Chemistry of Heterocyclic Compounds, Vol. 43, No. 6, 2007

PREPARATION OF 4-(AZOL-1-YL)BUTYRIC ACIDS BY THE INTERACTION OF AZOLES WITH γ-BUTYROLACTONE

A. L. Alekseenko and S. V. Popkov

The interaction of salts of imidazole, 1,2,4-triazole, benzimidazole, and 2-benzylbenzimidazole with γ-butyrolactone has been studied. Ab initio quantum-chemical calculations showed a preference for N-alkylation on interaction of azolates with γ-butyrolactone.

Keywords: 2-benzylbenzimidazole, benzimidazole, γ-butyrolactone, imidazole, 1,2,4-triazole, N-alkylation of azoles, quantum-chemical calculations.

It is known that many azolylalkanoic acids possess high biological activity, for example 8-(imidazol-1-yl)octanoic acid displays antiaggregation properties [1, 2]. 4-(Imidazol-1-yl)butyric acid is a GABA agonist [3]. High immunomodulating activity is displayed by estimulocel, 3-(benzimidazol-2-yl)propionic acid [4]. ω-Azolylalkanoic acids serve as starting materials for the synthesis of antiaggregation preparations [5].

The preparation of azolylalkanoic acids by the interaction of azolates and esters of ω-haloalkanoic acids with subsequent hydrolysis has been known for a long time [1-3, 6]. The interaction of heterocycles with γ-butyrolactone is comparatively seldom used for their N-alkylation [7-11]. The direction of cleavage the lactone at the acyl-oxygen or alkyl-oxygen bond is determined by the acid–base properties of the azole. Preference of fission of the alkyl-oxygen bond is aided by the use of the azolate, more nucleophilic than the azole, or an increase in temperature [7]. Products of N-alkylation of heterocycles are obtained in this way, *viz*. imidazol-1-yl-, pyrrol-1-yl-, and indol-1-ylbutyric acids [8-10].

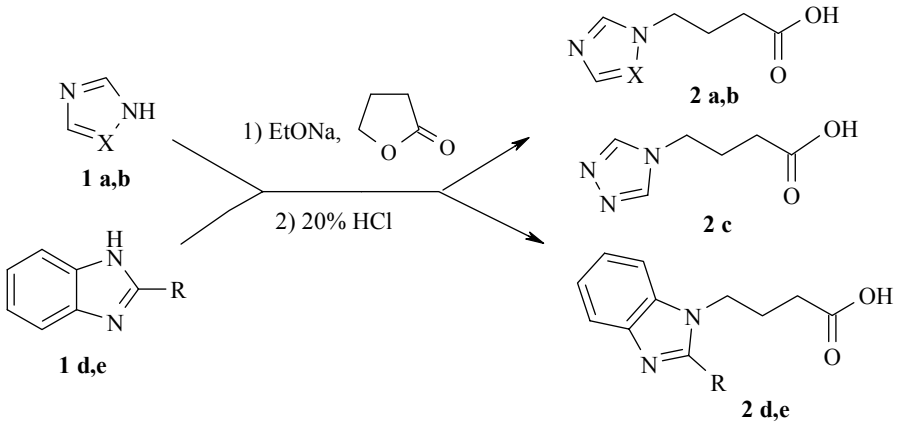
The condensation of imidazole, 1,2-4-triazole, benzimidazole, and 2-benzylbenzimidazole with γ-butyrolactone has been studied in the present work.

The interaction of imidazole with γ-butyrolactone in the presence of sodium sulfate catalyzed by concentrated sulfuric acid at 180°C, by analogy with the procedure given in a patent [12], led to significant resinification of the reaction mixture. The imidazolide of 4-(imidazol-1-yl)butyric acid was isolated in insignificant yield (16%) from the reaction mixture by high vacuum distillation, on hydrolysis of which the corresponding acid was obtained in 15% yield. On interacting the sodium salt of imidazole with a small excess of γ-butyrolactone at 120°C in the absence of solvent 4-(imidazol-1-yl)butyric acid (**2a**) is formed in 50% yield. The use of the potassium salt of imidazole did not lead to an increase in yield. On carrying out the interaction in a boiling mixture of xylenes the yield of acid **2a** was increased to 67%.

