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REACTIVITIES OF 5-, 6-, AND 7-(ENAMINO)INDOLES IN THE SYNTHESIS OF PYRROLOQUINOLINES

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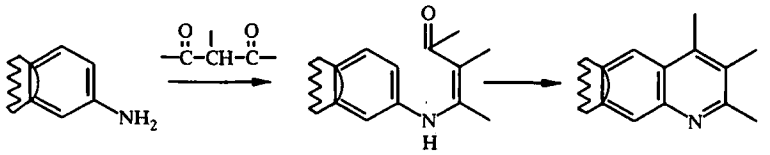
The concept of regioorientation is proposed for the annelation of the pyridine ring with the participation of 5-, 6-, and 7-aminoindoles. The conclusions based on the experimental data are supported by quantum-chemical calculations.

The production of quinoline and its derivatives is based on various types of pyridine ring closure with the participation of arylamines, hetarylamines, and β-dicarbonyl compounds [1]. Such processes include a condensation stage in which an enamine E is formed; this subsequently undergoes intramolecular cyclization under conditions of kinetic or thermodynamic control to form a quinoline system:



We have investigated the possibility of using 5-, 6-, and 7-aminoindoles in this sort of reaction in order to obtain pyrroloquinolines. Results from this research have been reported in a series of papers [2-22]. After analyzing the entire body of data, we have formulated a general concept of annelation of the pyridine ring to the benzene ring of the two-ring indole system, by the use of benzaminoindoles.

Enamines of aminoindoles undergo cyclocondensation more readily than do the enamines of anilines and naphthylamines. This is manifested most clearly in the acid cyclization of indolylenaminoketones, indolylenaminoaldehydes, and indolylamides of acetoacetic acid. These compounds are cyclized quite smoothly when they are refluxed in trifluoroacetic acid (and in some cases even at room temperature) [2-4, 9]. We should emphasize that the formation of a quinoline system when using analogous derivatives of aromatic amines requires heating in concentrated sulfuric acid [1]. This difference is apparently related to the influence of the pyrrole fragment, which not only increases the overall nucleophilicity of the benzene ring in the indoles, but also tends to stabilize the intermediate cation. Substituents in the pyrrole part of the molecule also influence the overall character of the process. Thus, the enamine of 2,3-dimethyl-5-aminoindole is cyclized in trifluoroacetic acid, even at room temperature; in contrast, cyclization of the analogous enamine of 2-methyl-5-aminoindole requires heating; this difference can apparently be attributed to a difference in the basicity of the compounds in the stage of the processes preceding the cyclization [4].

Substituents in the benzene ring of the enamine are not consistent in their influence on cyclization. A methyl group, the same as in the case of anilines, has practically no influence on the course of cyclization; in contrast, the presence of a methoxy group in various positions plays an important role in the ring formation process. Thus, enamines obtained from 7-methoxy-6-aminoindole are converted to pyrroloquinolines just as readily as are the corresponding unsubstituted or methyl-substituted analogs [17]. However, the derivatives of 6-methoxy-5-aminoindoles and 5-methoxy-6-aminoindoles, like the ani-

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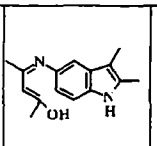
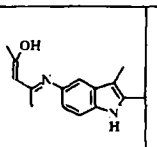
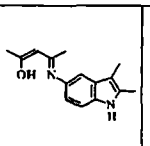
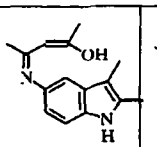
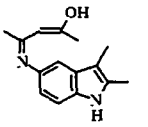
TABLE 1. Data from Quantum-Chemical Calculations of Isomers Id and Ig-k by Methods PM3, MNDO (in parentheses), and AM1 (in brackets)

Index	Id	Ik	Ig	Ih	Ii	Ij
Heat of formation, kcal/mole	-11,7 (3,4) [12,4]	-11,8 (3,5) [12,7]	-7,8 (5,7) [22,8]	-7,4 (5,0) [21,2]	-8,6 (5,6) [22,6]	-7,1 (4,8) [21,4
Dihedral angle $=CNC_{(5)}C_{(4)}$	110,4 (114,8) [129,1]	73,2 (64,8) [53,7]	136,5 (133,8) [151,8]	141,7 (144,8) [171,2]	54,8 (44,6) [3,6]	39,5 (67,9) [27,0]
Length of $C_{(4)}C_{(5)}$ bond, nm	0,1391 (0,1403) [0,1405]	0,1390 (0,1404) [0,1402]	0,1392 (0,1409) [0,1407]	0,1392 (0,1408) [0,1407]	0,1391 (0,1403) [0,1402]	0,1392 (0,1408) [0,1402]
Length of $C_{(5)}C_{(6)}$ bond, nm	0,1414 (0,1435) [0,1424]	0,1417 (0,1434) [0,1427]	0,1417 (0,1435) [0,1424]	0,1416 (0,1431) [0,1422]	0,1417 (0,1435) [0,1428]	0,1417 (0,1433) [0,1427]
Coefficient of $C_{(4)}$ atom in HOMO	0,112 (0,145) [0,111]	0,112 (0,140) [0,111]	0,155 (0,190) [0,147]	0,159 (0,176) [0,164]	0,157 (0,152) [0,144]	0,156 (0,201) [0,170]
Coefficient of $C_{(6)}$ atom in HOMO	0,002 (0,100) [0,012]	0,004 (0,104) [0,013]	0,001 (0,002) [0,021]	0,000 (0,065) [0,007]	0,001 (0,098) [0,022]	0,000 (0,009) [0,001]
Charge on $C_{(4)}$ atom	-0,067 (+0,036) [-0,109]	-0,050 (+0,001) [-0,105]	-0,096 (-0,042) [-0,134]	-0,100 (+0,021) [-0,135]	-0,086 (-0,017) [-0,143]	-0,078 (+0,005) [-0,124]
Charge on $C_{(6)}$ atom	-0,089 (-0,041) [-0,130]	-0,105 (-0,005) [-0,136]	-0,112 (-0,051) [-0,148]	-0,109 (-0,042) [-0,153]	-0,123 (-0,005) [-0,144]	-0,125 (-0,066) [-0,154]

TABLE 2. Certain Properties of the Most Important Conformers of the Enol Form of the Molecule I, Calculated by the PM3 Quantum-Chemical Method (energies in kcal/mole; k is the coefficient of the atom in the HOMO; q is its charge)

Property					
ΔHf	-3,3	-8,5	-8,5	-3,2	-2,3
θ, $C{=}NC_{(5)}C_{(4)}$	111,8	139,9	40,3	71,7	71,4
$kC_{(4)}$	0,156	0,142	0,137	0,157	0,158
$kC_{(6)}$	0,008	0,001	0,000	0,008	0,006
$qC_{(4)}$	-0,062	-0,047	-0,089	-0,080	-0,083
$qC_{(6)}$	-0,109	-0,120	-0,082	-0,093	-0,093

