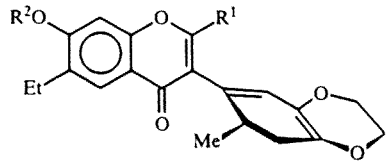
Chemistry of Heterocyclic Compounds, Vol. 32, No. 7, 1996

SYNTHESIS OF STERICALLY HINDERED BENZODIOXANE ANALOGS OF ISOFLAVONE AND A STUDY OF THEIR ATROPOISOMERISM

S. P. Bondarenko, A. V. Turov, and V. P. Khilya

Syntheses are reported for sterically hindered 2-substituted benzodioxane analogs of isoflavone. An optically active lanthanide shift reagent (LSR) was used to show that these products exist as mixtures of atropoisomers. The difference in the chemical shifts of the enantiomeric protons in the presence of the LSR may reach 2-3 ppm with decreasing temperature. Conclusions were drawn concerning the structure of the LSR—substrate adducts and their conformations.

Heterocyclic analogs of isoflavone display considerable biological activity and have been studied as potential drugs for the treatment of cardiovascular disease and dysfunction of the liver and pancreas [1, 2]. Benzodioxanes are promising compounds of this type, for which many natural analogs have been found. In particular, the benzodioxane fragment is found in silibin, which is an important natural hepatoprotector [3]. The biological activity of a compound is related to its optical activity. Thus, one of the four enantiomers of silibin displays high hepatoprotector activity and, thus, it was of interest to synthesize benzodioxane analogs of isoflavone possessing chirality. By analogy with benzofuran and thiazole analogs [4, 5], we may assume that derivatives containing substituents both at $C_{(2)}$ of the chromone system and $C_{(7)}$ of the benzodioxane fragment will prove chiral. Hence, we synthesized the following compounds:



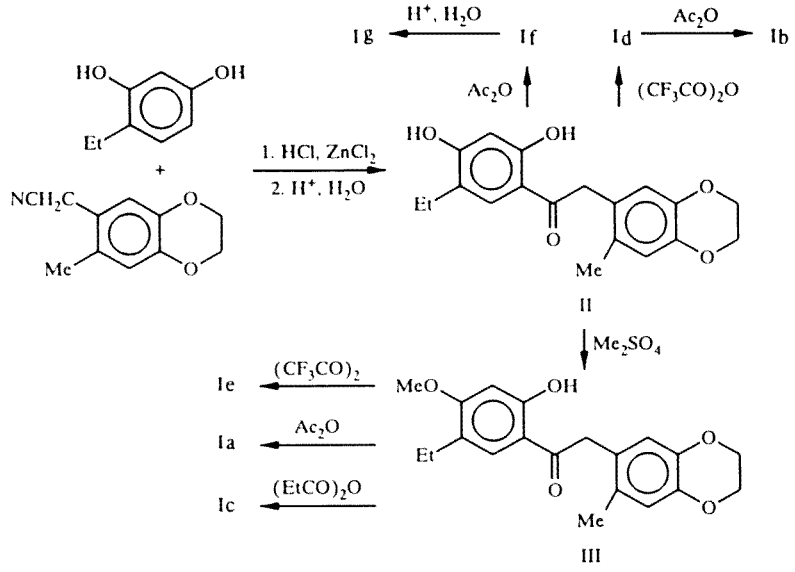
Ia–g

I a $R^1 = R^2 = Me$; b $R^1 = CF_3$, $R^2 = MeCO$; c $R^1 = Et$, $R^2 = Me$; d $R^1 = CF_3$, $R^2 = H$; e $R^1 = CF_3$, $R^2 = Me$; f $R^1 = Me$, $R^2 = MeCO$; g $R^1 = Me$, $R^2 = H$

Ketone II synthesized by the condensation of 6-cyanomethyl-7-methyl-1,4-benzodioxane and 4-ethylresorcin under conditions of the Hoesch reaction was used as the starting compound for the desired products. Ketone II and its methylation product III underwent heterocyclization with the anhydrides of acetic, trifluoroacetic, and propionic acids in the presence of base. The synthesis pathways for all the products are indicated in the scheme. Table 1 gives the PMR spectral data for these isoflavones. Assignment of the signals of the chromone fragment aromatic protons was not difficult since the signal for 5-H appears downfield (7.7-8.2 ppm) due to the effect of the unshared electron pair of the carbonyl oxygen atom. Assignment of the signals for 5-H and 8-H of the benzodioxane system is based on the small coupling constant of 8-H with the protons of the close-lying methyl group, leading to a decrease in the peak intensity of the signal relative to the signals of the other aromatic protons.

