QUANTUM-CHEMICAL INTERPRETATION OF RECYCLIZATION REACTIONS. 3.* AZAINDOLIZINES

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The rearrangements of a number of azaindolizines are examined within the framework of the previously developed [Khim. Geterotsikl. Soedin., No. 11, 1496 (1979); No. 3, 381 (1980)] method of quantum-chemical description. Allowance for the effect of functional substitution on all stages of the calculation was realized on the basis of the bonded variant of perturbation theory in the π-electron approximation by the MO LCAO self-consistent field (SCF) method. Replacement of the CH group by a nitrogen atom was examined as a source of perturbation in addition to the effect of functional substituents; a small perturbation parameter ($\Delta\alpha_N$) was obtained from a comparison of the chemical shifts of the protons and the energies of the lower singlet-singlet transitions of azaindolizines found within first-order (with respect to $\Delta\alpha_N$) perturbation theory [see Ref. Zh. Khim., 12B72 (1976) and 19B195 (1978)] with the experimental values and the values calculated by a direct method. It is shown that, in addition to rearrangements that take place with the ejection of the heteroatom from the aromatic ring and replacement by a carbon atom, this scheme describes recyclizations of the Dimroth type, satisfactorily reflecting their reversible character and the shift of the equilibrium in these rearrangements.

A method for the description of the recyclization reactions of the anhydro bases of α-methylpyridines and benzopyridines was developed in [1, 2]; the competitive formation of the anhydro bases, the ratios of the yields of which were estimated from the π-electron residual charges on the corresponding methylene groups, was regarded as the first step in this method. The positions of the attack on the anhydro base by the hydroxide ion and the weakest bond (the minimum π-bond order corresponds to it), the cleavage of which should occur during the reaction, were then determined from a calculation of the electron-density distribution of the most stable of these isomers. The anhydro bases with a cleaved (the corresponding resonance integral was assumed to be equal to zero) π bond were calculated, and the direction of cyclization, for which the positive long-range bond orders serve as reactivity indexes, was determined in the third step. Allowance for the effect of functional substitution in all steps of the calculation was realized on the basis of the bonded variant of perturbation theory in the MO LCAO self-consistent-field (SCF) method. Since replacement of the CH group in the conjugated system by a nitrogen atom can also be regarded as a perturbation [3], it can be described by means of the same scheme. In the present research we studied the effect of "aza substitution" on the recyclization reactions of this class of compounds within the framework of the developed approach in the case of a number of azaindolizines.

1. The reactivities of organic molecules within the framework of a static model are determined by the parameters of their electronic structures, direct information regarding which is rather difficult to obtain experimentally but relatively easy to obtain by the methods of quantum chemistry. The agreement between the calculated and experimental spectral characteristics usually serves as a criterion of the reliability of the electron-density distribution found, since it is precisely the calculation of the ground state of the molecules that serves as the basis of the determination of their physicochemical molecular properties. To describe the reactivities of azaindolizines within the framework of the scheme for allowance for the effect of aza substitution on the physicochemical properties one must therefore first estimate the small parameters of the perturbations of the CH groups ($\Delta\alpha_N$) that are replaced by nitrogen atoms. This can be accomplished by comparing

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*See [1, 2] for Communications 1 and 2.

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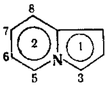
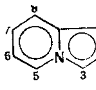
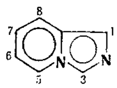
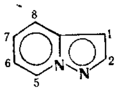
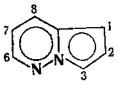
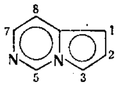
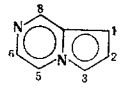
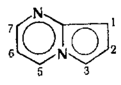
TABLE 1. π-Electron Ring Currents (i), Relative Diamagnetic Susceptibilities (χ'), and Proton Chemical Shifts (ppm) of Azaindolizines

