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CATALYTIC HYDROGENATION OF METHYL ESTERS OF SOME 1H-PYRAZOLINE-3-CARBOXYLIC ACIDS

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Hydrogenation over Raney nickel of the methyl ester of 1H-pyrazoline-3-carboxylic acid and also of its 4-phenyl and 5-methoxycarbonyl-substituted analogs, leads respectively to 3-aminopyrrolidin-2-one, its 4-phenyl- and 5-methoxycarbonyl derivatives, predominantly to the trans isomer. Under the same conditions 1-amino-4-methoxycarbonylpyrrolidin-2-one was obtained from 3,4-di(methoxycarbonyl)-1H-pyrazoline, but 3,4,5-tri(methoxycarbonyl)-1H-pyrazoline did not react.

Keywords: 3-aminopyrrolidin-2-ones, methyl esters of 1H-pyrazoline-3-carboxylic acids, Raney nickel, catalytic hydrogenation, cyclocondensation.

At the present time much attention is paid to the search for new regioselective and stereoselective methods for constructing the pyrrolidine ring, which is a pharmacophoric group of many pharmaceutical preparations (piracetam, oxiracetam, fenotropil) and physiologically active substances (domoic acid, oxazolomycin) [1-14]. Pyrrolidines with an amino group in position 3 are of special interest. For example, 3-aminopyrrolidin-2-one, linked with a norbornane fragment, displays antiarrhythmic, anti-inflammatory, analgesic, and nootropic activity and in the breadth of its therapeutic action exceeds the antiarrhythmic preparations used at the present time [15, 16].

The use of 1,3-dipolar cycloaddition of diazo compounds to olefins and subsequent catalytic hydrogenation of the resulting pyrazolinecarboxylic acid esters is one of the most promising approaches to the synthesis of 3-aminopyrrolidin-2-ones [15-18].

With the aim of obtaining new compounds of the series mentioned the hydrogenation has been studied in the present work of pyrazoline-3-carboxylic acid methyl ester (**1**), and also its 4-phenyl- (**2**), 5-methoxycarbonyl- (**3**), 4-methoxycarbonyl- (**4**), and 4,5-di(methoxycarbonyl)- (**5**) substituted analogs.

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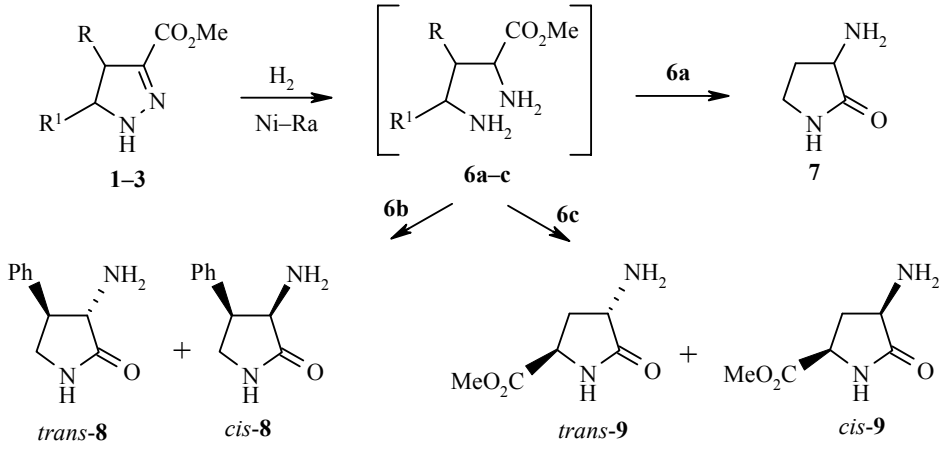
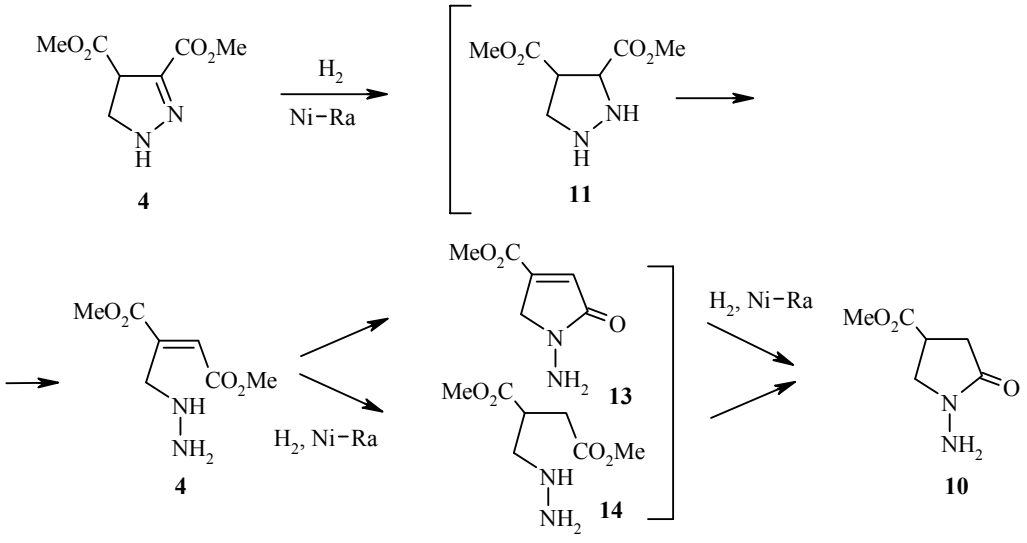
A preliminary search for optimum reaction conditions showed that the most effective was hydrogenation in methanol in the presence of Raney nickel at 100°C (hydrogen pressure 7.1 MPa, 5 h) [19], previously proposed for pyrazoline-3-carboxylic acid methyl ester linked with a norbornene fragment.

