# STUDY OF THE PROTOTROPIC TAUTOMERISM IN THE 1,2,4-TRIAZINO[2,3-a]BENZIMIDAZOL-(4H)-3-ONE SYSTEM

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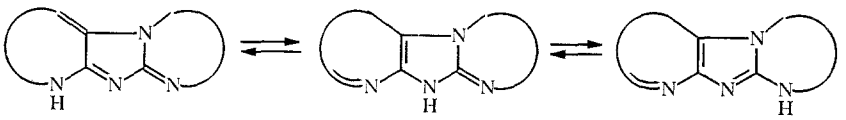
*The peri-prototropic tautomerism of 1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one in the gas and liquid phases was studied by IR and PMR spectroscopy, high-efficiency liquid chromatography, mass spectrometry, and photoionization. Analytical criteria were found for the fixed tautomeric forms of this compound, which permitted us to evaluate the nature of the methylation reaction carried out by different methods.*

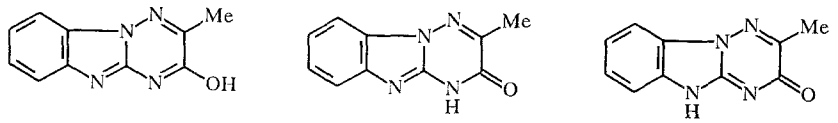
The ever increasing interest in fused imidazole systems (1,2,4-triazoles and tetrazoles) having a common nitrogen atom with the other azine or azole heterocycle is a function of their high biological activity (hypotensive, neuroleptic, diuretic, and anti-viral effects) [1-5] and their practical use as steel corrosion inhibitors, organic luminophores, dyes for polymer materials, and active media for lasers ("imitrines") [6-8]. The development of practical syntheses for such compounds requires detailed knowledge of their structural and chemical properties. The question of the possible existence of isomers or tautomers (A ⇄ B ⇄ C) among compounds with a guanidine or amidine fragment has virtually not been studied and remains open [9, 10].



A B C

In previous work on the mass-spectral fragmentation of such compounds, we found indications of prototropic tautomerism or isomerism when the hydrogen atom or heteroatom of one of the rings migrated to the nitrogen atom of the other ring (peri tautomerism or isomerism). Thus, the mass spectra of 4-substituted 2-methyl-7,8-diphenyl-imidazo[1,2-b]-1,2,4-triazepine [11] show ions of protonated phenylnitrile with m/z 104 along with diphenylaziridine ions with m/z 193.

In the present work, we studied the prototropic peri tautomerism or isomerism of 2-methyl-1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one (I), which theoretically may exist in forms $\Phi_1$—$\Phi_3$.



$\Phi_1$ $\Phi_2$ $\Phi_3$

Solution of this problem requires synthesis of fixed forms of tautomers $\Phi_1$—$\Phi_3$.

In this study, synthetic methods were developed, which permitted us to obtain representatives of forms $\Phi_2$ and $\Phi_3$ stabilized by a methyl group.

The representative of form $\Phi_2$, namely, 2,4-dimethyl-1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one (II) was synthesized by the condensation of diamine IV with pyruvic acid in 2-propanol [14]. Product II was also obtained by methylation of triazinobenzimidazolone I [15] using methyl iodide or dimethyl sulfate (see Experimental).

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TABLE 1. Physicochemical Indices of 1,2,4-Triazino[2,3-a]benzimidazol-3-ones (I)-(III)

| Compound | IR spectra $cm^{-1}$ with KBr | | PMR spectrum, δ, ppm | | | IR spectra $cm^{-1}$ with KBr | |
|---|---|---|---|---|---|---|---|
| | $\nu_{C=O}$ | $\nu_{NH}$ | C—$CH_3$, s, (3H) | —$CH_3$, s, (3H) | $H_{arom}$, m (4H) | min | purity, % |
| I | 1640 (s.)<br>1665* (s.) | 3220<br>3240 | 2,302 | — | 7,289...7,800 | 4,06 | 99,76 |
| II | 1680 (s.)<br>1685* (s.) | —<br>— | 2,371 | 3,560 | 7,266...7,777 | 11,02 | 99,78 |
| III | 1660 (s.)<br>1670* (s.) | —<br>— | 2,308 | 3,646 | 7,250...7,809 | 10,13 | 99,67 |

*Spectra taken in dioxane solution.