Molecule	Proton No.	Calc.		experimental
		direct	from perturbation theory	
I  $i_1=1,026$ $i_2=0,801$ $\chi'=1,481$	1	6,78	6,77*	6,28
	2	6,67	6,68	6,64
	3	7,03	7,02	7,14
	5	7,32	7,46	7,76
	6	6,95	7,04	6,31
	7	6,91	7,01	6,50
	8	7,12	7,21	7,29
II  $i_1=1,085$ $i_2=0,865$ $\chi'=1,581$	2	8,15	8,06	7,48
	3	7,11	7,05	7,48
	5	7,43	7,37	8,09
	6	7,04	6,98	6,65
	7	7,01	6,96	7,03
	8	7,69	7,60	7,51
III  $i_1=1,096$ $i_2=0,792$ $\chi'=1,518$	1	8,26	8,19	7,27
	3	8,41	8,46	7,97
	5	7,35	7,34	7,88
	6	6,96	6,97	6,47
	7	6,92	6,93	6,58
	8	7,16	7,15	7,34
IV  $i_1=1,015$ $i_2=0,844$ $\chi'=1,516$	1	6,79	6,81	6,38
	2	8,12	8,09	7,80
	5	7,88	7,81	8,39
	6	7,02	6,98	6,62
	7	7,01	6,96	6,97
	8	7,19	7,16	7,44
V  $i_1=1,039$ $i_2=0,775$ $\chi'=1,463$	1	6,88	6,82	6,31
	2	6,68	6,68	6,67
	3	7,51	7,51	7,52
	6	8,31	8,40	7,79
	7	6,94	6,95	6,32
	8	7,21	7,22	7,51
VI  $i_1=1,024$ $i_2=0,800$ $\chi'=1,478$	1	6,79	6,80	6,50
	2	6,69	6,70	6,94
	3	7,06	7,07	7,37
	5	8,82	8,80	8,84
	7	8,29	8,27	7,37
	8	7,12	7,13	7,37
VII  $i_1=1,032$ $i_2=0,790$ $\chi'=1,472$	1	6,85	6,85	6,85
	2	6,71	6,71	6,97
	3	7,07	7,08	7,46
	5	7,30	7,31	7,89
	6	8,30	8,30	7,58
	8	8,59	8,58	8,91
VIII  $i_1=1,034$ $i_2=0,804$ $\chi'=1,494$	1	7,77	7,29	—
	2	6,68	6,68	—
	3	6.60	7,04	—
	5	6.93	7,42	—
	6	6,92	7.01	—
	7	8,50	8,36	—

*Data from [6].

the chemical shifts of the protons and the energies of the lower singlet-singlet transitions found via this scheme (for example, see [4, 5]) with the experimental values and the values calculated by a direct method.

The results of a direct calculation by the method in [6] of the π-electron ring currents (i), the relative diamagnetic susceptibilities (χ'), and the chemical shifts (CS) of the protons are presented in Table 1. It is apparent from Table 1 that, upon the whole, the calculation satisfactorily reproduces the experimental data, although it does not agree with the assignment in [7] of the signals of the protons in the 2 and 5 positions in II and IV and the protons in the 1 and 5 positions in III. In the calculation it was assumed that the structures of the five- and six-membered rings in all of the investigated compounds are regular pentagons and hexagons with a bond length of 1.39 Å and that the coulombic integrals of the nitrogen atoms and the interelectron interaction integrals are the same as in [6], while the resonance integrals of the CN bonds in the six-membered ring are equal to the β_{CN} value of pyridine, and the resonance integrals of the CN bonds in the five-membered ring are equal to the β_{CN} value of pyrrole.