Under these conditions 3-aminopyrrolidin-2-one **7** was obtained in 84% yield from ester **1**, probably as a result of cyclocondensation of the intermediate diamine **6a**. Hydrogenation of the phenyl-substituted ester **2** was effected in quantitative yield to a mixture (1.5:1, here and subsequently from ^{1}H NMR spectra) of *trans* and *cis* isomers of 3-amino-4-phenylpyrrolidin-2-one (**8**). The predominant formation of the *trans* isomer **9** was also observed on reduction of the 5-methoxycarbonyl-substituted ester **3** (ratio *trans*-**9**:*cis*-**9**, 2.4:1). Probably such stereoselectivity is caused by the fact that the catalytic addition of hydrogen to the C=N double bond occurs mainly at the sterically least hindered side, in the *trans* position relative to the substituent in the ring.



1, 6a R = R^1 = H; **2, 6b** R = Ph, R^1 = H; **3, 6c** R = H, R^1 = CO_2Me

In difference to esters **1-3**, hydrogenation under the same conditions of 4-methoxycarbonyl-substituted ester **4** led to 1-amino-4-methoxycarbonylpyrrolidin-2-one **10** in 87% yield. The determining stage of the process is probably the conversion of pyrazolidine **11** into the dimethyl ester of 2-(hydrazinomethyl)fumaric acid (**12**) as a result of breaking of the ring at the N(2)–C(3) bond.



