Chemistry of Heterocyclic Compounds, Vol. 39, No. 10, 2003

STUDY OF THE STERIC STRUCTURE OF 7-ALKOXYALKYL-3-OXA-7-AZABICYCLO-[3.3.1]NONAN-9-ONES AND THEIR DERIVATIVES USING ^{1}H NMR SPECTROSCOPY

S. G. Klepikova[1], V. K. Yu[1], E. E. Fomicheva[1], R. D. Mukhasheva[1], K. D. Praliev[1], V. A. Solomin[1], and K. D. Berlin[2]

Using the ^{1}H NMR spectroscopic method it has been shown that 7-alkoxyalkyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ones and 7-alkoxyalkyl-3-oxa-7-azabicyclo[3.3.1]nonanes exist in deuterochloroform solution in a double chair conformation. 7-(3-Butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol is a 1:1 mixture of the two stereoisomeric alcohols. One of them exists in a double chair conformation having an equatorial hydroxyl group with relation to the piperidine ring and the other in a chair-boat conformation having an axial hydroxyl group which involves an intramolecular hydrogen bond with the unshared electron pair of the nitrogen atom.

Keywords: 7-alkoxyalkyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one derivatives, *chair-boat*, *chair-chair*, conformation, structure, ^{1}H NMR.

The synthesis of a huge number of novel organic compounds is due to the vital need to create efficient medicinal preparations and materials needed for agriculture. This problem is closely connected with a resolution of questions of the steric structure of the synthesized compounds since the effect of the different components of the active substrate on its biological activity is well known.

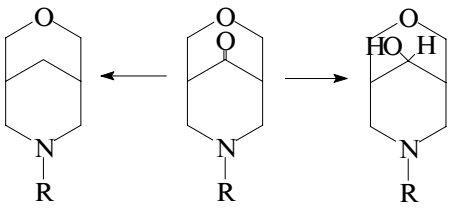
Using ^{1}H NMR spectroscopy and model compounds we show in this communication the steric structure of bicyclo[3.3.1]nonanes which contain an N-alkoxyalkylpiperidine joined with an oxacycle. 7-Alkoxyalkyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ones **1-3** [1] are prepared by the reaction of tetrahydro-4H-pyran-4-one with paraformaldehyde and ethoxyethyl-, ethoxypropyl- and butoxypropylamines in aceto-methanolic solutions. Reduction of the bicyclic ketones **2, 3** under Wolff–Kishner reaction conditions gives the corresponding 7-(3-ethoxypropyl)-, and 7-(3-butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonanes **4** and **5** [1]. In order to achieve a fuller spectroscopic picture of a compound in the 3-oxa-7-azabicyclo[3.3.1]nonane series the ketone **3** was reduced using sodium borohydride in isopropanol to yield the 7-(3-butoxypropyl)-3-oxa-7-azabicyclo-[3.3.1]nonan-9-ol (**6**) as a mixture of two stereoisomers.

Evidently, the results obtained would prove useful for carrying out a conformational investigation of newly synthesized bicyclo[3.3.1]nonane derivatives which contain atoms of nitrogen and oxygen in positions 3 and 7 and the compounds **1-6** studied by us proved convenient model substances.

---

[1] A. B. Bekturov Institute for Chemical Sciences, Ministry of Education and Science for the Kazakhstan Republic, Almaty 480100; e-mail: yu_vk@rambler.ru. [2] Oklahoma State University, Chemistry Faculty, Stillwater 74078, USA. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1562-1571, October, 2003. Original article submitted September 16, 2002.

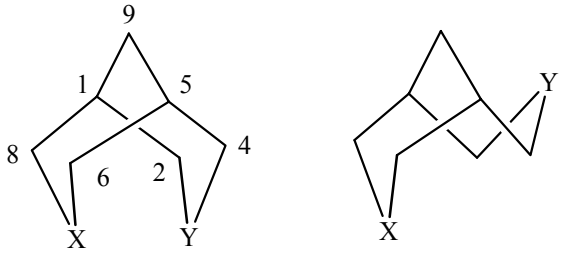
 0009-3122/03/3910-1376$25.00



4, **5** **1–3** **6**

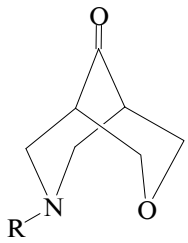
1 R = $(CH_2)_2OEt$, **2**, **4** R = $(CH_2)_3OEt$, **3**, **5**, **6** R = $(CH_2)_3OBu$

