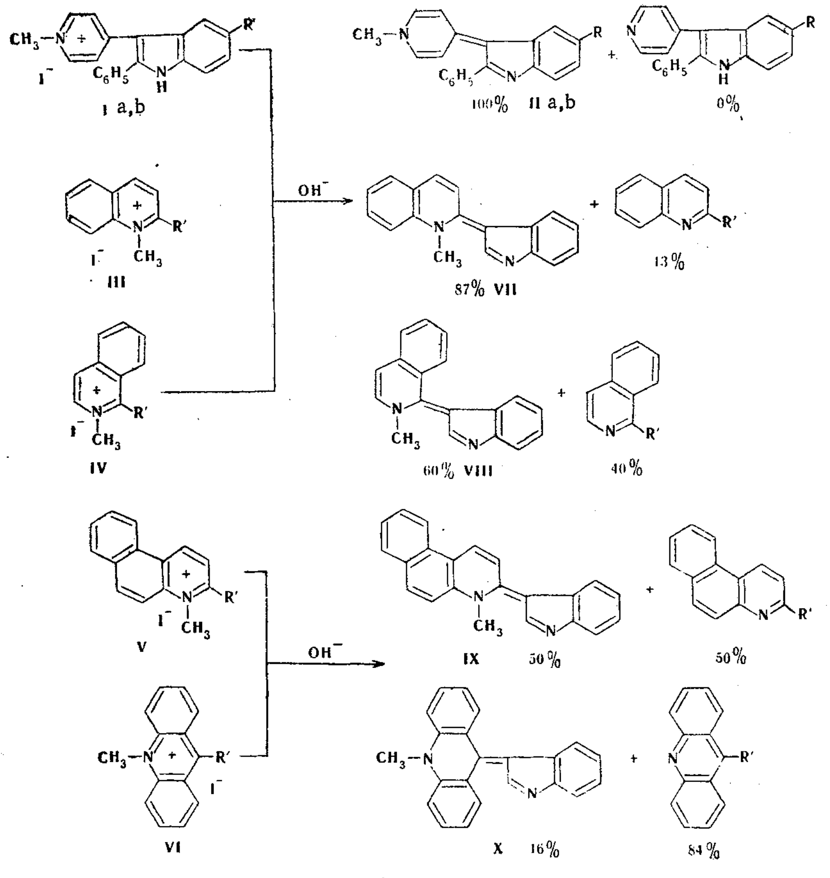
trans conformers, as compared with 59° for the cation of VI. In the calculations the resonance integral of the C−C interannular bond was, as usual, multiplied by cos θ.

The results of the calculation constitute evidence that a cis conformation is preferred for III and IV. Thus, for example, the calculated dipole moment of 3-(2-quinolyl)indole (the dihedral angles of the cis and trans conformations are 48 and 34°, respectively) in the cis conformation is 3.37 D. The experimental dipole moment [8] of this compound is 3.97 D. Calculation of the dipole moment in the trans conformation gave 1.44 D.



a R=H; b R=CH$_3$; R′=3-indolyl

The distributions of the electron densities of the investigated cations [see [6] for the 3-(4-pyridyl)indole cation (XI)] are presented in molecular diagrams 1-3 (Fig. 1), from which it follows that the highest positive charge in the III, IV, and XI cations is localized on the nitrogen atom in the indole ring (+0.34505, +0.34810, and +0.36024, respectively), while the highest positive charge in the IV cation is localized on the nitrogen atom in the pyridine ring (+0.35418). Let us note that since the π-electron charge on the nitrogen atom in the indole ring determines the tendency for detachment of a proton, while the charge on the nitrogen atom in the pyridine ring determines the tendency for dealkylation, the difference in the charges on these atoms should be symbatic to the ratio of the yields of the competitive deprotonation and dealkylation processes. In fact, the difference in the charges on the nitrogen atoms in the indole and pyridine rings decreases in the order XI > III > IV (+0.02104, +0.01838, and −0.00880, respectively), and the contribution of dealkylation processes increases in the same order.