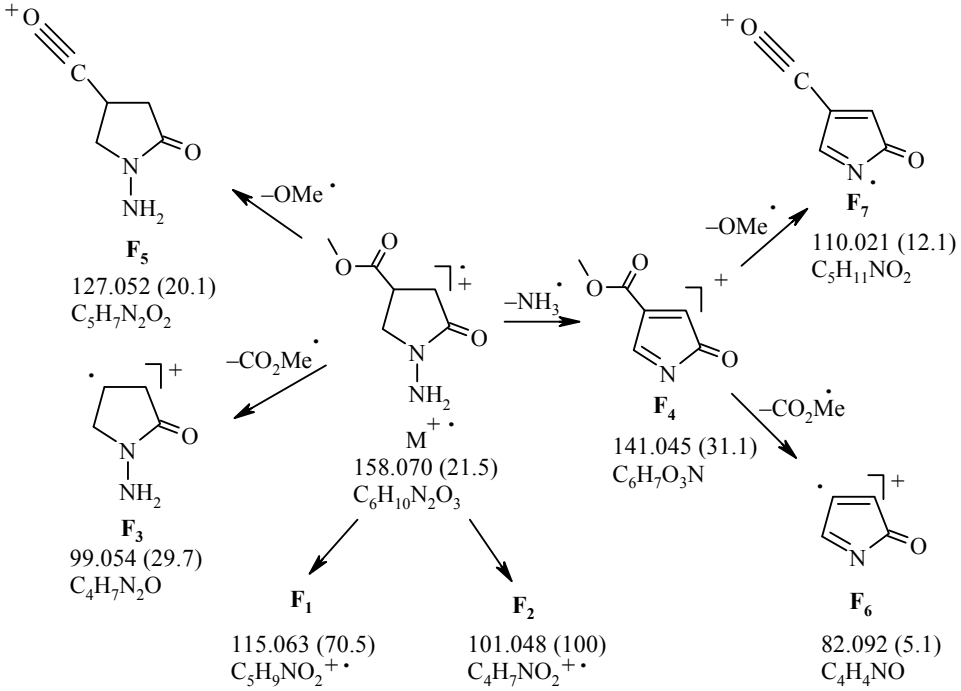
It should be mentioned that under the conditions of hydrogenating compounds **1-4,** 3,4,5-tri-(methoxycarbonyl)pyrazoline **5** (mixture of *trans* and *cis* isomers in a ratio of 9:1) did not undergo any conversion.

The composition and structure of the obtained new compounds **7-10** were confirmed by the results of elemental analysis, and also by data of IR spectra, ^{1}H, and ^{13}C NMR spectra. The presence in their IR spectra of an absorption band for the C=O group (in the 1640-1736 region) and for NH_2 (in the 2856-3424 cm^{-1} region) confirms the formation of an amino lactam fragment.

In the ^{1}H NMR spectra of pyrrolidones **7-9** there were broadened signals for the protons of the NH_2 group (at 1.5-2.2 ppm) and the NH ring fragment (6.8-7.7 ppm). In the case of N-aminopyrrolidone **10** the amino group is displayed at lower field (2.57 ppm), but the signal of the NH fragment was absent. The ^{13}C NMR spectra of all compounds **7-10** contain a signal for the carbon atom of the C=O ring fragment (at 178.2-180.8 ppm), but in the spectra of esters **9** and **10** a signal was also observed for the C=O group of the COOMe substituent (at 173.7-174.8 ppm). The presence in the NMR spectra of doubled signals for the H-3 and H-4 protons and the C(3), C(4) atoms in the case of compound **8**, and also the H-4 proton and the C(3), C(5) atoms for compound **9** show the formation of a mixture of two isomers. Comparison of the indicated spectra with the spectra of the known analogs make it possible to conclude that a *trans* configuration is the most probable for the main isomers of **8** and **9**. The coupling constant of the main isomer of 3-amino-4-phenylpyrrolidone (**8**) $J_{3,4}$ = 10.1 Hz, and of the minor $J_{3,4}$ = 7.4 Hz. The signals of the C(3) and C(4) atoms of the first were displaced relative to the signals of the analogous atoms of the second towards low field (by 3.11 and 5.63 ppm respectively). A similar picture was also observed in the spectra of the known analog 3-amino-1-benzyl-4-indolylpyrrolid-2-one [20]. The $J_{3,4}$ of its *trans* and *cis* isomers were 9.0 and 8.0 respectively, but the signals of the C(3), C(4) atoms of the *trans* isomer were displaced relative to the signals of the analogous atoms of the *cis* isomer towards low field (by 3.2 and 4.9 ppm respectively). It should also be noted that the coupling constants of *trans*-, and *cis*-3-amino-4-indolyl-5-(*tert*-butyldimethylsilyloxy)methylpyrrolid-2-one $J_{3,4}$ = 11.1 Hz [21], i.e. close to the $J_{3,4}$ coupling constants of the main isomer of **8**. In the spectra of the main isomer of 3-amino-5-methoxycarbonylpyrrolid-2-one (**9**), and also of the *trans* and *cis* isomers of its analogs 3-hydroxy- and 3-benzoyloxy-5-methoxy-carbonylpyrrolid-2-ones [22], the signals of the two H-4 protons have the form of two doublets of doublets of doublets. The similarity of the spectra of the main isomer of **9** and the *trans* isomers of the analogs is well shown from this signal, and also their difference from the spectra of the minor isomer of **9** and the *cis* isomers of the analogs. In the first the signals of the two H-4 protons are disposed significantly more closely (the distance between them is 0.2-0.4 ppm) than in the second (distance is equal to 0.8-0.9 ppm). In the first the coupling constants $J_{4,5}$ (at 6.3-8.3 Hz) differ significantly but for the second this difference is smaller (0.1-0.2 Hz). We also note that like the signals of atoms C(3), C(4) of the main isomer of **8**, the signals of the C(3), C(5) atoms of the main isomer of **9** are displaced relative to the signals of the analogous atoms of the minor isomer towards low field (by 0.25 and 0.90 ppm respectively).