4-(Benzimidazol-1-yl)- and 4-(2-benzylbenzimidazol-1-yl)butyric acids (**2d,e**) were obtained analogously by the interaction of the sodium salts of benzimidazole and 2-benzylbenzimidazole with γ-butyrolactone at 180°C in the absence of solvent in yields of 52 and 42% respectively (Scheme 1).

D. Mendeleyev University of Chemical Technology of Russia, Moscow 125047, Russia; e-mail: popkovsv@rctu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6. pp. 910-916, June, 2007. Original article submitted August 25, 2006.

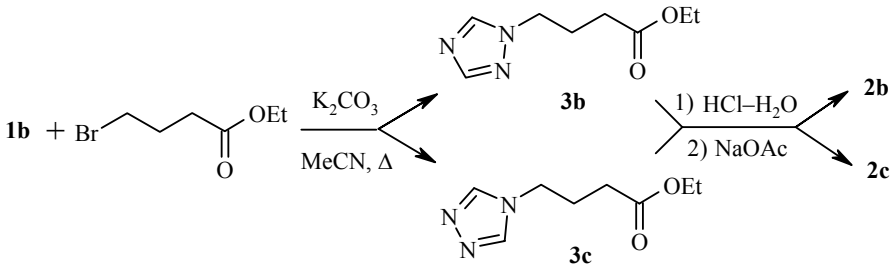
Scheme 1



1,2 a X = CH, **b** X = N, **d** R = H, **e** R = CH_2Ph

On alkylating the salt of 1,2,4-triazole with γ-butyrolactone a mixture of 4-(1,2,4-triazol-1-yl)butyric (**2b**) and 4-(1,2,4-triazol-4-yl)butyric acids (**2c**) was formed (93 : 7, according to ^{1}H NMR data), the separation of which was unsuccessful. The individual acids **2b** and **2c** were obtained by the classical method through the ethyl esters in two stages (Scheme 2). In the first stage, on interacting 1,2,4-triazole with ethyl 4-bromobutyrate in the presence of potassium carbonate a product was formed of both 1- and 4-substitution in a ratio of 10 : 1 (according to ^{1}H NMR data). On attempting to separate esters **3b** and **3c** by fractionation in vacuum only ester **3b** was successfully isolated. Probably the product of 4-alkylation **3c** is partially converted into the more thermodynamically stable 1-isomer **3b**.

Scheme 2



As it is known, products of 1-substitution are mainly formed on alkylation of 1,2,4-triazole as being the thermodynamically most stable [13]. Quantum-chemical calculations by the *ab initio* method on the RHF/6-31G* basis [14] for the isomeric ethyl triazolylbutyrates showed a higher stability (by 25.14 kJ/mol) for 4-(1,2,4-triazol-1-yl)butyrate **3b** in comparison with 4-(1,2,4-triazol-4-yl)butyrate **3c**. According to the data obtained experimentally the stability of 1,1-diphenyl-2-(1,2,4-triazol-1-yl)ethanol is greater by 17.45 kJ/mol than that of 1,1-diphenyl-2-(1,2,4-triazol-4-yl)ethanol [13]. No wonder that under distillation conditions at temperatures greater than 100^{o}C the 1-substitution product **3b** is distilled preferentially from the mixture of isomers.

Product **3c** was isolated from the mixture by column chromatography. Acids **2b** and **2c** were obtained in 89 and 55% yield respectively on hydrolysis of ethyl esters **3b** and **3c** in hydrochloric acid.