Taras Shevchenko Kiev University, 252033 Kiev, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 902-908, July, 1996. Original article submitted March 27, 1996.

0009-3122/96/3207-0767$15.00



Benzodioxane analogs of isoflavone Ia-Ig have a chirality axis along the bond of the heterocyclic fragments such that these compounds exist as mixtures of two atropoisomers. This may be seen for compounds soluble in apolar solvents and capable of coordination with lanthanide chelates using an optically active lanthanide shift reagent (LSR) containing the D-camphor-Eu(FBK)$_3$ residue [5]. Products Ia-Ic different in substituent R^1 were taken for the experiments. Substituent R^2 was found to have virtually no effect on coordination with the LSR. The signals of most of the protons in the PMR spectra of solutions containing the tested compound and the LSR are shifted downfield and are split into two components corresponding to the resultant two diastereomeric LSR—substrate adducts. The visible split increases with increasing molar fraction of the LSR and may reach 0.2-0.4 ppm at room temperature. The signal for 5-H of the chromone system and the signal for 7-CH_3 of the benzodioxane fragment are the most strongly split.

The positions of the signals in the PMR spectra depend to a great extent on the temperature. Figure 1 shows the temperature dependence for some of the proton signals of Ia. The specific lanthanide-induced shifts (LIS) obtained by extrapolation of the observed shifts to a 1:1 LSR:substrate molar ratio are used for the quantitative characterization of the shifts. These plots show that the difference in the chemical shifts of the diastereomeric protons increases sharply with decreasing temperature and may reach 2-3 ppm at 240 K (see Table 1). Upon further cooling, the signals broaden due to a breakdown in the conditions for fast exchange between the LSR-coordinated and free substrate molecules. We should note that the LIS values themselves decrease for many signals with decreasing temperature rather than increase as would be expected from the theory of pseudocontact LIS [6]. We attribute this finding to strong steric hindrance for coordination of the LSR with Ia-Ic and the circumstance that the 3-heteroaryl substituent in the chromone system at room temperature has a mean conformation not very favorable for coordination with the LSR. An energy barrier exists upon the approach of the LSR molecule to the substrate molecule at some distance from the coordination site created by the electron clouds of the close-lying substituents. An increase in the temperature increases the probability for overcoming this barrier. The conformation of the mobile fragments in the molecule may occur simultaneously as indicated by the complex form of the temperature dependence. Thus, curves with a maximum are observed for 5-H, while the temperature dependence curves for the 2-CH_3 protons of the enantiomer signals intersect. As previously seen for benzofuran derivatives [5], such curves indicate a change in the orientation of the 3-heterocyclic substituent with change in temperature.

The electron-donor capacity of the 2-R substituent in the chromone system has a large effect on the LIS in these products. Thus, the LIS values in the 2-methyl (Ia) and 2-ethyl derivatives (Ib) are similar, while they are much lower in going to trifluoromethyl derivative Ic, although the splittings of the signals of the diastereomeric protons are also quite evident (see Table 1). This effect is probably related to the electron-withdrawing effect of the trifluoromethyl group on the unshared electron pairs of the chromone carbonyl and, as a consequence, weakening of the coordination of Ic with the LSR. The temperature dependence of the LIS obtained for Ic show the same features as for Ia except that the range of the shift changes in the case of Ic are less by a factor of 2-3.

The structure and conformation of organic molecules in solution may be found using LSR [7]. Such calculations are based on the pseudocontact nature of the LIS and assumption of fast exchange between the coordinated and free substrate

