QUANTUM-CHEMICAL INTERPRETATION OF RECYCLIZATION REACTIONS.

5.* PYRROLYLPYRIDINES

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The ability of pyrrolylpyridines to undergo rearrangements is examined on the basis of a developed scheme for the quantum-chemical description of recyclization reactions. It is shown that the cations of the α and β isomers of pyridine can undergo recyclization to derivatives of 2-azaazulenes and indoles, respectively, while the γ isomers are incapable of undergoing rearrangements. The calculated data are compared with the available experimental data.

In previous papers of this series, within the framework of the bonded variant of perturbation theory and the π-electron approximation of the MO LCAO self-consistent field (SCF) method, we developed a method for the quantum-chemical description of cyclization and recyclization reactions, on the basis of which we examined the rearrangements of 1,2-dialkylpyridinium [3] and 1,2-dialkylisoquinolinium [4] ions, indolizine and azaindolizines [1], and a number of antiaromatic azines [5] and the photochemical isomerization of furan [2]. A distinctive feature of these reactions is the fact that the atoms that participate in the formation of the new bonds are found either in the transformed heterocycle [2, 5] or are bonded directly to it (see [1, 3, 4]). In the present paper the developed approach is extended in the case of pyrrolylpyridines to recyclization of the pyridine ring with the participation of the nucleophilic center located one C—C bond away from it.

The results of the quantum-chemical calculation of the electron densities (with the parametrization in [1-5]) of all of the possible isomers of pyrrolylpyridines fused via the carbon atoms are presented in Table 1. Since we assume that the reaction proceeds under the influence of nucleophiles, in Table 1 we present only the π-electron charges of the most electrophilic centers that determine, within the framework of a static model (for example, see [6]), the position of nucleophilic attack. Since the long-range bond orders serve as reactivity indexes in recyclization reaction [1-5], only the orders of the newly formed and cleaved bonds are presented in Table 1. It is apparent from Table 1 that the bond orders and the charges are more equalized in the 1'H tautomers (A) of all of the investigated systems as compared with the 1H tautomers (B), in which a quinoid structure is observed, and there are higher π-electron positive charges on the C_2 and C_6 atoms of the pyridine ring (except for V and VI) than in the A structures.

The existence of large positive long-range bond orders depends substantially on the mode of fusion of the pyridine and pyrrole rings. It is apparent from Table 1 that they are high only in the β isomers of pyridine and do not depend on the position of the nitrogen atom in the pyrrole ring. The charges on the carbon atoms of the pyrrole ring are negative in all cases both in the A forms and in the B forms, i.e., the pyrrole ring should not undergo nucleophilic attack.

These data indicate that only the 1H tautomers of I and II are capable of recyclization, the result of which should be indole derivatives. However, let us emphasize that the tautomer A⇄B equilibrium for all of the examined compounds should, according to the results of the calculation, be shifted markedly to favor A. Thus the transition from B to A leads to a gain in π-electron energy of ∿81 kJ/mole for the α isomers of pyridine, as compared

*See [1, 2] for Communications 3 and 4.

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TABLE 1. Residual π-Electron Charges of the Electrophilic Centers and Orders of the Cleaved and Newly Formed Bonds in Pyrrolylpyridines