These bicyclic molecules can assume *double chair*, *chair-boat*, or *double boat* forms depending on the overall stabilization and destabilization of the electronic and steric factors which are determined by their geometry in each specific case [2]. The geometry is governed both by the properties of the bicyclic system itself, the heteroatoms occurring in its skeleton, and by the substitutents. On the one hand, introduction of nitrogen and oxygen atoms into the 3 and 7 positions suppresses the steric repulsion of the *endo*-hydrogen atoms in the *double chair* conformation and leads to its stabilization. On the other hand, there arise dipole-dipole, orbital, and steric repulsions between the heteroatoms which favor the appearance of a *chair-boat* form. However, despite the presence of the unbonded interactions, the *double chair* conformation is more stable than the *chair-boat* conformation (as follows from calculations and experimental data [2] for 3,7-diazabicyclo[3.3.1]nonanes and compounds containing two oxygen atoms or an oxygen and sulfur atom). Compounds with two sulfur atoms have a *chair-boat* structure.

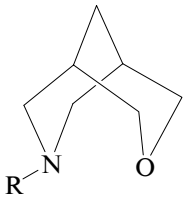


^{1}H NMR spectroscopy is generally used to determine the steric structure of the bicyclo[3.3.1]nonanes in solution and the basis of this is the well known dependence of a vicinal proton spin-spin coupling constant on dihedral angle [3]. The values of the vicinal constants for the interaction of the protons 1- and 5-H with neighbors in the *double chair* conformation of 3,7-dihetero analogs are 1-7 Hz [4, 5]. This observed spread is due not only to the value of the dihedral angle but also the bond length between the carbon atoms, the valence angles, and the electronegativity values of series of heteroatoms or substituents and is determined by the structural features of the molecule as a whole. A striking example of this is the effect of the geometry of the bonded protons relative to the heteroatom in the ring. In 4-phenyl-1,3-dioxane [3] with a *chair*-like configuration of the ring the equatorial-axial constant for the proton in the *trans* position to the oxygen atom is J = 2.9 Hz and differs from the axial-equatorial constant for the proton in the *cis* position where J = 5.1 Hz. Since the same value of the constants (2.9-3.6 and 5.6-6.5 Hz) is also observed for the *trans* isomers of N-substituted 2,5-dimethyl-4-piperidones [6] the values of the vicinal constants should be used cautiously and it is necessary to bear in mind the data obtained for compounds close in composition and structure. The observation in the spectrum of any vicinal constant with $J >$ 9 Hz points to the presence of a *boat* form for the ring with typically shielded ethane fragments. In this case the dihedral angle between the proton situated at the ring junction and the *pseudo*-equatorial is close to zero and, as follows from the Karplus curve, J = 9-12 Hz [7]. It should be noted that the *chair*-like ring in the *chair-boat* conformation is much less distorted than in the *double chair* conformation and in geometry must be close to the geometry of the corresponding six-membered heterocycle.

We report below the analysis of the spectrum of 7-(3-butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**3**) since the decarbonylation product **5** and the secondary alcohol **6** could be synthesized from it. The arguments for ketones **1** and **2** are similar.



