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EFFECT OF AZA SUBSTITUTION ON THE FORMATION OF ANHYDRO BASES OF QUINOLYLINDOLES

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The reaction of quaternary salts of 3-(2-quinoxalinyl)indoles with hydroxylamine was investigated. It was established that the presence of a second pyridine nitrogen atom in the ring increases the positive π-electron charge on the nitrogen atom of the quinoxaline ring and, as a consequence of this, markedly increases the contribution of dealkylation.

The NH group of indole is deprotonated by the action of quaternary salts of 3-pyridylindoles, and stable anhydro bases of pyridylindoles are formed [1]. As a result of annellation of the pyridine ring, two competitive processes, viz., deprotonation of the NH group and dealkylation of the pyridine nitrogen atom, take place in the reaction of quaternary salts of benzopyridylindoles with alkali [2]. The ratio of the products of these processes cannot be explained by steric factors, and the direction of the reaction is primarily due to the distribution of the changes of the corresponding cations [2].

Since the introduction of a nitrogen atom into the molecule changes the electron density distribution and may change the ratio of the yields of these competitive processes, it seems of interest to investigate the effect of aza substitution in 3-(2'-quinolyl)indole methiodide (I) on the direction of the reaction of the quaternary salt with hydroxide ion; as in [3], in the quantum-chemical calculations we will describe the effect of aza substitution within the framework of the bonded variant of perturbation theory in the self-consistent-field (SCF) MO LCAO method.

Since the ratio of the indicated competitive processes is determined by the difference in the π-electron charges on the nitrogen atoms in the indole and pyridine rings [2], the effect of aza substitution on the direction of this reaction in the I cation can be described within the framework of the approach being developed here by the difference in the atom–atom mutual polarizabilities, viz., $\pi_{i1}-\pi_{i1'}$, where i is the position at which substitution takes place. The 1 position corresponds to the indole nitrogen atom, while the 1' position corresponds to the quinoline nitrogen atom. The results of calculation of these indexes are presented in Table 1, from which it is apparent that the greatest change in the magnitude of the π-electron charge on the nitrogen atom in the quinoline fragment of the molecule is produced by aza substitution of the $C_{4'}$ atom; the charge on the nitrogen atom in the indole ring remains virtually unchanged. The π-electron positive charge on the nitrogen atom in the quinoline ring decreases in the case of aza substitution of the carbon atoms in the 6, 5, 3, and 6' positions, whereas the charge on the nitrogen atom in the indole ring increases or remains unchanged. The increase in the charge on the nitrogen atom in the quinoline ring in the case of aza substitution of the C_2 atom is compensated by a pronounced increase in the charge on the nitrogen atom in the indole ring. It follows from Table 1 that the degree of dealkylation

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TABLE 1. Atom–Atom Mutual Polarizabilities of the 2-(3'-Indolyl)quinolinium Cation

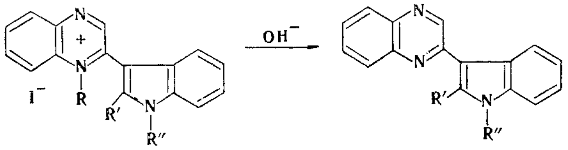
	2	7	6	5	4	3′	4′	8′	7′	6′	5′
π'_{i1}	−0,010	0,000	0,002	0,002	−0,001	0,001	−0,061	−0,014	−0,011	0,006	−0,06
π_{i1}	−0,071	−0,013	−0,006	0,000	0,000	0,000	−0,002	−0,001	−0,002	−0,001	0,00
$\pi_{i1}-\pi'_{i1}$	−0,061	−0,013	−0,008	−0,002	0,001	−0,001	0,059	0,0013	0,009	−0,007	0,06

in the case of aza substitution of the carbon atoms in the quinolylindole should decrease in the following order:

$$4'\gg 8'>7'>5'>4\geqslant \text{quinolylindole}\geqslant 3'\geqslant 5>6=6'>7\gg 2.$$

The extreme terms stand out most markedly in this series, and a study of them is therefore of greatest interest. Thus in the reaction of 3-(2'-quinoxalinyl)indole methiodide (II) with alkali the degree of dealkylation should be substantially higher than in the case of I, whereas in the case of 2'-(1-H-indazol-3-yl)quinoline the primary pathway in the reaction with alkali should be the formation of the corresponding anhydro base, and dealkylation of the pyridine nitrogen atom will proceed with greater difficulty than in the case of I. According to the data in Table 1, substitution in the remaining positions of both the indole and quinoline rings should have a substantially smaller effect on the ratio of the products of the competitive processes.