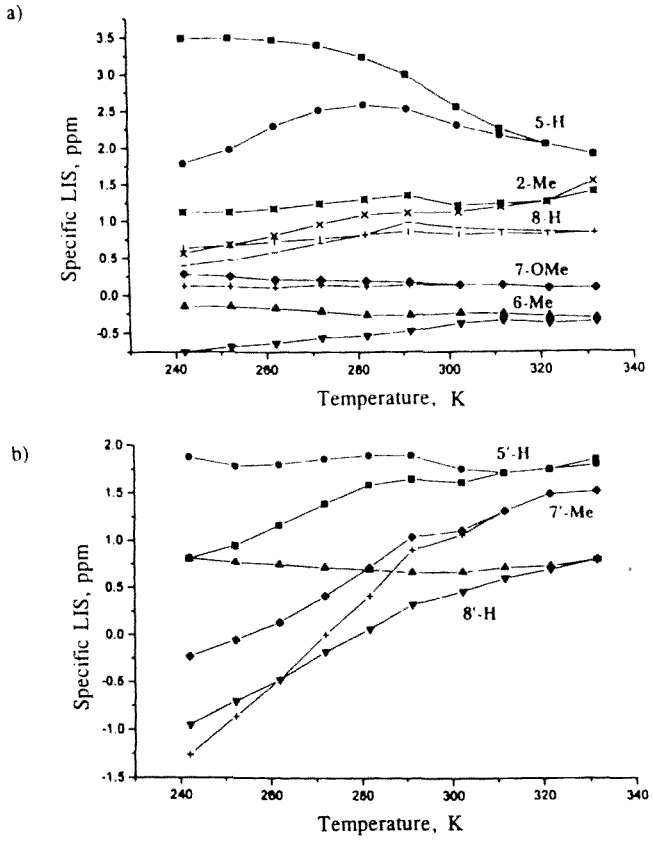


Fig. 1. Temperature dependence of LIS obtained for the adduct of Ia with $Eu(HFBK)_3$: *a*) for signals of the chromone fragment protons and *b*) for the benzodioxane fragment signals (the proton related to the curve is indicated next to each curve).

molecules, in which there is effective axial symmetry of the LSR—substrate adduct. In this case, the McConnel—Robertson equation in its simplest form may be used [8]:

$$\Delta H_i = K(3\cos^2\theta_i - 1)/r_i^3, \quad (1)$$

where θ_i and r_i are the polar coordinates of the proton in the adduct assuming that the coordination site of the molecule is at the origin, ΔH_i are the calculated LIS, and K is the constant for all protons of the adduct.

The structure of the LSR—substrate adduct may be found by determining a point near the coordination site, at which the value of K for the protons in the molecule have minimal scatter [9].

The geometrical structure of the adducts of optically active LSR with racemates of chiral compounds has not been studied. In addition to the complexity of such PMR spectra, this failure is related to the circumstance that the LSR in many cases form adducts lacking effective axial symmetry [10] such that satisfactory agreement of the calculated and experimental LIS cannot be achieved. We carried out the corresponding calculations for Ia according to our previous work [9]. These calculations were successful since, on one hand, the given compound has a large number of inequivalent proton groups, each of which may be used for the calculations, and, on the other, the LSR—substrate adducts in this case prove not very stable due to steric hindrance, which increases the rate of exchange between the coordinated and noncoordinated substrate molecules such that the condition of effective axial symmetry of the adducts is achieved. The standard deviation of the K values in Eq. (1) calculated for the protons using our previous method [9] was used for the correlation parameter of the calculated and experimental LIS values. The calculation results showed that the europium ion in the adduct is found in the plane of the chromone system at a distance of 2.6-2.7 Å from the carbonyl oxygen atom. The europium ion in the adduct is displaced by

TABLE 1. PMR Spectral Data for Benzodioxane Analogs of Isoflavone

Compound	Chromone fragment proton signals						Benzodioxane fragment proton signals			
	2-R^1	5-H	6-Et		7-R^2	8-H	2,3-CH_2	5-H	7-CH_3	8-H
Ia	2,17	7,96	1,23	2,70	3,93	6,79	4,25	6,62	2,02	6,79
Ia + LSR*	1,12	3,49	-0,15		0,28	0,63	0,23	1,88	-0,23	0,81
	0,56	1,79	-0,75		0,12	0,40	0,07	0,81	-1,26	-0,92
Ib	—	8,11	1,26	2,68	2,40	7,35	4,26	6,79	2,01	6,60
	—	0,5	-0,05	-0,0	0,27	0,31	0,1	0,1	0,05	0,31
Ib + LSR*	—	0,27	0,05	-0,08	0,27	0,24	0,1	0	-0,05	0,19
Ic	2,48, 1,21	7,95	1,21	2,70	3,94	6,82	4,26	6,78	2,03	6,62
Ic + LSR*		3,56			0,22	0,63	0,25	1,75	0	0,49
		1,90			0,13	0,50	0,25	0,77	-1,16	-0,29
Id	—	7,79	1,19	2,65	11,2	6,96	4,26	6,66	1,93	6,79
Ie	—	7,95	1,23	2,71	3,96	6,90	4,25	6,61	2,02	6,77
If	2,19	8,11	1,26	2,64	2,39	7,21	4,26	6,62	2,03	6,80
Ig	2,12	7,72	1,19	2,63	10,71	6,81	4,25	6,59	1,03	6,78

*Specific LIS values are given for the diastereomeric Eu(FOD)$_3$—substrate adducts at 242 K.