Since the relative diamagnetic susceptibility serves as one of the quantitative characteristics of aromaticity (for example, see [8]), from the data in Table 1 it is easy to construct a scale of aromaticity that, with allowance for the results in [6], has the following form: pyrrole < 5-azaindolizine (V) < 7-azaindolizine (VII) < 6-azaindolizine (VI) ≤ indolizine (I) < 8-azaindolizine (VIII) < 3-azaindolizine (IV) < 2-azaindolizine (III) < benzimidazole < 1-azaindolizine (III) < 1H-indazole. Let us note that in the calculation of indolizine in [6] the resonance integrals of all of the CN bonds were assumed to be the same as for pyrrole, and this led to a somewhat overstated χ' value with respect to the data in the present study. The chemical shifts of indoli-

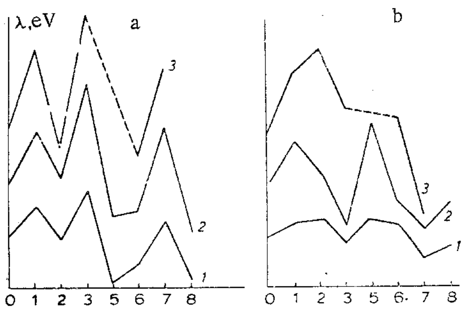


Fig. 1. Effect of the position of the nitrogen atom* in azaindolizines on the energies of the transitions of the α (a) and p (b) bands: 1) calculation from perturbation theory; 2) direct calculation; 3) experimental data.

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*Unsubstituted indolizine is designated by 0.

zine found in [6] are presented in Table 1 for comparison and depend only slightly on a change in the parametrization.

It follows from the scale of aromaticity that replacement of the CH group of indolizine by a nitrogen atom in the five-membered ring leads to an increase in the aromaticity (compare with χ') of the molecule as compared with indolizine, while in the case of a six-membered ring it leads to a decrease in the aromaticity, with the exception of substitution in the 8 position. However, let us emphasize that the χ' values of azaindolizines display relatively little variation (from 1.463 to 1.581). The aromaticities of the individual rings can be estimated from the π-electron ring currents. It follows from Table 1 that the aromaticity of the five-membered ring increases in the case of introduction of a nitrogen atom in both five- and six-membered rings, with the exception of IV and VI, while the aromaticity of the six-membered ring decreases; the introduction of a nitrogen atom in the 1 and 3 positions of the five-membered ring of indolizine constitutes an exception in this case.

The energies of the lower singlet–singlet transitions, which were determined as the eigennumbers of the Hartree–Fock ground state stability matrixes [8], which is equivalent to allowance for all of the singly and some of the doubly excited configurations, were found on the basis of a calculation of the ground states of the investigated systems. The calculated values are in satisfactory agreement with the experimental values: I 3.54 (3.58),* 4.27 (4.21); II 3.75 (4.00), 4.56 (4.43); III 3.57 (3.60), 4.40 (4.53); IV 3.93 (4.13), 4.20 (4.29); V 3.43 (–), 4.61 (–); VI 3.44 (3.59), 4.36 (4.38); VII 3.77 (3.75), 4.15 (4.43); VIII 3.35 (–), 4.29 eV (–) (the experimental data from [10-12] are presented in parentheses). It is apparent from these data that replacement of the carbon atoms in the 1, 3, and 7 positions in indolizine by a nitrogen atom is accompanied by a hypsochromic shift of the long-wave band. The second band is less sensitive to aza substitution, the hypsochromic shift of which is observed when a nitrogen atom is introduced in the 1, 2, and 5 positions. This sequence of the spectral lines in the case of aza substitution of indolizine is in good agreement with the experimental results, which is graphically apparent in Fig. 1.

