Chemistry of Heterocyclic Compounds, Vol. 44, No. 11, 2008

^{1}H NMR SPECTROSCOPY IN THE STUDY OF THE THREE-DIMENSIONAL STRUCTURE OF 7-ALKOXYALKYL-3-THIA-7-AZABICYCLO-[3.3.1]NONAN-9-ONES AND SOME OF THEIR DERIVATIVES

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

^{1}H NMR spectroscopy was used to establish that 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones and their decarbonylated derivatives in deuterochloroform solution exist in the double chair conformation. The predominantly formed secondary alcohols isomers have preferred double chair conformation with the hydroxyl group equatorial relative to the plane of the piperidine ring. On the other hand, the epimeric alcohols have predominant boat-chair conformation; the piperidine ring takes the boat form due to intramolecular hydrogen bonding between the unshared electron pair of the nitrogen atom and hydroxyl group proton.

Keywords: 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]non-9-one and its derivatives, conformational analysis, ^{1}H NMR spectra.

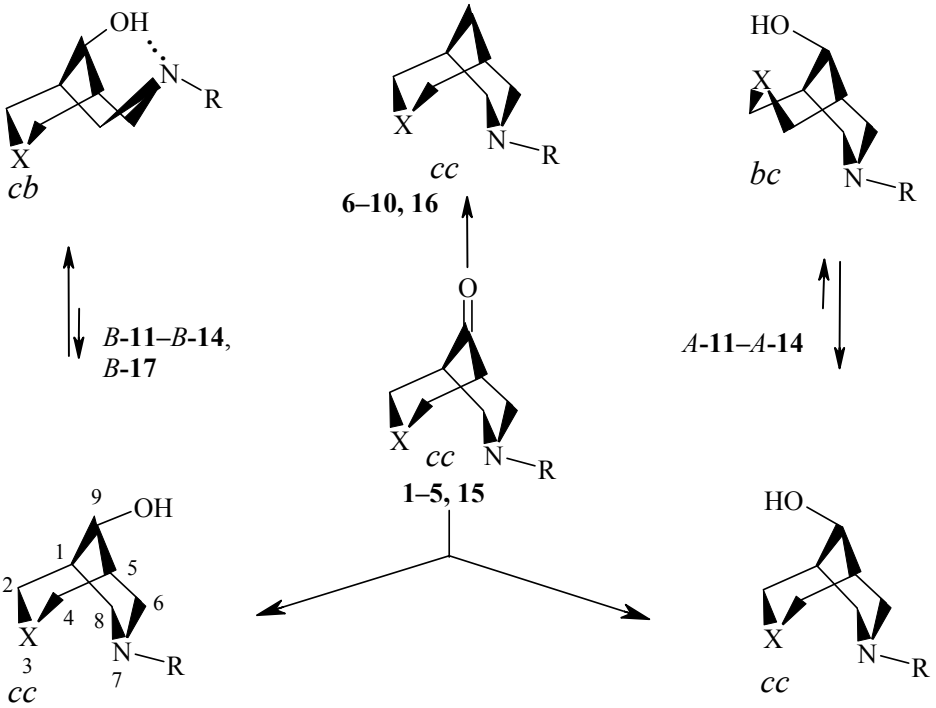
The study of the three-dimensional structure of bicyclic compounds containing important biogenic elements such as oxygen, nitrogen, and sulfur holds interest not only in regard to the search for new physiologically active compounds but also for the development of conformational analysis and stereochemistry. We have described the synthesis of a series of 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]non-9-ones, their deoxygenated derivatives, and derived secondary alcohols [1]. In the present work, we have determined the three-dimensional structure of these compounds using high resolution ^{1}H NMR spectroscopy. We studied ketones **1-5** with various substituents at the nitrogen atom, their reduced analogs **6-10**, and secondary alcohols **11-14**. The chemical shifts and coupling constants for the individual stereoisomers isolated from alcohols **11** and **12** were used to interpret the rather complex spectra of alcohols **13** and **14**, each of which is a mixture of two isomers that could not be separated.