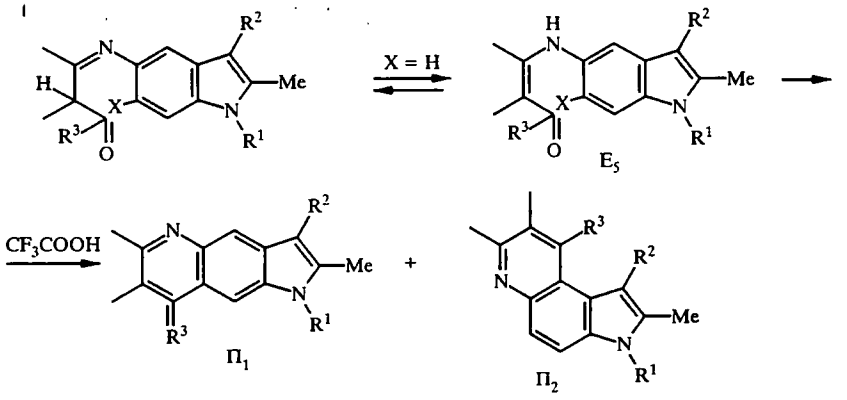
lines, are far more difficult to cyclize; i.e., a methoxy group in the meta-position relative to the site of electrophilic attack has a deactivating effect [19, 20]. In spite of certain differences in the reactivities of indole derivatives that reflect differences in the distribution of electron density in the benzene ring, the ring formation processes in derivatives of aminoindoles, the same as in the series of anilines and naphthylamines, all have a common character of intramolecular electrophilic attack.

If there are two free ortho-positions in the enaminoindole, the process of primary attack should be the determining factor in the direction of cyclization, since the transition states of both the angular and linear isomers are similar. In fact, the orientation of ring formation corresponds to the known relationships of electrophilic substitution in the benzene ring of indoles. It is known that indoles with electron-donor substituents (for example, 5-hydroxyindoles or 5-methoxyindoles) are nitrated in position 6, with initial protonation of the pyrrole ring [23]. Aminomethylation of these same models in weakly acidic or neutral media [24] proceeds in position 4. In our case, for the enamines of the E_5 type, synthesized from 5-aminoindoles, the pyrrole part is not protonated; and the electrophilic attack by the carbon atom of the carbonyl group is directed primarily toward posi-

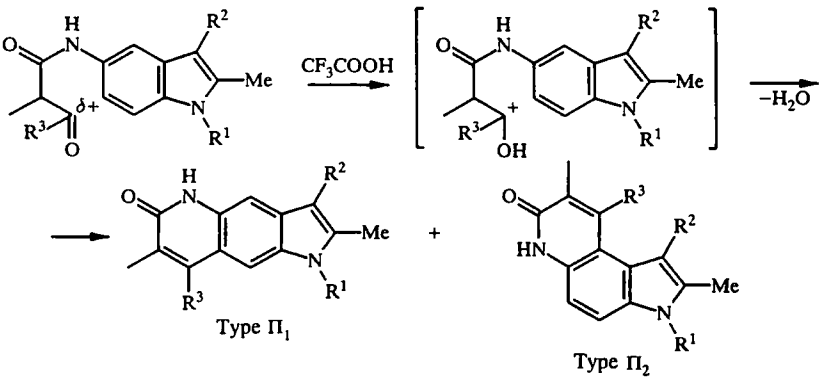
TABLE 3. Heats of Formation of Isomeric Products from Heterocyclization of Type E_5 Enaminoketone and Its Homologs, Calculated by Methods PM3, MNDO (in parentheses) and AM1 (in brackets)

Pyrroloquinolines	R^1 = H, R^2 = R^3 = Me	R^1 = R^2 = R^3 = Me	R^1 = R^2 = R^3 = H	R^1 = R^2 = H, R^3 = Me
Linear, Type Π_1	31,2 (35,5) [58,6]	30,0 (39,5) [63,6]	48,8 (49,8) [72,8]	40,6 (44,5) [72,8]
Angular, Type Π_2	35,0 (42,5) [63,0]	34,0 (46,5) [68,5]	44,9 (46,2) [69,5]	37,4 (43,2) [63,9]

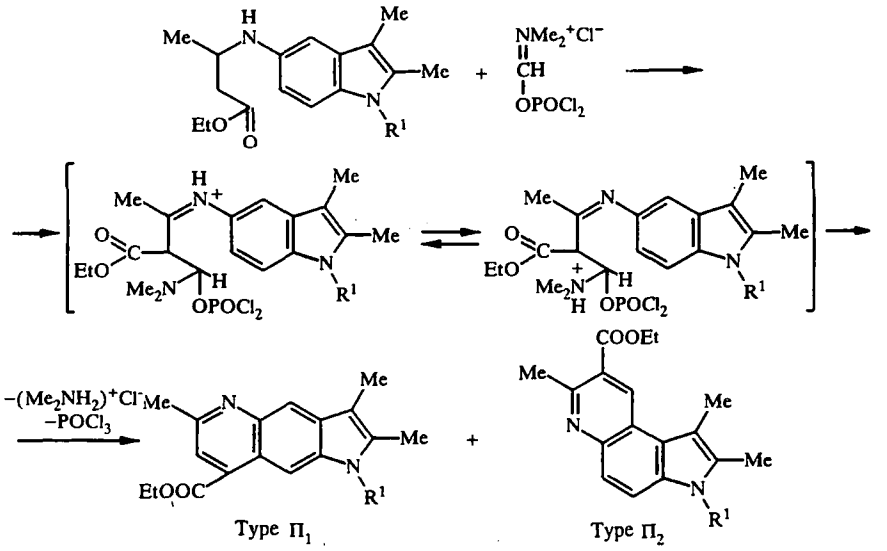
tion 4, with the formation of angular isomers of the Π_2 type (R^2 = H, R^3 = Me, Ph; or R^2 = Me, R^3 = H). Supporting evidence for this statement may be found in the PMR spectra of the original enamines taken in trifluoroacetic acid: In the case of compounds with a free β-position, the spectra do not exhibit any signals from protons of the β-methylene group. However, the peri-effect of substituents on the $C_{(3)}$ carbon atom in the pyrrole ring and at the carbonyl carbon atom makes such cyclization considerably more difficult, favoring the preferential or exclusive formation of the linear isomer of the Π_1 type as a result of ring closure through position 6 (R^1 = H, Me, R^2 = Me, R^3 = Me, Ph) [4, 12]. If a methyl group is present in the enaminoketone at position 7 of the indole, a blocking ortho-effect of this substituent is manifested, leading to the formation of a mixture of the angular and linear pyrroloquinolines, with the latter predominating [22]. Thus, the steric influence of peri-substituents in ring closure is greater than the ortho-interaction.



