12. N. L. Allinger and E. L. Iliel (eds.), *Selected Problems of Stereochemistry* [Russian translation], Mir, Moscow (1970).
13. S. Ley, B. Lygo, F. Sternfeld, and A. Wonnacott, *Tetrahedron*, **42**, 4333 (1986).
14. H. Peterson, H. Brandeis, and R. Fikentscher, GFR Patent, No. 1,230,805; *Chem. Abstr.*, **66**, 46435 (1967).

INVESTIGATION OF COMPLEX FORMATION AND RELATIVE REACTIVITY OF PYRROLOQUINOLINES AND PYRROLOISOQUINOLINES BY MEANS OF NMR SPECTROSCOPY

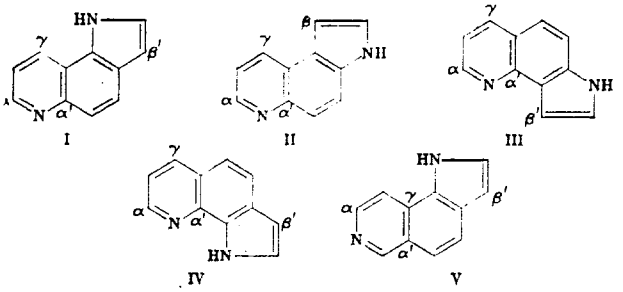
S. N. Krasnokutskii, L. N. Kurkovskaya, and N. N. Suvorov

UDC 547.836.3'759.04:543.422.25

The series of isomeric pyrroloquinolines and pyrroloisoquinolines has been studied by means of multinuclear NMR spectroscopy. It is shown that in inert media all of the compounds form complexes of the NH · · · H type, cyclic or linear, depending on the type of annelation of the pyrrole ring. A spectroscopic estimation of their proton-donating and proton-accepting properties has been made. The protonation (deuteration) of the pyrrole fragment of the methiodides of the pyrroloquinolines has been studied. A reaction profile of the protonation of the pyrroloquinolines as a function of the acidity of the medium has been obtained. A comparative evaluation of the reactivity of the pyrroloquinolines has been carried out.

According to [1-3], the isomeric pyrroloquinolines to be discussed, 1H-pyrrolo[2,3-f]quinoline (I), 3H-pyrrolo[3,2-f]quinoline (II), 3H-pyrrolo[2,3-h]quinoline (III), 1H-pyrrolo[3,2-h]quinoline (IV), and 1H-pyrrolo[2,3-f]isoquinoline (V), display a different reactivity in electrophilic and nucleophilic substitution reactions. For a number of reasons related to the conditions of preparation and isolation of the pyrroloquinolines, it does not appear possible to compare the reactivities of the entire series of compounds (I-V) from the yields of a single kind of reaction. Nor do the available quantum chemical calculations by the MOKh and RMKh methods permit a judgment of the relative reactivities of compounds I-V [4].

The purpose of the present work was to seek sound criteria affording an explanation and, possibly, a prediction of the relative reactivities of the isomers. Since the molecules investigated possess two nitrogen atoms, one of which is a proton-donating and the other a proton-accepting center, a potential criterion for evaluating differences in the chemical behavior of compounds I-V could be information obtained by studying the acid-base reaction with formation of complexes of the NH · · · H type. The stability of the complex is related to the extent of the change in the electron density in the π-rich (indole) and π-deficient (pyridine) fragments of the molecules of the different isomers. This, in turn, must be reflected in their reactivity, first in electrophilic substitutions (for example protonation of the β'-carbon atom of the pyrrole ring), and second in nucleophilic substitutions (the Chichibabin reaction).



D. I. Mendeleev Chemical Technological Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 237-244, February, 1991. Original article submitted July 11, 1989.