TABLE 2. Results of the Alkylation of 2-Methyl-1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one

| Method | Reagent | II/III/isomer ratio | | Yield, % |
|---|---|---|---|---|
| | | according to PMR data | according to HELC | |
| A | $CH_3I$ | Only II | | 61 |
| B | $CH_3I$ | Only II | | 67 |
| C | $(CH_3)_2SO_4$ | Only II | | 57 |
| D | $CH_3I$ | 3,5 : 1 | 4,7 : 1 | 43* |
| E | $CH_3I$ | 1,5 : 1 | 3,4 : 1 | 54* |
| F | $CH_2N_2$ | 2,3 : 1 | 3,6 : 1 | 58* |

*Total yield of N-methylation products.

2,5-Dimethyltriazinobenzimidazolone (III, form $\Phi_3$) was synthesized by the condensation of 1,2-diamino-3-methylbenzimidazolium iodide (V) [16] with pyruvic acid since the direct methylation of I to give pure tricyclic III could not be achieved.

The PMR and high-efficiency liquid chromatography data (Tables 1 and 2) indicate that the methylation of tricyclic derivative I gives a number of products. Thus, the alkylation of I by methyl iodide in DMF, sodium methylate, or excess dimethyl sulfate (methods A-C) leads exclusively to II. In contrast, the reaction of the potassium salt of tricyclic derivative I with methyl iodide in acetone (method D) or of neutral I in methanol/DMSO (method E) leads to the formation of a mixture of II and III with the predominance of II. Such an effect with the formation of an analogous product mixture was observed in the methylation of I by diazomethane (method F) (Table 1, Scheme 1).

Scheme 1

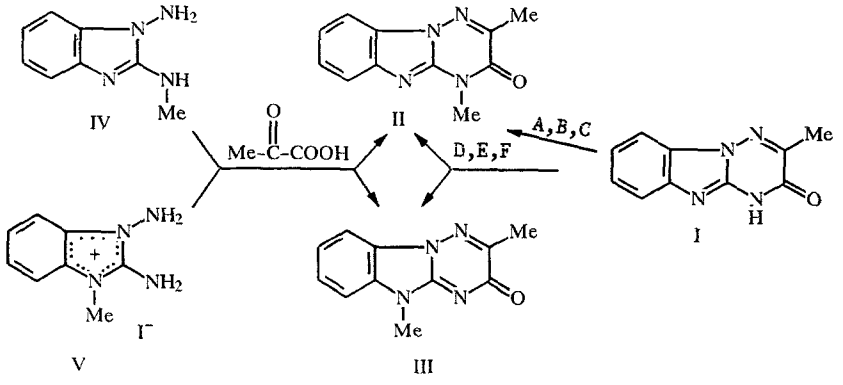


TABLE 3. Mass Spectral and Photoionization Data for I-III

| Ions | Mass spectra of compounds (rel. int., %) | | | Methylation products, mixture of II and III | | | Photoionization, eV | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | method | | | | | |
| | I | II | III | D | E | F | I | II | III |
| $[M+1]^+$ | 201 (14) | 215 (14) | 215 (3) | 215 (16) | 215 (10) | 215 (12) | | | |
| $[M]^{+\cdot}$ | 200 (100) | 214 (100) | 214 (23) | 214 (100) | 214 (77) | 214 (80) | 7,82 (IE) | 7,64 (IE) | 7,79 (IE) |
| $[M-CO]^+$ | 172 (12) | 186 (4) | — | — | — | — | 11,58 (AE) | 12,00 (AE) | — |
| $[M-CH_2CN]^+$ | 160 (36) | 174 (4) | 174 (8) | 174 (10) | 174 (10) | 174 (10) | | | |
| $[M-CH_3CN]^+$ $[A]^{+\cdot}$ | 159 (38) | 173 (27) | 173 (100) | 173 (56) | 173 (100) | 173 (100) | 9,47 (AE) | 11,50 (AE) | 8,86 (AE) |
| $[A-CO]^+$ | 131 (52) | 145 (15) | 145 (6) | 145 (6) | 145 (5) | 145 (6) | 10,18 (AE) | 11,55 (AE) | — |
| $[A-CO, -H]^+$ | 130 (2) | — | 144 (30) | 144 (8) | 144 (12) | 144 (10) | | | |
| $[A-NCO]^+$ | 117 (16) | — | — | — | — | — | | | |
| $[A-CO, -HCN]^+$ $[C]^{+\cdot}$ | 104 (48) | 118 (24) | 118 (42) | 118 (34) | 118 (38) | 118 (36) | | | |
| $[A-CO, -N_2]^+$ | 103 (16) | 117 (8) | 117 (5) | 117 (6) | 117 (5) | 117 (7) | | | |
| $[A-CO, -RCN]^+$ $[B]^{+\cdot}$ | 90 (17)* | 104 (29) | 104 (10) | 104 (15) | 104 (15) | 104 (14) | | | |
| $[B-HCN]^+$ | 77 (40) | 91 (5) | 91 (10) | 91 (11) | 91 (10) | 91 (12) | | | |
| $[A-CO, -N_2, -HCN]^+$ | — | 90 (13) | 90 (26) | 90 (23) | 90 (22) | 90 (25) | | | |