Let us emphasize that the marked intensification of the dealkylation process for the VI cation is evidently associated with the large amount of steric hindrance of the N-methyl group (the distance from the N-methyl group to the hydrogen atom in the 1 position of acridine is 2.42 Å, and the sum of the van der Waals radii is 5.2 Å), while the formation of anhydro base X is associated with localization of the large π-electron charge on the nitrogen atom in the indole ring (Fig. 1). The importance of dealkylation increases significantly when the N-methyl group is replaced by an ethyl, isopropyl, or nonyl group in the 3-(2-quinolyl)indole salts; this is associated with an increase in the steric hindrance. In the latter case an anhydro base was observed only by chromatography even under very mild conditions.

As in the case of the anhydro bases of 3-(4-pyridyl)indole [6], the formation of anhydro bases II and

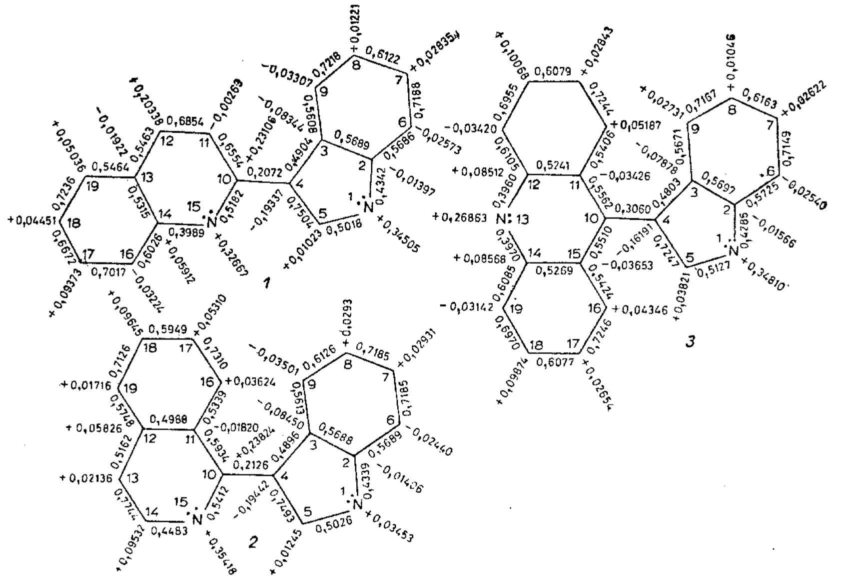


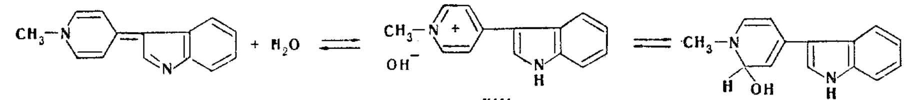
Fig. 1. Molecular diagrams: 1) 3-(2-quinolyl)indole cation; 2) 3-(1-isoquinolyl)indole cation; 3) 3-(9-acridinyl)indole cation.

TABLE 1. Anhydro Bases of Pyridylindoles

Compound	mp, deg C[a]	R_f[b]	UV spectrum, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
IIa	195 (dec.)	0,30[B]	426 (4,35)	84.3	5.8	9,8	$C_{20}H_{16}N_2$	84,5	5,6	9,9	99
IIb	251—252	0,32	426 (4,65)	84,8	5.7	9.6	$C_{21}H_{18}N_2$	84,6	6,0	9,4	99
VII	173—174	0,35	510 (4,59)	84,0	5,2	11,1	$C_{18}H_{14}N_2$	83,7	5,4	10,9	87
VIII	185—186	0,31	515 (4.71)	83,5	5,6	10,7	$C_{18}H_{14}N_2$	83,7	5,4	10,9	60
IX	201—202	0,36	521 (4,38)	85,6	5,4	9,3	$C_{22}H_{16}N_2$	85,7	5,2	9,1	50
X	250—251	0,40	550 (4,39)	85,8	5,1	9,0	$C_{22}H_{16}N_2$	85,7	5,2	9,1	16

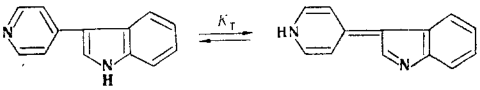
[a] From acetonitrile. [b] System B. [c] System A.