TABLE 1. Characteristics of Compounds **2a-e**, **3b,c**

Compound	Empirical formula	Found, % / Calculated, %			mp, ºC,	Reaction conditions		Yield, %
		C	H	N		*t*, ºC	τ, h	
2a	$C_7H_{10}N_2O_2$	54.58 / 54.54	6.80 / 6.54	17.98 / 18.17	134-136 (138 [7])	120 / 140*	3 / 2.5	50 / 67
2b	$C_6H_9N_3O_2$	46.42 / 46.45	5.70 / 5.85	27.27 / 27.08	142-143 / 132-133*[2]	100 / 140	2 / 2	79 / 89
2c	$C_6H_9N_3O_2$	46.40 / 46.45	5.78 / 5.85	27.16 / 27.08	145-146	100	2	55
2d	$C_{11}H_{12}N_2O_2$	64.79 / 64.69	5.97 / 5.92	13.70 / 13.72	146-147	180	0.5	52
2e	$C_{18}H_{18}N_2O_2$	73.73 / 73.45	6.42 / 6.16	9.44 / 9.52	153-154	180	1.5	42
3b	$C_8H_{13}N_3O_2$	52.55 / 52.45	7.09 / 7.15	22.89 / 22.94	—*[3]	80	8	75
3c	$C_8H_{13}N_3O_2$	52.40 / 52.45	7.12 / 7.15	23.14 / 22.94		80	8	—*[4]

* Reaction was carried out in a mixture of xylenes.
*[2] Mixture of acids **2b** and **2c** in a ratio 93 : 7.
*[3] bp 139-142°C (0.08 mm Hg).
*[4] Mixture of esters before fractionation consisted of **3b** and **3c** in a ratio 91 : 9.

TABLE 2. Spectral Characteristics of Compounds **2a-e**, **3b,c**

Compound	IR spectrum, ν, cm^{-1}	^{13}C NMR spectrum, δ, ppm*
2a	3390 (OH), 1680 (C=O), 1518 (CH=N azol.), 1282 (C–O)	26.16 ($C_{(3)}$), 30.66 ($C_{(2)}$), 45.28 ($C_{(4)}$), 119.28 ($C_{(5)}$ imidaz.), 128.29 ($C_{(4)}$ imidaz.), 137.22 ($C_{(2)}$ imidaz.), 173.83 ($C_{(1)}$)
2b	3400 (OH), 1705 (C=O), 1516 (CH=N azol.), 1288 (C–O)	24.42 ($C_{(3)}$), 29.93 ($C_{(2)}$), 47.38 ($C_{(4)}$), 143.58 ($C_{(5)}$ triaz.), 150.96 ($C_{(3)}$ triaz.), 173.26 ($C_{(1)}$)
2c	3410 (OH), 1712 (C=O), 1522 (CH=N azol.), 1290 (C–O)	25.66 ($C_{(3)}$), 30.49 ($C_{(2)}$), 43.64 ($C_{(4)}$), 143.24 ($C_{(3)}$, $C_{(5)}$ triaz.), 173.61 ($C_{(1)}$)
2d*	3400 (OH), 1700 (C=O), 1500 (CH=N azol.), 1270 (C–O)	24.99 ($C_{(3)}$), 30.66 ($C_{(2)}$), 43.41 ($C_{(4)}$), 110.32 ($C_{(7)}$ benzimidaz.), 119.46 ($C_{(4)}$ benzimidaz.), 121.50 ($C_{(5)}$ benzimidaz.), 122.32 ($C_{(6)}$ benzimidaz.), 133.75 ($C_{(7')}$ benzimidaz.), 143.39 ($C_{(3')}$ benzimidaz.), 143.96 ($C_{(2)}$ benzimidaz.), 173.77 ($C_{(1)}$)
2e	3400 (OH), 1708 (C=O), 1512 (CH=N azol.), 1286 (C–O)	24.56 ($C_{(3)}$), 30.41 ($C_{(2)}$), 32.85 (CC_6H_5), 42.35 ($C_{(4)}$), 110.08 ($C_{(7)}$ benzimidaz.), 118.54 ($C_{(4)}$ benzimidaz.), 121.50 ($C_{(5)}$ benzimidaz.), 121.89 ($C_{(6)}$ benzimidaz.), 126.62 ($C_{(4)}$ arom.), 128.52 ($C_{(2)}$, $C_{(6)}$ arom.), 128.71 ($C_{(3)}$, $C_{(5)}$ arom.), 134.96 ($C_{(1)}$ arom.), 136.92 ($C_{(7')}$ benzimidaz.), 142.06 ($C_{(3')}$ benzimidaz.), 153.22 ($C_{(2)}$ benzimidaz.), 173.86 ($C_{(1)}$)
3b	1728 (C=O), 1270, 1138 (C–O)	14.122 ($OCH_2\underline{C}H_3$), 24.947 ($C_{(3)}$), 30.543 ($C_{(2)}$), 48.403 ($C_{(4)}$), 60.633 ($O\underline{C}H_2CH_3$), 143.150 ($C_{(5)}$ triaz.), 152.033 ($C_{(3)}$ triaz.), 172.322 ($C_{(1)}$)
3c	1730 (C=O), 1270, 1142 (C–O)	—

