Kinetics of hydrolysis of five-membered *C*-nitroheterocycles: pyrazole, imidazole, 1,2,4-triazole, and isoxazole derivatives

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Alkaline hydrolysis of mono- and dinitro derivatives of five-membered heterocycles, *viz.*, pyrazole, imidazole, 1,2,4-triazole, and isoxazole, is accompanied by the elimination of the nitro group in the form of a nitrite anion. The hydrolysis kinetics was studied by the polarographic and photometric methods. The experimentally determined hydrolysis rate constants depend on the nature of the heterocycle. A possible mechanism for hydrolytic transformations of the compounds under study was proposed on the basis of the calculated thermodynamic parameters of the reaction ($\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$).

Key words: *C*-nitro derivatives of five-membered heterocycles, pyrazole, imidazole, isoxazole, nitrite anion, NO-donor activity, xanthine oxidase, free activation energy, activation entropy, activation enthalpy, Gibbs energy.

Some nitro compounds[1—3] are exogenic generators of nitrogen oxide. The activity of *O*-nitro (nitroesters[1]) and *N*-nitro compounds (in particular, *N*-nitropyrazoles[4]) in the formation of NO is well known. Many aliphatic *C*-nitro derivatives can also evolve NO under hydrolytic conditions.[1] In addition, it is known that some *C*-nitroheterocycles, such as medicines of the nitrofuran[5,6] and nitroimidazole[7,8] series, can exhibit the NO-donor activity. However, no systematic studies in the area of *C*-nitro compounds functioning as nitrogen oxide donors were performed.

In the present work, we studied *C*-nitro derivatives of pyrazole, imidazole, 1,2,4-triazole, and isoxazole (**1—16**) as potential NO donors.

It is known that one of the routes for synthesis of nitrogen oxide in the organism is the nitrite-nitrate-xanthine oxidase method. Xanthine oxidase is capable of catalyzing NO generation under anaerobic conditions, using nitrite ions as the substrate.[9] In a recent publication[10] the problem of heterocyclic ring opening under hydrolytic conditions is considered. It was indicated that these processes can occur *via* both the non-enzymatic mechanism and enzymatic catalysis. It seemed of interest to study the ability of these compounds to generate a nitrite ion under alkaline hydrolysis conditions and to reveal the effect of the heterocycle nature and number of nitro groups in the heterocycle structure on the efficiency of elimination of the nitro group in the form of NO_2^-.

Results and Discussion

Compounds **1—15** were synthesized according to Scheme 1.

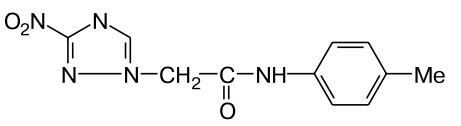
Acid chlorides (see Scheme 1) were synthesized by reflux of the corresponding compounds **17a—c** [11] and **17d** [12] in excess $SOCl_2$ and further used without additional purification. The nitration of 5-methyl-3-isoxazolecarboxylic acid (**18**) with sodium nitrate in H_2SO_4 afforded nitro acid **17e** (Scheme 2). 1-(*p*-Methoxyphenyl)carbamidomethyl-3,4-dinitro-5-methoxypyrazole (**10**) has been described elsewhere.[13]

Acid **17e** * decomposes gradually on storage and, hence, it was converted into acid chloride. The latter was used to synthesize amide **15** without additional purification.

When studying the alkaline hydrolysis of synthesized compounds **1—16**, the formation of the nitrite anion was found, which is one of markers of nitrogen oxide formation and whose yield depends strongly on the heterocycle nature (Table 1).

* ^{1}H NMR data (δ, DMSO-d_6): 2.3 (s, 3 H).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2719—2725, December, 2005.