*$[A - NCO, - HCN]^+$ for I.

In the first stage of this study, it was necessary to check the existence of forms $\Phi_1$—$\Phi_3$ for I in solution and in the gas phase and also estimate the activation barrier ($\Delta G^{\neq}$) upon going from one form to another in order to determine whether this is a tautomeric or isomeric effect.

IR and PMR spectroscopy and mass spectrometry were used to detect forms $\Phi_1$—$\Phi_3$. The IR spectra of I in the crystal and dioxane solution show bands for the carbonyl and imino groups (see Table 1). No $\nu_{OH}$ band at 3300-3600 $cm^{-1}$ was observed. The PMR spectrum did not show a broad signal for a hydroxyl proton. The PMR spectra of the methylation products obtained by methods D-F did not show a methoxy group signal (see Table 1).

The mass spectrum of tricyclic derivative I lacks a peak for the $[M - H]^+$ ion characteristic for compounds containing a hydroxyl group in an aromatic system such as hydroxyquinolines [17]. The mass spectra of the products obtained by methods D-F did not show loss of a methyl radical, CHO˙, or $CH_2O$ from $M^+$ or other fragmentation ions resulting from the $M^+$ form of $\Phi_1$ (Table 3).

The data given in Tables 1-3 exclude the possibility that I exists in form $\Phi_1$ in any aggregate state and this narrows the question to identification of forms $\Phi_2$ and $\Phi_3$ (tautomers or isomers). Also, no *o*-methyl derivative was found in the methylation products of structurally similar 6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazine [9].

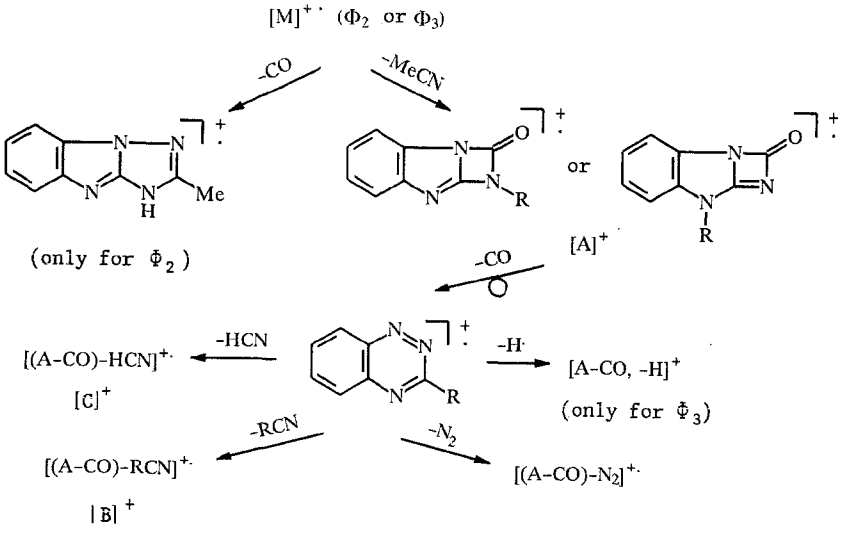
Photoionization data were used to measure the energy parameters related to the transition of one form to another ($\Phi_2 \rightarrow \Phi_3$) [17]. The differences in the ionization energies (IE) of II and III is $0.15 \pm 0.2$ eV (3.46 kcal/mole or 14.475 kJ/mole) (see Table 3), which clearly indicates the tautomeric nature of the observed transformations (for isomers, $\Delta G^{\neq} >$ 20-25 kcal/mole [18]).