VII-X is accompanied by a strong bathochromic shift (~100 nm) of the principal band of the $\pi-\pi^*$ transition. On passing to neutral aqueous media a pronounced change in the color and in its conversion to pale-yellow in all cases was noted even visually; the absorption curve becomes wider and close to the absorption curve of the starting quaternary salt. This is evidently explained by the fact that the strongly nucleophilic anhydro base (XII, for example) adds a proton reversibly to the indolenine nitrogen atom [6] as the site of the highest negative π-electron charge, thereby undergoing conversion to quaternized form XIII, which can add a hydroxide ion covalently and also reversibly to give pseudo base XIV:

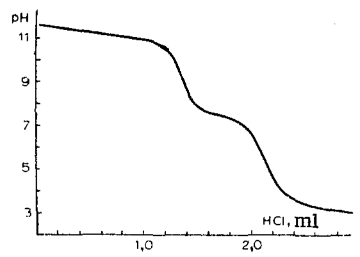


XII XIII XIV

The somewhat depressed pK_a value of XII determined by a spectrophotometric method [6] is explained by hydration processes that take place in aqueous solutions of the anhydro bases. During the measurement of the pK_a value of this compound by a potentiometric method we observed two sharp pH inflections on the titration curve (Fig. 2); this constitutes evidence for the presence of two bases, viz., the anhydro base and its hydrated form, in the system. Judging from the position of the inflections on the titration curve, the pK_a value of anhydro base XII is 11.25 while the pK_a value of its hydration product is 7.30. Potentiometric titration of VII-X in dilute aqueous alcohol solutions gave titration curves with two inflections; the corresponding pK_a values of these compounds are presented in Table 2. Let us note that anhydro bases VII-X and XII are fixed structures of the B type in tautomeric equilibrium:



A B



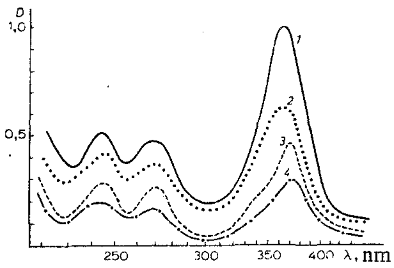


Fig. 2 Fig. 3

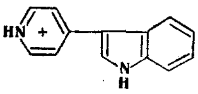
Fig. 2. Titration curve of an aqueous alcohol solution of the 3-(4-pyridyl)indole anhydro base.

Fig. 3. UV spectra: 1) 3-(4-pyridyl)indole in 0.1 N HCl solution; 2) 3-(4-pyridyl)indole in concentrated H_2SO_4; 3) 1-methyl-4-(3-indolyl)pyridinium iodide in concentrated H_2SO_4; 4) 1-methyl-4-(3-indolyl)pyridinium iodide in methanol.

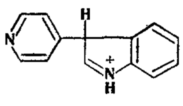
TABLE 2. Basicities and Indexes of the Aromatic Character of Pyridylindoles (A) and Their Anhydro Bases (B)

Compound	Form A				Form B				K_T	ΔG, kcal/mole	$\Delta\chi^\pi$	ΔJ	
	pK_a	induced π-electron currents			pK_a	induced π-electron currents							
		pyridine ring	pyrrole ring	benzene rings		pyridine ring	pyrrole ring	benzene firngs				pyridine ring	pyrrole ring
3-(4-Pyridyl)-indole	5,55	0,95	0,78	1,06	11,25	0,39	0,39	0,93	$1{,}99 \cdot 10^{-6}$	7,76	0,94	0,56	0,39
3-(2-Quinolyl)-indole	4,87	1,06	0,81	1,06; 1,06	9,75	0,62	0,63	0,95; 1,00	$1{,}32 \cdot 10^{-5}$	6,65	0,72	0,44	0,18
3-(1-Isoquinolyl)indole	4,60	1,07	0,82	1,06; 1,04	9,60	0,67	0,69	0,97; 0,99	$0{,}89 \cdot 10^{-5}$	6,88	0,63	0,40	0,13
3-(2-Benzoquinolyl)indole	4,45	—	—	—	9,95	—	—	—	$3{,}16 \cdot 10^{-6}$	7,50	—	—	—
3-(9-Acridinyl) indole	4,45	1,04	0,81	1,06; 1,06 1,06	9,87	0,41	0,39	1,19; 0,95 0,95	$3{,}8 \cdot 10^{-6}$	7,39	1,64	0,65	0,42