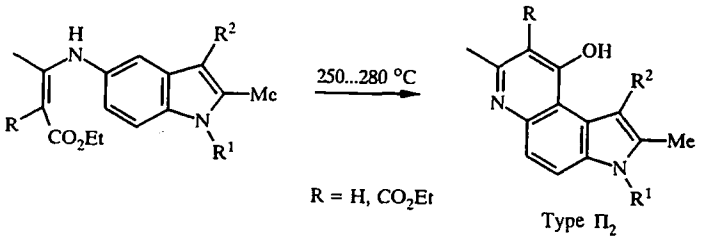
An enamine with a carbonyl group, activated by acid, undergoes cyclodegradation, as does its completely protonated form. This is evidenced by the PMR spectra of the enaminoketones in DMSO with the addition of CF_3COOH, where the enamine form is not observed (no signal of a vinyl proton). Apparently, analogous processes under the influence of an acid are also characteristic for the indolylamides of acetoacetic acid.



Also incorporated into the proposed scheme is the formation of pyrroloquinolines from aminocrotonates under the conditions of the Vilsmeier reaction. The reaction apparently begins with attack by the Vilsmeier complex on the most highly nucleophilic carbon atom of the aminocrotonate. The intermediate cation that is formed is cyclized electrophilically, with the attack of the electrophile directed primarily at position 4 of the indole, forming an angular pyrroloquinoline of the Π_2 type. Substituents on the attacking carbon atom and in the β-position of the pyrrole ring (H, Me) do not offer any steric hindrance to ring formation [10, 21, 22].



In the conversion of enamines to pyrroloquinolines under conditions of thermodynamic cyclization, we should expect that the steric hindrance to ring formation will be overcome. In fact, the angular pyrroloquinoline of the Π_2 type with phenyl and methyl groups in the peri-positions (R^2 = Me, R^3 = Ph) is formed when the corresponding enaminoketone is refluxed in Dowtherm (the linear isomer of the Π_1 type is also formed) [4]. The cyclization of indolylaminocrotonates and malonates (the former upon refluxing in biphenyl, the latter in Dowtherm) leads to the exclusive formation of angular pyrroloquinolines of the Π_2 type, regardless of the steric requirements of the substituent R^2 (H, Me) [6, 9, 21, 22].

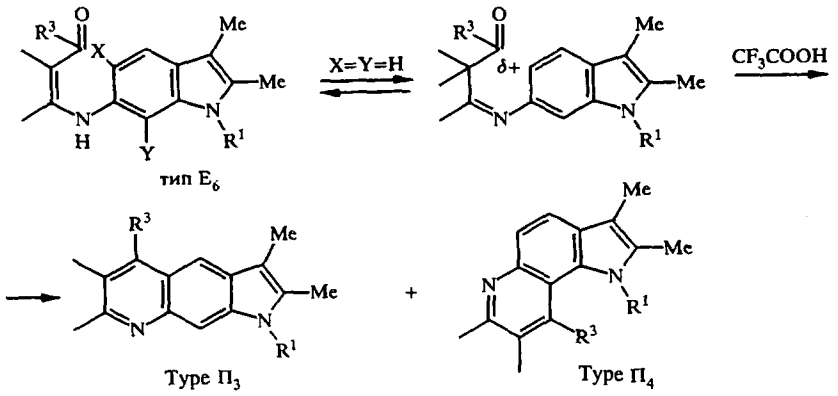


Thus we see that here also, position 4 of the benzene ring of enaminoindoles proves to be the more reactive position.

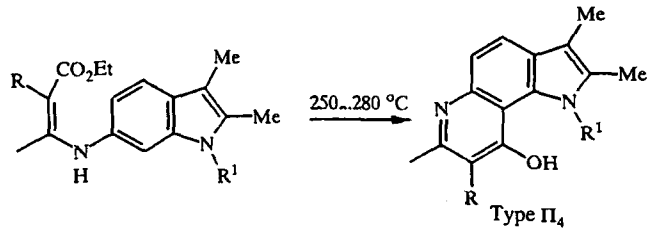
For derivatives of 6-aminoindole (the enamines E_6), we also observe preferential cyclization with participation of the $C_{(7)}$ atom (R^1 = H, R^2 = H, Me, Ph) (compare the aminomethylation of 6-hydroxyindoles in position 7 and the nitration of the same models in position 5); we also observe the strong influence of steric factors when a substituent is present on the pyrrole nitrogen atom, leading to the exclusive formation of a linear pyrroloquinoline of the Π_3 type as a result of cyclization through position 5 (R^1 = Me, R^2 = Me, Ph) [2, 4]. We should note that the steric requirements of the substituents R^1 and R^2 in the case of formation of the angular pyrroloquinolines of the Π_4 are expressed more strongly than in the formation of Π_2 type compounds from the enamines E_5. Thus, we were completely unable to obtain pyrroloquinolines of the Π_4 type with substituents R^1 = Me and R^2 = Me or Ph, whereas the analogous angular structures of the Π_2 type are formed in the cyclization of 5-enaminoindoles E_5, although with great difficulty [15].

The behavior of the 6-indolylamides of acetoacetic acid in the cyclization reaction is analogous to that of the enaminoketones [9].

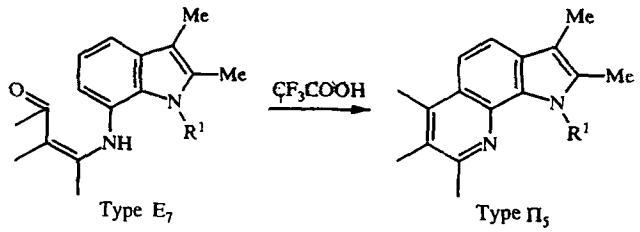
Thermolysis of indolyl-6-aminocrotonates and malonates also indicates the higher reactivity of position 7 of the indole. Here, regardless of the character of the substituent R^1, the corresponding pyrroloquinolines of the Π_4 type with angular connection of the rings are always formed, the same as in the case of the indolyl-5-aminocrotonates [6, 9].



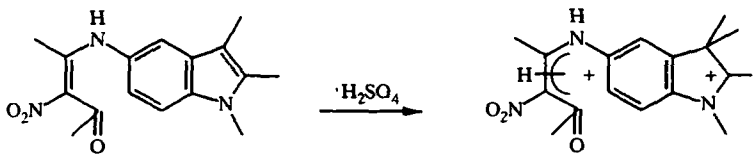
The formation of pyrroloquinolines of the $П_5$ type from indolyl-7-enaminoketones (E_7), whether or not a methyl substituent is present on the pyrrole nitrogen atom, confirms the preferential direction of electrophilic attack through the $C_{(6)}$ carbon atom, not the $N_{(1)}$ nitrogen atom [14].