The structure of compound **10** was also confirmed by data of mass spectra, in which a peak was recorded for the molecular ion of *m/z* 158.070 (21.5%) of composition $C_6H_{10}N_2O_3$ (calculated 158.16). The breakdown of this ion was in accordance with the rules for the mass spectral behavior of esters and pyrrolidines [23, 24]. Interpretation of the spectrum was carried out based on concepts of charge localization and the unpaired electron [24]. Diagnostic fragments are formed on breaking the heterocycle (fragments $\mathbf{F_1}$, $\mathbf{F_2}$) and fission of substituents ($\mathbf{F_3}$, $\mathbf{F_4}$). On localizing the charge on the carbonyl carbon atom of the ester group not only is fission of the C–C bond ($[M\text{-}CO_2CH_3]^+ \rightarrow \mathbf{F_3}$) brought about but also a C–O bond is broken ($[M\text{-}OCH_3]^+ \rightarrow \mathbf{F_5}$). Analogous processes were observed on breakdown of the secondary ion $\mathbf{F_4}$: ($\mathbf{F_4} - (CO_2CH_3)^+ \rightarrow \mathbf{F_6}$; $\mathbf{F_4} - (OCH_3)^+ \rightarrow \mathbf{F_7}$).

The character of the substitution of the studied pyrazolines **1-4** shows a decisive effect on their reactivity on hydrogenation over Raney nickel and determines the direction of conversion of the pyrazolidine ring formed as an intermediate. Its breakdown at the N–N or C(3)–N bond leads to a 3- or 1-aminopyrrolidin-2-one.



EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300 and 75 MHz respectively) spectrometer in $CDCl_3$, C_6D_6, or CD_3OD, internal standard was TMS. The IR spectra were recorded on UR 20 and Specord M 80 instruments in a thin film or in nujol. The mass spectra were recorded on a high resolution Thermo Finnigan MAT 95 XP spectrometer at an ionizing voltage of 70 eV (temperature of ionizing chamber 250°C, temperature of direct insertion 50-270°C, heating rate 10°C/min). The precise values of mass numbers of fragments formed in the source were measured with the aid of a procedure for comparing peaks with a standard (perfluorokerosene). Melting points were determined on a Boetius microstage. Elemental analysis of compounds was carried out on a CHN analyzer from HEKAtech Gmbh Analysen–technik's Euro-EA. Preparative separation was effected on a column of 70-320 mesh silica gel from Lancaster.

The initial compounds **1-5** were synthesized by known procedures [17, 25].

Catalytic Hydrogenation of Pyrazolines (General Method). A solution of pyrazoline **1-5** in MeOH (50 ml) and Raney nickel, obtained from nickel–aluminum (1:1) alloy (0.1 g), was kept in a rotating steel autoclave of volume (100 ml) at 100°C and H_2 pressure 7.09 MPa for 5 h. The reaction mixture was then cooled, filtered, and the filtrate evaporated.