Molecule	i–k	1'H tautomer	1H tautomer	Cation	
				starting structure	open form ($\beta_{1,6}=0$)
3-(3'-Pyrrolyl)pyridine	2—2	0,0608	0,1377	0,1478	0,3205
	4—4	0,0260	0,1147	0,1598	0,2212
	6—6	0,0656	0,0546	0,1664	0,1417
	1—2	0,6654	0,5307	0,5137	0,5273
	1—6	0,6561	0,4983	0,5156	0,1892
	2'—6	0,1197	0,1145	0,1115	0,1226
	4'—6	0,0826	0,0895	0,0712	0,0762
3-(2'-Pyrrolyl)pyridine	2—2	0,0522	0,1518	0,1301	0,3114
	4—4	0,0322	0,1081	0,1567	0,2146
	6—6	0,0734	0,0463	0,1684	0,1412
	1—2	0,6659	0,5345	0,5124	0,5274
	1—6	0,6553	0,4937	0,5174	0,1914
	3'—6	0,1202	0,1209	0,1144	0,1295
2-(2'-Pyrrolyl)pyridine	2—2	0,0605	0,1587	0,1354	0,2231
	4—4	0,0400	0,0794	0,1627	0,1937
	6—6	0,0803	0,1061	0,1589	0,1047
	1—2	0,6124	0,4316	0,4462	0,4342
	1—6	0,6641	0,4573	0,4722	0,1225
	3'—6	0,0224	0,0684	0,1004	0,1200
2-(3'-Pyrrolyl)pyridine	2—2	0,0724	0,1652	0,1661	0,2703
	4—4	0,0317	0,0849	0,1631	0,2027
	6—6	0,0737	0,1051	0,1624	0,1157
	1—2	0,6198	0,4329	0,4676	0,4641
	1—6	0,6645	0,4547	0,4844	0,1375
	2'—6	0,0208	0,0744	0,1015	0,1256
	4'—6	0,0156	0,0510	0,0605	0,0630
4-(3'-Pyrrolyl)pyridine	2—2	0,0727	0,0774	0,1649	0,2786
	4—4	0,0357	0,1345	0,1277	0,2089
	6—6	0,0761	0,0788	0,1706	0,1406
	1—2	0,6551	0,4270	0,4812	0,4894
	1—6	0,6543	0,4255	0,4816	0,1386
	2'—6	−0,1063	−0,0235	−0,1041	−0,1390
	4'—6	−0,0637	−0,0140	−0,0539	−0,0626
4-(2'-Pyrrolyl)pyridine	2—2	0,0762	0,0774	0,1649	0,2644
	4—4	0,0218	0,1345	0,1277	0,1671
	6—6	0,0847	0,0786	0,1706	0,1367
	1—2	0,6543	0,4255	0,4816	0,4820
	1—6	0,6549	0,4270	0,4812	0,1250
	3'—6	−0,0265	−0,0998	−0,1051	−0,1357

with 145 kJ/mole for the β isomers and 106 kJ/mole for the γ isomers, and is virtually independent of the position of the nitrogen atom in the pyrrole ring.

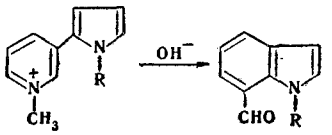
Since the difference in the aromaticities of the tautomeric forms is intimately related to the tautomeric equilibrium constants [7, 5], the shift of the tautomeric equilibrium to favor the A forms should also be manifested in the calculation of the diamagnetic molecular properties, which serve as one of the quantitative characteristics of aromaticity [5, 8]. In fact, for example, on passing from IA to IB the relative π-electron diamagnetic susceptibility changes from 1.38 to 1.07, and the induced π-electron ring current in the pyridine ring changes from 0.921 to 0.673, as compared with a change from 0.696 to 0.598 in the pyrrole ring. A comparison of the calculated and experimental UV spectra also provides evidence for predominance of the A form. Thus, for example, for the IIA tautomer the calculation gives λ_{max} = 297 nm, as compared with 656 nm for the IIB tautomer and the experimental value of 288 nm [9].

Thus in order to bring about the recyclization of pyrrolylpyridines one must synthesize fixed structures IB and IIB or activate the 1'H tautomers of all of the examined molecules by the introduction of substituents or quaternization of the pyridine nitrogen atom.

A calculation of the atom–atom and atom–bond mutual polarizabilities showed that only the introduction of electron-acceptor substituents in the 3 and 5 positions of the pyridine

ring of the A forms of the investigated compounds increases the positive charges on the C_2 and C_6 atoms appreciably, thereby promoting attack by nucleophiles, while the orders of the 1—2 and 1—6 bonds are virtually insensitive to the effect of substituents.

It is apparent from Table 1 that quaternization of the A forms of I-VI leads to an increase in the positive π-electron residual charges on the carbon atoms and weakening of the orders of the C—N bonds in the pyridine ring, which favors opening of the pyridine ring. After ring opening (see Table 1), the long-range bond orders increase as compared with the unopened forms. The V and VI systems constitute exceptions in this case, inasmuch as the negativity of the long-range bond orders in them (in both the neutral and cationic forms, including the open form) constituted evidence, within the framework of the developed approach, for the impossibility of their recyclization. β-Substituted pyridines should undergo recyclization to indole derivatives:



