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ACID–BASE CHARACTERISTICS OF 5-DIAZOIMIDAZOLE DERIVATIVES

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The transformation of 5-diazoimidazoles containing a carboxamide, ethoxycarbonyl, or nitro group at position 4 into diazonium salts was studied by UV and IR spectroscopy. It was shown by means of model compounds and chemical transformations that nitrosamines are involved in the transformation.

Study of the acid–base transformations of certain diazo compounds of the azole series into the corresponding diazonium salts has made it possible to obtain the pK_a values of these compounds [1]. For 5-diazoimidazole-4-carboxamide (Ia) it was shown that at pH 1, 2.5, and 7 it exists in the form of the diazonium salt, diazo compound, and diazohydroxide respectively [2].

The present communication is devoted to a study of the specific characteristics of the acid–base equilibrium in 5-diazoimidazole derivatives at acidities H_0 −3.38 to −0.02 and in the range of pH 0-10.

We studied the IR and UV spectra of the amide (Ia), ethyl 5-diazoimidazole-4-carboxylate (Ib), and 5-diazo-4-nitroimidazole (Ic) under various conditions. 4-Ethoxycarbonylimidazole-5-diazonium tetrafluoroborate (II) was synthesized from the imidazole (Ib) as model compound, and its spectra were recorded. The data are given in Table 1.

As seen from Table 1, in strongly acidic media (H_0 −1.9-0) the diazoimidazoles (Ia, b) change into the corresponding diazonium salts (IIIa, b). This is demonstrated by the shift of the frequency for the stretching vibrations of the diazo group in the IR spectra by 40-60 cm^{-1} toward larger values. [They approximate to the frequency for the vibrations of the diazonium group in the model compound (II).] In the UV spectra, recorded under the same conditions, a hypsochromic shift of the long-wave absorption maximum by 30 nm is observed. At pH 1 the IR spectrum of the ester (Ib) contains bands for the vibrations of both the diazo and the diazonium groups.

Thus, the presented data indicate that compound (Ib) in 1-5 N hydrochloric acid exists in the form of the diazonium salt (IIIb). At pH 1 there is an equilibrium between the salt (IIIb) and the diazo compound (Ib). At pH 5-9.2 only compound (Ib) is present in the solution.

The existence of ranges of pH in which 5-diazoimidazoles and the corresponding diazonium salts exist in the solution makes it possible to determine the pK_a values of the diazonium salts as NH acids. For this purpose the UV spectra of compounds (Ia, b) in 5-0.01 N hydrochloric acid and also of 5-diazo-4-nitroimidazole (Ic) in 50, 20, 10, 5, and 2.5% sulfuric acid (H_0 −3.38, −1.01, −0.31, −0.02, and 0 respectively) and in water were studied. Here it was unexpectedly found that the spectral curves of solutions of compounds (Ia, b) did not pass through an isobestic point (Figs. 1, 2). A similar pattern was observed for solutions of diazonitroimidazole (Ic) (Fig. 3). This could be explained by the slow establishment of an equilibrium between the two tautomeric forms (A and B) of the diazonium salts (III) and also by the participation of the diazo compound (I) in an equilibrium. However, only one band for the stretching vibrations of the diazonium group and not two was observed in the IR spectra of solutions of the diazoimidazole (Ib) in 5, 1, and 0.1 N hydrochloric acid. Consequently, under these conditions at least other compound is present in the equilibrium in addition to the diazonium salt and the diazo compound. It can be supposed that this is the product from the decomposition of the diazo compound, formed while the spectrum is being recorded. In fact, in the case of the amide (Ia) at pH 7-10 the spectral pattern changed rapidly, and its cyclization to 2-azahypoxanthine (IV), detected in the solution by TLC, was observed. This transformation was complete after 10 min at pH