* imidaz. – imidazole, triaz. – triazole, benzimidaz. – benzimidazole.

TABLE 3. Spectral Characteristics of Compounds **2a-e**, **3b,c**

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
2a	1.91 (2H, q, *J* = 6.8, $\underline{CH_2}CH_2CO$); 2.15 (2H, t, *J* = 6.8, $\underline{CH_2}CO$); 3.97 (2H, t, *J* = 7.2, CH_2N); 6.89 (1H, s, H-4 imidaz.); 7.16 (1H, s, H-5 imidaz.); 7.62 (1H, s, H-2 imidaz.); 9.5 (1H, br. s, COOH)
2b	1.99 (2H, q, *J* = 7.0, $\underline{CH_2}CH_2CO$); 2.21 (2H, t, *J* = 6.4, $\underline{CH_2}CO$); 4.20 (2H, t, *J* = 7.0, CH_2N); 7.96 (1H, s, H-3 triaz.); 8.50 (1H, s, H-5 triaz.); 12.21 (1H, br. s, COOH)
2c	1.98 (2H, q, *J* = 7.5, $\underline{CH_2}CH_2CO$); 2.20 (2H, t, *J* = 7.5, $\underline{CH_2}CO$); 4.05 (2H, t, *J* = 7.0, CH_2N); 8.54 (2H, s, H-3,5 triaz.); 12.25 (1H, br. s, COOH)
2d*	2.02 (2H, q, *J* = 7.0, $\underline{CH_2}CH_2CO$); 2.23 (2H, t, *J* = 7.0, $\underline{CH_2}CO$); 4.26 (2H, t, *J* = 7.0, CH_2N); 7.12-7.35 (2H, m, H-5,6, benzimidaz.); 7.63 (2H, t, H-4,7, benzimidaz., *J* = 8.7); 8.21 (1H, s, H-2 benzimidaz.); 12.22 (1H, br. s, COOH)
2e	1.75 (2H, q, *J* = 7.3, $\underline{CH_2}CH_2CO$); 2.26 (2H, t, *J* = 6.9, $\underline{CH_2}CO$); 4.18 (2H, t, *J* = 7.7, CH_2N); 4.31 (2H, s, CH_2Ph); 7.12-7.26 (3H, m, 3CH arom.); 7.27-7.40 (4H, m, 2CH arom., 2CH benzimidaz.); 7.48-7.67 (2H, m, H-4,7, benzimidaz.)
3b	1.19 (3H, t, *J* = 7.4 $\underline{CH_3}CH_2O$); 2.15 (2H, q, *J* = 7.4, $\underline{CH_2}CH_2CO$); 2.25 (2H, t, *J* = 6.6, $\underline{CH_2}CO$); 4.07 (2H, q, *J* = 7.4, CH_2O); 4.20 (2H, t, *J* = 6.6, CH_2N); 7.88 (1H, s, H-3 triaz.); 8.00 (1H, s, H-5 triaz.)
3c	1.26 (3H, t, *J* = 7.4, $\underline{CH_3}CH_2O$); 2.15 (2H, q, *J* = 6.6, $\underline{CH_2}CH_2CO$); 2.33 (2H, t, *J* = 6.6, $\underline{CH_2}CO$); 4.13 (2H, q, *J* = 7.4, CH_2O); 4.23 (2H, t, *J* = 6.6, CH_2N); 8.16 (2H, s, H-3,5 triaz.)