20-30° from the direction of the C=O bond toward 5-H due to the steric hindrance caused by the 3-benzodioxane substituent. The calculated LIS values are in good accord with the experimental data for an adduct of this structure.

The LIS values were also used for conformational analysis of Ia. In this case, we calculated the structure of the adduct and determined the minimum standard deviation for different trial orientations of the benzodioxane substituent starting from its flat *Z* conformation ($\varphi = 0$). The conformation with the global minimum of standard deviation corresponds to the best correlation of the calculated and experimental LIS values. Figure 2 shows our curves for the adduct of Ia with the LSR at two temperatures. At 332 K, the minimum on the curve for standard deviation vs. torsion angle is found at the mutually perpendicular orientation of the heterocyclic fragments. A similar conformation also obtains for the adduct with one of the enantiomers at 242 K. Molecule Ia has precisely this conformation according to a molecular mechanics calculation. However, the structure of the adducts of the LSR with the other enantiomer in this case differs considerably. The curve for the standard deviation on the torsion angle has a minimum at $\varphi = 60°$. Thus, there are different interactions of the LSR with the enantiomers of Ia. In one of the enantiomers, which more readily forms an adduct with the LSR and for which higher LIS values are found, the conformation of the benzodioxane substituent is virtually the same as in the noncoordinated molecule. In the other enantiomer, the benzodioxane substituent is twisted upon formation of the adduct with the LSR. Since the change in the orientation of the substituent requires an expenditure of energy, a less stable adduct with the LIS is formed and the LIS value is lower. A change in conformation of the substrate upon complexation of the LSR with one of the antipodes accounts for the complex temperature curves for the LIS values and pronounced anisochronicity of the signals of the diastereomeric protons with decreasing temperature.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WP-100SY spectrometer at 100 MHz in deuterochloroform. The temperature measurements were carried out using a B-VT 1000 thermostabilization block. The precision of the temperature measurements was ±1°C. TMS was used as the internal standard. Eu(HFBK)$_3$ was used as the LSR without additional treatment.

6-Cyanomethyl-7-methyl-1,4-benzodioxane. A sample of 44 g (0.22 mole) 6-chloromethyl-7-methyl-1,4-benzodioxane was added dropwise with stirring to a solution of 17 g (0.26 mole) potassium cyanide in 80 ml DMF. The reaction mixture was heated to 70°C and stirred vigorously for 11 h. The precipitate was filtered off and the solvent was distilled off at reduced pressure using a water pump. The product was distilled in vacuum to give 32.2 g (78%) product with bp 110-115°C

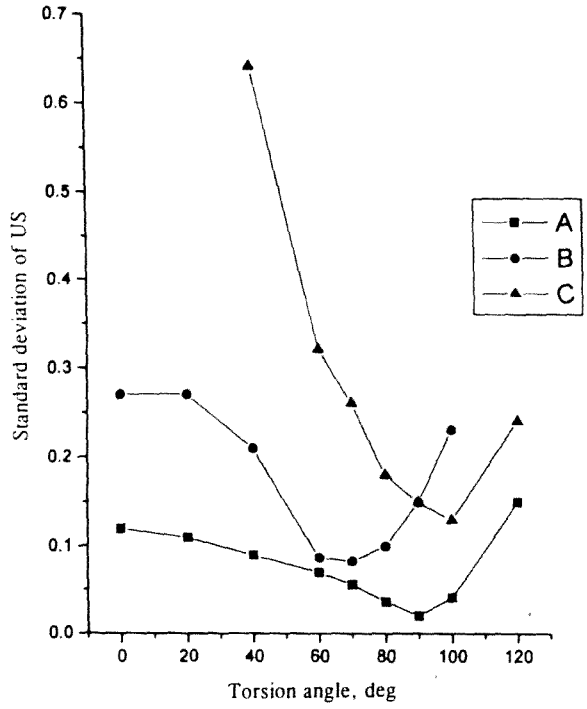


Fig. 2. Conformational analysis of the adducts of Ia with $Eu(HPBK)_3$: *A*) dependence of the standard deviation on the torsion angle between the heterocyclic fragments of Ia obtained at 242 K for the diastereomer with the higher LIS, *B*) the same for the other diastereomer, *C*) dependence of the standard deviation on the torsion angle obtained at 332 K (the signals of the diastereomeric protons coincide).