0009-3122/91/2702-0194$12.50

TABLE 1. Enthalpies of Association (ΔH_{as}) and Chemical Shifts of Protons of the NH Group and β'-H of Compounds I-V

Compound	$\Delta H_{as} \pm 1.5$ kJ/mole*1	Chemical shifts, δ, ppm*2					
		NH∞	NH*3	NH*4	β'-H	β'-H*3	β'-H*4
I	−14,4	8,85	8,44	8,31	6,75	6,62	6,62
II	−19,7	8,53	8,38	8,38	7,10	6,69	6,65
III	−14,4	8,53	8,38	8,38	7,34	6,93	6,65
IV	−24,3; −24,1*5	9,63	9,22	8,84	6,72	6,59	6,59
V	−24,3	8,95	8,54	8,41	6,77	6,64	6,64

*1Calculated by the limiting slopes method.
*2Obtained in $CDCl_3$ at infinite dilution and with correction for anisotropic [8, 9], steric [10], and other contributions.
*3With correction for ring current.
*4With allowance for ring current, steric factors, and the effect of the unshared electron pair.
*5By Lippert's method [7].

TABLE 2. Values of pK_a

Compound	pK_a*	pK_a**	pK_a***	Compound	pK_a*	pK_a**	pK_a***
Pyridine		4,43	5,23 [13]	IV	5,09 [2]	3,90	4,70
Quinoline		4,18	4,94 [13]	V	6,70	5,68 [3]	
Isoquinoline		4,57	5,40 [13]			5,71	6,51
I	5,92 [2]	4,92	5,72	VI		4,12	4,92
	5,72			VII		5,39	6,19
II	6,19 [2]	5,00	5,80	VIII		3,55	4,35
III	5,97 [2]	5,00	5,80				

*Data measured by UV spectroscopy (±0.12 pK_a units).
**Data measured by potentiometric titration for a 1:1 water/alcohol system, 25°C (±0.07 pK_a units).
***Data presented are for potentiometric titration with an allowance of a 0.80 pK_a unit correction (water, 25°C).

The presence in one molecule of a π-rich and a π-deficient nucleus leads to a restructuring of the entire π-system. The result is to strengthen both the proton-donating and proton-accepting properties of the molecule with the formation of a stable, intermolecular complex of the NH · · · N type [5]. This was confirmed by the course of the concentration and temperature dependencies of the δ_{NH} chemical shift in the NMR spectra. The high solubility of compound IV in $CDCl_3$ (~0.8 M) compared to the solubility of the other isomers (≤0.04 M) and a favorable geometry allowed one to suppose for it a different kind of self-association than for the remaining pyrroloquinolines. Indeed, the ^{15}N-NMR data (with the natural isotopic content) give evidence of this. Thus, in pyridine-d_6, which precludes the formation of intermolecular self-associates, the CS [chemical shifts] of the nitrogen atoms of the pyridine and pyrrole fragments of compound I are equal to −64.8 and −238.9 ppm, respectively, and the CS of isomer IV are −82.3 and −235.4 ppm, respectively. The drawing together of the CS of the nitrogen atoms in the spectrum of compound IV indicates an equalization of the bonds in the =N—C—C—NH fragment and the large, strong-field shift of the CS of the pyridine nitrogen indicates a significant increase in the electron density at the expense of the π-donating imino group as well as the probable transfer of the proton along the NH · · · N bond, as shown for 7-azaindole, which forms cyclic dimers [6].