So far as we could observe, the character of the acidic agent does not have any influence on the direction of cyclization. The use of zinc chloride or polyphosphoric acid as the cyclizing agent (with heating at 120-140°C) leads to the same pyrroloquinolines as with trifluoroacetic acid, but with smaller yields [2-4]. An increase of the acidity of the medium, i.e., the use of concentrated H_2SO_4, might change the direction of cyclization as a result of protonation of the pyrrole ring.

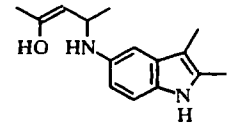
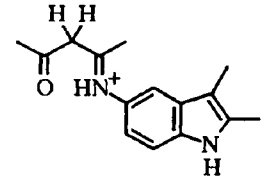
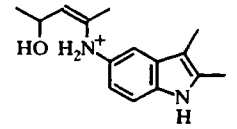
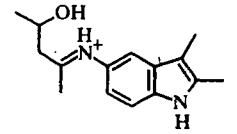
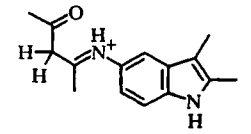
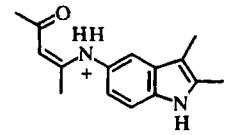
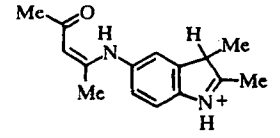


However, such assumptions proved to be unjustified. The α-methyl derivative of an indolyl-5-enaminoketone of the E_5 type, even in sulfuric acid, gives primarily the angular isomer; and enamines of nitromalonic dialdehyde are not cyclized at all in concentrated H_2SO_4 [7]. The PMR spectra indicate the presence of a dication species:



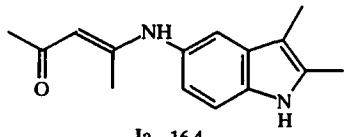
With the aim of elucidating the cyclization mechanism and determining how substituents on the indole ring and on the enamine fragment influence the regiochemistry of thermal and acid-catalyzed cyclization and the relative reactivities of the compounds, we perform semiempirical quantum-chemical calculations of the original compounds, their protonated forms, and the reaction products. In these calculations, we used the AM1, MNDO, and PM3 methods [25-29], by means of the MOPAC 7.0 program package. The calculations were performed with complete optimization of geometry for all parameters, using the keywords GNORM = 0.01 and VECTORS. In conformationally mobile systems, semiempirical methods usually lead to localization of multiple minima on the potential energy surface of the system; therefore, each isomer was optimized several

TABLE 4. Energies (kcal/mole) of Isomeric Protonated Forms of the Enaminoketone I, Calculated by Different Quantum-Chemical Methods

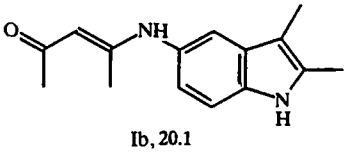
Isomer	AM1	MNDO	PM3
	148,2	141,9	130,5
	151,3	151,3	129,2
	162,1	166,4	134,4
	148,5	142,3	130,8
	151,6	151,2	129,2
	162,1	166,5	134,3
	159,8	164,5	133,6

times, using different original geometries. In addition, we analyzed the deepest energy minimum on the potential energy surface corresponding to the particular conformation. As model compounds entering into the heterocyclization reaction, we selected enaminocarbonyl compounds I (Type E_5, $R^1 = X = H$, $R^2 = R^3 = Me$) and II (Type E_6, $X = Y = R^1 = H$, $R^2 = R^3 = Me$), synthesized on the basis of 5- and 6-aminoindoles, respectively. These compounds are conformationally mobile; also, they can exist in the form of cis- and trans-isomers and two tautomeric enols (with a fragment of 1-aza-1,3-dien-4-ol and 4-amino-1,3-dien-2-ol). Therefore, the first stage of our theoretical study consisted of an investigation of the relative stabilities of different conformers of the enamine I, using the AM1 method. The energies of these conformers, in kcal/mole, are shown in the reaction scheme.

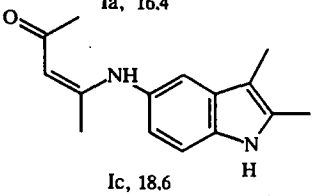
It can be seen from our data that the most important conformations for the 5-substituted enaminoketone I are the structures Id and Ik — which are stabilized through the formation of an intramolecular hydrogen bond and are global minima on the potential energy surface — and also the structures Ig-j — which are "reaction conformers," i.e., those specific conformations in which the molecule must exist in order to accomplish independently the stage of heterocyclization through the atom $C_{(4)}$ (Ig, h) or $C_{(6)}$ (Ii, j). Therefore, these isomers of the molecule I were also studied by the use of the MNDO and PM3 calculation schemes. The results are presented in Table 1.