1–3



4, 5

The values for the chemical shifts and spin-spin coupling constants for the protons in compounds **1-3** are given in Table 1. The signals for the cyclic protons do not overlap and are quite well resolved thus readily allowing us to make assignments and prove the conformation of the investigated compounds. The high field signal at 2.53 ppm is assigned to the protons at 1- and 5-H and appear as a complex multiplet with a half width of 12 Hz. From their position in the spectrum and the values of their vicinal constants (6.0 and 2.7 Hz) the next two double doublets with chemical shifts of 2.91 and 3.13 ppm are assigned respectively to the axial and equatorial protons of the piperidine ring having the *chair* form. These results are virtually identical to the coupling constant values of 5.6-6.3 and 2.1 -3.0 and chemical shift values of 2.76-2.93 and 2.99-3.10 ppm for the axial and equatorial protons in 3,7-disubstituted 3,7-diazabicyclo[3.3.1]nonan-9-ones which exist in a double *chair* conformation [8]. Two double doublets with small vicinal constants of 2.7 and 1.0 Hz are seen to lower field at 3.87 and 4.21 ppm and these are typical of axial and equatorial protons in a tetrahydo-4H-pyran ring found in the *chair* form. This is comparable with the value of the equatorial-axial constant of J = 2.0 Hz in the 2,6-diphenyltetrahydro-4H-pyran-4-one chosen by us as a model. In the study [9] it was shown that the compound has a *chair*-like ring configuration with equatorially positioned phenyl groups. The value of the equatorial-equatorial constant is usually less than an equatorial-axial and hence should be less than 2.0 Hz. In the spectra of compounds **1-3** there is not a single large vicinal constant in the range 9-12 Hz. The values of the constants found point to a *chair*-like form for the piperidine and tetrahydro-4H-pyran rings. Thus the analysis of the data obtained from the ^{1}H NMR spectra and a comparison with the literature allows us to conclude that the ketones **1-3** exist in the double *chair* conformation. It should be noted that the exchange of the nitrogen atom for oxygen does not lead to a marked change in the chemical shifts and vicinal constants for the protons of the piperidine ring as does a change of the substitutent on the nitrogen.

The signals for the 2-, 4- and 6-, 8-H protons in the spectra of the 3-oxa-7-azabicyclo[3.3.1]nonanes **4** and **5** differ from the signals of the corresponding protons in the spectra of the ketones **2** and **3** by an additional splitting and they appear as a double triplets. The structure of the triplets is poorly resolved due to the small value of the constant and is more clearly observed for the axial protons. The appearance of a small splitting, close in value to the vicinal constant, is possible as a result of the spin spin interaction of protons separated through four bonds and which are formed thanks to the transfer of the interaction *via* a planar, *zig-zag* configuration. An addition splitting occurs for the axial and equatorial signals relative to the plane of the piperidine ring with the 9-H protons. Thus, in place of the expected doublet of triplets for the equatorial 9-H proton, the spectrum shows a doublet of quintets. The transfer of remote spin-spin coupling between the axial 4-H_a and 6-H_a (2H_a and 8-H_a) protons, the equatorial 9-H_e proton and equatorial 6-, 8-H protons, and the axial 9-H_a and equatorial 2-, 4-H protons can only occur in a *double chair* conformation. The absence of vicinal constants greater than 9 Hz also confirms that the compounds examined **4** and **5** exist in a *double chair* conformation. The assignment of signals and spin-spin coupling values are given in Table 2.

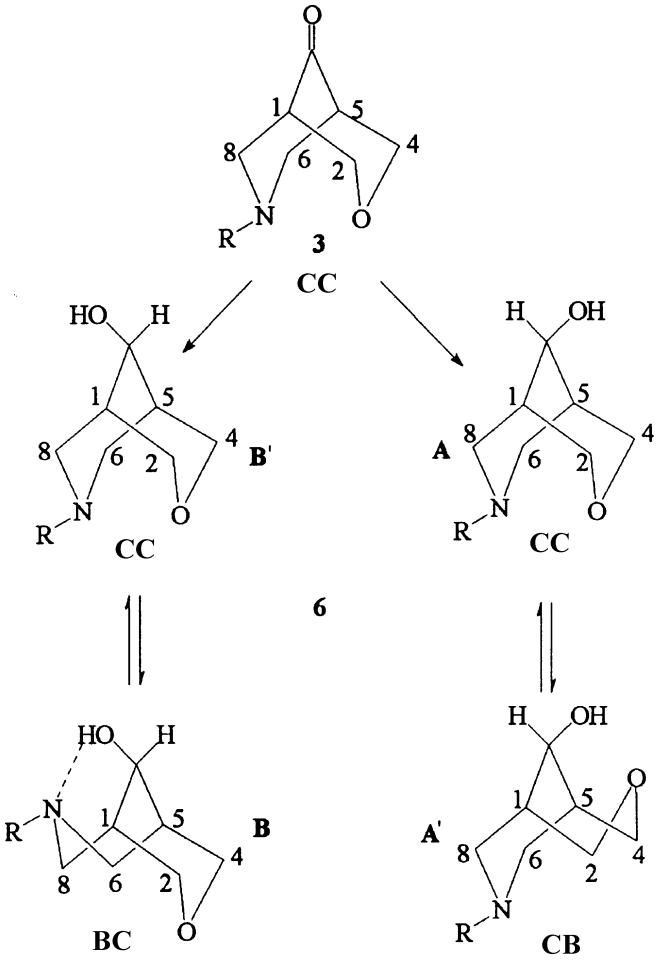
TABLE 1. ^{1}H NMR Spectra of 7-(2-Ethoxyethyl-, 3-Ethoxypropyl-, and 3-Butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]-nonan-9-ones (**1-3**)