In the general case, the introduction of a methyl group into an aryl or hetaryl system reduces the IE by 0.2-0.5 eV (17]. Thus, IE = $7.82 \pm 0.02$ eV for I is closer to form $\Phi_2$ (see Table 3). The data in Table 2 indicate the predominant existence of form $\Phi_2$.

Model compounds II and III are readily distinguished by their spectral and chromatographic characteristics (see Tables 1 and 3), which facilitates the assignment of the fusion products to forms $\Phi_2$ or $\Phi_3$.

A mass-spectral study of I and its fixed forms II and III shed light on the differences in the fragmentation of the isomers and energetics of some reactions of common decomposition processes and indicated a logical relationship between structure and the nature of its dissociative ionization. Table 3 shows that there are no apparent differences in the decomposition of I-III upon electron impact. A exception is found for the $[A - CO - H]^+$ ion, which is specific for III. In contrast, this process is hardly observed for I ($J_{130} = 2\%$). Furthermore, differences are noted in the intensities of the $[M]^+$, $[M - CO]^+$, and $[A]^+$ ions for N-methyl derivatives II and III. Thus, a tautomer of form $\Phi_3$ may be detected in the mass spectrum of tricyclic derivative I only after methylation and subsequent separation of the mixture. In contrast, the form of tautomer $\Phi_2$ is best observed in the mass spectrum of I relative to the $[M - CO]^+$ ion (Scheme 2).

Scheme 2




The energy required for contraction of the triazine ring in I and II to a triazole ring upon elimination of CO from $[M]^{+\cdot}$ is rather large: ΔE (energy for formation of the $[M - CO]^+$ ions) = AE (threshold energy for appearance of the ion) − IE (molecular ionization energy) is 362.829 kJ/mole for I and 420.727 kJ/mole for II. The clear difference in the energetics of this process (0.6 eV) is attributed to the effect of the methyl group [14]. Hence, the structures of the $[M - CO]^+$ ions in the case of I and II should be considered approximately the same (see Table 3).

The following energies are required for the formation of ion $[A]^{+\cdot}$ according to the ΔE values determined: 159.220 kJ/mole for I, 372.478 kJ/mole for II, and 103.252 kJ/mole for III, which presupposes a different set of structural forms. The subsequent loss of an $N_2$ molecule from $[A]^{+\cdot}$ (MSVR — [perhaps secondary radical mass spectrometry]: measured 103.0427 for I, 117.0571 and 117.0583 for II and III, respectively) presupposes that one of the structural forms for the $[A - CO, - N_2]^+$ ion has 1,2,4-benzotriazine structure, which arises as the result of a rearrangement. This hypothesis is supported by the low value of ΔE for the process $[A]^{+\cdot} - CO$ in the case of II (4.825 kJ/mole).

The formation of an ion with m/z 90 for I does not fit into the general decomposition pathway in the framework of the proposed fragmentation scheme based on the metastable ion spectra [19] (see Table 3). In this case, the pathway for ion generation is as follows: $[A]^{+\cdot} - NCO - HCN$, which is confirmed by metastable transitions.

The differences noted in the fixed forms of II and III, including the intensities of the individual ion peaks, does not lead to a quantitative evaluation of the tautomeric forms of I in the gas phase. However, comparison of the intensities of the individual ions in methylated derivatives II and III permits us to carry out a mass-spectral evaluation of the isomer ratio in the products of the methylation of tricyclic derivative I (according to methods D-F). For example, comparison of the intensities of the $[(A - CO) - H]^+$ ions in the mass spectra of the methylation products and of pure III yields an approximate ratio of isomers II and III. The II:III ratio in the products obtained is 70:30 when method D is used and 60:40 when methods E and F are used. Thus, the tendency for predominance of form $\Phi_2$ is retained in the gas phase.

This study for 1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one showed the existence of peri-prototropic tautomerism, indicated the predominant tautomer form in the crystalline, liquid, and gas phases, and shed light on the methylation reaction.