3-Aminopyrrolidin-2-one (7). Product **7** (0.85 g, 84%) was obtained from ester **1** (1.3 g, 10.14 mmol) as colorless crystals of mp 105-106°C (sublimes). IR spectrum, ν, cm^{-1}: 720, 916, 1008, 1040, 1240, 1264, 1288, 1376, 1460, 1676, 2856-3336. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.65 (2H, br. s, NH_2); 1.78-1.81 (1H, m, H-4); 2.42-2.47 (1H, m, H-4); 3.22-3.35 (2H, m, H-5); 3.47 (1H, dd, $^3J_{cis}$ = 8.3, $^3J_{trans}$ = 10.1, H-3); 7.06 (1H, br. s, NH). ^{13}C NMR spectrum (CD_3OD), δ, ppm: 30.96 (C-4); 38.76 (C-5); 52.16 (C-3); 179.58 (C-2). Found, %: C 47.95; H 8.10; N 28.00. $C_4H_8N_2O$. Calculated, %: C 47.99; H 8.05; N 27.98.

***trans*- and *cis*-3-Amino-4-phenylpyrrolidin-2-one (8).** A mixture (0.6 g, 99%) (1.5:1) of the *trans* and *cis* isomers of product **8** was obtained from ester **2** (0.7 g, 3.42 mmol) as colorless crystals of mp 208-209°C (from a benzene–ether mixture). IR spectrum, ν, cm^{-1}: 704, 760, 1168-1196, 1256, 1440, 1496, 1600,

1712-1736, 3032-3256. Found, %: C 68.20; H 6.80; N 15.88. $C_{10}H_{12}N_2O$. Calculated, %: C 68.16; H 6.86; N 15.90. The ratio of isomers was determined from the ratios of the areas of the signals of the H-3 protons of the *trans* and *cis* isomers in the ^{1}H NMR spectrum of a mixture.

***trans*-8.** ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.49 (2H, br. s, NH_2); 2.89 (1H, ddd, $J_{4,3}$ = 10.1, $J_{4,5}$ = 8.7, $J_{4,5}$ = 8.4, H-4); 3.02-3.17 (2H, m, H-5); 3.39 (1H, d, $J_{3,4}$ = 10.1, H-3); 7.06-7.22 (5H, m, C_6H_5); 7.60 (1H, br. s, NH). ^{13}C NMR spectrum (C_6D_6), δ, ppm: 45.50 (C-5); 50.99 (C-4); 59.06 (C-3); 127.21 (C Ph); 128.71 (C Ph); 128.83 (C Ph); 140.39 (C Ph); 178.25 (C-2).

***cis*-8.** ^{1}H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.49 (2H, br. s, NH_2); 2.98 (1H, ddd, $J_{4,3}$ = 7.4, $J_{4,5}$ = 9.3, $J_{4,5}$ = 9.2, H-4); 3.02-3.17 (2H, m, H-5); 3.46 (1H, d, $J_{3,4}$ = 7.4, H-3); 7.06-7.22 (5H, m, C_6H_5); 7.65 (1H, br. s, NH). ^{13}C NMR spectrum (C_6D_6), δ, ppm: 45.36 (C-4); 45.47 (C-5); 55.95 (C-3); 127.27 (C Ph); 128.71 (C Ph); 128.83 (C Ph); 139.00 (C Ph); 179.06 (C-2).

***trans*- and *cis*-3-Amino-5-methoxycarbonylpyrrolidin-2-one (9).** A mixture (2.4 : 1) (0.55 g, 86%) of the *trans* and *cis* isomers of product **9** was obtained as a colorless oily liquid from ester **3** (0.75 g, 4 mmol). IR spectrum, ν, cm^{-1}: 756, 800, 1016, 1096, 1440, 1688, 2880-2960, 2960-3424. Found, %: C 45.63; H 6.25; N 17.75. $C_6H_{10}N_2O_3$. Calculated, %: C 45.57; H 6.37; N 17.71. The ratio of isomers was determined from the ratio of the total areas of the signals of the two H-4 protons of the *trans* and *cis* isomers in the ^{1}H NMR spectrum of the mixture.