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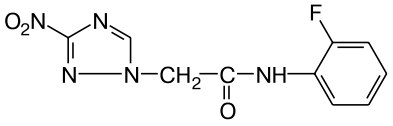

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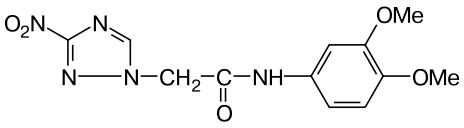

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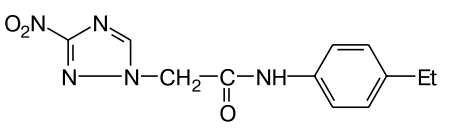

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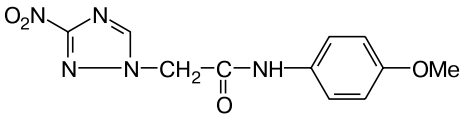

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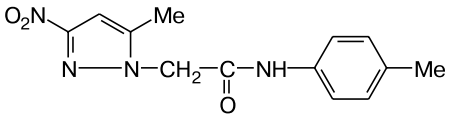

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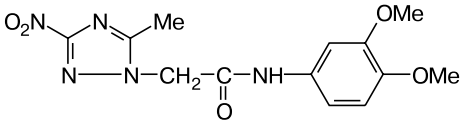

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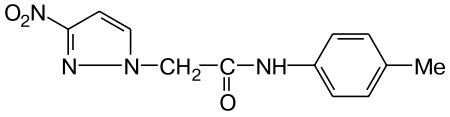

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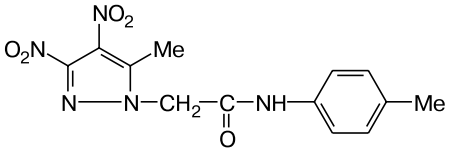

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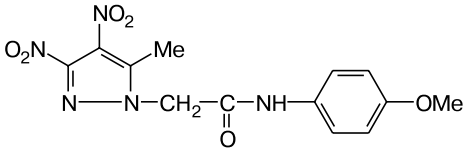

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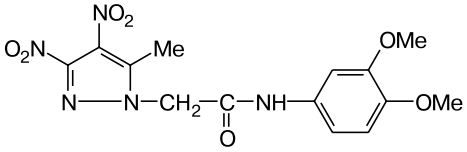

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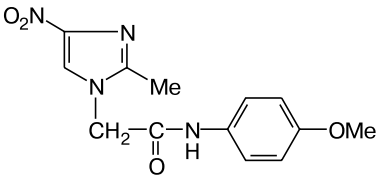

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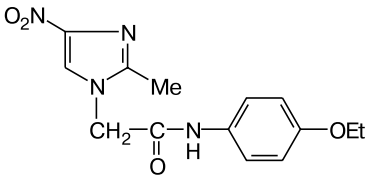

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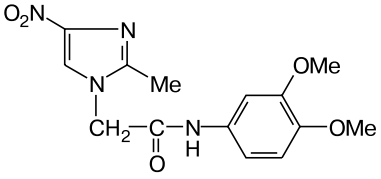

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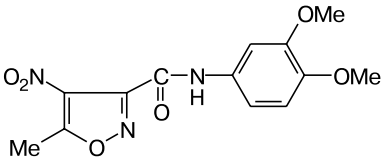

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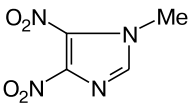