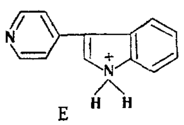
The tautomeric equilibrium constants (K_T) and the aromaticities of these compounds are then intimately associated with the peculiarities of compounds A and B [9]. However, a necessary condition for this is the requirement of the formation of a common cation (or anion) from both tautomers A and B [9]. The most likely site of protonation in the 3-(4-pyridyl)indole molecule is the pyridine nitrogen atom; however, one must also take into account protonation in the β position of the indole ring, especially since cases of β protonation of indole [10], particularly 3-phenylindole [11], which has a structure similar to that of 3-pyridylindole, are known. It is true that a process of this sort is less favorable, since β protonation of the indole ring proceeds with disruption of the aromaticity of the system. In addition to this, one must also take into account N-protonation of the pyrrole part of the molecule, since this process also takes place in the reaction of indole with mineral acids. [10]. Finally, one must also examine the possibility of diprotonation. Thus, one should assume the formation of C–F ions in acidic media for 3-(4-pyridyl)indole:



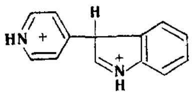
C



D



E



F

However, since the UV spectrum of 3-(4-pyridyl)indole XV in 0.1 N HCl solution is similar to the spectrum of methiodide XVI in methanol (Fig. 3), this constitutes evidence for protonation in a dilute solution of acid XV at the nitrogen atom of the pyridine ring to give ion C. The absorption curves of XV and XVI in concentrated sulfuric acid are identical and do not differ from the spectrum of XVI in methanol. This fact excludes the possibility of secondary protonation. In addition, the spectrum of XII in acid is similar to the spectrum of XVI in methanol. This indicates that XI and XV form a common cation and that one can consequently use the pK_a method for the calculation of K_T. This conclusion is confirmed by quantum-chemical calculation of the electron density distributions in XV and XII. The highest negative π-electron charge in XV is localized on the pyridine nitrogen atom, while the highest negative π-electron charge in XII is localized on the nitrogen atom in the indole ring [6].

Calculation of the tautomeric equilibrium constants from pK_a data [12] (Table 2) showed that the $A \rightleftarrows B$ tautomeric equilibrium is shifted to favor A; the change in the aromaticity on passing from A to B (ΔG) correlates satisfactorily with the calculated (by the method in [13]) aromaticity indexes, viz., the change in the relative diamagnetic susceptibilities ($\Delta\chi^n = \chi A^{\pi} - \chi^{\pi}_{B}/\chi_{C_6H_6}$) and the change in the induced π-electron ring currents (ΔI) in the pyrrole and pyridine rings (Table 2).

EXPERIMENTAL

The UV spectra of solutions (c 10^{-5} mole/liter) of the compounds in methanol, water, 0.1 N HCl, and concentrated H_2SO_4 were recorded with a Specord UV-vis spectrophotometer. The pK_a values were determined with a pH-340 pH meter by titration of 10^{-3} M solutions of the compounds in a 10% solution of methanol with a 10^{-2} M solution of hydrochloric acid and a 10^{-2} M solution of sodium hydroxide. The pK_a values were assumed to be equal to the pH values at the half-neutralization point. Chromatography was carried out in a loose thin layer of aluminum oxide (activity II) with elution with chloroform–benzene–hexane (30 : 6 : 1) (A) and chloroform–benzene–hexane–methanol (30 : 6 : 1 : 5) (B) systems; the chromatograms were developed with iodine vapors.

1-Methyl-2-(2-phenyl-3-indolenylidene)-1,2-dihydropyridine. A solution of 1.2 g (3 mmole) of 1-methyl-2-(2-phenyl-3-indolyl)pyridinium iodide in 15 ml of a 10% methanol solution of NaOH was maintained at 50°C for 5 min, after which it was cooled and diluted with water, and the precipitate was removed by filtration and recrystallized from acetonitrile to give 0.7 g (83%) of a product with mp 159-160°C and R_f 0.49 (A). UV spectrum, λ_{max} (log ε): 253 (4.5); 310 (4.4); 430 HM (4.2). Found: C 84.1; H 5.8; N 9.7%. $C_{20}H_{15}N_2$. Calculated: C 84.5; H 5.6; N 9.8%.

Anhydro bases IIa,b and VII-X, the characteristics of which are presented in Table 1, were similarly obtained.

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