* imidaz. – imidazole, triaz. – triazole, benzimid. – benzimidazole.

In the IR spectra of the obtained azolylbutyric acids **2a-e** an absorption band for the carbonyl group is observed at 1680-1712 cm^{-1}, and for the hydroxyl at 3390-3410 cm^{-1}. On analyzing the NMR spectra of the isomeric acids **2b** and **2c** it should be mentioned that the triazole methine proton of the 4-substituted product is displayed as a singlet at 8.54 ppm of double intensity, like the $C_{(5)}H$ methine proton (8.50 ppm) of acid **2b**, analogously located between nitrogen atoms of pyridine and pyrrole types. In the ^{13}C NMR spectrum the signal of the methylene group bonded to the azole of the isomeric butyric acids **2b** and **2c** is observed at lower field (47.38 ppm) for the 1-substituted product in comparison with acid **2c** (43.64 ppm). Data of elemental analysis and NMR and IR spectroscopy given in EXPERIMENTAL confirm the structure of the compounds obtained.

With the aim of determining the applicability of the quantum-chemical method for predicting the direction of the interaction of azoles with γ-butyrolactone leading to products of N-alkylation or N-acylation, quantum-chemical calculations were carried out of the energy characteristics (ΔH_f, E_{total}). The calculations were carried out by the semiempirical PM3 method with the HyperChem 6.03 set of programs [15] with complete optimization of the geometry of the molecules. For the determination of ΔH of a reaction this method is most applicable since the heat of formation is a parameterizable property [14]. A more precise calculation of the structures of the compounds was carried out by the Hartree-Fock method on the 6-31G* basis. For molecules with closed electron shells the formalism of the restricted Hartree-Fock (RHF) method was used. The calculations of anions were carried out with the unrestricted Hartree-Fock (UHF) method.

The calculations showed that on interacting γ-butyrolactone with neutral azoles alkylation was more favourable than acylation, although on the whole the values of ΔH_p did not exceed 30 kJ/mol. Consequently under similar conditions products of acylation of azoles, imidazolides of 4-hydroxybutyric acids, were obtained and isolated together with 4-(imidazol-1-yl)butyric acids by the authors of [7]. Starting from the calculated charges on the $C_{(2)}$ and $C_{(5)}$ atoms of the lactone (q_2 = 0.787, q_5 = 0.004) the product of N-acylation is the product of kinetic control, since the nucleophilic opening of the lactone ring occurs probably as a result of attack at the most electropositive atom $C_{(2)}$ of the lactone. On subsequent heating the most stable product of

TABLE 4. Quantum-Chemical Calculations of the Interaction of γ-Butyrolactone with Azoles and Azolates by Semiempirical and Nonempirical Methods (PM3 and 6-31G*)

Compound	$\Delta H_p/\Delta E_{total}$, kJ/mol				$\Delta\Delta H_p/\Delta\Delta E_{total}$, kJ/mol*	
	Alkylation		Acylation			
	PM3	6-31G*	PM3	6-31G*	PM3	6-31G*
Neutral molecules						
1a	-24.83	-7.54	2.53	9.22	-27.36	-16.76
1b	-25.58	-21.37	14.64	28.91	-40.23	-50.28
1d	-26.69	-7.54	0.88	7.95	-27.57	-15.49
Ions						
1a'*[2]	-196.22	-96.37	-179.82	115.23	-16.40	-211.60
1b'	31.07	-77.10	-4.37	156.71	35.44	-233.80
1d'	35.75	-57.82	66.26	58.14	-30.51	-115.96

* $\Delta\Delta H_p/\Delta\Delta E_{total} = \Delta H_p/\Delta E_{total(alkylation)} - \Delta H_p/\Delta E_{total(acylation)}$.
*[2] **1a′,b′,d′** are the azolates of azoles **1a,b,d** respectively.