The results of treating the data for compound IV by the least-squares method give evidence for the formation of just such a cyclic dimer, whereas for the remaining compounds in $CDCl_3$ solution, linear-type dimerization occurs:

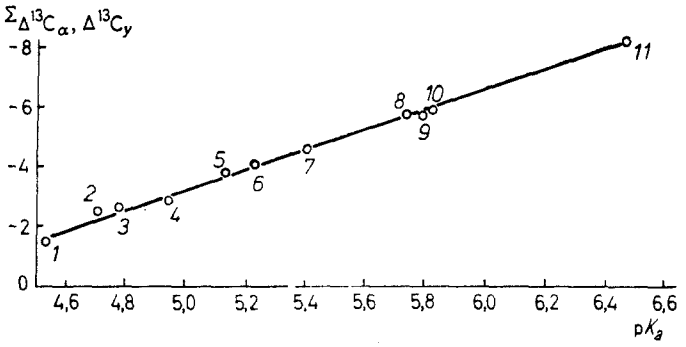


Fig. 1. Values of pK_a measured by means of ^{13}C-NMR: 1) phenanthridine; 2) compound IV; 3) 1H-pyrrolo[2,3-c]phenanthridine; 4) quinoline; 5) 1H-pyrrolo[3,2-i]phenanthridine; 6) pyridine; 7) isoquinoline; 8) compound I; 9) compound III; 10) compound II; 11) compound V.

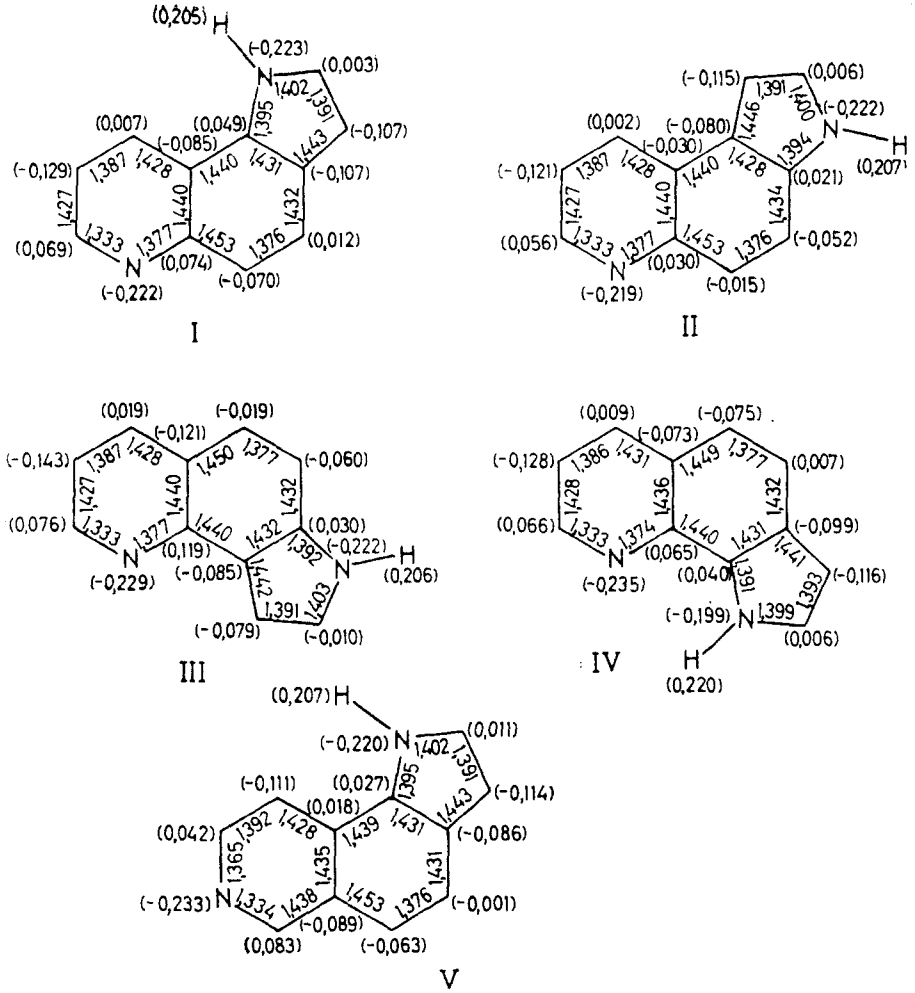
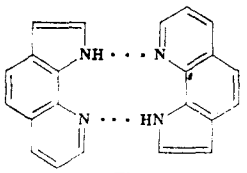
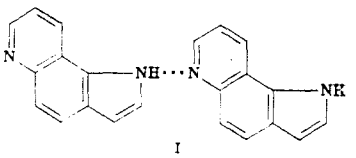


Fig. 2. Charges on the atoms and bond lengths in pyrroloquinolines I-IV and pyrroloisoquinoline V, calculated by the MNDO method.