***trans*-9.** ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 2.15 (2H, br. s, NH_2); 2.16 (1H, ddd, J^2 = 13.0, $J_{4,3}$ = 10.1, $J_{4,5}$ = 9.3, H-4); 2.53 (1H, ddd, J^2 = 13.0, $J_{4,3}$ = 8.3, $J_{4,5}$ = 2.0, H-4); 3.54 (1H, dd, $J_{3,4}$ = 10.1, $J_{3,4}$ = 8.3, H-3); 3.76 (3H, s, CH_3); 4.23 (1H, dd, $J_{5,4}$ = 9.3, $J_{5,4}$ = 2.0, H-5); 6.80 (1H, br. s, NH). ^{13}C NMR spectrum (CD_3OD), δ, ppm: 34.93 (C-4); 51.71 (CH_3); 54.0 (C-3,5); 174.43 (CO); 180.77 (C-2).

***cis*-9.** ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.81 (1H, ddd, J^2 = 12.4, $J_{4,3}$ = 9.5, $J_{4,5}$ = 9.1, H-4); 2.15 (2H, br. s, NH_2); 2.74-2.83 (1H, m, H-4); 3.54 (1H, dd, $J_{3,4}$ = 7.3, $J_{3,4}$ = 9.5, H-3); 3.76 (3H, s, CH_3); 4.21-4.26 (1H, m, H-5); 6.80 (1H, br. s, NH). ^{13}C NMR spectrum (CD_3OD), δ, ppm: 34.93 (C-4); 51.71 (CH_3); 53.10 (C-5); 53.75 (C-3); 173.74 (CO), 180.12 (C-2).

1-Amino-4-methoxycarbonylpyrrolidin-2-one (10). Compound **15** (0.81 g, 87%) was obtained from ester **4** (1.1 g, 5.9 mmol) as a pale-blue oil, converting into a dark-blue amorphous powder of mp 105°C (decomp.). IR spectrum. ν, cm^{-1}: 676, 1200, 1440, 1640-1728, 2952, 3016-3272. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 2.57 (2H, br. s, NH_2); 3.36-3.45 (1H, m, H-4); 3.50-3.64 (2H, m, H-3); 3.72 (3H, s, CH_3); 3.72-3.77 (2H, m, H-5). ^{13}C NMR spectrum (CD_3OD); δ, ppm: 33.91 (C-3); 39.46 (C-4); 45.41 (C-5); 52.60 (CH_3); 174.81 (CO); 178.59 (C-2). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 158 (22) $[M]^+$, 141 (31) $[M\text{-}NH_3]^+$, 127 (20) $[M\text{-}OMe]^+$, 115 (71) $[M\text{-}CHON]^+$, 110 (12) $[M\text{-}NH_3\text{-}OMe]^+$, 101 (100) $[M\text{-}C_2H_3ON]^+$, 99 (30) $[M\text{-}CO_2Me]^+$, 82 (5) $[M\text{-}NH_3\text{-}CO_2Me]^+$. Found, %: C 45.63; H 6.38; N 17.84. $C_6H_{10}N_2O_3$. Calculated, %: C 45.57; H 6.37; N 17.71.

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REFERENCES

1. A. Lebedev, *Khim. Geterotsikl. Soedin.*, 803 (2007). [*Chem. Heterocycl. Comp.*, **43**, 673 (2007)].
2. N. K. Yee, Y. Dong, S. R. Kapadia, and J. J. Song, *J. Org. Chem.*, **67**, 8688 (2002).
3. P. W. Smith, A. R. Whittington, K. N. Cobley, A. Jaxa-Chamiec, and H. Finch, *J. Chem. Soc., Perkin Trans. 1*, 21 (2001).
4. F. Felluga, V. Gombac, G. Pitacco, and E. Valentin, *Tetrahedron: Asymmetry*, 15, 3323 (2004).
5. B. Clique, C. Anselme, D. Otto, N. Monteiro, and G. Balme, *Tetrahedron Lett.*, **45**, 1195 (2004).