## EXPERIMENTAL

The IR spectra were taken for KBr pellets and dioxane solutions on an IKS-22 spectrometer. The PMR spectra were taken on a Bruker WH-90 spectrometer in DMSO-$d_6$ with TMS as the internal standard. The electron impact mass spectra were taken on a Finnigan HSQ-30 mass spectrometer with continuous sample inlet into the ion source. The ionization energy was 70 eV. The MSVR were taken on the same spectrometer under the same conditions ($M/\Delta M$ = 15,000, with as the standard). The mass spectra of the metastable ions were taken using the DADI technique in a second fieldless space [19]. The photoionization was carried out on MS-1302 mass spectrometer with a hydrogen lamp as the source of ionizing photons. The ionization efficiency curves were taken with simultaneous recording of the optical spectrum of the hydrogen lamp in the range from 6 to 13 eV. The IE and AE were determined with an error of $\pm 0.02$ and $\pm 0.03$ eV, respectively, as the energies of the photons corresponding to the inflection points on the photoionization efficiency curves [20]. The products of the methylation of I were analyzed by high-efficiency liquid chromatography on a Bruker ZC-21 chromatograph using a UV detector at $\lambda$ = 270 nm and a 250 × 4.0-mm column with Spherisorb ODS inverted phase adsorbent (5 $\mu$m particle diameter). The mobile phase was a mixture of 60 vol. % methanol and 40 mole % 0.05 M phosphate buffer at pH 7.5. The flow rate of the mobile phase was 1 ml/min.

The elemental analysis data for C, H, and N corresponded to the calculated values.

A sample of 1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one (I) was obtained according to Day [15], 1-amino-2-methylaminobenzimidazole (IV) was obtained according to Kuz'menko [14], and 1,2-diamino-3-methylbenzimidazolium iodide (V) was obtained according to Kuz'menko [16].

**1,2-Dimethyl-1,2,4-triazino[2,3-a]benzimidazol-(4H)-3-one (II).** A solution of 0.32 g (2 mmoles) 1-amino-2-methylaminobenzimidazole and 0.26 g (3 mmoles) pyruvic acid in 25 ml 2-propanol was heated at reflux for 3 h and cooled. The precipitate was filtered off as white needles, mp 233-235°C (from ethanol), which corresponded to the data of Kuz'menko [14]. $M^+$ 214.

**Methylation of I** (see Table 2). **A.** A sample of 0.22 ml (3.6 mmoles) methyl iodide was added with stirring to a solution of 0.6 g (3 mmoles) I in 8 ml freshly distilled dimethylformamide, heated on a steam bath for 14 h, and cooled. Then, 0.21 g (1.5 mmole) anhydrous potassium carbonate was added and the mixture was heated for 2 h. The mixture was filtered and washed with 50% ethanol to give colorless crystals with mp 233-235°C (from ethanol). $M^+$ 214.

**B.** A sample of 0.6 g (3 mmoles) I was dissolved in 20 ml sodium methylate prepared from 0.1 g (4.5 mmoles) metallic sodium and 20 ml methanol and 0.64 g methyl iodide was added with stirring. The solution was stirred for 2.5 h and concentrated in vacuum down to 5 ml. The precipitate was filtered and washed with 50% ethanol to give colorless needles with mp 233-235°C (from ethanol) $M^+$ 214.

**C.** A sample of 0.6 g (3 mmoles) I in 3 ml dimethyl sulfate was stirred on a steam bath for 4 h. The solution was cooled, poured into 50 ml 3% sodium bicarbonate with stirring, and left for 12 h. The precipitate of II was filtered off as colorless needles with mp 233-235°C (from ethanol). $M^+$ 214.

**D.** A solution of 0.6 g (3 mmoles) I and 0.22 g (4 mmoles) potassium hydroxide in 10 ml water was evaporated to dryness at reduced pressure. The residue was suspended in 5 ml dry acetone and filtered. The precipitate was suspended in 25 ml acetone and 0.2 ml (3 mmoles) methyl iodide was added. The mixture was stirred for 1 h at 20°C and then heated at reflux for 3 h. The precipitate was filtered off and the solution was concentrated at reduced pressure. The precipitate of a mixture of II and III was filtered off.

**E.** A sample of 0.2 g (1 mmole) I was dissolved in a mixture of 10 ml methanol and 2 ml DMSO. The solution was heated to 100°C and 0.28 g (2 mmoles) methyl iodide was added. The mixture was stirred for 3 h and then cooled. The precipitate of a mixture of II and III was filtered off.

**F.** An ethereal solution of diazomethane was added dropwise with rapid stirring to a solution containing 0.2 g (1 mmole) I in 15 ml methanol and 2 ml DMSO according to a standard procedure [21]. The solvent was removed by distillation in vacuum provided by a water pump at 30-35°C.