The coefficients of the effect of chemical substitution on the proton magnetic shielding (K_{ij}) and on the energies of the lower singlet–singlet transitions of indolizine were calculated by the methods in [4, 5] to describe the spectral characteristics of azaindolizines within the framework of perturbation theory. Since the change in the chemical shift of the i-th proton when the j-th CH group is replaced by a nitrogen atom is linearly related to K_{ij} ($\Delta\delta_i = K_{ij}\Delta\alpha_N$), this makes it possible to find $\Delta\alpha_N$ from the calculation of K_{ij} and a knowledge of $\Delta\delta_i$. The use of the NMR spectra together with the UV spectra makes it possible to estimate this value more reliably, since a sufficiently large set of experimental data is encompassed in this case. The method of least squares gives a value of 1.30 eV for $\Delta\alpha_N$ with a correlation coefficient of 0.95. It is apparent from Table 1, in which, in addition to the results of direct calculation, the chemical shifts found within the framework of this scheme are presented, that the patterns of the positions of the signals of the protons in the NMR spectra of azaindolizines obtained by various methods virtually coincide with one another.

Calculation of the UV spectra of the azaindolizines with the use of the same $\Delta\alpha_N$ value by the method in [5] gave the following energies of the lower $\pi-\pi^*$ transitions for II-VIII, respectively: α band 3.58, 3.55,

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*In [6] the calculated energy of this transition was 3.48 eV.

3.60, 3.48, 3.50, 3.56, and 3.47 eV; p band 4.28, 4.29, 4.25, 4.29, 4.25, 4.23, and 4.25 eV. These data are in satisfactory agreement with the experimental values [10-12] and the results of direct calculation and correctly reflect the sequence of the spectral shifts as a function of the position of the nitrogen atom in the azaindolizines (Fig. 1).

Thus, the good agreement between the calculated (within the framework of the bonded variant of perturbation theory in the MO LCAO SCF method) spectral characteristics of azaindolizines and the experimental values and the values obtained by direct calculation constitutes evidence for the reliability of the charge distribution obtained via this scheme and makes it possible to draw conclusions regarding the reactivities of these compounds on the basis of calculation of only one indolizine molecule, the charge distribution of which and the atom–atom and atom–bond mutual polarizabilities are presented in Table 2.

These data (together with the polarizabilities $\pi_{4,4} = +0.235$, $\pi_{9,9} = +0.460$, and $\pi_{4,9} = -0.048$) make it possible to find the electron-density distribution in any azaindolizine molecule (and to describe any functional substitution) from the formulas

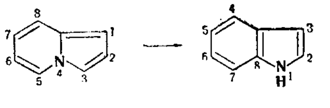
$$q_i = q_i^0 + \sum_k \pi_{ik} \Delta\alpha_k; \qquad P_{ij} = P_{ij}^0 + \sum_k \pi_{ij,k} \Delta\alpha_k,$$

where q_i and q_i^0(P_{ij}, P_{ij}^0) are the charges (bond orders) in the substituted and unsubstituted molecules, π_{ik} and $\pi_{ij,k}$ are the atom–atom and atom–bond mutual polarizabilities, $\Delta\alpha_k$ is a parameter that characterizes the substituent (or the nitrogen atom), and the summation is performed over all of the substituting groups.

Let us note that, as expected, the $\Delta\alpha_N$ value has the same sign as $\Delta\alpha_{NO_2}$, although it is smaller in absolute magnitude. This constitutes evidence for the identical effects of the nitro group and the ring nitrogen atom on the spectral characteristics and the reactivities of the organic compounds, particularly on recyclization reactions. For example, using the formulas and tables in [1] it is easy to show that the anhydro bases of pyrimidines should undergo recyclization to pyridines, while sym-triazines should undergo recyclization to diazines, in agreement with the experimental data [13-16]. In fact, the long-range 6–7 bond order is $0.4282 + 0.088 \cdot 0.2465 \cdot 1.30 = 0.4571$ when the carbon atom in the 3 position in 1-methyl-2-methylene-1,2-dihydropyridine is replaced by a nitrogen atom, while the order of the cleaved bond is $P_{1,6} = -0.1417$. Similarly in the case of simultaneous replacement of the carbon atoms in the 3 and 5 positions by nitrogen atoms these bond orders are $P_{6,7} = 0.4991$ and $P_{1,6} = -0.1827$. 1,2,4,6-Tetramethyl-sym-triazinium iodide should also undergo rearrangement readily, since the orders of the 6–7 and 1–6 bonds in its anhydro base are, respectively, +0.6670 and −0.4620. It can similarly be shown (with the aid of the tables in [2]) that 2-methylquinazoline salts should undergo recyclization to quinolines with corresponding bond orders $P_{1,6} = -0.1359$ and $P_{6,7} = +0.423$.