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)											
	1-, 5-H_e (m)*	2-, 4-H_a (dd)	2-, 4-H_e (dd)	6-, 8-H_a (dd)	6-, 8-H_e (dd)	10-CH_2, t	11-CH_2	12-CH_2	13-CH_3, 13-CH_2	14-CH_3, 14-CH_2	15-CH_2	16-CH_3
1	2.52	3.87 (*J* = 11.1; *J* = 2.7)	4.22 (*J* = 11.1; *J* = 1.0)	3.01 (*J* = 11.4; *J* = 6.0)	3.21 (*J* = 11.4; *J* = 2.7)	2.64 (*J* = 6.0)	3.56 (*J* = 6.0)	3.47 (*J* = 6.9) quart.	1.18 (*J* = 6.9) t			
2	2.53	3.86 (*J* = 11.1; *J* = 2.7)	4.20 (*J* = 11.1; *J* = 1.0)	2.91 (*J* = 11.1; *J* = 6.0)	3.13 (*J* = 11.1; *J* = 2.7)	2.45 (*J* = 7.2)	1.75 (*J* = 6.8) quint.	3.46 (*J* = 6.9) t	3.45 (*J* = 6.9) quart.	1.17 (*J* = 6.9) t		
3	2.53	3.87 (*J* = 11.1; *J* = 2.7)	4.21 (*J* = 11.1; *J* = 1.0)	2.91 (*J* = 11.1; *J* = 6.0)	3.13 (*J* = 11.1; *J* = 2.7)	2.45 (*J* = 7.2)	1.74 (*J* = 6.9) quint.	3.45 (*J* = 6.6) t	3.45 (*J* = 6.6) t	1.53 (*J* = 6.9) quint.	1.35 (*J* = 7.2) sext.	0.90 (*J* = 7.2) t

* Δδ (signal halfwidth) = 12.0 Hz.

TABLE 2. ^{1}H NMR Spectra of 7-(3-Ethoxypropyl and 3-Butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonanes (**4, 5**)

Com-pound	Proton chemical shifts, δ, ppm (spin spin coupling, *J*, Hz)													
	1-, 5-H_e (m)	2-, 4-H_a (dt)	2-, 4-H_e (dt)	6-, 8-H_a (dt)	6-, 8-H_e (dt)	9-H_a (*J* = 11.7, dm)	9-H_e (*J* = 11.7, dm)	10-CH_2 (*J* = 7.2, t)	11-CH_2 (quint.)	12-CH_2 (*J* = 6.9)	13-CH_2 (t)	14-CH_3, 14-CH_2	15-CH_2	16-CH_3
4	1.72 Δδ = 13.0	3.74 (*J* = 11,1; *J* = 2.4; *J* = 2.4)	3.92 (*J* = 11.1; *J* = 2.4; *J* = 2.4)	2.28 (*J* = 11.1; *J* = 3.0; *J* = 3.0)	3.03 (*J* = 11.1; *J* = 2.7; *J* = 2.7)	1.59	1.79	2.36	1.80 (*J* = 6.9)	3.45 quart.	3.46 (*J* = 6.9)	1.18 (*J* = 6.9) t		
5	1.71 Δδ = 13.0	3.74 (*J* = 11.1; *J* = 2.4; *J* = 2.4)	3.91 (*J* = 11.1; *J* = 2.4; *J* = 2.4)	2.27 (*J* = 10.8; *J* = 2.1; *J* = 2.1)	3.03 (*J* = 10.8; *J* = 2.4; *J* = 2.4)	1.59	1.79	2.35	1.79 (*J* = 6.9)	3.44 t	3.39 (*J* = 6.6)	1.53 (*J* = 6.9) quint.	1.35 (*J* = 7.2) sext	0.90 (*J* = 7.2) t