We experimentally confirmed predominance of dealkylation in the reaction of II with alkali. Thus we isolated 3-(2'-quinoxalinyl)indole (IIIa) when we refluxed IIa, b in an aqueous alcohol solution of alkali, and we were unable to establish the formation of an anhydro base even by chromatography. The structure of IIIa was proved by alternative synthesis [4]:



II a-d

III a,c,d

II, III a $R=CH_3$; $R'=R''=H$; b $R=C_2H_5$; $R'=R''=H$; c $R=C_2H_5$; $R'=H$; $R''=CH_3$;
d $R=C_2H_5$; $R'=CH_3$; $R''=H$

Compound IIIa was also obtained by reaction of 3-(2'-quinoxalinyl)indole (IIb) with hydroxide ion. The quaternary salts of 1-methyl-3-(2'-quinoxalinyl)indole (IIc) and 2-methyl-3-(2'-quinoxalinyl)indole (IId) behave similarly in alkaline media and give the corresponding bases (IIIc, d).

A direct calculation† of the 3-(2'-quinoxalinyl)indole cation (Fig. 1) shows that a greater amount of positive charge is localized on the nitrogen atom in the 1' position in the six-membered ring than on the nitrogen atom in the five-membered ring; the difference in the π-electron charges turns out to be even greater in absolute value than for the 3-(1'-isoquinolyl)indole cation [2] (−0.0111 and −0.0088, respectively). These data, with allowance for the results in [2], indicate that in the series of cations of 3-pyridylindole I and 3-(1'-isoquinolyl)indole II [sic] the yields of the corresponding anhydro bases in the case of reaction with alkali will decrease and, correspondingly, the yields of dealkylation products will increase. Let us emphasize that the annexation of an indole residue has virtually no effect on the ratio of the charges on the quaternized nitrogen atoms of the quinoline and quinoxaline cations (compare [2, 5] and the data in the present paper).

Since the acid–base transformations of salts of pyridylindoles are displayed most clearly in changes in the UV spectra, which constitute a reliable method for the detection of anhydro bases [1, 2], we made an attempt to record the anhydro base of 3-(2'-quinoxalinyl)indole by recording the UV spectra of II and III at various pH values. We found that the quaternization of III is accompanied by an ~100 nm bathochromic shift of the long-wave transition band,

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†The calculation was made with the parameters and by the method in [1].

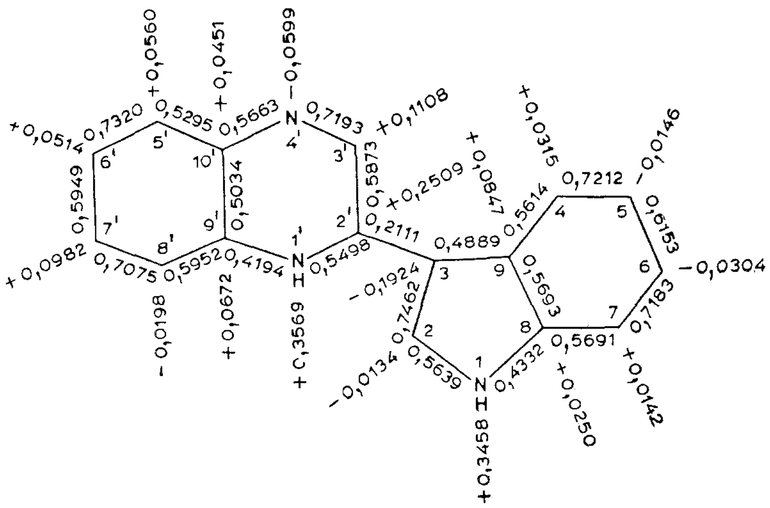

Fig. 1. Molecular diagram of the 3-(2'-quinoxalinyl)indole (IIIa) cation.