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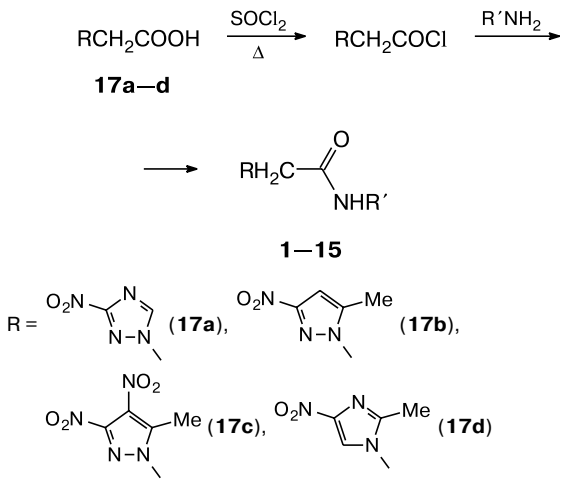
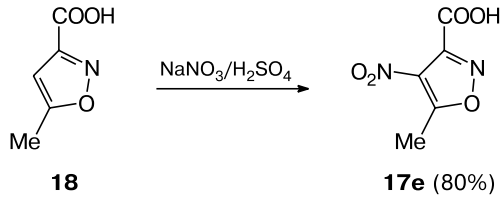
In principle, two main routes of nitrite anion elimination are possible under these conditions. The first route is *ipso*-substitution characterized by the formation of the corresponding σ-complex followed by the elimination of the NO_2^- anion. The second route includes the preliminary heterocycle opening and dearomatization of the system followed by the liberation of the nitrite anion from the non-heterocyclic precursor.

To compare activities of compounds **1—16** as potential NO-donors, let us compare the aromaticity parameters of the basic heterocycles, whose derivatives are studied in the present work.

Scheme 1



Scheme 2



According to calculations, isoxazole is least aromatic among other five-membered heterocycles.[14] The mechanism of isoxazole opening under the action of alkali was studied in detail,[15] and the order of decreasing aromaticity is as follows: benzene > 1,2,4-triazole > pyrazole > > imidazole > isoxazole.[16]

On heating solutions of mononitro derivatives of 1,2,4-triazole **1—5** in 0.1 *M* NaOH containing 10% etha-

Table 1. Yield of the nitrite anion due to hydrolytic transformations of amides **1—16** in a 10% aqueous-alcohol solution of 0.1 *M* NaOH

Amide	*T*/°C	*t*/min	Yield (%)	Amide	*T*/°C	*t*/min	Yield (%)
1	40	60	0	**9**	40	60	6.7
		120	0			120	10
	70	60	0.8		70	60	18.6
		120	2.1			120	28.1
2	40	60	0	**10**	40	60	6.5
		120	0			120	10.4
	70	60	0.9		70	60	19
		120	1			120	27.3
3	40	60	0	**11**	40	60	7
		120	1.2			120	12
	70	60	2.9		70	60	17.9
		120	3.5			120	27
4	40	60	1	**12**	40	60	0
		120	1.3			120	0
	70	60	2		70	60	0.7
		120	3.2			120	1.0
5	40	60	0.5	**13**	40	60	0
		120	1.2			120	0.1
	70	60	2.3		70	60	0.6
		120	2.9			120	1.32
6	40	60	0	**14**	40	60	0
		120	0			120	0.5
	70	60	0.8		70	60	1.2
		120	0.9			120	2
7	40	60	0	**15**	40	60	5
		120	0			120	7
	70	60	1.3		70	60	9
		120	1.5			120	16
8	40	60	0	**16**	40	60	103*
		120	0			120	108*
	70	60	0.8		70	60	125*
		120	1.3			120	130*

* The yield of the nitrite anion more than 100% in the case of the dinitroimidazole derivative is a consequence, probably, of the quantitative elimination of the first nitro group and the onset of consumption of the second group.

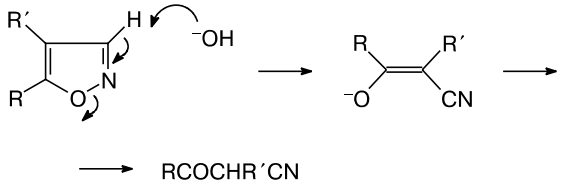
Table 2. Rate constants (k_{av}) at different temperatures for derivatives of dinitropyrazole **10**, isoxazole **15**, and dinitroimidazole **16**