Interesting results were obtained for compound **6**. It was found that the sample is a mixture of equal amounts of the two epimeric alcohols. With the help of double resonance and a change in solvents from chloroform to benzene it was possible to carry out a complete assignment of the signals and to determine the constants (see Table 3). The values found for the vicinal constants show that one of the stereoisomers **6A** has a *double chair* (CC) conformation with the hydroxyl group equatorially placed relative to the piperidine ring whereas the stereoisomer **6B** has a *chair-boat* conformation (CB) and an axial OH group with the *boat* form involving the nitrogen atom. The stabilization of this *chair-boat* conformation occurs because of the formation of an intramolecular hydrogen bond between the hydroxyl group proton and the lone electron pair of the nitrogen atom (as found previously by us for diazabicyclo[3.3.1]nonan-9-ols [8]). The cyclic protons of isomer **6A** occur in the spectrum as four double doublets and one unresolved multiplet with a half-width of 12.0 Hz. The largest of the vicinal constants is 3.6 Hz and this unambiguously shows that the conformation is a *double chair*. The cyclic protons of the isomer **6B** occur as three double doublets with small vicinal constants, a triplet with a broadened component in the centre, and a doublet of multiplets. The last two signals have the same constant of J = 10.5 Hz. Such a large spin-spin coupling can be found only for a *boat*-like ring hence these signals, judged by their structure, intensity, and chemical shift values, must be assigned to a *pseudo*-equatorial proton of the piperidine ring in a *boat* form and a proton placed on the joined rings. The obtained data for the isomer **6B** thus supports a *chair-boat* conformation. Hence the distinctive features present for the *chair-boat* conformation (rarely observed in solution) are the simultaneous presence in the ^{1}H NMR spectra of the studied

TABLE 3. ^{1}H NMR Spectra of the Stereoisomeric 7-(3-Butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ols (**6A-6B**)

Com-pound	Proton chemical shifts, δ, ppm, (spin-spin coupling, *J*, Hz)												
	1-, 5-H_e	2-, 4-H_a (dd)	2-, 4-H_e (dd)	6-, 8-H_a	6-, 8-H_e (dd)	9-H (t)	10-CH_2 (*J* = 7.2, t)	11-CH_2 (*J* = 6.9, quint.)	12-CH_2 (*J* = 6.9, t)	13-CH_2 (*J* = 6.6, t)	14-CH_2 (*J* = 6.9, quint.)	15-CH_2 (*J* = 7.2, sext.)	16-CH_3 (*J* = 7.2, t)
6A	1.77 (Δδ = 12.0) m	4.15 (*J* = 11.1; *J* = 2.4)	3.74 (*J* = 11.1) 1.0	2.26 (*J* = 11.1) 1.0 dd	3.03 (*J* = 11.1; *J* = 1.8)	3.73 (*J* = 3.6)	2.36	1.75	3.42	3.38	1.53	1.35	0.90
6B	2.18 (*J* = 10.5) dm	3.45 (*J* = 10.8) *J* = 1.0)	3.77 (*J* = 10.8) 1.0	3.10* (*J* = 11.1; *J* = 10.5) t	2.47*[2] (*J* = 11.1; *J* = 2.1)	3.65 (*J* = 2.7)	2.39	1.77	3.45	3.39	1.53	1.35	0.90

* For the *chair-boat* conformation the protons are pseudoaxial.

*[2] For the *chair-boat* conformation the protons are pseudoequatorial.

3,7-diheterobicyclo[3.3.1]nonane derivatives of a triplet for the *pseudo*-equatorial protons of the *boat*-like heterocycle and a doublet of multiplets for the protons found in the joined rings with an overall vicinal constant $J > 9.0$ Hz.