Bicyclo[3.3.1]nonanes and their 3,7-dihetero analogs exist in solution as one of four forms: *double chair* (*cc*), *chair-boat* (*cb*), *boat-chair* (*bc*), and *double boat* (*bb*) or as a mixture in conformational equilibrium [2]. The predominant configuration is determined not only by the overall electronic and steric factors within these

---

[1]A. B. Bekturov Institute of Chemical Sciences, Ministry of Education and Science, Republic of Kazakhstan, Almaty 480100, Kazakhstan; e-mail: yu_vk@rambler.ru. [2]Chemistry Department, Oklahoma State University, Stillwater, Oklahoma 74078, USA, e-mail: berlin.d.kenneth@okstate.edu. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1716-1725, November, 2008. Original article submitted June 8, 2004. Revised version submitted September 3, 2008.

molecules but also depends on external conditions. Hence, we should be careful in assuming that the structures established for the crystalline state and calculated for the gaseous state actually exist in real solutions. If the energy difference between the *double chair* and *chair-boat* conformers is slight (on the order of only 1.5 kcal/mol) [3], a change in the solvent, temperature, or concentration can shift the equilibrium toward another form.



1–**14** X = S, **15**–**17** X = N$(CH_2)_2$OEt; **1**, **6** R = $(CH_2)_2$OMe; **2**, **7**, **11** R = $(CH_2)_2$OEt; **3**, **8**, **12** R = $(CH_2)_3$OEt; **4**, **9**, **13** R = $(CH_2)_3$OBu; **5**, **10**, **14** R = $(CH_2)_3$OPr-*i*

^{1}H NMR spectroscopy permits us to determine which of the forms in solution is predominant. Structural information is found in the vicinal constants, which are characteristic and described by the Karplus equation [4]. Coupling constants J = 1-7 Hz for 3,7-dihetero analogs of bicyclo[3.3.1]nonane are known to correspond to equatorial-equatorial or equatorial-axial interactions of protons in *chair*-like rings [5, 6], while J = 9-12 Hz correspond to interactions of protons H-1 and H-5, located equatorially as a consequence of a given ring fusion, with pseudoequatorial protons of a *boat*-like ring [2, 7]. The observation of a large vicinal constant J > 9 Hz is a reliable criterion for the existence of the *chair-boat* conformation in solution. Thus, the establishment of the three-dimensional structure reduces to the proper assignment of the NMR signals and determination of the vicinal coupling constants of the protons at the ring fusion with adjacent protons.

The spectra of ketones **3-5** are rather readily analyzed although the signals of the cyclic protons are found in a narrow range and partially overlap. These results permitted us to decipher the more complex spectra of ketones**1** and **2**. The geminal constant for six-membered compounds with a sulfur atom in the ring, as a rule, is greater than for nitrogen analogs. Hence, of the four doublet of doublets, two signals with geminal constant 13.2 Hz were assigned to the equatorial and axial protons of the sulfur-containing ring, while the two other signals with J = 11.1 Hz were assigned to the corresponding protons of the piperidine ring. The correctness of this assignment was also indicated by the finding that the chemical shifts and coupling constants of the piperidine ring methylene protons in the ketones studied hardly differ from the analogous values for 3,7-diazabicyclo[3.3.1]nonan-9-ones with the same substituents, which as already determined [8], exist in

TABLE 1. [1] NMR Spectra of 7-Alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones **1-5** and **15**

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)											
	H*e*-1, -5, (m, Δδ, Hz)*	H*a*-2,-4 (dd)	H*e*-2,-4 (dd)	H*a*-6,-8 (dd)	H*e*-6,-8 (dd)	10-CH_2 (t)	11-CH_2	12 CH_3, 12-CH_2	13-CH_3, 13-CH_2, 13-CH	14-CH_3, 14-CH_2	15-CH_2	16-CH_3
1	2.83 (16.0)	3.16 (13.2; 3.9)	3.19 (13.2; 4.2)	2.85 (11.1; 5.4)	3.15 (11.1; 2.0)	2.65 (5.6)	3.51 (5.6) t	3.38 s				
2	2.80 (16.0)	3.11 (13.2; 4.8)	3.23 (13.2; 3.9)	2.83 (11.1; 4.8)	3.15 (11.1; 2.0)	2.66 (5.7)	3.54 (5.7) t	3.48 (6.9) q	1.19 (6.9) t			
15	2.54 (16.0)	2.87 (11.1; 6.3)	3.10 (11.1; 2.1)	2.87 (11.1; 6.3)	3.10 (11.1; 2.1)	2.62 (6.0)	3.52 (6.0) t	3.47 (6.9) q	1.18 (6.9) t			
3	2.81 (18.0)	3.12 (13.2; 6.9)	3.21 (13.2; 4.5)	2.71 (11.1; 4.8)	3.09 (11.1; 2.4)	2.49 (6.9)	1.74 (6.6) q	3.48 (6.6) t	3.47 (6.9) q	1.19 (6.9) t		
4	2.80 (18.0)	3.13 (12.9; 6.9)	3.21 (12.9; 4.2)	2.71 (11.7; 5.1)	3.08 (11.7; 2.0)	2.48 (7.2)	1.73 (6.9) q	3.47 (6.6) t	3.40 (6.6) t	1.54 (6.9) q	1.35 (7.2) sext	0.91 (7.2) t
5	2.80 (18.0)	3.12 (13.2; 7.2)	3.22 (13.2; 4.2)	2.70 (11.1; 4.8)	3.08 (11.1; 2.8)	2.484 (6.6)	1.72 (6.6) q	3.47 (6.6) t	3.54 (6.0) sept	1.14 (6.0) d		