Compound	k_{av}/s^{-1} at temperature/°C				
	25	35	40	50	70
10	—	$4.4 \cdot 10^{-5} \pm 2.6 \cdot 10^{-6}$	$9.4 \cdot 10^{-5} \pm 8.5 \cdot 10^{-6}$	$3.5 \cdot 10^{-4} \pm 3.5 \cdot 10^{-5}$	—
15	$3.1 \cdot 10^{-5} \pm 4.6 \cdot 10^{-6}$	—	$9.3 \cdot 10^{-5} \pm 1.1 \cdot 10^{-6}$	—	$3.9 \cdot 10^{-4} \pm 6.2 \cdot 10^{-5}$
16	—	$2.3 \cdot 10^{-3} \pm 3.1 \cdot 10^{-4}$	$5.0 \cdot 10^{-3} \pm 5.0 \cdot 10^{-4}$	$3.1 \cdot 10^{-5} \pm 4.6 \cdot 10^{-6}$	—

nol at 70 °C for 180 min, the isolation of the nitrite anion depends weakly on the basic heterocycle. For derivatives of nitropyrazole **6—8** and nitroimidazole **12—14**, the yield of NO_2^- is ~2%, while its yield for nitrotriazole is somewhat higher (~3%). Storage of nitroisoxazole derivative **15** under these conditions leads to a considerable degradation of the starting molecule, and NO_2^- is formed in 16% yield.

Under similar conditions, the isoxazole cycle cleavage proceeds[15] *via* Scheme 3.

Scheme 3



In the present work, we studied the degradation of *N*-(3,4-dimethoxyphenyl)carbamoyl-4-nitro-5-methylisoxazole (**15**). The rate constants were determined under assumption that the process is a pseudo-monomolecular reaction (since the main reagent, *viz.*, alkali, is taken in a high excess). Although the degree of decomposition of compound **15** with nitrite anion elimination is relatively high, on a fairly long heating in a great excess of alkali the degradation of this isoxazole derivative can also occur in other directions. This uncertainty decreases the accuracy of determination of reaction rate constants and, hence, thermodynamic parameters. It was found that the differences in the kinetic parameters (reaction rate constants) exceed 10%, and the average constant values (k_{av}), available from the spectrophotometric and polarographic measurements, were used for further calculations.

We attempted to use the k_{av} values to analyze a possible mechanism of NO_2^- elimination. The k_{av} values obtained at different temperatures for compounds **10**, **15**, and **16** are given in Table 2. The thermodynamic parameters calculated from these data are presented in Table 3.

A relatively low free activation enthalpy can be attributed to a small energy consumption needed to cleave the N—O bond and open the isoxazole cycle, which possesses, as already mentioned, the lowest aromaticity in the series of five-membered heterocycles. The high negative activation entropy indicates the formation of a highly ordered transition state.[17]

Table 3. Free energy ($\Delta G^{\neq}$), enthalpy ($\Delta H^{\neq}$), and free entropy ($\Delta S^{\neq}$) of activation of the hydrolytic cleavage of compounds **10**, **15**, and **16**

Compound	$\Delta G^{\neq}$	$\Delta H^{\neq}$	$-\Delta S^{\neq}$
	kcal mol^{-1}		/cal mol^{-1} K^{-1}
10	24.1±3.0	26.8±2.7	8.6±0.3
15	24.4±2.5	11.1±1.5	41.8±1.2
16	13.2±1.2	12.1±1.2	30.2±1.5

The general presumable scheme of elimination of the nitro group in the form of NO_2^- on heating of derivative **15** in the presence of alkali can be presented as Scheme 4.