The model compounds 3,7-di(2-ethoxyethyl)-3,7-diazabicyclo[3.3.1]nonan-9-ol [8] and tetrahydro-4H-pyran-4-ol [10] were used for the determination of the steric structure of the alcohols. The chemical shifts and the constants for the protons of the piperidine ring of isomer **6B** agree quite well with those found for the protons of the *boat*-like ring in 3,7-di(2-ethoxyethyl)-3,7-diazabicyclo[3.3.1]nonan-9-ol. As shown previously [8], this compound exists in the *chair-boat* conformation in deuterochloroform, the *boat* form occurring in the ring with the axial OH group. The tetrahydro-4H-pyran-4-ol has a *chair*-like form with an equatorial hydroxyl group and models the geometrical parameters of the oxygen-containing ring in the studied isomers quite well and, therefore, the chemical shifts and constants. In fact, the chemical shifts (3.61 and 3.79 ppm) for the axial and equatorial protons next to the oxygen atom and the vicinal constants for the interaction of these protons with the equatorial neighbors (2.4 and 2.1 Hz) agree quite well with those for the isomer **6B**. It should be noted that, for the tetrahydropyran-4-ol, J = 2.4 Hz and differs from the other axial-equatorial constant J = 5.1 Hz. As shown above, the position of the oxygen atom relative to the discussed fragments affects the constant. Hence it is necessary to use these values with care, and bear in mind the nature of the studied and model compounds, when determining the geometry.

Analysis of the ^{1}H NMR spectra of the studied compounds has shown that the 7-alkoxyalkyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ones and 7-alkoxyalkyl-3-oxa-7-azabicyclo[3.3.1]nonanes exist in deuterochloroform solution in the *double chair* conformation. The secondary alcohol **6** exists as a 1:1 mixture of two stereoisomers. One of them occurs in a double *chair* conformation with an equatorial hydroxyl group relative to the piperidine ring and the other in a *chair-boat* conformation with an axial hydroxyl group which experiences an intramolecular hydrogen bond with the unshared electron pair on the nitrogen atom.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury-300 instrument (300 MHz) using $CDCl_3$.

7-(3-Butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (6). A mixture of $NaBH_4$ (0.82 g, 22 mmol) and 7-(3-butoxypropyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**3**) (0.9 g, 3.5 mmol) in isopropanol (10 ml) was stirred for 20 h at about 20°C. Solvent was evaporated and water (10 ml) was added to the residue. The aqueous solution was extracted with ether (3 × 20 ml) and the combined extracts were dried over Na_2SO_4. The ether solutions were filtered and the solvent was evaporated to give a light yellow oil which was refluxed for 10 min in hexane (30 ml). The solvent was decanted off and evaporated in vacuo to give compound **6** (0.81 g, 89%) as light yellow, amorphous crystals with mp 60-67°C and R_f 0.57 and 0.39 (aluminium oxide, benzene–ethanol, 15:1). Found, %: C 65.43; 65.40; H 10.38; 10.55; N 5.58; 5.83. $C_{14}H_{27}NO_3$. Calculated, %: C 65.42; H 10.57; N 5.44.

REFERENCES

1. E. E. Fomicheva, R. D. Mukhasheva, V. K. Yu, K. D. Praliev, and K. D. Berlin, *Izv. MON RK, NAN RK, Ser. Khim.,* No. 6, 26 (2001).
2. N. S. Zefirov, *Usp. Khim.,* **44**, 413 (1975).
3. H. Günther, *Introductory Course in NMR Spectroscopy* [Russian translation], Mir, Moscow (1984), p. 478.

4. G. L. Garrison, K. D. Berlin, B. J. Scherlag, R. Lazzara, E. Patterson, T. Fazekas, S. Sangiah, Chen Chun-Lin, F. D. Schubot, and D. Van der Helm, *J. Med. Chem.*, **39**, 2559 (1996).
5. K. D. Berlin, S. Tyagi, A. Rahaman, F. Qiu, L. M. Raff, L. Venkatramani, M. A. Khan, D. van der Helm, V. Yu, and K. D. Praliev, *Phosphorus, Sulfur, Silicon,* **148**, 97 (1999).
6. N. S. Prostakov, A. A. Fomichev, N. I. Golovtsov, V. A. Rezakov, and A. V. Varlamov. *Zh. Org. Khim.*, **21**, 2313 (1985).
7. R. A. Appleton, S. C. Egan, J. M. Evans, S. H. Graham and J. R. Dixon, *J. Chem. Soc.*, 1110 (1968).
8. N. A. Ismagulova, *Authors Abstract, Dissertations of Candidates in Chemical Sciences,* Almaty (2000).
9. C. A. R. Baxter and D. A. Whiting, *J. Chem. Soc.*, 1174 (1968).
10. P. Arjunan, K. D. Berlin, Ch. L. Barnes, and D. van Helm, *J. Org. Chem.*, **46**, 3196 (1981).