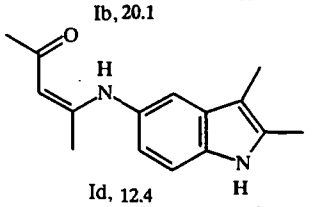
Ia, 16.4



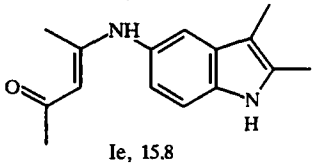
Ib, 20.1



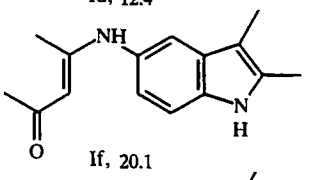
Ic, 18.6



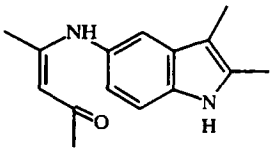
Id, 12.4



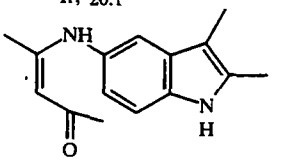
Ie, 15.8



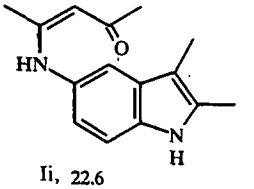
If, 20.1



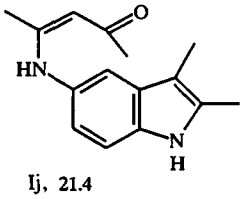
Ig,. 22.8



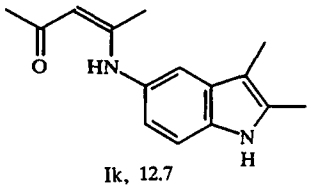
Ih, 21.2



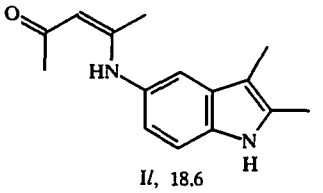
Ii, 22.6



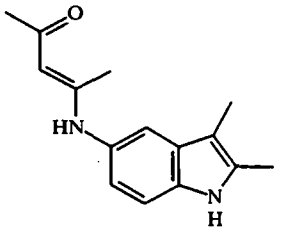
Ij, 21.4



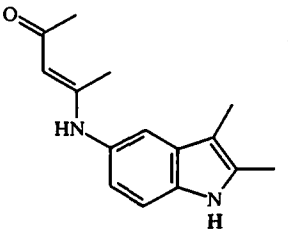
Ik, 12.7



Il, 18.6



Im, 16.4



In, 20.1

From the data presented in Table 1, it can be seen that the MNDO method greatly understates the difference between energies of the conformers stabilized by a hydrogen bond (Id, k) and the conformers Ig-j. The same sort of results were obtained for other isomers. Thus, according to the MNDO calculations, the isomer Im is less stable than Ik by only 0.9 kcal/mole, whereas the corresponding values when the AM1 and PM3 methods are used are 3.7 and 2.4 kcal/mole. This can be attributed to the well-known incapability of the MNDO method for describing the formation of hydrogen bonds, so that the use of this method for the purposes of the present work is questionable. Meanwhile, the presence of an intramolecular hydrogen bond is the specific reason why, in obtaining the enaminoketone I and its analogs, only the Z-isomers are formed [5, 18].

It should be noted that the enaminoketone fragment is quite strongly inclined (tilted) relative to the indole plane (the effect is most pronounced in the hydrogen-bonded isomers Id and Ik), and the angle of inclination in the "reaction" conformers Ig-j is 40-50° within the framework of the MNDO and PM3 methods. This angle is greatly different from the angle that is found when the AM1 method is used. As can be seen from Table 1, the magnitude of the angle of inclination proves to be important not so much in itself as in its influence on the charges on the atoms and the coefficients of the atoms in the frontier

TABLE 5. Results of PM3 Quantum-Chemical Calculations of Conformers of Protonated Forms of Enaminoketone I (energies in kcal/mole; k is the coefficient of the atom in the HOMO; q is the charge of the atom)

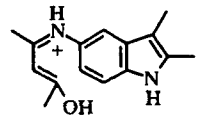
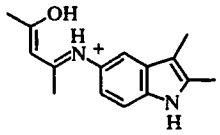
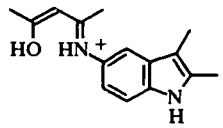
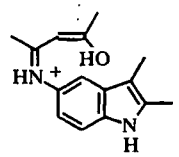
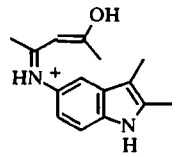
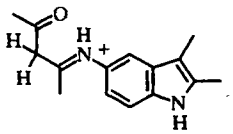
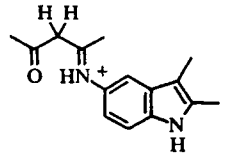
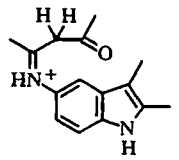
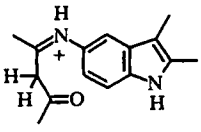
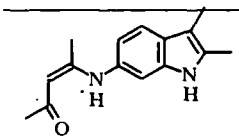
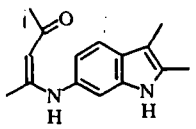
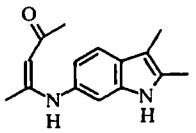
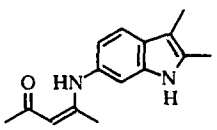
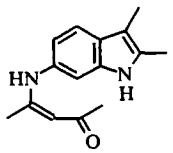
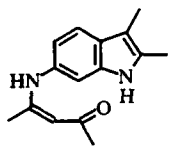
Isomer	ΔHf	$\theta_{C=NC(5)C(4)}$	$kC_{(4)}$	$kC_{(6)}$	$qC_{(4)}$	$qC_{(6)}$
1	2	3	4	5	6	7
	135,2	139,1	0,076	0,080	0,026	-0,070
	130,8	125,7	0,078	0,080	0,017	-0,080
	130,5	53,2	0,078	0,081	0,017	-0,078
	135,0	39,1	0,077	0,082	0,028	-0,074
	138,2	44,8	0,073	0,081	0,031	-0,084
	129,2	133,9	0,071	0,082	0,040	-0,073
	129,2	45,8	0,072	0,086	0,031	-0,067
	132,3	40,3	0,073	0,086	0,023	-0,062
	132,2	139,4	0,070	0,081	0,049	-0,080

TABLE 6. Heats of Formation of Isomeric Products from Heterocyclization of Enaminoketone IIa and Its Homologs, Calculated by Methods PM3, MNDO (in parentheses), and AM1 (in brackets)

Pyrroloquinolines	$R^1 = R^2 = R^3 = Me$	$R^1 = R^2 = R^3 = Me$	$R^1 = R^2 = R^3 = H$	$R^1 = R^2 = H$, $R^3 = Me$
Linear, Type Π_3	31,0 (35,4) [58,3]	30,2 (39,0) [63,4]	48,5 (49,8) [72,7]	40,3 (44,3) [66,0]
Angular, Type Π_4	29,3 (35,4) [56,4]	34,7 (46,5) [68,7]	45,4 (46,5) [69,5]	38,3 (43,9) [63,7]

TABLE 7. Results of PM3 Quantum-Chemical Calculations of Conformers of Enaminoketone IIa (energies in kcal/mole; k is the coefficient of the atom in the HOMO; q is the charge on the atom)

Isomer	ΔHf	θ, $C=NC_{(6)}C_{(7)}$	$kC_{(5)}$	$kC_{(7)}$	$qC_{(5)}$	$qC_{(7)}$
	-11,7	112,0	0,002	0,103	-0,129	-0,118
	-7,9	144,8	0,002	0,132	-0,159	-0,149
	-7,3	147,4	0,009	0,131	-0,150	-0,151
	-11,7	71,7	0,003	0,104	-0,143	-0,102
	-8,0	46,3	0,000	0,132	-0,163	-0,130
	-8,0	43,4	0,002	0,132	-0,162	-0,140

orbitals (both of which are highly dependent on this dihedral angle, as a result of differences in the degree of conjugation between the enaminoketone and the aromatic system of the indole). In the literature, we have already noted considerable differences in describing conformational equilibria by different semiempirical methods. Thus, the results from calculations by the MNDO method (and also PM3) are better than those obtained with the AM1 method and are consistent with experimental data on the axial-equatorial equilibrium in substituted cyclohexanes, which are the standard model for describing conformational equilibria.