IV



I

The values of the thermodynamic parameters of compound IV calculated by Lippert's method and the method of limiting slopes [7] agree. This is an indication of their reliability. Because of the limited solubility of the other isomers, it was only possible to get values of the enthalpy of self-association ΔH_{as} by the method of limiting slopes (Table 1). In terms of the enthalpies of self-association, the isomers form the series I $\approx$ III < II < V $\approx$ IV.

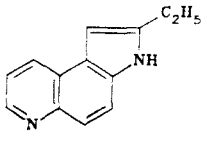
The proton-donating abilities of the NH group were estimated, starting from a calculation of the anisotropic [8, 9] and steric [10] contributions and the contribution of the unshared pair of electrons on the nitrogen atom of the pyridine ring to the CS of the monomer δ_{NH}^{∞} for infinitely dilute solutions of compounds I-V in $CDCl_3$ (Table 1). The contribution of the unshared pair of electrons was estimated from a comparison of the CS of the β'-H protons of isomers II and III, taking account of the greater sensitivity of the δ_{NH} CS in accordance with the data in [11].

The proton-accepting abilities of the pyridine fragment in the series of compounds I-V were characterized by the values of pK_a, which was determined both from ^{13}C-NMR data [12] and by potentiometric titration (previously obtained values of pK_a for some of the isomers differed with moderate precision ($\pm$0.4 pK_a units) [13]).

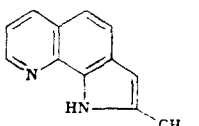
In measuring the pK_a by the ^{13}C-NMR, the values of the total changes of the CS of the α- and γ-carbon atoms of the pyridine fragment were used when the nitrogen of those fragments was protonated by trifluoroacetic acid in $CDCl_3$. The method proposed is particularly suited for compounds that are insoluble in water or alcohol. The pK_a values of the parents (quinoline, pyridine, isoquinoline) of the compounds investigated give a linear slope (Fig. 1). An increase in the pK_a takes place over the series of compounds: IV < I $\leq$ III $\leq$ II < V. These data agree with the pK_a values obtained by potentiometric titration (Table 2) and with the series obtained in a study of the dynamics of salt formation by the collapse of the doublet lines due to the $J_{CH_\alpha,NH}$ spin–spin interaction of the pyridine fragment at a given pH of the medium in the −10 to +50°C temperature range [12]. The measurements of pK_a by potentiometric titration were carried out in 50% aqueous ethanol because of the low solubility of the substances in water. The resultant data were then extrapolated to an aqueous solution at 25°C by the addition of 0.8 pK_a units. As standards to find the correction coefficient, quinoline, pyridine, and isoquinoline were used [14].

The pK_a values (Table 2) for isomers I-III differ insignificantly. Isomer IV is an exception; steric hindrance on the pyrrole ring side hinders protonation or solvation of the cation and lowers the value of the pK_a (4.70), as noted for some benzoquinones [14]. This could also be the result of a negative inductive effect of the nearby pyrrole imine group [15].