**2,5-Dimethyl-1,2,4-triazino[2,3-a]benzimidazol-(5H)-3-one (III).** A solution of 0.87 g (3 mmoles) 1,2-diamino-3-methylbenzimidazolium iodide and 0.35 ml (4 mmoles) pyruvic acid in 15 ml anhydrous butanol was heated at reflux for 1.5 h, filtered, and concentrated at reduced pressure down to 5 ml. The precipitate of III was filtered off as colorless needles with mp 276-277°C (from ethanol). $M^+$ 214.

## REFERENCES


1. B. A. Priimenko, S. N. Garmash, N. A. Klyuev, N. I. Romanenko, and V. V. Kirichenko, Khim. Geterotsikl. Soedin., No. 1, 32 (1983).
2. N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, A. N. Chervinskii, N. A. Klyuev, and V. V. Kirichenko, Khim.-Farm. Zh., No. 4, 427 (1986).
3. A. A. Tumashov, Reactions of Condensed Nitropyrimidines with C-Nucleophiles [in Russian], Chemical Sciences Candidate's Dissertation, Sverdlovsk (1989).
4. B. A. Priimenko, B. A. Samura, E. A. Skul'skaya, D. A. Troshin, and S. N. Garmash, Khim.-Farm. Zh., No. 12, 1456 (1983).
5. B. A. Priimenko, B. A. Samura, S. N. Garmash, N. A. Klyuev, and N. I. Romanenko, Khim.-Farm. Zh., No. 2, 32 (1983).
6. M. V. Povstyanoi, V. P. Kruglenko, A. A. Timoshin, N. A. Klyuev, I. I. Grandberg, and Yu. Yu. Stoilov, Izv. TSKhA, No. 5, 155 (1984).
7. V. A. Korolenko, M. V. Povstyanoi, V. A. Eres'ko, and V. F. Voloshin, Zashchita Metallov, **18**, 800 (1982).
8. V. P. Kruglenko, O. A. Logunov, A. V. Startsev, Yu. Yu. Stoilov, and M. V. Povstyanoi, Kvantovaya Élektronika, 7, 2136 (1980).
9. E. N. Ulomskii, V. L. Rusinov, O. N. Chupakhin, G. L. Rusinov, A. I. Chernyshev, and G. G. Aleksandrov, Khim. Geterotsikl. Soedin., No. 11, 1543 (1987).
10. N. A. Klyuev, V. G. Baklykov, and V. L. Rusinov, Khim. Geterotsikl. Soedin., No. 1, 116 (1992).
11. V. P. Kruglenko, N. S. Patalakha, P. B. Kurapov, N. A. Klyuev, V. A. Idzikovskii, I. I. Grandberg, and M. V. Povstyanoi, Khim. Geterotsikl. Soedin., No. 5, 694 (1985).
12. V. L. Rusinov, A. Yu. Petrov, O. N. Chupakhin, N. A. Klyuev, and G. G. Aleksandrov, Khim. Geterotsikl. Soedin., No. 5, 682 (1985).
13. M. V. Povstyanoi, N. A. Klyuev, E. Kh. Dank, V. A. Idzikovskii, and V. P. Kruglenko, Zh. Org. Khim., **19**, 433 (1983).
14. T. A. Kuz'menko, V. V. Kuz'menko, A. F. Pozharskii, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 8, 1070 (1988).
15. R. I-fu Ho and R. Day, J. Org. Chem., **38**, 3084 (1973).
16. V. V. Kuz'menko, T. A. Kuz'menko, A. F. Pozharskii, V. N. Doron'kin, N. L. Chikina, and S. S. Pozharskaya, Khim. Geterotsikl. Soedin., No. 2, 218 (1989).
17. N. A. Klyuev, Izv. Severo-Kavkaz. Nauchn. Tsentra Vysshei Shkoly, **13**, 50 (1989).
18. V. I. Minkin, L. P. Olekhnovich, and Yu. A. Zhdanov, Molecular Design of Tautomeric Systems [in Russian], Izd. Rostovsk. Gos. Univ., Rostov-on-the-Don (1977), p. 27.
19. N. A. Klyuev, É. N. Istratov, R. A. Khmel'nitskii, V. P. Suboch, V. L. Rusinov, and V. A. Zyryanov, Zh. Org. Khim., **13**, 1501 (1977).
20. N. A. Klyuev, A. K. Sheinkman, and A. N. Smirnov, Khim. Geterotsikl. Soedin., No. 6, 812 (1976).
21. A. N. Kost (ed.), General Organic Chemistry Laboratory Textbook [Russian translation], Mir, Moscow (1965), pp. 484, 532.