2. Indolizine can be regarded as a fixed anhydro base, since the 1-R-2-methylene-1,2-dihydropyridine structural fragment can be isolated in its molecule. The quantum-chemical description of its recyclization should therefore begin with the determination of the site of attack by the nucleophile. It follows from the molecular diagram of indilizine (Table 2)* that considerable positive π-electron charge is localized on the nitrogen atom, whereas the negative charges are localized on all of the carbon atoms except C_8. This explains the high stability of indolizine with respect to nucleophilic agents, while the calculated values of the residual π-electron charges and atom–atom self-polarizabilities indicate the electrophilic attack on the indolizine ring should occur primarily in the 3 and 1 (and subsequently 2) positions of the five-membered ring. These conclusions are confirmed by the experimental data (see [17]).

Thus, unsubstituted indolizine should not undergo recyclization under alkaline conditions, although the long-range 1–5 bond order is rather high ($P_{1,5} = +0.1571$), and the lowest bond order in the molecule ($P_{4,5} = 0.3890$) is relatively small; this constitutes evidence for the possibility of thermal rearrangement of indolizine to indole. The reverse rearrangement of indole to indolizine is unlikely, since the 1–4 bond order in in-



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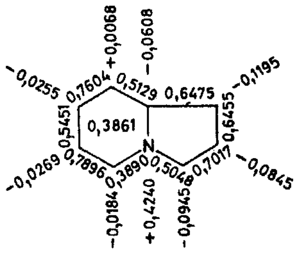
*Let us note that the distribution of the π-electron density in the indolizine molecule depends only slightly on the parametrization used (for example, see [6]) and coincides in its general features with the distribution previously obtained by the Hückel [18] and CNDO/2 [19] methods (let us note that the long-range bond orders were not examined in these studies).

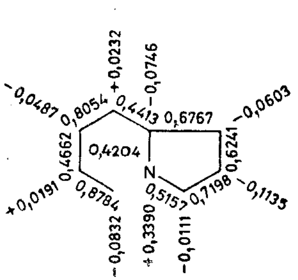
TABLE 2. Molecular Diagrams of the Self- and Mutual Polarizabilities of Indolizine (1) and Its Open Form (2) (in Units of $-0.2465\ \mathrm{eV}^{-1}$)

$P_{1,5} = 0.1571$ 1



	1	2	3	5	6	7	8
1	−0,501						
2	+0.185	−0,471					
3	−0,003	+0,231	−0,520				
5	+0,036	+0,001	+0,068	−0,579			
6	+0,003	+0,018	+0,001	+0,311	−0,478		
7	+0,060	+0,001	+0,058	−0,031	+0,125	−0,503	
8	−0,000	+0,021	−0,015	+0,151	−0,015	+0,284	−0,520
9	+0,188	−0,001	+0,103	−0,003	+0,035	−0,007	+0,097
4	+0,034	+0,015	+0,078	+0,047	+0,002	+0,015	−0,003
1—2	+0,057	+0,035	−0,070	−0,033	+0,018	−0,024	+0,011
2—3	−0,064	+0,025	+0,034	+0,040	−0,019	+0,023	−0,007
3—4	+0,037	−0,074	+0,090	−0,079	+0,020	−0,040	+0,013
4—5	−0,043	+0,025	−0,085	+0,076	−0,061	+0,019	−0,029
5—6	+0,021	−0,021	+0,033	+0,007	+0,010	−0,013	+0,002
6—7	−0,028	+0,016	−0,034	−0,025	+0,012	+0,016	+0,000
7—8	+0,009	−0,014	+0,009	+0,024	−0,005	+0,016	−0,009
8—9	−0,112	+0,019	−0,009	−0,032	+0,009	−0,031	+0,010
9—1	+0,038	−0,041	+0,049	+0,025	−0,024	+0,017	−0,021
4—9	−0,083	+0,011	−0,100	+0,002	+0,021	+0,008	+0,019
1—5	+0,003	−0,034	+0,025	−0,045	+0,051	−0,004	+0,026