TABLE 8. Results of PM3 Quantum-Chemical Calculations of Conformers of Protonated Form of Enaminoketone IIa (energies in kcal/mole; k is the coefficient of the atom in the HOMO; q is the charge on the atom)

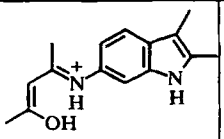
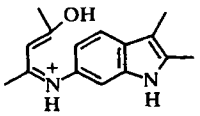
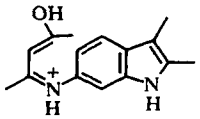
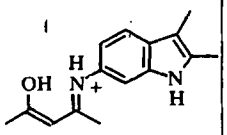
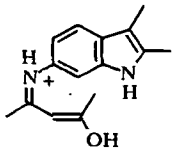
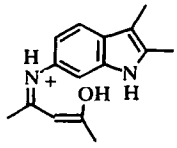
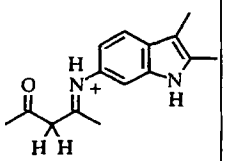
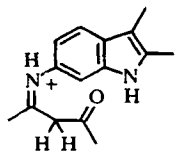
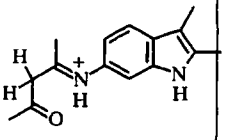
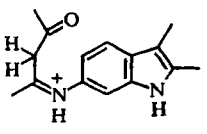
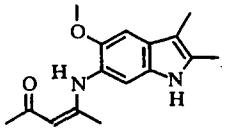
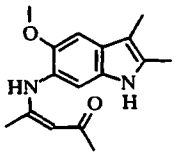
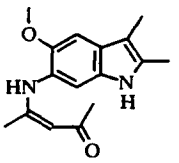
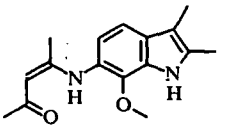
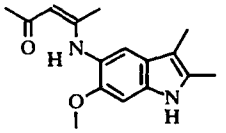
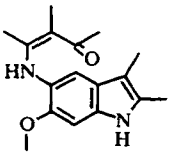
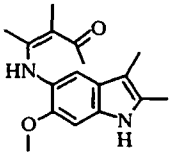
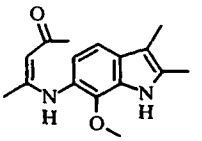
Isomer	ΔH_f	$\theta_{C=NC_{(6)}C_{(7)}}$	$kC_{(5)}$	$kC_{(7)}$	$qC_{(5)}$	$qC_{(7)}$
1	2	3	4	5	6	7
	131,9	123,5	0,051	0,058	-0,120	-0,035
	136,6	139,6	0,050	0,056	-0,112	-0,029
	139,8	139,7	0,050	0,054	-0,115	-0,041
	132,1	55,3	0,052	0,059	-0,119	-0,040
	139,1	51,5	0,052	0,053	-0,124	-0,025
	139,3	67,6	0,053	0,051	-0,143	-0,024
	131,1	34,3	0,048	0,053	-0,026	-0,106
	134,6	41,3	0,050	0,055	-0,101	-0,033
	130,4	144,0	0,049	0,052	-0,116	-0,014
	133,5	138,1	0,046	0,051	-0,122	-0,004

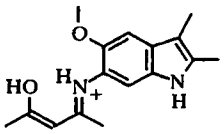
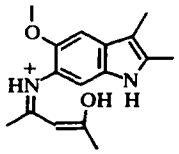
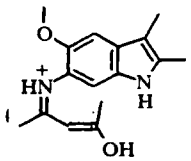
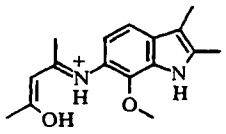
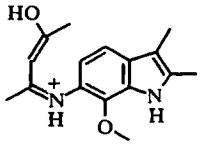
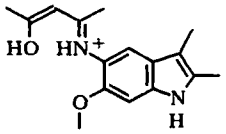
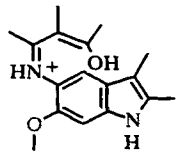
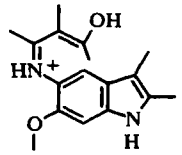
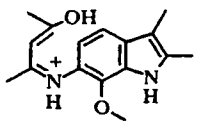
TABLE 9. Results of PM3 Quantum-Chemical Calculations of Conformers of Methoxy-Substituted Enaminoketones V and VI (energies in kcal/mole; k is the coefficient of the attacked carbon atom in the HOMO; q is the charge on the atom)

Conformer	ΔHf	k	q
	-47,3	0,089	-0,055
	-43,8	0,130	-0,102
	-44,1	0,132	-0,119
	-47,2	0,003	-0,118
	-47,7	0,087	-0,007
	-42,5	0,088	-0,002
	42,3	-0,091	0,016
	-43,0	0,000	-0,113

After looking at all the differences found in describing the geometry and energies of the isomers of molecule I, we can conclude that the PM3 method is the most adequate (suitable) for analysis of the series of compounds in which we are interested. The results obtained with the PM3 method will provide the main basis for subsequent discussion, although we will also present some data obtained by other methods.

In the case of thermal cyclization of enamines of the E_5 and E_6 types, the most probable mechanism through which the process is accomplished is the enolization of the enaminoketone to the corresponding azadienol, with a subsequent electrocyclic reaction. The regiochemistry of electrocyclization will depend on the contributions of the $C_{(4)}$ and $C_{(6)}$ atoms to

TABLE 10. Results of PM3 Quantum-Chemical Calculations of Conformers of Protonated Form of Methoxy-Substituted Enaminoketones V and VI (energies in kcal/mole; k is the coefficient of the attacked carbon atom in the HOMO; q is the charge on the atom)

Conformer	ΔH_f	k	q
1	2	3	4
	93,1	0,066	-0,015
	98,0	0,066	-0,007
	100,4	0,061	0,006
	95,4	0,058	-0,110
	102,4	0,072	-0,093
	91,8	0,074	-0,031
	96,0	0,073	0,051
	98,7	0,070	0,060
	99,7	0,062	-0,093

the population of the HOMO, and also on the heat effects of the two competing reactions. It can be seen from Table 1 that for all of the conformers of the enaminoketone I, according to the data obtained by the PM3 method, the contribution of the $C_{(4)}$ atom to the HOMO ($k \sim 0.1$) is far greater than the contribution of the $C_{(6)}$ atom ($k \sim 0$). However, since the electrocyclization reaction is possible only after the formation of the enol species, we also performed calculations of the isomers of the corresponding azadienol. It can be seen from the data of Table 2 that the enol form of the molecule I is less stable than the keto form by 3.3 kcal/mole; this lower stability is even more evident for the "reaction conformers" Ig-j, which can in themselves enter into the electrocyclization reaction. In contrast to the keto form, we find that in the enol form, the angle of inclination of the substituent in the hydrogen-bonded conformation (40°) is smaller than in the "reaction" form (70°). Here, the conformers that are inclined on the side of the atoms $C_{(4)}$ and $C_{(6)}$ have practically identical energies. On this basis, we can conclude that this particular factor cannot play any sort of a role in determining the regiochemistry of the reaction. The orbital and charge characteristics of the $C_{(4)}$ and $C_{(6)}$ atoms upon transition from the keto to the enol form undergo very little change. As before, the contribution of the $C_{(4)}$ atom to the HOMO is far greater than that of $C_{(6)}$ atom, which makes hardly any contribution.