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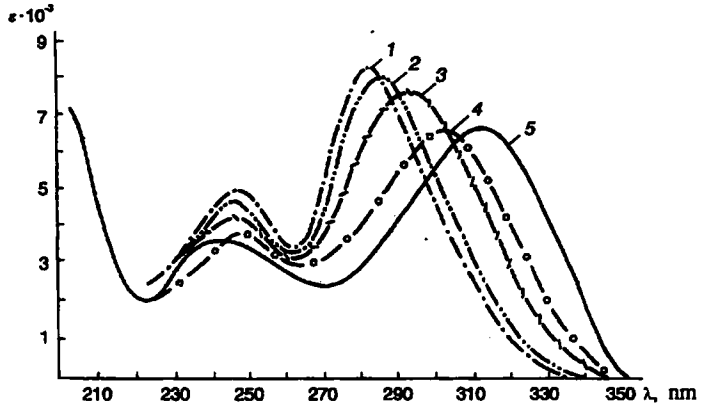


Fig. 1. UV spectra of the diazoimidazole (Ia) in: 1) 1-5 N hydrochloric acid; 2) 0.75 N hydrochloric acid; 3) 0.5 N hydrochloric acid; 4) 0.1 N hydrochloric acid; 5) water.

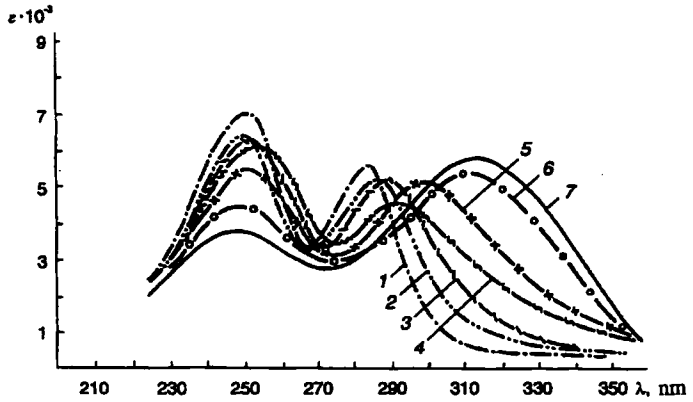


Fig. 2. UV spectra of the diazoimidazole (Ib) in: 1) 1-5 N hydrochloric acid; 2) 0.75 N hydrochloric acid; 3) 0.5 N hydrochloric acid; 4) 0.1 N hydrochloric acid; 5) 0.05 N hydrochloric acid; 6) 0.01 N hydrochloric acid; 7) water, pH 9.2; 0.1 N sodium hydroxide.

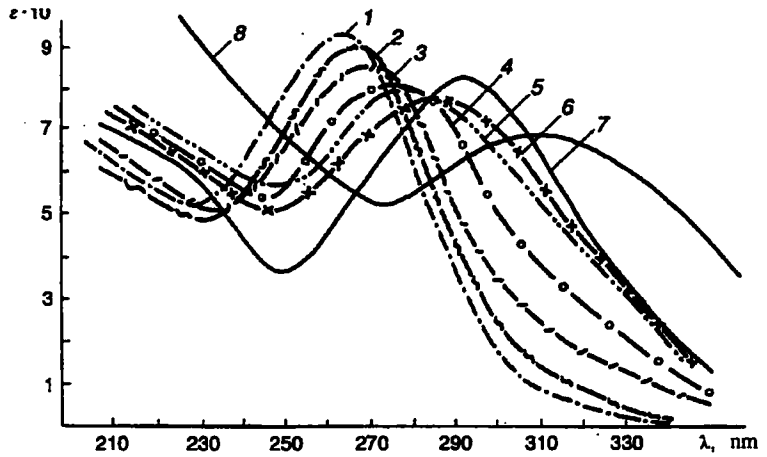
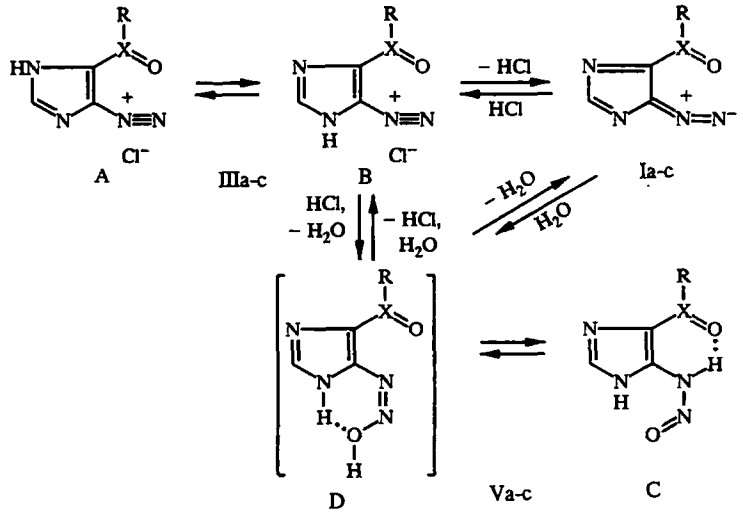