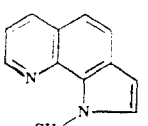
The results of quantum chemical MNDO calculations [16] (Fig. 2) demonstrate another series of basicities, predicting a greater value for isomers III and especially IV, which are sterically hindered systems. This is also supported by a study of their alkylsubstituted derivatives. It was shown that the introduction of alkyl substituents in the pyrrole fragment of isomers II and IV (compounds VI and VII, respectively) led to different increments in pK_a (Table 2): ΔpK_a 0.39 (II), 0.22 (IV), while replacement of the NH group by N-CH_3 in compound IV (compound VIII) even led to a decrease in pK_a (4.35). Maps of the distribution of the molecular electrostatic potential [12] confirm the difficulty a protonating agent has in approaching the pyridine nitrogen atom in isomers III and IV.



VI



VII



VIII

Thus, the order of the change in CS of the monomers δ_{NH}^{∞} (Table 1) agrees qualitatively with the order of change in the basicity of the pyridine nucleus in the compounds studied, except for isomer IV, for which the NH-group proton is the most acidic (8.84 ppm) and the pyridine nitrogen atom is, conversely, the least basic (pK_a 4.70). Apart from the reasons mentioned, this last could also be the result of a proton transfer along the H bonds of the cyclic dimer of IV with the formation of a bipolar ion.

In connection with this, one would expect pyrroloquinoline IV to behave anomalously in electrophilic substitution reactions compared to the other isomers. Data confirming this hypothesis were obtained from the

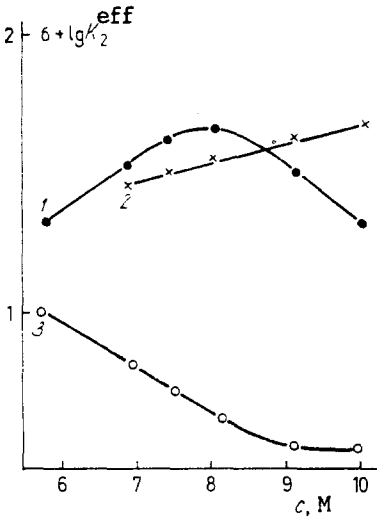
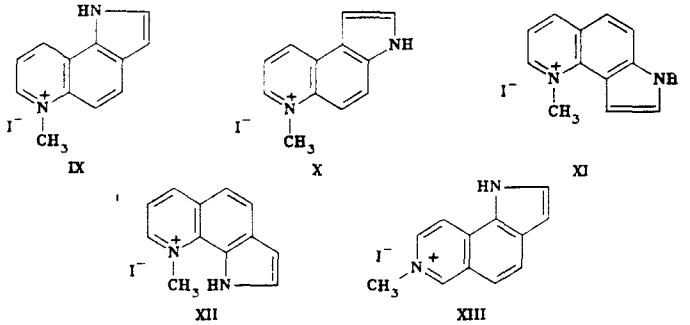


Fig. 3. Dependence of the rate of deuteration of isomers I (1), IV (2), and V (3) in the β'-C position on the concentration of CD_3COOD at 90°C.

TABLE 3. Thermodynamic Activation Parameters of the Methiodides of Pyrroloquinones and Pyrroloisoquinoline I-V

Compound	$E_a \pm 1.2$ kJ/mole	$\Delta S^{\neq} \pm 3.3$ J/mole·K
IX	36,9	−175,9
X	39,5	−173,5
XI	38,2	−173,2
XII	26,8	−216,2
XIII	45,2	−163,0

position of the β'-C signal on the deuteration, as a model of electrophilic substitution, of the methiodides of the pyrroloquinolines and pyrroloisoquinoline (compounds IX-XIII).

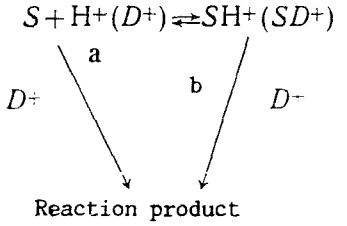


A study of the known salts precluded self-association and protonation of the nitrogen atom in the pyridine nucleus in an acidic medium. The rate of deuteration of isomers IX-XIII in CD_3COOD + D_2O was monitored by the ratio of the decreasing intensity of the signal from the β'-H of the pyrrole ring and a reference signal in the spectrum. The change in the reaction rate constant was examined over the 50-110°C temperature range. The thermodynamic parameters of isomers IX-XIII were calculated (Table 3). Along with the lowest activation energy, compound XII has the largest entropy factor, which is explained by the steric hindrances to the deuteration process. In fact, according to the MNDO calculation for compound XII, the NH group proton extends at a 27.8° angle from the molecular plane. This agrees with the PMR data, which show the disappearance of the SSCC with the imine group in the pyrrole fragment [17].