This recyclization when R = CH_3 has been observed experimentally [10]. Let us emphasize that, in contrast to the recyclizations of 1,2-dialkylpyridinium and 1,2-dialkylisoquinolinium ions and indolizines and azaindolizines [1, 3, 4], in pyrrolylpyridines the order of the bond undergoing cleavage in the open structure is somewhat greater than the order of the newly formed π bond. The low yields of the desired product and the more severe conditions for its production in the recyclization of cations I and II as compared with the rearrangements described in [1, 3, 4] are consequences of this. Thus, for example, cation II undergoes recyclization under alkaline conditions at 150°C after 60-70 h with a product yield less than 20%, while, let us say, 1,2,6-trimethyl-3-nitropyridinium iodides undergo rearrangement at room temperature after 24 h in aqueous alcoholic alkali. It is apparent from Table 1 that cation I has positive orders of both the 2'—6 and the 4'—6 bonds, i.e., its recyclization to both an indole and an isoindole is possible. However, since $P_{2'-6} > P_{4'-6}$, the yield of the isoindole will be substantially lower than that of the indole. Let us note that a calculation of the atom—bond mutual polarizabilities shows that the introduction of electron-donor substituents in the 1', 4', 5, and 6 positions of cations I and II leads to an increase in the long-range bond orders in the open form, i.e., it promotes recyclization of these compounds. The introduction of electron-donor substituents in the 1 position, although it does somewhat decrease the positive long-range bond order, loosens the 1—6 bond, thereby promoting opening of the cation at this bond.

Insofar as the α derivatives of pyridine are concerned, the development of positive orders of the 3'—6 bond for cation III and of the 2'—6 and 4'—6 bonds for cation IV indicates that the recyclization of these cations to 2-azaazulene derivatives is possible.

Condensation of the pyrrole ring at the 4'—5' bond in II and of the benzene ring does not change the qualitative characteristics of the electron density distribution. However, the long-range bond orders in all forms of 2-(3-indolyl)pyridine (VII) are increased as compared with the II structures (+0.1365 for VIIA, +0.1509 for VIIB, and +0.1341 for the cation), whereas in the open form of the cation (+0.2551) they become greater than the order of the cleaved bond (+0.1525). Consequently, cation VII will undergo rearrangement with formation of the product in higher yield and under milder conditions than cation II; this is in complete agreement with the experimental data (compare [10] and [11]). The introduction of electron-donor groups in the 1, 4, and 5 positions of the pyridine ring of cation VII increases the long-range bond order and promotes its recyclization to a carbazole derivative.

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BROMINATION OF δ-KETO AMIDES

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It is demonstrated that 3,5-dibromo-3,4-dihydropyridones are formed in the bromination of derivatives of δ-keto amides. The course of the bromination was investigated in the case of N-substituted and N-unsubstituted δ-keto amides. Dibromo-3,4-dihydropyridones were converted to the corresponding monobromopyridones. The stabilities of the compounds obtained were studied by subjecting them to thermal analysis. The structures of the compounds obtained were confirmed by their PMR, IR, and UV spectra.

We have previously shown that δ-keto amides I undergo intramolecular cyclization to dihydro-2-pyridone derivatives under the influence of acids or bases [1]. N-Alkyl-substituted δ-keto amides II do not form a dihydropyridone ring (III) under similar conditions because of steric hindrance. This paper is devoted to a study of the bromination of N-alkyl- and N-unsubstituted δ-keto amides in order to synthesize bromo derivatives of dihydro-2-pyridones.

The bromination of N-alkyl-δ-keto amides II with a twofold excess of bromine in chloroform or in acetic acid at room temperature leads to 1-alkyl-3,5-dibromo-3-(N-alkylcarbamoyl)-4,6-diphenyl-3,4-dihydro-2-pyridones (VIII). The UV and IR spectra of pyridones VIII (Table 1) are similar to those obtained for nitrogen-unsubstituted 3,4-dihydro-2-pyridones [1, 2], and this indicates that they have a dihydro structure. The PMR spectra of VIII (Table 2) contain, in addition to signals of protons of two phenyl and alkyl groups and an exocyclic amide group, singlets at 4.63-4.66 ppm, which correspond to the 4-H proton, and this confirms the presence of bromine in the 3 and 5 positions of the pyridone ring.

γ-Bromo-δ-keto amides IV are formed initially in the reaction of δ-keto amides II with 2 moles of bromine. This is confirmed by the bromination of amides II with an equivalent amount of bromine, as a result of which we obtained γ-butyrolactones V [3], which are capable of being formed only from γ-bromo-substituted δ-keto amide IV. The subsequent bromination of IV takes place in the α position to give α,γ-dibromo-substituted δ-keto amides VII, which, in contrast to IV, undergo cyclization to pyridones VIII. The bromine atom in the α position in amide VII promotes both spatial drawing together of the N-alkylamido and δ-carbonyl groups and hydrolysis of the N-alkylamido group. The spatial drawing together, which is responsible for the production of bromo derivatives of dihydropyridones VIII rather than lactones VI, which can be obtained only by bromination of lactone V, is the decisive factor in this case.

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