TABLE 2. Energies of the Lower Singlet—Singlet Transitions

Compound	Calculated, eV	Experimental, eV
IIIa	3,53, 4,40	3,76, 4,20
IIIa cation	2,48, 3,22	2,43, 3,37
IIIa dication	1,82	2,17

while the spectra of II obtained in alkaline media, contrary to our expectations, are characterized by a hypsochromic shift of the long-wave band of the π—π* transition. This constitutes evidence that the anhydro base of 3-(2'-quinoxalinyl)indole is not formed in alkaline media. This is also indicated by the calculated (by the method in [6]) energies of the lower singlet—singlet transitions, which are in good agreement with the experiment data (Table 2).

One may draw a conclusion regarding the direction of protonation of IIIa from a comparison of the calculated and experimental UV spectra. Protonation takes place at the nitrogen atom in the 1' position in weakly acidic solutions (for example, in 0.01 N hydrochloric acid). The spectrum calculated for the 1'H-2'-(3-indolyl)quinoxalinium ion, which is in agreement with the spectrum obtained experimentally (Table 2), attests to this, whereas for the 4'H-2'-(3-indolyl)quinoxalinium ion the calculated values of the lower singlet—singlet transitions (1.49 and 3.56 eV) are not in agreement with the experimental values.

Both nitrogen atoms of the quinoxaline ring are protonated in concentrated sulfuric acid to give the 2'-(3-indolyl)quinoxalinium dication, for which the calculated UV spectrum is similar to the experimental spectrum (see Table 2).

A calculation of the localization of the perturbations by the method in [7] showed that the long-wave absorption band of the π—π* transition in the spectrum of IIa is due primarily to perturbation of the quinoxaline ring (84% of the perturbation is localized on this nucleus), while the second absorption band is due primarily to perturbation of the molecule as a whole. However, the long-wave absorption band in the IIa cation corresponds to perturbation of the molecule as a whole, while the second band corresponds to perturbation of the quinoxaline ring (95%).

A study of the second extreme member of the series [2'-(1H-indazol-3-yl)quinoline], for which the formation of anhydro bases should be characteristic, is proposed for the future.

EXPERIMENTAL

The UV spectra of solutions of the compounds in methanol, water, 0.01 N HCl, 0.01 M NaOH, and concentrated H_2SO_4 were recorded with a Specord UV-Vis spectrophotometer. 1-Ethyl-2-(3-

TABLE 3. 3-(2'-Quinoxalinyl)indole Derivatives

Compound	mp, °C (isopropyl alcohol)	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIa	310[a]	52,9	3,8	10,7	$C_{17}H_{14}N_3$	52,7	3,6	10,8	45
IIc	252—253[a]	54,8	4,2	10,3	$C_{19}H_{18}N_3$	54,9	4,3	10,1	40
IId	241—242[a]	55,1	4,0	9,8	$C_{19}H_{18}N_3$	54,9	4,3	10,1	42
IIIb	154—155[b]	78,9	5,3	16,6	$C_{17}H_{13}N_3$	78,7	5,0	16,2	85
IIIc	147—148[b]	79,0	4,9	15,9	$C_{17}H_{13}N_3$	78,7	5,0	16,2	90

[a] From isopropyl alcohol. [b] From acetone.

indolyl)quinoxalinium iodide (IIb) was obtained by the method in [8]. The other quaternary salts of 3-(2'-quinoxalinyl)indoles, the principal characteristics of which are presented in Table 3, were similarly obtained.

3-(2'-Quinoxalinyl)indole (IIIa). A mixture of 1.5 g (3.5 mmole) of IIb, 4 g of KOH, 10 ml of water, and 20 ml of ethanol was heated at 40-50°C for 10 min, after which the ethanol was removed by distillation, and the precipitate was removed by filtration and recrystallized from acetone to give 0.81 g (80%) of a product with mp 209-210°C (mp 208-209°C [4]).

The other 3-(2'-quinoxalinyl)indoles (IIIc, d), the principal characteristics of which are presented in Table 3, were similarly obtained.

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