A study of the kinetics of protonation (deuteration) of compounds I-V in the β' position with changing pH of the medium graphically illustrates the soundness of choosing the quaternary salts as the objects of deuteration. It

is known [18] that the reaction mechanism of electrophilic substitution does not change when NH is replaced by NMe, and hence the reaction profile must be the same. For convenience of discussion, the experimental results are shown in the form of the graph (Fig. 3) presented in [18].

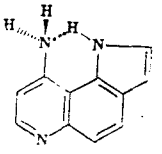
Analysis of the curves (Fig. 3) showed that for the least-basic compound IV (pK_a 4.70), in the range of acidity under consideration, the neutral substrate S takes part in the reaction, the rate of which grows because of the increasing activity (concentration) of the electrophilic agent (D^+). In this case, path *a* is the one realized:



Conversely, for the most basic pyrroloisoquinoline V (pK_a 6.57), the participant in the reaction is either the cation (SH^+), which is inert toward electrophiles, or the neutral molecule (S), which is active but present in low concentration, and the reaction follows path b. Of the two isomers close in basicity, I and III (Table 2), pyrroloquinoline I (pK_a 5.74) was studied. For it, the transition from the neutral to the protonated form was observed as the pH increased. The rate constant for the reaction for the protonated (deuterated) forms of I and V is comparable to the constant for the corresponding methiodides of these compounds (10^{-5} sec^{-1}, 90°C).

Analysis shows that the ordering in the series obtained by studying the basicities of molecules I-V (pK_a), the acidities (δ_{NH^∞}), the enthalpies of self association (ΔH_{as}), the activation energies for deuteration in the β' position (E_a) qualitatively agree with one another with the exception of isomer IV, for which structural features and the mutual influence of the nitrogen atoms determine another kind of self-association as well as an increased reactivity toward electrophilic substitution. From the data we obtained, the isomers form the following series with respect to the tendency toward electrophilic substitution: V < II ≈ I ≈ III < IV. This agrees with the yields of electrophilic substitution reactions [2, 3].

The relationship found affords an explanation also of the different tendency of compounds I-V toward nucleophilic substitution reactions. In fact, for the most basic (and consequently easily protonated) pyrroloisoquinoline V, the Chichibabin reaction goes most readily of all, and even α-hydroxy derivatives are obtained in good yield [3]. This is not observed in the case of the pyrroloquinoline isomers. For the latter it was possible to obtain α- and γ-amine derivatives with sodium amide in xylene. The α- and γ-derivatives are obtained in different ratios depending on the type of isomer [2]. The role of the mobility of the NH proton, of its ability to self-associate, is doubtless important since the Chichibabin reaction does not go with the NMe analogs. Nor does it go in liquid ammonia [2], which blocks the NH group proton. The presence of the NH···H complex strengthens the electrophilicity of the α- and γ-carbon atoms [5], orienting the NH group in both these positions while the geometric factor of the proximity of C_α (to which the NH_2 in azines is usually directed) to the pyridine nitrogen is not so important here because it is probable that an "inner salt" forms with a transfer of charge into the complex. The increase in the basicity of the pyrroloquinolines IV < I ≲ III ≲ II ~ V promotes the formation of the Na salt in the same order, and the inherent mobility of the NH proton promotes the splitting out of a hydride ion [14]. Salt formation (or protonation) at the pyridine nitrogen atom primarily depletes the electron density of the γ-carbon atom [5]. In connection with this, the growth of the content of γ-amine derivative also takes place in the same order [2]: for slightly basic compound IV, $\alpha >> \gamma$, for isomers II and III the α- and γ-isomers are about equal in amount, and for compound I an exception is found — the content is $\gamma > \alpha$ because of the formation of an intramolecular hydrogen bond by the mobile, pyrrole proton with the amine group, NH···NH_2 (δ_{NH} 13.50 ppm), as was shown by us at low temperatures.