Fig. 3. UV spectra of the nitrodiazoimidazole (Ic) in: 1) 50% sulfuric acid; 2) 20% sulfuric acid; 3) 10% sulfuric acid; 4) 5% sulfuric acid; 5) 2.5% sulfuric acid; 6) 1.5% sulfuric acid; 7) water; 8) the spectrum of 4-nitro-5-nitrosomethyl-aminoimidazole (X) in water.

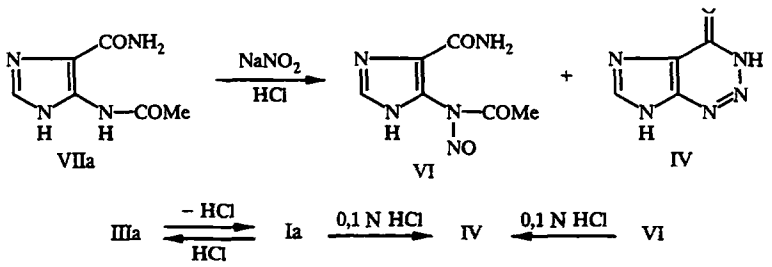
9.2 and 10. However, the UV spectra of the ester (Ib) and the nitro derivative (Ic) in 1, 0.1, and 0.01 N hydrochloric acid did not change as a result of holding at room temperature for 0.5-1 h. The spectra of solutions of the same compounds in 10% sulfuric acid at room temperature did not change for 3 h, while those in water did not change for 72 h. Changes were also not observed in the spectrum of the ester (Ib) after 24 h at pH 9.2. Impurities were not detected by TLC after holding in these solutions.



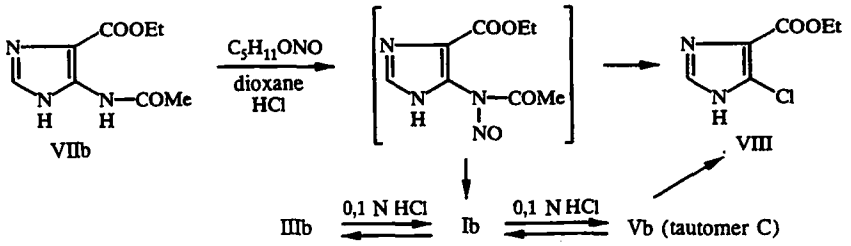
I, III, V a X = C, R = NH_2; b X = C, R = OEt; c X R = N→O

Thus, the investigated data indicate that a compound the IR spectrum of which does not contain absorption bands in the region of 2100-2300 cm^{-1} takes part in the equilibrium. This compound may be either the nitrosamine (V) (form C) or, which is less likely, its tautomer (form D).

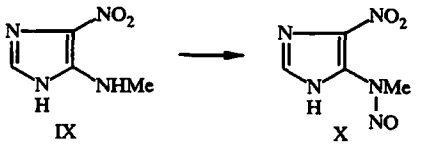
The model compound 5-N-nitrosoacetylaminoimidazole-4-carboxamide (VI), formed together the cyclization product (IV) during the treatment of 5-acetamidoimidazole-4-carboxamide (VIIa) with sodium nitrite in hydrochloric acid, was synthesized in order to confirm the presence of the nitrosamine in the equilibrium mixture. The IR spectrum of the amide (VI) contained a band for the vibrations of the nitrosoamino group at 1555 cm^{-1}, while the UV spectrum contained three absorption maxima at 250, 300, and (low intensity) 380 nm. Compound (VI) was also obtained during the nitrosation of the acetamide (VIIa) by isoamyl nitrite in dioxane, and in this case the main product at 40°C was the imidazotriazinone (IV).