N-alkylation is formed. In the case of imidazole for example its stability is greater by 16.76 kJ/mol (6-31G* method). In calculations of the interaction of azolate ions with γ-butyrolactone the thermal effects grew significantly (almost by an order of magnitude). Under these conditions the acylation reaction becomes energetically unfavoured. The increase of enthalpy is from 58 to 156 kJ/mol depending on the type of azolate ion, and on the other hand, an appreciable reduction of enthalpy occurs on alkylation of azolate ions. The gain is from 57 to 96 kJ/mol. Evidently this is linked with the stability of the final anions. The 4-azolylbutyrates are stabilized as a result of delocalization of the negative charge in the carboxylate anion, unlike the unstable isomeric anions, *viz*. the 4-azolyl-4-oxobutylates. Alkylation products of azoles are therefore formed on interacting γ-butyrolactone with azolates as a result of thermodynamic control. The results of semiempirical (PM3) and nonempirical *ab initio* (6-31G* basis) calculations are very different. On interacting with imidazolate or benzimidazolate alkylation is more favored than acylation by 16 and 30 kJ/mol respectively. In the case of triazolate anion the semiempirical calculation shows that acylation is energetically more favored by 35 kJ/mol. The refined nonempirical method of calculation (6-31G*) indicates a significant energy gain in the case of alkylation compared with acylation of anions of imidazole, 1,2,4-triazole, and benzimidazole at $\Delta\Delta E_{total}$ amounting to -212, -234, and -115 kJ/mol respectively.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 (200 and 50 MHz respectively) instrument in $(CD_3)_2SO$, shifts were measured relative to TMS. The IR spectra were obtained on a Specord M-80 instrument in thin films in nujol. The progress of reactions and the purity of products were checked by TLC on Silufol UV-254 plates in chloroform–methanol, 10 : 1. Spots were detected in UV light and by iodine vapor and the modified Dragendorf reagent [16]. Silica gel Acros 35/70 was used for column chromatography. The physicochemical constants of previously described compounds were close to or coincided with literature data.

Interaction of Imidazole with γ-Butyrolactone. A. γ-Butyrolactone (10.32 g, 0.12 mol) was added to freshly obtained sodium imidazolate [17] (9.0 g, 0.1 mol), the mixture was stirred for 3 h at 110-120°C, neutralized with the calculated amount of 20% hydrochloric acid (16.7, 0.1 mol), the solvent was distilled off, and the residue was recrystallized from isopropyl alcohol. 4-Imidazol-1-ylbutyric acid (**2a**) (3.9 g, 30%) was obtained.

B. γ-Butyrolactone (9.46 g, 0.11 mol) and xylene mixture (20 ml) were added to freshly obtained sodium imidazolate [17] (9.0 g, 0.1 mol), and the mixture was stirred while boiling for 2.5 h. Processing was analogous. Compound **2a** (8.6 g, 67%) was obtained.

Compounds 2d,e were obtained analogously (see Table 1).

Interaction of Ethyl 4-Bromobutyrate with 1,2,4-Triazole. A. Freshly calcined potassium carbonate (34.5 g, 0.25 mol) in acetonitrile (175 ml) was added to 1,2,4-triazole (17.25 g, 0.25 mol) and the mixture was heated to boiling. Ethyl 4-bromobutyrate (35.8 ml, 48.77 g, 0.25 mol) was added dropwise with stirring, and the mixture boiled with stirring for 8 h, then cooled. The solid was filtered off, and washed with acetonitrile (2×20 ml). The filtrate was evaporated, and the residue distilled in vacuum, collecting the fraction of bp 139-142°C (0.08 mm Hg). The ethyl ester of 4-(1,2,4-triazol-1-yl)butyric acid (**3b**) (34.32 g, 75.0%) was obtained having n_D^{20} 1.4735. A portion of the reaction mass (5.0 g) was separated by column chromatography (eluent chloroform–methanol, 10 : 1). Compound **3c** (0.44 g) was obtained having n_D^{20} 1.4826.