6. J. Flisinska, S. Lesniak, and R. Nazarski, *Tetrahedron*, **60**, 8181 (2004).
7. J. M. D. Storey, *Tetrahedron Lett.*, **41**, 8173 (2000).
8. O. Kitagawa, M. Fujita, M. Kohriyama, H. Hasegawa, and T. Taguchi, *Tetrahedron Lett.*, **41**, 8539 (2000).
9. D. Berger and W. Imhof, *Tetrahedron*, **56**, 2015 (2000).
10. S. A. Ebrik, B. Rigo, C. Vaccher, M. P. Vaccher, N. Flouquet, M. Debaert, and P. Berthelot, *J. Heterocycl. Chem.*, **35**, 579 (1998).
11. D. Gunn, C. Akuche, J. Baryza, and M.-L. Blue, *Bioorg. Med. Chem. Lett.*, 15, 3053 (2005).
12. J. C. Clayden, F. E. Knowles, and I. R. Baldwin, *J. Am. Chem. Soc.*, **127**, 2412 (2005).
13. T. J. Donohoe, J. Y. K. Chiu, and R. E. Thomas, *Org. Lett.*, **9**, 421 (2007).
14. C. T. Hoang, V. H. Nguyen, V. Alezra, and C. Kouklovsky, *J. Org. Chem.*, **73**, 1162 (2008).
15. V. A. Gorpinchenko, E. A. Yatsynich, D. V. Petrov, L. T. Karachurina, R. Yu. Khisamutdinova, N. Zh. Baschenko, V. A. Dokichev, Yu. V. Tomilov, M. S. Yunusov, and O. M. Nefedov, *Khim.-farm. Zh.*, **39**, No. 6, 9 (2005).
16. D. V. Petrov, V. A. Gorpinchenko, E. A. Shafikova, F. S. Zarudii, N. Zh. Baschenko, R. Yu. Khisamutdinova, N. S. Makara, V. A. Vakhitov, Yu. V. Vakhitova, Chzhan Veimu, R. I. Alimbekov, V. A. Dokichev, Yu. V. Tomilov, and O. M. Nefedov, Rus. Pat. 2281938; *Byull. Izobret.*, No. 23 (2006).
17. A. Levai, *J. Heterocycl. Chem.*, **39**, 1 (2002).
18. I. V. Kostyuchenko, E. V. Shulishov, V. A. Korolev, V. A. Dokichev, and Yu. V. Tomilov, *Izv. Akad. Nauk, Ser. Khim.*, 2482 (2005).
19. V. A. Gorpinchenko, D. V. Petrov, S. L. Khursan, V. A. Dokichev, and Yu. V. Tomilov, *Khim. Getrerotsikl. Soedin.*, 1301 (2009). [*Chem. Heterocycl. Comp.*, **45**, 1039 (2009)].
20. M. Boisbrun, L. Jeannin, L. Toupet, and J.-Y. Laronze, *Eur. J. Org. Chem.*, 3051 (2000).
21. E. Dardennes, A. Kavacs-Kulyassa, A. Renzetti, J. Sapi, and J. Laronze, *Tetrahedron Lett.*, **44**, 221 (2003).
22. L. J. Heinz, W. H. W. Lunn, R. E. Murff, J. W. Paschal, and L. A. Spangle, *J. Org. Chem.*, **61**, 4838 (1996).
23. A. T. Lebedev, *Mass Spectrometry in Organic Chemistry* [in Russian], Binom, Moscow (2003), p. 493.
24. P. B. Terentiev and A. P. Stankevicius, *Mass Spectrometric Analysis of Biologically Active Nitrogen Bases* [in Russian], Mokslas, Vil'nyus (1987), p. 280.
25. N. A. Anisimova, L. I. Deiko, and V. M. Berestovskaya, *Selected Methods of Synthesis and Modification of Heterocycles*, Vol. 1 [in Russian], IBS PRESS, Moscow (2003), p. 7.