$P_{1,5} = 0.1824$
$P_{4,5} = 0.0863$ 2



	1	2	3	5	6	7	8
1	−0,508						
2	+0,168	−0,464					
3	−0,022	+0,244	−0,529				
5	+0,054	−0,002	+0,088	−0,676			
6	−0,000	+0,004	−0,011	+0,386	−0,454		
7	+0,070	+0,004	+0,069	−0,056	+0,085	−0,517	
8	+0,000	+0,006	−0,020	+0,176	−0,012	+0,330	−0,530
9	−0,022	+0,244	+0,120	−0,014	+0,014	−0,010	+0,066
4	+0,028	+0,033	+0,060	+0,044	−0,011	+0,024	−0,017
1—2	+0,026	+0,052	−0,020	−0,036	+0,003	−0,028	+0,002
2—3	−0,028	+0,034	−0,030	+0,039	−0,004	+0,026	−0,002
3—4	+0,022	−0,097	+0,089	−0,060	+0,011	−0,041	+0,020
4—5	−0,047	+0,019	−0,053	+0,013	−0,001	+0,014	+0,007
5—6	−0,008	−0,003	−0,016	+0,068	−0,003	−0,013	−0,013
6—7	+0,011	+0,004	+0,020	−0,066	−0,013	+0,011	+0,019
7—8	−0,019	−0,006	−0,030	+0,050	+0,007	+0,037	−0,019
8—9	+0,034	+0,011	+0,047	−0,123	−0,001	−0,051	−0,005
9—1	+0,008	−0,051	+0,007	+0,039	−0,002	+0,027	+0,006
9—4	−0,088	+0,026	−0,115	+0,003	+0,002	+0,011	−0,002
1—5	+0,019	−0,025	+0,015	+0,006	−0,020	+0,018	−0,002

dole is low (0.053), while the 1–8 and 4–9 bond orders are rather high (0.437 and 0.561). Activation of indolizine by the introduction of substituents is necessary for its recyclization under alkaline conditions.

Substituents in the indolizine molecule can change the distribution of the π-electron density significantly. Thus, it is apparent from the atom–atom self- and mutual polarizabilities (Table 2) that the C_5 position undergoes the greatest change in charge. The presence of electron-acceptor substituents in the 6 and 8 positions of indolizine (for example, a nitro group, $\Delta\alpha$ = 8.07 eV) changes the sign of the π-electron charge in the 5 position; thus, for example, it becomes equal to +0.603 for 6-nitroindolizine and +0.283 for 8-nitroindolizine. This explains the ease of the reaction of 6- and 8-nitroindolizines with nucleophiles; 6-nitroindolizine should undergo nucleophilic substitution more readily than the 8-nitro isomer, and this is in agreement with the experimental data [20]. The introduction of electron-acceptor groups in the 1 and 3 positions has a similar effect. Electron-donor substituents in all of these positions increase the negative charge on the C_5 atom and make nucleophilic attack at this site unlikely. The introduction of substituents in the 2 position has virtually no effect on the charge on the carbon atom in the 5 position, while the probability of attack on the C_5 atom by a nucleophile increases when electron-donor functional groups are introduced in the 7 position. However, the presence of electron-acceptor groups in the 7 position decreases the probability of nucleophilic substitution in the 5 position even as compared with unsubstituted indolizine. The introduction of several functional groups should be considered additively.