Thus, the investigations carried out demonstrate an increase in the basicity in the pyridine fragment because of the decrease in the electron density in the π-rich pyrrole portion of the molecule. This allows one to explain, and to some degree to predict, the relative reactivity of the isomeric pyrroloquinolines and pyrroloisoquinolines in electrophilic and nucleophilic substitution reactions.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker WP-200-SY high-resolution NMR spectrometer. For the ^{1}H and ^{13}C nuclei, TMS served as an internal standard. For ^{15}N, a 1.0 M solution of $H^{15}NO_3$ in D_2O was the internal standard. The kinetics parameters were processed on an SM-4 computer, and the quantum chemical calculations on an ES-1061 computer.

The authors thank their co-worker at the Irkutsk Polytechnical Institute, D. K. Danovich, for carrying out the quantum chemical calculations by the MNDO method.

LITERATURE CITED

1. V. P. Shabunova, Zh. F. Sergeeva, R. N. Akhvlediani, A. M. Vasil'ev, N. B. Gorelova, and N. N. Suvorov, *Khim.-farm. Zh.*, No. 6, 53 (1978).
2. R. N. Akhvlediani, V. P. Shabunova, I. A. Morozova, T. A Volodina, and N. N. Suvorov, *Zh. Org. Khim.*, **17**, 1542 (1981).
3. T. F. Ponasenkova, R. N. Akhvlediani, V. V. Dikopolova, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, No. 4, 495 (1984).
4. A. M. Vasil'ev, Candidate's Dissertation, Moscow (1982).
5. L. N. Kurkovskaya, S. N. Krasnokutskii, V. P. Shabunov, R. N. Akhvlediani, and N. N. Suvorov, *Zh. Org. Khim.*, **22**, 1546 (1986).
6. L. N. Yakhontov and A. A. Prokopov, *Usp. Khim.*, **49**, 814 (1980).
7. I. P. Gragerov, V. K. Pogorelyi, and I. F. Franchuk, *The Hydrogen Bond and Fast Proton Exchange* [in Russian], Naukova Dumka, Kiev (1978).
8. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *High-Resolution Nuclear Magnetic Resonance Spectroscopy*, Vol. 1, Pergamon (1966), p. 565.
9. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *High-Resolution Nuclear Magnetic Resonance Spectroscopy*, Vol. 2, Pergamon (1966), p. 56.
10. B. V. Cheney, *J. Am. Chem. Soc.*, **90**, 5386 (1968).
11. P. J. Black, R. D. Brown, and M. L. Hefferman, *Austr. J. Chem.*, **20**, 1305 (1967).
12. S. N. Krasnokutskii, Candidate's Dissertation, Moscow (1988).
13. A. P. Gryaznov, Candidate's Dissertation, Moscow (1977).
14. A. F. Pozharskii, *Theoretical Foundations of Heterocyclic Chemisty* [in Russian], Khimiya, Moscow (1985).
15. M. Charton, *J. Org. Chem.*, **30**, 3341 (1965).
16. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4 (1977).
17. L. N. Kurkovskaya, V. P. Shabunova, R. N. Akhvlediani, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, No. 12, 1643 (1983).
18. J. H. Ridd, in: *Physical Methods in Heterocyclic Chemistry*, A. R. Katritzky (ed.), Vol. 4, Academic Press, New York (1977), p. 55.