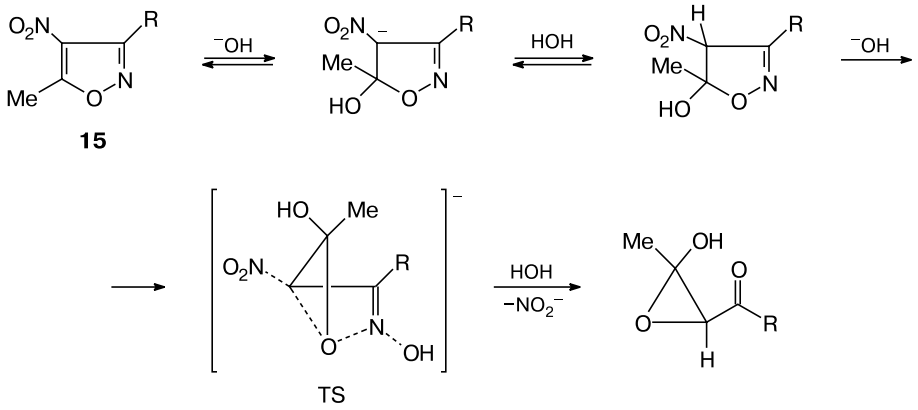
Evidently, the intensity of interaction with nucleophilic reagents should increase sharply with an increase in the number of electron-withdrawing groups in the heterocycle. On going from mono- to dinitro derivatives, nitrite anion elimination due to the nucleophilic attack becomes much more probable.

The reaction rate constants obtained by the study of the alkaline degradation of compound **10** are given in Table 2. The thermodynamic parameters of the process calculated from these data are presented in Table 3. The amount of the nitrite ion reaches 27%, which is much higher than that for the mononitro derivatives. In this case, a rather high activation enthalpy indicates a probable bond cleavage in the transition state. A comparatively low negative activation entropy indicates that the bond is almost cleaved and the transition state is similar to the final structure (Scheme 5). Due to this, the entropy value of the transition state is similar to that of the initial state.

The behavior of 1-methyl-4,5-dinitroimidazole (**16**) differs so strongly from that of pyrazole derivative **10** that this cannot be explained by the difference in the nature of substituents in position 1. For example, compound **16** exhibits the fast (within approximately 12 min at 50 °C) and qualitative elimination of the nitrite anion. In addition, the next step of interaction is a much slower process: degradation of the intermediate that formed with withdrawal of one more nitro group as the second nitrite anion.

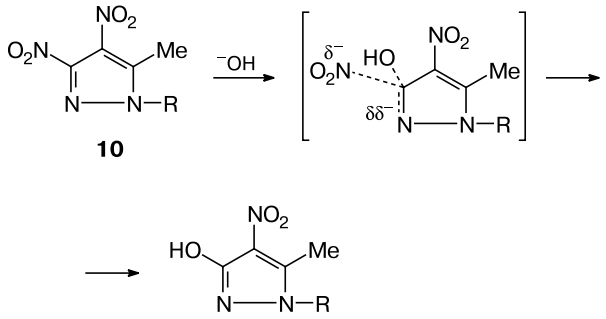
In this case, the reaction mechanism differs from the mechanism of degradation of pyrazole derivative **10**. For compound **16**, the activation enthalpy is much lower,