On the basis of these data, we can expect that the thermal cyclization of the molecule I should proceed preferentially or exclusively through position 4 of the indole fragment; this is in complete agreement with the experimental data [6, 8, 9, 21]. The relatively low selectivity of the reaction is explained on the basis that in the case of the molecule I, the product of cyclization through the $C_{(4)}$ atom, the tetramethyl derivative IV ($R^1 = R^2 = R^3 = Me$) of an angular pyrroloquinoline of the Π_2 type, is 3.8 kcal/mole less stable than its linear isomer, the tetramethylpyrroloquinone III ($R^1 = R^2 = R^3 = Me$) of the Π_1 type that is obtained by cyclization through the $C_{(6)}$ atom (see Table 3). This is explained by steric interaction between the methyl group in position 3 of the indole fragment and the methyl group in the enaminoketone fragment for the angular isomer obtained by cyclization through the $C_{(4)}$ atom. The importance of this repulsion can be demonstrated in the example of homologs that do not have even one of these methyl groups (see Table 3). In this case, the angular isomer of the pyrroloquinoline already proves to be more stable by 3-4 kcal/mole. In fact, the heterocyclization of the enaminoketone of 2-methylindole goes forward with the formation of a single isomer [2, 4].

Differences in energy parameters are also manifested in products from cyclization of the enamine of 2,3,7-trimethyl-5-aminoindole, Type E_5 ($R^2 = X = Me$), in which peri-interaction (in a linear pyrroloquinoline of the Π_1 type) competes with ortho-repulsion (in the angular isomer of the Π_2 type), but to a lesser degree. The ratio of pyrroloquinolines of the Π_1 and Π_2 types in the reaction mixture is consistent with the MNDO-calculated heats of formation [$\Delta H_{f(\pi\text{-}1)}$] = 57.9 kcal/mole; [$\Delta H_{f(\pi\text{-}2)}$] = 58.7 kcal/mole.

In performing heterocyclization under conditions of acid catalysis, there is still a possibility (the same as before) of enolization with a subsequent electrocyclic reaction; hence it is evident that the most probable mechanism is a reaction of electrophilic substitution with attack by the activated carbonyl carbon atom through one of the ortho-positions of the benzene ring of the indole. It is known that the position of attack by an electrophile on an aromatic system is determined mainly by the charges on the atoms and their contributions to the HOMO population. In most aromatic systems, these two factors act in the same direction; sometimes however, the attack of the electrophile may be directed to more than one position. In this case, we can speak of orbital or charge control of the regiochemistry of the course of the reaction, depending on which of the factors has the greatest influence. From analysis of the data obtained in quantum-chemical calculations of the neutral molecule E_1, it can be seen that in this case we are dealing specifically with the case in which the orbital and charge control direct the attack of the electrophile to different positions on the benzene ring of the indole: The contribution of the $C_{(4)}$ atom to the HOMO is far greater than that of the $C_{(6)}$ atom, but the latter carries a greater negative charge. In most cases in which the charge and orbital controls act in opposite directions, the relative importance of these quantities becomes the decisive factor. Thus, the difference in charges of the $C_{(4)}$ and $C_{(6)}$ atoms, according to the results of the PM3 quantum-chemical calculations, is rather insignificant, whereas the contributions of these atoms to the HOMO population differ substantially; the contribution of the $C_{(6)}$ atom is close to zero, while that of the $C_{(4)}$ atom is greater than 0.1. Consequently, we should expect in this case that electrophiles will attack through position $C_{(4)}$, not through $C_{(6)}$; this is in agreement with experimental data on electrophilic substitution in derivatives of 5-hydroxyindoles and 5-aminoindoles [23, 24].

Since analysis of the regiochemistry of acid-catalyzed intramolecular heterocyclization on the basis of data calculated for the neutral molecule can hardly be justified, we performed quantum-chemical calculations of protonated forms of the molecule I. There are several possible sites of protonation in the enaminoketone I; therefore, we made a study of the possible protonated isomers.

It can be seen from Table 4 that the ranking of stability of various isomers of the protonated enaminoketone I depends on which semiempirical method is used. According to the AM1 and MNDO calculations, the isomer protonated through the oxygen atom is the most stable; however, the PM3 calculations predict a higher stability for the isomer protonated through the carbon atom in the α-position to the carbonyl group. All three methods predict that both of these isomers will be far more stable than isomers protonated through the $C_{(3)}$ atom of the indole fragment or through the nitrogen atom. According to the PM3 results, the charge on the carbonyl carbon atom for the isomer protonated through the oxygen atom (regardless of the geometry of the conformer) is 0.20 ± 0.01; for the isomer protonated through the carbon atom, the charge will be 0.31. This means that the latter must be more susceptible to electrophilic attack on the aromatic ring.

The other two semiempirical methods also gave a greater positive charge on the carbonyl carbon atom in the case of the isomer protonated through the carbon atom. The data indicate that protonation of the enaminoketone I is possible through either the oxygen or carbon atom, a conclusion that is consistent with the observation of partial introduction of a deuterium label into the product when the reaction is performed in a medium of deuterosulfuric acid [30]. In the subsequent reaction, it is most probable that the cation protonated through the oxygen enters into the cyclization reaction (this will lead to aromatic products of reaction without further rearrangement). Therefore, we performed calculations of the conformers for each of the two isomers, with the aim of determining their orbital and charge characteristics, which might then be used as a basis for predicting the regiochemistry of the electrophilic regiocyclization reaction.

It can be seen from Table 5 that under acid-catalyzed conditions, the reaction of electrophilic cyclization must proceed primarily or exclusively through the $C_{(6)}$ atom; the contributions of the $C_{(4)}$ and $C_{(6)}$ atoms to the HOMO are approximately equal, but the $C_{(4)}$ carries a positive charge, the $C_{(6)}$ atom a negative charge. In this case, we can expect that the regiochemistry of the reaction should be determined primarily by charge control, and hence the reaction will proceed mainly through the $C_{(6)}$ atom.

The analog of molecule I without a methyl group in position 3 is cyclized far more slowly, giving mainly the product of attack at the $C_{(4)}$ atom. We had noted above that this compound is the more stable compound in the case of this particular substrate. Also, quantum-chemical calculations show that removal of the methyl group in position 3 results in an increased contribution of the $C_{(4)}$ atom to the HOMO up to a value of 0.102, with very little change in the contribution of the $C_{(6)}$ atom; this also favors heterocyclization through position $C_{(4)}$. At the same time, the positive charge on the $C_{(4)}$ atom, as before, hinders cyclization through the $C_{(4)}$ atom; this is evidently the explanation for the lower reactivity of this compound in comparison with the enamine of 2,3-dimethyl-5-aminoindole.