An analysis of the atom–bond mutual polarizabilities shows that although electron-acceptor substituents (for example, NO_2) in the 1, 3, 6, and 8 positions intensify the electrophilicity of the 5 position, they also strengthen the 4–5 bond somewhat, hindering, as it were, its cleavage. Attack by a rather strong nucleophile such as OH^- is therefore necessary for the formation of an open form with cleavage of the 4–5 bond, and attack by a weaker nucleophilic agent such as piperidine does not lead to ring opening but rather to replacement of the hydrogen atom [20]. Let us note that the introduction of a nitro group in the 2 position weakens the 4–5 bond and thereby promotes the formation of the open form without affecting the charge on the C_5 atom.

It follows from molecular diagram 2 (Table 2) that the 1–5 bond order, which serves as a reactivity index in reactions involving cyclization of the open form, prevails over the 4–5 bond order, and this determines the direction of cyclization. It is apparent from Table 2 that the introduction of electron-acceptor functional groups in the 2, 6, and 8 positions (in contrast to the 1 and 3 positions) strengthens the 1–5 bond and weakens the 4–5 bond. Electron-donor substituents have the opposite effect.

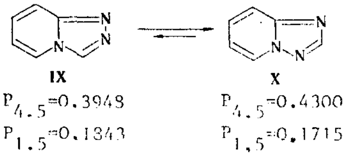
Thus, all of the material set forth above makes it possible to assert that recyclization to the corresponding indoles with cleavage of the 4–5 bond and the formation of a 1–5 bond is possible for 6- and 8-nitroindolizines. The recyclization should proceed more readily and the yield of products for 6-nitroindolizine should be higher than for 8-nitroindolizine. All of this is in complete agreement with the experimental data [21]. Let us note that since the long-range positive bond orders in indolizine are somewhat smaller than in the anhydro bases of 2-picoline and 1- and 3-alkylisoquinolines, while the order of the cleaved bond is greater (see [1, 2]), the yields of the products of recyclization of indolizines should be lower than the yields of 2-alkylpyridinium and 1-alkylisoquinolium salts; this is also in agreement with the experimental data (compare [21-23]). This rearrangement should also be realized for 3-nitroindolizine. The presence of electron-acceptor groups in the 3,6, and 8 positions and of an electron-donor group in the 7 position should facilitate the recyclization. A nitro group in the 2 position promotes rearrangement only when electron-acceptor groups are present in one (or several) of the 3, 6, or 8 positions.

Thus, the activating effect of substituents on the recyclization reactions of the molecules is threefold in nature. First, a substituent activates attack on the molecule by the nucleophile by changing the electron-density distribution; second, it promotes ring opening by weakening the bond undergoing cleavage (in this case its π-electron order is decreased); third, a substituent may increase the rate of cyclization of the open form (it may increase the corresponding long-range bond order). Allowance for all of these factors is necessary in the quantum-chemical description of the recyclization reactions. Let us note that, depending on the structure of the molecule and the character of the substituting group, the latter may have a different effect on these three processes. For example, a substituent may promote nucleophilic addition and hinder ring opening or, in the open form, may hinder cyclization. The specific effect of a functional group depends on its numerical $\Delta\alpha$ values and the magnitudes of the charges, bond orders, and mutual polarizabilities of the molecule.

3. It follows from an examination of the UV and NMR spectra of the azaindolizines that replacement of the CH group by a nitrogen atom is equivalent to the introduction of a weak electron-acceptor substituent in

this position. The effect of the ring nitrogen atom on the recyclization of azaindolizines is therefore similar to the effect of electron-acceptor functional groups. Thus, for example, the introduction of a nitrogen atom in place of the carbon atom in the 7 position leads, in conformity with the experimental data [24], to nucleophilic attack in the 8 position (in which case $q_8 = +0.09$, and $q_5 = -0.028$). Nucleophilic attack in 6-azaindolizine (VI) should take place at the C_5 atom, whereas in 8-azaindolizine (VIII) it should take place at C_7. In 5-azaindolizine (V) attack by a nucleophilic agent should be directed to the 6 position or to C_8 (the charges on these atoms are +0.073 and +0.055, respectively. Unsubstituted 1- and 2-azaindolizines should be resistant to recyclizations, since $q_5 < 0$. All of the monoazaindolizines have little inclination to undergo rearrangements because of the smallness of $\Delta\alpha_N$, and activation of these compounds is necessary for their recyclization.