* Δδ – halfwidth signal.

TABLE 2, [1]H NMR Spectra of Compounds **6-10** and **16**

Compound	Chemical shifts, δ, ppm. (SSCC, *J*, Hz)													
	H*e*-1,-5 (m, Δδ, Hz)	H*a*-2,-4 (dd)	H*e*-2,-4 (dm)	H*a*-6,-8 (dd)	H*e*-6,-8 (dt)	H*a*-9 (dt)	H*e*-9 (dm)	10-CH_2 (t)	11-CH_2	12-CH_3, 12-CH_2	13-CH_3, 13-CH_2, 13-CH	14-CH_3, 14-CH_2	15-CH_2	16-CH_3
6	2.09 (19.0)	3.00 (12.9; 6.0)	22.63 (12.9; 2.7)	2.40 (11.1; 3.9)	2.84 (11.1; 2.0)	1.55 (12.9; 3.9)	1.77 (12.9)	2.50 (6.0)	3.53 (6.0) t	3.35 s				
7	2.08 (19.0)	3.00 (13.2; 6.3)	2.64 (13.2; 2.7)	2.39 (11.1; 3.9)	2.84 (11.1; 2.0)	1.53 (12.6; 3.9)	1.78 (12.6)	2.50 (6.3)	3.57 (6.6) t	3.50 (6.9) q	1.19 (6.9) t			
16	1.88 (18.0)	2.53 (11.4; 6.0)	2.96 (11.4; 1.5)	2.53 (11.4; 6.0)	2.96 (11.4; 1.5)	1.55 br. m	1.82 br. m	2.51 (6.3)	3.56 (6.3) t	3.49 (6.9) q	1.18 (6.9) t			
8	2.7 (15.0)	3.01 (13.2; 6.0)	2.63 (13.2; 2.4)	2.26 (11.1; 3.6)	2.83 (11.1; 1.5)	1.51 (12.9; 3.9)	1.80 (12.9)	2.30 (6.9)	1.74 (6.9) q	3.51 (6.6) t	3.47 (6.9) q	1.19 (6.9) t		
9	2.08 (19.0)	3.02 (13.2; 6.0)	2.64 (13.2; 2.4)	2.27 (10.8; 3.3)	2.83 (10.8; 1.5)	1.52 (12.9; 3.9)	1.81 (12.9)	2.31 (6.9)	1.74 (6.6) q	3.51 (6.6) t	3.42 (6.6) t	1.55 (6.9) q	1.37 (7.2) sext	0.91 (7.2) t
10	2.07 (19.0)	3.01 (13.2; 6.0)	2.62 (13.2; 2.4)	2.29 (11.1; 3.9)	2.84 (11.1; 1.5)	1.53 (12.6) 3.9	1.79 (12.6)	2.31 (6.6)	1.67 (6.6) q	3.51 (6.6) t	3.56 (6.0) sept	1.14 (6.0) d		