The problem of regioselectivity of the heterocyclization reaction is also critical for substrates of the E_6 type. Therefore, we performed quantum-chemical calculations of compounds IIa (X = Y = H, R^1 = H) and IIb (R^1 = Me) and the corresponding products of cyclization (Tables 6 and 7).

It can be seen from Table 6 that, the same as for the substrate I, the angular isomer that is obtained with heterocyclization through the $C_{(7)}$ atom is more stable than the linear isomer, the product of cyclization through the $C_{(5)}$ atom, when there is no steric interaction between the substituent on the nitrogen atom and the substituent in position 4 of the pyrroloquinoline that is formed. However, the difference in stability of the two isomers of the pyrroloquinolines of the II_3 and II_4 types in the case of compound II is smaller than for the isomer I that we examined previously. In contrast, in the case of the N-methylated indole, the product of heterocyclization through the $C_{(7)}$ atom of the indole ring is 4.4 kcal/mole less stable than its linear isomer.

In the example of substrate I, we showed that the relative stability of the two possible products of cyclization is an important factor, but not the sole factor, determining the regioselectivity of the reaction. Therefore, we calculated the basic characteristics of the most important conformers of the molecule IIa and its protonated form.

From Tables 7 and 8 it follows that in the neutral form, the contribution of the $C_{(7)}$ atom to the HOMO is far greater than that of the $C_{(5)}$ atom, and the charges on these two atoms are approximately equal. This is analogous to the data obtained for the substrate I. In exactly the same way, protonation leads to equalization of the contributions of the $C_{(5)}$ and $C_{(7)}$ atoms to the HOMO, an increase of the negative charge on the $C_{(5)}$ atom, and a decrease of the charge on the $C_{(7)}$ atom. In contrast to substrate I, the $C_{(7)}$ atom still carries an appreciable negative charge, which makes it possible that electrophilic attack will occur at both atoms. The two other semiempirical methods give similar results; however, when they are used, the contributions of the $C_{(5)}$ and $C_{(7)}$ atoms are greatly different, even in the protonated form of the substrate IIa. When the AM1 method is used, the contribution of the $C_{(5)}$ atom to the HOMO is 0.13-0.19 depending on the conformer, while the contribution of the $C_{(7)}$ is 0.35-0.41. When the MNDO method is used, the respective contributions are 0.29-0.33 and 0.52-0.53.

Summarizing these results, we can say that the quantum-chemical calculations indicate that electrophilic attack on the nonprotonated form of the substrate IIa, and also thermal cyclization of this substrate, should proceed exclusively through the $C_{(7)}$ atom, not through the $C_{(5)}$ atom. Acid-catalyzed heterocyclization is possible in both directions. Here, on the basis of the similar coefficients of the $C_{(5)}$ and $C_{(7)}$ atoms in the HOMO, we can expect to obtain comparable quantities of isomeric pyrroloquinolines of the types II_3 and II_4. The larger negative charge on the $C_{(5)}$ atom in the protonated form of the substrate is a factor directing the reaction toward the formation of the product that is less thermodynamically stable; however, in contrast to substrate I, charge control does not prevent attack through the $C_{(7)}$ atom, forming a compound that is 2 kcal/mole more stable than the linear pyrroloquinoline. Therefore, the predominant reaction product should be the angular isomer of the II_4 type; this is in agreement with the experimental data [4, 9]. The introduction of a substituent into position 1 of the original indole leads to reversal of the thermodynamic stabilities of the two isomeric pyrroloquinolines, without having any significant effect on the charge or orbital characteristics of the molecule. As a result, both charge control and the enthalpy factor direct the cyclization reaction to the $C_{(5)}$ atom, and this leads to the formation of a single product of cyclization, the linear pyrroloquinoline of the II_4 type.

It has been established [19, 20] that the 6-methoxy derivative of the 5-enaminoketone and the 5-methoxy derivative of the 6-enaminoketone, under conditions of acid catalysis, are cyclized more poorly than their analogs that do not contain a methoxy group. The same effect has been noted for reactions of ortho-methoxyanilines and has been described as a deactivating influence of the electronegative oxygen atom as a result of an inductive effect [31]. At the same time, 7-methoxy-6-enaminoindole is far more readily subjected to acid-catalyzed heterocyclization. The efficiency of this reaction is comparable to the ease of cyclization of the enaminoketone without the methoxy group [17]. In order to explain these results, we undertook a quantum-chemical study of the properties of Type E_6 enamines of these methoxy derivatives V (R^1 = Y = H, R^2 = R^3 = Me, X = OMe) and VI (R^1 = X = H, R^2 = R^3 = Me, Y = OMe) and also their protonated forms (Tables 9 and 10).

From an analysis of the data presented in Tables 9 and 10, it can be seen that in the case of the 5-methoxy-6-enaminoketone E_4, the contribution of the $C_{(7)}$ atom to the HOMO of the neutral molecule in the "reaction" conformers is 0.13, i.e., practically the same as the corresponding value for the substrate II. The negative charge on the $C_{(7)}$ atom in the molecule V is somewhat smaller, but still greater than 0.1 in absolute magnitude. Hence we can expect that in the case of thermal cyclization or in the interaction with an external electrophile in a neutral medium, the substrate V should react almost as easily as its analog II without the methoxy group. However, protonation of the substrate V results in a substantial increase of the contribution of the $C_{(7)}$ atom to the HOMO; and, still more important, it leads to loss of the negative charge on this atom. In the "reaction" conformers, the charge on this atom remains approximately equal to zero. This is the specific explanation for the low reactivity of 5-methoxy-6-(3-oxo-1-methylbutylidenamino)indole V in acid-catalyzed heterocyclization in comparison with the substrates I and II, which do not contain methoxy groups. This effect is still more pronounced in the case of the 6-methoxy-5-enaminoketone VII. Here, in the "reaction" conformers, the attacked $C_{(4)}$ atom carries a positive charge of 0.05-0.06. Evidently, attack by the electrophilic reagent on the positively charged atom is hindered as a consequence of strong Coulomb repulsion, and the substrate VII clearly reacts more poorly in comparison with its analog without a methoxy group, of the E_5 type. In the case of the 7-methoxy-6-enaminoketone VI, the situation is the direct opposite: The attacked $C_{(5)}$ atom carries a significant negative charge, both in the most stable conformer and in the "reaction" conformers. The contribution of this atom to the HOMO is also lower in comparison for this same atom in the substrates I and II, which do not contain methoxy groups. Thus, the results of the quantum-chemical calculations completely support the conclusions based on experimental data regarding the actual distribution of electron density in the indole ring and regarding the specific influence of a 7-methoxy substituent.

On the whole, based on the material we have set forth here, we can conclude that the quantum-chemical calculations are not only in good agreement with the experimental data, but that they offer a means for revealing the fine features of the influence of the character of substituents in the indole ring of isomeric enamines, and the influence of the reaction conditions, on the regioorientation of annelation of a pyridine ring to the benzene fragment of the indole bicyclic molecule.

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