B. Hydrochloric acid (6 M, 126 ml, 0.76 mol) was added to ethyl 4-(1,2,4-triazol-1-yl)butyrate (14.79 g, 80.8 mmol) and the mixture boiled with stirring for 2 h, and evaporated. The residue was dissolved in water (35 ml), and sodium acetate trihydrate (10.99 g, 80.8 mmol) was added in portions, the mixture was cooled, and filtered. The solid was washed with water (2×7 ml), and dried in a desiccator over phosphoric anhydride. 4-(1,2,4-triazol-1-yl)butyric acid (**2b**) (9.89 g, 79%) was obtained having mp 142-143°C (lit. mp 137-138°C [18]).

4-(1,2,4-triazol-4-yl)butyric acid (**2c**) (0.24 g, 55%) was obtained by an analogous procedure on hydrolysis of ethyl 4-(1,2,4-triazol-4-yl)butyrate (0.44 g).

REFERENCES

1. K. Iizuka, K. Akahane, D. Momose, M. Nakazawa, T. Tanauchi, M. Kauvamura, I. Okyama, I. Kajiwara, Y. Iguchi, T. Okada, K. Taniguchi, T. Miyamoto, and M. Hayashi, *J. Med. Chem.*, **24**, 1139 (1981).
2. T. Kamijo, R. Yamamoto, H. Harada, and K. Iizuka, *Chem. Pharm. Bull.*, **312**, 1213 (1983).
3. M. Varasi, G. Tarzia, F. Luzzani, L. Gallico, and D. Barone, *Farmaco*, **42**, 425 (1987).
4. S. V. Sibiryak, Yu. V. Sorokin, R. F. Sadykov, and V. M. Dianov, *Khim.-farm. Zh.*, **24**, No. 11, 19 (1990).
5. V. N. Zhuravlev, S. V. Popkov, E. G. Lobanova, and A. L. Aleekseenko, in *XII Russian National Congress "Man and Medicine"*, Abstracts, Moscow (2005), p. 753.
6. K. Iizuka and K. Akahane, GB Patent 2016452; *Chem. Abstr.*, **93**, 114514 (1980).
7. O. K. Shevchenko, A. T. Ayupova, and G. G. Galust'yan, *Khim. Geterotsikl. Soedin.*, 1491 (1992). [*Chem. Heterocycl. Comp.*, **28**, 1274 (1992)].
8. B. R. Lahue, S.-M. Lo, Z.-K. Wan, G. H. Woo, and J. K. Snyder, *J. Org. Chem.*, **69**, 7171 (2004).
9. J.-H. Li and J. K. Snyder, *J. Org. Chem.*, **58**, 516 (1993).
10. S. C. Denson, J.-H. Li, and J. K. Snyder, *J. Org. Chem.*, **57**, 5285 (1992).
11. H. Krzikalla and W. Alt, DR Patent 743661; *Chem. Zentralblatt*, **115**, 1152 (1944).
12. H. Haussmann and H. Kaltschmidt, DB Patent 882093; *Chem. Zentralblatt*, **125**, 10133 (1954).
13. T. W. Bentley, L. M. Howle, and P. J. Wareham, *Tetrahedron*, **48**, 7869 (1992).
14. V. I. Minkin, B. Ya. Simkin, and R. M. Minyaev, *Theory of Molecular Structure* [in Russian], Feniks, Rostov-on-Don (1997), p. 237.
15. HyperChem 6.03. *Trial Version.* http\\www.hyper.com

16. M. Sharshunova, V. Shvarts, and Ch. Mikhalets, *Thin-Layer Chromatography in Pharmacy and Clinical Biochemistry, Part 2* [Russian translation], Mir, Moscow (1980), p. 583.
17. D. A. Karachev and S. V. Popkov, *Khim. Geterotsikl. Soedin.*, 1161 (2005). [*Chem. Heterocycl. Comp.*, **41**, 987 (2005)].
18. A. Baba, N. Kawamura, H. Makina, Y. Ohta, S. Taketomi, and T. Sohda, *J. Med. Chem.*, **39**, 5176 (1996).