The latter is also formed during treatment of compounds (Ia) and (VI) in 0.1 N hydrochloric acid. This does not contradict the idea that the nitrosamine (Va) may participate in the equilibrium but is also not a deciding argument in its favor. Sufficiently convincing evidence for the presence of the supposed equilibrium in compounds (Ib) and (Vb) was obtained during an attempt at the nitrosation of ethyl 5-acetamidoimidazole-4-carboxylate (VIIb) with isoamyl nitrite in dry dioxane saturated with HCl. Under these conditions ethyl 5-chloroimidazole-4-carboxylate (VIII), identical with a sample synthesized by the method in [3], was obtained instead of the expected nitrosamine compound. The same product was obtained when a solution of the diazo compound (Ib) in 0.1 N or 1 N hydrochloric acid was kept at room temperature for 18 days. The authors [3] reported that compound (Ib) does not enter into the Sandmeyer reaction even in the presence of copper monochloride. At the same time it is well known that nitrosamines are readily transformed into the corresponding chlorine derivatives in hydrochloric acid [4, 5].



Thus, the third partner in the equilibrium between the diazonium salt (IIIb) and the diazo compound (Ib) is the nitrosoamino compound (Vb). We also confirmed the presence of the nitrosamine to a certain degree by the nitrosation of 4-nitro-5-methylaminoimidazole (IX). In the UV spectrum of the synthesized 4-nitro-5-N-nitrosomethylaminoimidazole (X) there is a single absorption band at 315 nm (Fig. 3), which can fully explain the absence of an isobestic point in the spectra of compound (Ic) in sulfuric acid solutions of various concentrations and in water.



The obtained data make it possible to determine the limiting pH values at which the various forms of the diazoimidazoles exist and to reach a conclusion that the previously reported [2] conversion of the diazo compound (Ia) into the diazohydroxide (Va) (tautomer D) at pH 7 is unlikely.

EXPERIMENTAL

The IR spectra were recorded on a Beckmann IR-4260 instrument in tablets with potassium bromide or (in the case of solutions) in silver bromide cuvettes. The UV spectra were recorded on Beckmann 26 and Specord M40 instruments (at pH 9.2-10, $NaHCO_3-Na_2CO_3$ buffer). The PMR spectra were obtained on a Bruker WP-80 instrument (80 MHz) in DMSO-d_6 solution with TMS as internal standard. The purity of the compounds was monitored by TLC on Silufol UV-254 plates with 4:1:1 *n*-butanol–acetic acid–water (a) and 3:1 chloroform–ethanol (b) as eluants.

Compounds (Ia-c) were obtained by the respective methods in [6-8]; the amide (VIIa) and the ester (VIIb) were synthesized as described earlier [9], 4-nitro-5-aminoimidazole was obtained according to [10], and 2-azahypoxanthine was obtained by the method in [6]. Analytically and chromatographically pure samples were used for the spectral investigations.

The results of elemental analysis for C, H, N, and Cl correspond to the calculated data.

4-Ethoxycarbonylimidazole-5-diazonium Tetrafluoroborate (II). To a solution of 1.0 g (7 mmole) of compound (Ib) in 50 ml of absolute ether we added 5 ml of boron trifluoride etherate and 1 ml of 40% hydrofluoroboric acid. The reaction mixture was stirred at room temperature for 2 h. The oily layer that formed was separated and rubbed with absolute ether, and the crystals of the product (II) were filtered off. The yield was 0.4 g (27%); mp 216-218°C (decomp. with explosion); R_f 0.8 (a). Found %: C 28.0; H 3.0; N 22.2. $C_6H_7BF_4N_4O_2$. Calculated %: C 28.4; H 2.8; N 22.1.

The data from the UV and IR spectra are given in Table 1.

2-Azahypoxanthine (IV). A. We dissolved 0.1 g (0.83 mmole) of the diazoimidazole (Ia) in 10 ml of 0.1 N sodium hydroxide or 10 ml of $Na_2CO_3-NaHCO_3$ buffer solution with pH 9.2. After 10 min the reaction mixture was acidified to pH 3 with concentrated hydrochloric acid and cooled to 0-3°C. The precipitated product (IV) was filtered off and crystallized from water. The yield was 0.09 g (90%); mp 210°C (decomp.); R_f 0.64 (a). UV spectrum (water), λ_{max} (log ε): 213 (3.91), 245 (3.73), 280 nm (3.65). The product was identical (mp, UV spectrum, R_f) with compound (IV) synthesized by the method in [6].