TABLE 3. ^{1}H NMT Spectra of Compounds **11-14** and **17**

Alcohol	Chemical shifts, δ, ppm (SSCC, *J*, Hz)													
	H*e*-1,-5	H*a*-2,-4 dd	H*e*-2,-4 dd	H*a*-6,-8*	H*e*-6, -8*[2] dd	H*a*-9 t	H*e*-9 t	10-CH_2 t	11-CH_2	12-CH_3, 12-CH_2	13-CH_3, 13-CH_2, 13-CH	14-CH_3, 14-CH_2	15-CH_2	16-CH_3
A-**11**	2.19 (Δδ 15.0) m	3.15 (13.2; 7.8)	2.73 (13.2; 2.7)	2.35 (11.4; 2.4) dd	2.88 (11.4; 1.2)	3.66 (3.9)	—	2.52 (6.0)	3.54 (6.0) t	3.49 (6.9) q	1.19 (6.9) t			
B-**11**	2.58 (11.4) dm	2.31 (13.8; 3.0)	2.93 (13.9; 2.4)	3.11 (11.4) t	2.73 (11.4; 4.2)	—	3.32 (2.7)	2.55 (5.7)	3.51 (5.7) t	3.47 (7.2) q	1.18 (7.2) t			
B-**17**	2.17 (10.2) dm	2.15 (11.1; 1.5)	2.74 (11.1; 2.7)	3.02 (10.2) t	2.57 (10.2; 2.4)	—*[3]	—*[3]	2.49 2.52 (6.0)	—*[3]	—*[3]	1.18 1.18 (6.9)	—	—	
A-**12**	2.22 (Δδ 15.0) m	3.09 (13.5; 7.8)	2.78 (13.5; 2.4)	2.22 (11.4; 2.1) dd	2.82 (11.4; 1.2) dd	3.64 (4.2)	—	2.35 (6.6)	1.72 (6.6) q	3.50 (6.6) t	3.47 (6.9) q	1.19 (6.9) t		
B-**12**	2.57 (10.2) dm	2.31 (13.8; 3.0)	2.93 (13.8; 2.1)	3.07 (10.2) t	2.62 (10.2; 3.9)	—	3.32 (2.7)	2.41 (6.6)	1.73 (6.6) q	3.46 (6.6) t	3.43 (6.9) q	1.18 (6.9) t		
A-**13**	2.21 (Δδ 15.0) m.	3.17 (13.2; 7.8)	2.70 (13.2; 2.4)	2.27 (10.8; 2.4) dd	2.89 (10.8; 1.5)	3.69 (4.2)	—	2.35 (6.6)	1.74 (6.6) q	3.50 (6.6) t	3.42 (6.6) t	1.54 (6.9) q	1.36 (7.2) sext	0.91 (7.2) t
B-**13**	2.59 (10.5) dm	2.33 (13.8; 3.0)	2.95 (14.1; 2.1)	3.09 (10.5) t	2.64 (10.5; 3.9)	—	3.34 (2.1)	2.43 (6.6)	1.74 (6.6) q	3.39 (6.6) t	3.32 (6.6) t	1.54 (6.9) q	1.36 (7.2) sext	0.91 (7.2) t
A-**14**	2.19 (Δδ 15.0) m	3.15 (13.8; 7.8)	2.71 (13.8; 2.1)	2.23 (10.8; 2.4) dd	2.86 (10.8; 1.5)	3.67 (3.6)	—	2.35 (6.6)	1.70 (6.6) q	3.50 (6.6) t	3.55 (6.0) sep	1.14 (6.0) d		
B-**14**	2.56 (10.8) dm	2.31 (14.1; 3.0)	2.94 (14.1; 1.8)	3.08 (10.8) t	2.63 (10.8; 3.6)	—	3.33 (2.4)	2.41 (6.6)	1.71 (6.6) q	3.41 (6.6) t	3.51 (6.6) sep	1.13 (6.6) d		

* The protons are pseudoequatorial for the *chair-boat* conformation.

*[2] The protons are pseudoaxial for the *chair-boat* conformation.

*[3] Overlap of signals.

deuterochloroform solution in *double chair* conformation. For comparison, the data for 3,7-di(2-ethoxyethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (**15**) are given in Table 1. The vicinal coupling constants found for ketones **1-5** J = 2.0-7.2 Hz are typical for *chair*-like rings. The equatorial-axial coupling constants J = 6.9-7.2 Hz indicate compression of the sulfur-containing ring, while the configuration of the piperidine ring (4.8-5.4 Hz) is closer to ideal than the configuration of ketone **15**, for which this coupling constant is 6.3 Hz. The signal of the protons at the ring fusion is an unresolved multiplet $\Delta\delta$ = 16-18 Hz, which also indicates a *double chair* conformation for ketones **1-5**.