Scheme 4



TS is transition state

Scheme 5



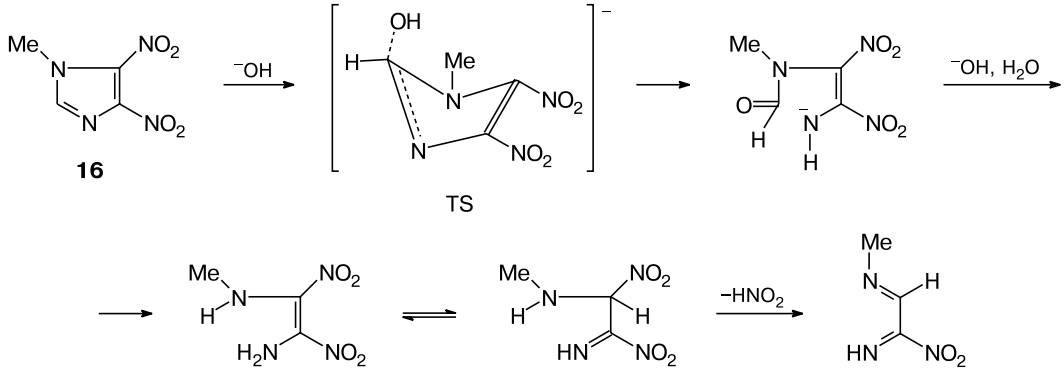
R = *p*-$MeOC_6H_4NHCOCH_2$

while the activation entropy is expressed by a considerable negative value as for mononitroisoxazole derivative **15**. The imidazole cycle is much less aromatic than the triazole and pyrazole cycles. The results obtained for compound **16** can be interpreted on the basis of the following assumption. Under the conditions of attack of the hydroxyl anion, the primary step of imidazole cycle degradation is imidazole ring opening (Scheme 6), which occurs in the rate-determining step of the process of NO_2^- group elimination. Similar reactions of imidazole cycle opening under hydrolytic and other conditions with elimination of nitrogen oxide in the form of the nitrite anion are described in literature.[1–3]

It should be mentioned in conclusion that the above-presented schemes require additional proves and should be considered presently as presumable. The main result of the present work is the reliably determined experimental fact that the studied *C*-nitro- and especially dinitroazole derivatives can eliminate the nitrite anion. A possibility of its elimination is determined by the structural features and stability of these derivatives under the conditions of nucleophilic attack.

The process of nitrite anion elimination was studied on heating in alkali, *i.e.*, under the conditions far from physicological. In many cases it remains unknown how the hydrolysis of heterocycles occurs in the organism. However, for thiazolidine derivatives, the cycle cleavage is known to be catalyzed by enzyme 5-oxo-L-prolinase. Our experiments represent a model process conducted under non-physicological conditions. However, it cannot

Scheme 6



TS is transition state

be excluded that that the compounds under study can be sources of NO in the organism as well, because the rates of the processes and yields of final products increase multiply under enzymatic catalysis conditions. The fact of determination of significant amounts of the nitrite anion during degradation of five-membered nitroheterocycles suggests substantially that these compounds can be generators of nitrogen oxide in the living organism as well.

From this point of view, it is important that the compounds of the type under study and their analogs can liberate the nitrite anion and are of significant interest due to their biological activity.

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-300 instrument. Chemical shifts are presented relative to Me_4Si. The course of the reaction and purity of substances were monitored by TLC on Silufol UV-254 plates.

5-Methyl-4-nitro-3-isoxazolecarboxylic acid (17e). Sodium nitrate (7.1 g) was added with stirring at room temperature for 30 min to a solution of 5-methyl-3-isoxazolecarboxylic acid (Acros, 7.0 g, 0.055 mol) in concentrated H_2SO_4 (100 mL). The reaction mixture was stored for 8 h at 50 °C, then poured into ice (400 g), extracted with ether (2×100 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo*, and the residue was crystallized from 1,2-dichloroethane. The yield was 7.5 g (79%).

Synthesis of amides 1—15 (general procedure). A solution of acid (0.001 mol) in $SOCl_2$ (10 mL) was refluxed for 4 h, an excess of $SOCl_2$ was evaporated, and a solution of amine (0.001 mol) in MeCN (10 mL) was added. The mixture was heated to boiling and left to stand for 16 h. The resulting mixture was diluted with water (20 mL), and the precipitate that formed was filtered off, washed with 10% NH_3 and water, and dried in air.

In all cases, the yields of amides were 90—95%. The melting points and ^{1}H NMR and elemental analysis data for the synthesized compounds are collected in Table 4.

The kinetic parameters were measured by the photocolorimetric and polarographic methods.