B. A suspension of 0.1 g (0.83 mmole) of the diazoimidazole (Ia) in 25 ml of 0.1 ml of 0.1 N hydrochloric acid was stirred at room temperature for 24 h. The reaction mixture was evaporated under vacuum, and the residue was crystallized from water. The yield was 0.085 g (85%). The product was identical with the sample obtained by method A.

TABLE 1. UV and IR Spectra of Compounds (Ia-c, II)

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν (N_2 or N_2^+), cm^{-1}	Conditions
Ia	245 (3,6); 312 (3,76)		H_2O
		2200	KBr
		2180	$CHCl_3$
	250 (3,9); 285 (3,71)	2242	5 N HCl
Ib	240 (3,5); 312 (3,8)	2180	H_2O
	244 (3,55); 312 (3,83)		H_2O, pH 9,2
		2170	KBr
		2165	$CHCl_3$
	250 (3,85); 280 (3,75)	2240	5...1 N HCl
	253 (3,77); 290 (3,52)	2240, 2180	0,1 N HCl
Ic	297 (3,95)		H_2O
		2220	KBr
	265 (3,98)		50% H_2SO_4
II	251 (3,93); 280 (3,68)		Acetonitrile
		2265	KBr

C. A suspension of 0.2 g (1 mmole) of compound (VI) in 20 ml of 1 N hydrochloric acid was stirred at room temperature for 24 h. The reaction mixture was evaporated under vacuum, and the residue was crystallized from water. The yield was 0.075 g (54%). The product was identical with the sample obtained by method A.

5-N-Nitrosoacetylaminoimidazole-4-carboxamide (VI). A. To a suspension of 1.3 g (7.7 mmole) of compound (VIIa) in 6 ml of a 50% solution of sodium nitrite at 0-5°C we added dropwise 10 ml of 10% hydrochloric acid. The reaction mixture was stirred at the same temperature for 2 h. The precipitate of the original compound and the azapurine (IV) was filtered off. The filtrate was extracted with chloroform, and the extract was dried over anhydrous sodium sulfate and evaporated. The residue was rubbed with ether, and the crystals of the product (VI) were filtered off. The yield was 48 g (28%); mp 182°C; R_f 0.56 (a), 0.76 (b). IR spectrum, cm^{-1}: 1685 (CO), 1670 (amide), 1555 (NO). UV spectrum (ethanol), λ_{max} (log ε): 250 (3.87), 300 (3.65), 380 (3.01). Found %: C 36.4; H 3.7; N 35.8. $C_6H_7N_5O_3$. Calculated %: C 36.6; H 3.6; N 35.5.

B. To a solution of compound (VIIa) in 40 ml of glacial acetic acid and 40 ml of absolute dioxane at 40-45°C we added isoamyl nitrite until an excess of nitrous acid had formed. The reaction mixture was kept at the same temperature for 1.5-2 h, and the solvents were evaporated under vacuum. The residue was dissolved in 3 ml of ethanol and chromatographed in system (a) on a plate (20 × 40 cm) with a thin layer of silica gel (50-100 μ). The bands were developed in UV light. Compound (VI) was extracted with chloroform from the band with R_f 0.5 ± 0.1. The solvent was evaporated under vacuum. The yield was 0.05 g (20%). The product was identical with the sample obtained by method A (mp, IR and UV spectra).

From the silica gel band with R_f 0.7 ± 0.1 with ethanol we extracted 0.09 g (62%) of 2-azahypoxanthine (IV), identical with an authentic sample (mp, IR and UV spectra).