Activation can be accomplished not only by the introduction of functional groups but also by replacement of the CH groups by nitrogen atoms. The presence of two nitrogen atoms in addition to a nodal nitrogen atom leads to recyclization, as, for example, in the case of the recyclization of sym-triazolo[4,5-a]pyridine to sym-triazolo[1,5-a]pyridine

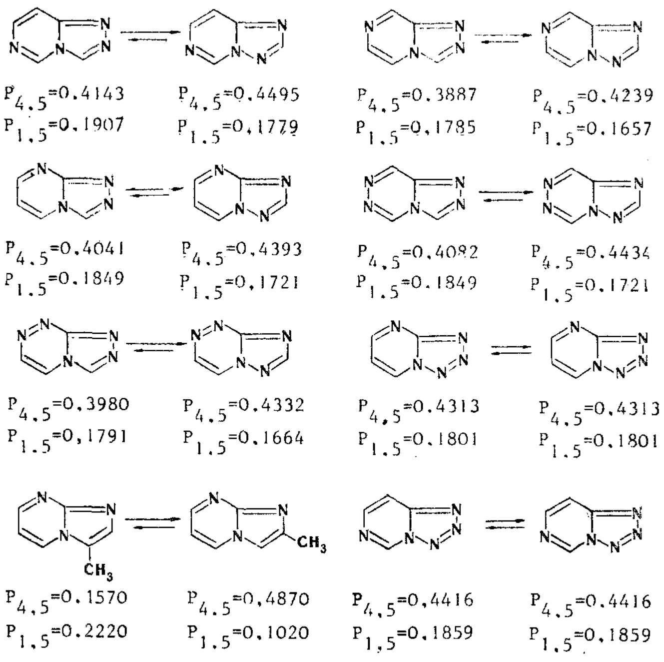

IX

X

although still under rather severe conditions (10% NaOH, refluxing for 24 h) [25]. The orders of the cleaved 4–5 bonds of the starting molecule and the long-range 1–5 bond orders in its open form are presented in the scheme next to the formulas of the compounds. Similar values are also presented for the reaction product. The closeness of $P_{4,5}$ and $P_{1,5}$, respectively, in structures IX and X constitutes evidence for the reversibility of this reaction, although their numerical values indicate a shift of this equilibrium to favor the X form. It follows from the calculation that activation of IX by the introduction of an NO_2 group in the 8 position facilitates the recyclization considerably (10% NaOH, refluxing for 30 min) [26]. Activation of 3,8-diazaindolizine leads to attack by the nucleophile on the C_5 atom and to its subsequent recyclization [27].

Let us note that the recyclization of azaindolizines that contain a nitrogen atom in the 1 position occurs with retention of the nodal nitrogen atom, in connection with which it is reversible and bears the name of the Dimroth rearrangement [28].

The presence of three or more nitrogen atoms facilitates the recyclization to an ever greater extent. All of these possible rearrangements can be readily described within the framework of the evolved approach. The results of the calculation are reflected in the following scheme:



The equilibria of these rearrangements are shifted to the right, in agreement with the available experimental data [28-34].

Thus, the method developed in this research makes it possible to describe a rather large amount of experimental material on the recyclization reactions of azaindolizines (as well as azapicolines and azaalkylisoquinolines) on the basis of quantum-chemical calculation of a small number of starting molecules and to uncover the principal structural regularities in the recyclization reactions of these compounds.

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