The signals of the cyclic protons in the spectra of reduced analogs **6-10** do not overlap. This circumstance permits us to determine the required characteristics (Table 2). The spectrum of 7-(2-ethoxyethyl)-3-thia-7-azabicyclo[3.3.1]nonane (**7**) has a multiplet at 2.08 ppm with $\Delta\delta$ = 19 Hz belonging to protons H-1 and H-5. The shape of this multiplet indicates that both rings are *chair*-like. The most downfield signal at 3.00 ppm with splitting 13.2 and 6.3 Hz are related to the axial protons of the sulfur-containing ring. The equatorial protons give a doublet (13.2 Hz) of doublets (2.7 Hz) and the components of the latter also have slight splitting due to long-distance spin-spin coupling with proton H-9, which is axial to the plane of the piperidine ring. The signal of the equatorial protons at 2.84 ppm for the piperidine ring is a doublet (11.1 Hz) of triplets (2.0 Hz). The complication of the structure of the signal also results from long-distance planar zigzag coupling with equatorial proton H-9. The doublet (11.1 Hz) of doublets (3.9 Hz) at 2.39 Hz is related to axial protons. The observed chemical shifts and coupling constants of the signals for protons H-6 and H-8 correlate rather well with the values given in Table 2 for 3,7-(2-ethoxyethyl)-3,7-diazabicyclo[3.3.1]nonane (**16**), which has *double chair* conformation [8]. There is no transmission of long-range coupling between axial protons of the heterocycles H*a*-4 and H*a*-6 (H*a*-2 and H*a*-8) in these compounds, in contrast to compounds with oxygen and nitrogen heteroatoms [9]. Thus, the vicinal coupling constants 1.5-6.3 Hz indicate that reduced analogs **6-10** in deuterochloroform solution exist predominantly in *double chair* conformation. We should note that the sulfur-containing ring, as in ketones **1-5**, is compressed (6.0-6.3 Hz), while the piperidine ring acquires are more proper form (3.3-3.9 Hz).

Data for 3,7-di(2-ethoxyethyl)-3,7-diazabicyclo[3.3.1]nonan-9-ol (*B*-**17**) (Table 3) were used to assign the signals in the spectra of the individual epimeric alcohols *A*-**11** and *B*-**11**. In previous work [10], we established that this secondary alcohol has *chair-boat* conformation, which is energetically more favorable than the *double chair* conformation due to intramolecular hydrogen bonding between the unshared electron pair of the nitrogen atom and hydrogen atom of the hydroxyl group oriented axially relative to the piperidine ring. Proof for the *chair-boat* conformation lies in the concurrent presence of a triplet and doublet of multiplets with identically large splitting (10.2 Hz), which were assigned to the pseudoaxial protons and protons at the ring fusion.

The spectrum of stereoisomer *B*-**11** showed signals analogous in both position and shape: a triplet at 3.11 ppm with splitting 11.4 Hz and doublet (11.4 Hz) of multiplets at 2.58 ppm. These data unequivocally indicate a *boat*-like form of the piperidine ring with an axial hydroxyl group. This conformation has optimal conditions for intramolecular hydrogen bonding, which stabilizes the unstable *boat* form. The pseudoaxial protons give a doublet (11.4 Hz) of doublets (4.2 Hz) at 2.73 ppm. Two doublet of doublets at 2.31 and 2.93 ppm with geminal coupling constant 13.8 Hz and vicinal coupling constants 3.0 and 2.4 Hz, respectively, belong to axial and equatorial protons H-2 and H-4. The small vicinal coupling constants indicate ideal *chair*-like form of the sulfur-containing ring, which may arise only in the *chair-boat* conformation when there are no nonbonding interactions between S(3) and N(7). The signal for proton H-9 is a triplet at 3.32 ppm with J = 2.7 Hz. Thus, stereoisomer *B*-**11** in deuterochloroform solution exists in the *chair-boat* conformation with an axial hydroxyl group relative to the plane of the piperidine ring present in *boat* form due to intramolecular hydrogen bonding. Hence, the hydroxyl group is in an equatorial position in epimer *A*-**11**.