The solutions under study with a concentration of 10^{-4}—10^{-3} mol L^{-1} in the presence of an 0.1 *M* solution of NaOH and 10% alcohol were maintained for 3—4 h at three temperatures: 23, 40, and 70 °C. Samples for photocolorimetric and polarographic studies were taken at certain time intervals

Table 4. Physicochemical properties of compounds **1—15**

Compound	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR data (DMSO-d_6, δ)
		C	H	N		
1	188	50.82 50.57	4.08 4.24	26.81 26.81	$C_{11}H_{11}N_5O_3$	2.3 (s, 3 H); 5.3 (s, 2 H); 7.2, 7.5 (both d, 2 H each); 8.9. 10.4 (both s, 1 H each)
2	135	45.17 45.29	2.83 3.04	26.07 26.41	$C_{10}H_8FN_5O_3$	5.3 (s, 2 H); 7.2 (m, 3 H); 7.9 (m, 1 H); 8.9, 10.4 (both s, 1 H each)
3	195	46.86 46.91	4.29 4.26	22.38 22.79	$C_{12}H_{13}N_5O_5$	3.7 (s, 6 H); 5.3 (s, 2 H); 6.9, (both d, 2 H each); 7.3, 8.9, 10.4 (all s, 1 H each)
4	147	52.34 52.36	4.66 4.76	25.63 25.44	$C_{12}H_{13}N_5O_3$	1.2 (t, 3 H); 2.6 (q, 2 H); 5.3 (s, 2 H); 7.2, 7.5 (both d, 2 H each); 8.9, 10.4 (both s, 1 H each)
5	126	47.47 47.66	4.08 4.00	24.56 26.26	$C_{11}H_{11}N_5O_4$	3.8 (s, 3 H); 5.3 (s, 2 H); 6.9, 7.5 (both d, 2 H each); 8.9, 10.4 (both s, 1 H each)
6	177	57.03 56.93	5.10 5.14	20.07 20.43	$C_{13}H_{14}N_4O_3$	2.2, 2.3 (both s, 3 H each); 5.1 (s, 2 H); 6.9 (s, 1 H); 7.2, 7.5 (both d, 2 H each); 10.3 (s, 1 H)
7	60	58.25 58.31	5.51 5.60	19.50 19.44	$C_{14}H_{16}N_4O_5$	1.2 (t, 3 H); 2.3 (s, 3 H); 2.6 (q, 2 H); 5.1 (s, 2 H); 6.9 (s, 1 H); 7.2, 7.5 (both d, 2 H each); 10.3 (s, 1 H)
8	186	53.89 53.79	4.82 4.86	19.11 19.30	$C_{13}H_{14}N_4O_4$	2.3 (s, 3 H); 5.1 (s, 2 H); 6.9 (d, 3 H); 6.9 (s, 1 H); 7.5 (d, 2 H); 10.3 (s, 1 H)
9	209	48.94 48.91	4.00 4.10	22.12 21.93	$C_{13}H_{13}N_5O_5$	2.3, 2.7 (both s, 3 H each); 5.2 (s, 2 H); 7.2 (d, 2 H); 7.5 (d, 2 H); 10.3 (s, 1 H)
10	172	47.01 46.57	3.91 3.87	21.04 20.89	$C_{13}H_{13}N_5O_6$	2.6 (s, 3 H); 5.2 (s, 2 H); 6.9, 7.5 (both d, 2 H each); 10.2 (s, 1 H)
11	174	45.77 46.03	3.94 4.14	18.97 19.17	$C_{14}H_{15}N_5O_7$	2.6 (s, 3 H); 3.7 (s, 6 H); 5.3 (s, 2 H); 6.9, 7.1 (both d, 1 H each); 7.3 (d, 2 H); 10.3 (s, 1 H)
12	251	57.04 56.93	5.14 5.05	20.11 20.43	$C_{13}H_{14}N_5O_4$	2.2, 2.3 (both s, 3 H each); 5.0 (s, 2 H); 7.1, 7.5 (both d, 2 H each); 8.3, 10.3 (both s, 1 H each)
13	250	58.08 58.33	5.54 5.59	19.64 19.43	$C_{14}H_{16}N_4O_3$	1.2 (t, 3 H); 2.6 (q, 2 H); 5.0 (s, 2 H); 7.2 (d, 2 H); 7.5 (d, 2 H); 8.3, 10.3 (both s, 1 H each)
14	250	52.45 52.50	5.16 5.04	17.47 17.49	$C_{14}H_{16}N_4O_5$	2.3 (s, 3 H); 3.7 (s, 6 H); 5.0 (s, 2 H); 6.9, 7.1 (both d, 1 H each); 7.3, 8.3, 10.3 (all s, 1 H each)
15	205	51.99 52.34	4.26 4.71	13.47 13.08	$C_{14}H_{15}N_3O_6$	2.9 (s, 3 H); 3.8 (s, 6 H); 7.0, 7.2 (both d, 1 H each); 7.3, 11.0 (both s, 1 H each)