Ethyl 5-Chloroimidazole-4-carboxylate (VIII). To a solution of 0.31 g (1.58 mmole) of compound (VIIb) in 45 ml of absolute dioxane, saturated with dry hydrogen chloride, we added dropwise 0.25 ml (2 mmole) of isoamyl nitrite. The reaction mixture was kept at room temperature for 1.5 h, the solvent was evaporated under vacuum at 50-60°C, and a solution of sodium carbonate was added to the residue to pH 6. The precipitated ethyl 5-chloroimidazole-4-carboxylate (VII) was filtered off, washed with water and with alcohol, and crystallized from water. The yield was 0.16 g (58%); mp 178°C; R_f 0.34 (a), 0.67 (b). IR spectrum, cm^{-1}: 1720 (CO), 670 (C−Cl). UV spectrum (ethanol), λ_{max} (log ε): 238 nm (4.05). PMR spectrum (δ, ppm): 7.84 (1H, s, CH); 4.28 (2H, q, CH_2); 1.29 (3H, t, CH_3). Found %: C 41.5; H 4.0; N 16.2; Cl 20.2. $C_6H_7ClN_2O_2$. Calculated %: C 41.3; H 4.0; N 16.1; Cl 20.3.

The product was identical (mp, IR and UV spectra) with a sample synthesized from ethyl 1-benzyl-5-chloroimidazole-4-carboxylate by the method in [3]. In the filtrate after separation of compound (VII) two substances giving a color reaction with *o*-phenylenediamine were detected by TLC (system a). One of them (R_f 0.85) coincided on the chromatogram with the diazo compound (Ib), while the second (R_f 0.75) was possibly a nitrosoamino compound. However, it was not possible to isolate these compounds by TLC.

B. A solution of 0.1 g (0.7 mmole) of the diazo compound (Ib) in 50 ml of 0.1 or 1 N hydrochloric acid was kept at 20-22°C for 18 days until the initial compound (Ib) had disappeared according to TLC, and it was then evaporated under vacuum. The residue was dissolved in ethanol and filtered. The filtrate was evaporated to dryness under vacuum, and the residue was crystallized from water. The yield was 0.06 g (49.5%). The product was identical with a sample of the compound synthesized by method A (mp, IR and UV spectra).

4-Nitro-5-N-nitrosomethylaminoimidazole (X). To a suspension of 0.6 g (4.2 mmole) of 5-methylamino-4-nitroimidazole in 2.5 ml of 5 N sulfuric acid, cooled to −5°C, we added 2.9 g (4.2 mmole) of sodium nitrite in 5 ml of water. The reaction mixture was kept at the same temperature for 1 h, and the precipitated product (X) was filtered off, washed with water, and dried under vacuum. The yield was 0.59 g (82%); mp 155-157°C (decomp.); R_f 0.8 (a), 0.66 (b). IR spectrum, cm^{-1}: 1370, 1525 (NO_2), 1500 (NO). UV spectrum (in water), λ_{max} (log ε): 315 nm (3.67). Found %: C 27.8; H 3.1; N 40.8. $C_4H_5N_5O_3$. Calculated %: C 28.1; H 2.9; N 40.0.

REFERENCES

1. J. Vilarassa, E. Melendes, and J. Elguero, Tetrahedron Lett., No. 17, 1609 (1974).
2. J. K. Horton and M. F. G. Stevens, J. Chem. Soc. Trans. Perkin I, No. 5, 1433 (1981).
3. T. Brown, G. Shaw, and J. Durant, J. Chem. Soc. Trans. Perkin I, No. 10, 2310 (1980).
4. H. Gehlen and J. Dost, Annalen, **665**, 144 (1968).
5. Yu. Yu. Morzherin, E. V. Tarasov, and V. A. Bakulev, Khim. Geterotsikl. Khim., No. 4, 554 (1994).
6. J. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, J. Org. Chem., **26**, 2396 (1961).
7. J. F. Shealy, C. A. Krauth, R. Pitillo, and D. E. Hunt, J. Pharm. Sci., **56**, No. 1, 147 (1967).
8. V. S. Mokrushin, I. S. Selezneva, T. A. Pospelova, V. K. Usova, S. M. Malinskaya, G. M. Anoshina, T. É. Zubova, and Z. V. Pushkareva, Khim.-farm. Zh., No. 3, 303 (1982).
9. V. S. Mokrushin, T. A. Pospelova, V. A. Bakulev, E. F. Golovina, S. L. Nikolaeva, and Z. V. Pushkareva, Khim. Geterotsikl. Khim., No. 2, 247 (1984).
10. V. S. Mokrushin, N. A. Belyaev, M. Yu. Kolobov, and A. N. Fedotov, Khim. Geterotsikl. Khim., No. 6, 808 (1983).