The spectrum of secondary alcohol *A*-**11** has three doublet of doublets with small vicinal coupling constants (1.2-2.7 Hz), one doublet of doublets with vicinal coupling constant 7.8 Hz, and a multiplet with $\Delta\delta$ = 15 Hz, which indicates predominant *double chair* conformation. The large coupling constants (7.8 Hz) for protons H-2 and Hα-4 of the sulfur-containing ring may indicate that this ring is either slightly compressed [2] or the *chair-chair* conformer is in rapid equilibrium with a *boat-chair* conformer and the ring with the sulfur

atom takes the *boat* form. The existence of a *boat-chair* conformer is not excluded due to possible intramolecular hydrogen bonding between the proton of the hydroxyl group and the sulfur atom. This question remains open and additional study is required for its resolution. However, the difference between $J = 7.8$ and $J = 11.4$ Hz (for the *boat* in isomer *B*-**11**) suggests that a *double chair* conformation with compression of the thiane ring and ideal form of the piperidine ring (1.2 and 2.4 Hz) is preferred. The triplet at 3.66 ppm with splitting 3.9 Hz is assigned to proton H-9.

We note that the signals for protons H-9 in the spectra of isomers *A*-**11** and *B*-**11** are not overlapped by other signals. These signals are shifted relative to each other by 0.34 ppm and have different coupling constants (3.9 and 2.7 Hz). In this regard, these signals may be taken as analytic in the quantitative analysis of unseparated mixtures of epimeric secondary alcohols **13** and **14**. The integral intensities of these signals were used to establish the 2:1 ratio of stereoisomers *A* and *B*. This ratio indicates the more favorable conditions for the formation of isomer *A*.

Our study using high resolution ^{1}H NMR spectroscopy showed that ketones **1-5** and reduced analogs **6-10** in deuterochloroform solution exist predominantly in the *double chair* conformation, in which the thiane ring is more compressed than the piperidine ring. Predominantly formed secondary alcohols *A*-**11** – *A*-**14** have preferred *double chair* conformation with the hydroxyl group equatorial relative to the piperidine ring. By analogy to the ketones, the sulfur-containing ring is compressed, while the piperidine ring has proper chair form. The epimeric alcohols, *B*-**11** – *B*-**14** exist predominantly in the *chair-boat* conformation; the piperidine ring has *boat* form due to intramolecular hydrogen bonding between the unshared electron pair of the nitrogen atom and the proton of the axial hydroxyl group. In this case, the thiane ring has proper chair-like form.

These distinguishing characteristics are useful for determining the three-dimensional structure of these newly synthesized derivatives and interpreting the spectra of mixtures.

EXPERIMENTAL

The ^{1}H NMR spectra of the compounds studied in $CDCl_3$ were taken on a Varian Mercury-300 spectrometer at 300 MHz.

REFERENCES

1. V. K. Yu, K. D. Praliev, E. E. Fomicheva, R. D. Mukhasheva, and S. G. Klepikova, *Khim. Geterotsikl. Soedin.*, 585 (2006). [*Chem. Heterocycl. Comp.*, **42**, 512 (2006)].
2. N. S. Zefirov, *Usp. Khim.*, **44**, 413 (1975).
3. 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).
4. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *NMR Spectroscopy in Organic Chemistry* [in Russian], Khimiya, Leningrad (1983), 268 pp.
5. A. Palanisamy and K. D. Berlin, *J. Org. Chem.*, **46**, 3196 (1981).
6. N. S. Pantaleo, D. van der Helm, K. Ramarajian, B. R. Bailey, and K. D. Bailey, *J. Org. Chem.*, **46**, 4199 (1981).
7, R. A. Apleton, S. G. Egan, J. M. Evans, S. H. Graham, and J. R. Dixon, *J. Chem. Soc.*, 1110 (1968).
8. N. A. Ismagulova, Thesis for Candidate of Chemical Sciences, Almaty (2000).
9. S. G. Klepikova, V. A. Solomin, K. D. Praliev, N. A. Ismagulova, V. K. Yu, T. K. Iskakova, and K. D. Berlin, *Khim. Geterotsikl. Soedin.*, 586 (2003). [*Chem. Heterocycl. Comp.*, **39**, 504 (2006)].
10. S. G. Klepikova, V. K. Yu, E. E. Fomicheva, R. D. Mukhasheva, K. D. Praliev, V. A. Solomin, and K. D. Berlin, *Khim. Geterotsikl. Soedin.*, 1562 (2003). [*Chem. Heterocycl. Comp.*, **39**, 1376 (2006)].