(at first, at an interval of 10 min and then every half an hour). Three or more entries were carried out at each temperature.

The Griess procedure[18] was used for the photocolorimetric determination of the yield of the nitrite anion: formation of a colored azo dye due to diazotization followed by azocoupling. A 2% solution of sulfanilic acid in 1 *M* HCl was used as a diazo component, and an 0.3% aqueous solution of α-naphthylethylenediamine hydrochloride served as an azo component.

The absorbance of colored solutions was determined on a KFK-3-01 photoelectrocolorimeter, which makes it possible to measure the absorbance in the wavelength interval from 200 to 900 nm. Cells with an optical path length of 1 cm were used. The absorption maximum of colored solutions was detected at 542 nm. The yield of nitrite in percentage was calculated from the ratio of the absorbance of solutions under study to the absorbance of the series of solutions of sodium nitrite with a specified concentration.

Polarographic studies were carried out on a dropping mercury electrode with the parameters $\tau = 2.2$ s, $m = 1$ mg s^{-1} *via* the three-electrode scheme on a PU-1 polarograph (Belarus) in the dc and differential-impulse polarographic mode. An XY Recoder 4103 two-coordinate recorder (Czechia) was used to detect polarograms. A saturated calomel electrode served as reference. Measurements were conducted in a temperature-controlled cell at 25—50 °C. Before polarogram recording, air oxygen was preliminarily removed from solutions in the cell by purging with an inert gas (argon).

The yield of NO_2^- during hydrolysis of the compounds under study was determined by a decrease of the four-electron reduction wave of the nitro group in time.

Once a linear dependence of the wave height (H) on the working solution (C) (polarographic method) or that of the absorbance (A) on C (spectrophotometric method) was established for a concentration interval of 10^{-5}—10^{-3} mol L^{-1}, the hydrolysis rate constants were calculated as for a quasi-monomolecular reaction of the first order, because alkali for hydrolysis is taken in an amount by two—three orders greater than the amount of the compound under study.

The reaction rate constants were determined by the graphical method from a slope of the plot $-\ln H_{lim}/H$ (or $-\ln A_{lim}/A$) *vs.* t (H is the height of the polarographic wave, A is the absorbance, and t is time/min). The experimental values corresponding to the initial linear regions of the kinetic curves were taken into account in calculations (in a time interval of 10—60 min).

The activation enthalpy and entropy values were calculated by the formulas[19]:

$$\Delta H^{\neq} = \Delta G^{\neq} - RT,$$

$$\Delta S^{\neq} = [\ln k - \ln(kT/h) + (E - RT)/(RT)]R,$$

where $\Delta H^{\neq}$ is the free activation enthalpy (kcal mol^{-1}), $\Delta G^{\neq}$ is the free activation energy (kcal mol^{-1}), $\Delta S^{\neq}$ is the free activation entropy (cal mol^{-1} K^{-1}), E is the activation energy (kcal mol^{-1}), k is Boltzmann constant ($0.33 \cdot 10^{-23}$ cal K^{-1}), T is the absolute temperature (K), k is the rate constant (s^{-1}), h is Planck's constant ($13.744 \cdot 10^{-34}$ cal s), and R is the gas constant (2.02 cal mol^{-1} K^{-1}).

The average values of the rate constants obtained after three—four entries at each temperature were used in calculations. The relative errors, being ±10% on the average, were calculated for each value.

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Received January 19, 2005;
in revised December 7, 2005