(0.2-0.25 mm Hg). PMR spectrum in $CDCl_3$: 2.37 (3H, s, 7-CH_3), 4.24 (2H, s, 6-CH_2CN), 4.53 (4H, s, 2,3-CH_2), 6.70 (1H, s, 8-H), 6.84 (1H, s, 5-H).

α-(7-Methyl-6-benzodioxan-1,4-yl)-2,4-dihydroxy-5-ethylacetophenone (II). A rapid stream of dry hydrogen chloride was passed through a solution of 18.9 g (0.1 mole) 6-cyanomethyl-7-methyl-1,4-dioxane in 34 ml absolute ether with stirring for 15 min. Then, a solution of 15.2 g (0.11 mole) dry 4-ethylresorcin and 8 g (0.06 mole) fused zinc chloride in 23 ml absolute ether was added. Then, hydrogen chloride was bubbled into the solution for 3 h at 0°C and an additional 4 h at room temperature. The reaction mixture became a thick mass and was left overnight. The ethereal layer was poured off. The oil was introduced into 400 ml hot water and heated at reflux for 2 h. After cooling, the precipitated oil was triturated with ice until it completely crystallized. The product was washed with water on the filter until the wash water was at pH 7 and recrystallized from aqueous methanol to give 15.5 g (47%) II as colorless needles, mp 161-162°C. PMR spectrum in $CDCl_3$: 12.36 (1H, s, 2-OH), 6.68 (1H, s, 3-H), 10.61 (1H, s, 4-OH), 2.51 (2H, q, ^3J = 7 Hz, 6-CH_2CH_3), 1.15 (2H, t, 6-CH_2CH_3), 4.23 (2H, s, α-CH_2), 4.20 (4H, s, 2′,3′-CH_2), 6.34 (1H, s, 5′-H), 2.08 (3H, s, 7′-CH_3), 6.68 (1H, s, 8′-CH_3).

α-(7-Methyl-6-benzodioxan-1,4-yl)-2-hydroxy-4-methoxy-5-ethylacetophenone (III). A sample of 4.14 g (30 mmoles) freshly roasted potassium carbonate and 1.15 ml (10 mmoles) dimethyl sulfate were added to a solution of 3.28 g (10 mmoles) ketone II in 70 ml absolute benzene and the mixture was heated at reflux for 5 h. Potassium carbonate was filtered off and benzene was evaporated. The product was crystallized from ethanol to give 2.5 g (73.5%) III as colorless, shiny needles, mp 139°C. PMR spectrum in $CDCl_3$: 12.47 (1H, s, 2-OH), 6.68 (1H, s, 3-H), 3.87 (3H, s, 4-OCH_3), 2.53 (2H, q, ^3J = 7 Hz, 6-CH_2CH_3), 1.15 (3H, t, 6-CH_2CH_3), 4.27 (2H, s, α-CH_2), 4.20 (4H, s, 2′,3′-CH_2), 6.51 (1H, s, 5′-H), 2.08 (3H, s, 7′-CH_3), 6.68 (1H, s, 8′-CH_3).

2-Methyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-acetoxychromone (If). A mixture of 3.28 g (10 mmoles) ketone II, 4.46 ml (50 mmoles) acetic anhydride, and 5.6 ml (40 mmoles) triethylamine was heated at 125-130°C for 10 h. The reaction mixture was poured into ice water containing 1.7 ml (70 mmoles) hydrochloric acid. The precipitate was filtered

off and washed with water until there was no pyridine odor to give 2.96 g (76%) If as colorless plates, mp 174-175°C (dec., from cyclohexane).

2-Methyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-hydroxychromone (Ig). A solution of 2.5 g (6.3 mmoles) 7-acetoxychromone If in 100 ml methanol was heated at reflux for 10 h and then, 30 ml warm water was added to the reaction mixture. Cooling gave 2 g (91%) Ig as colorless needles, mp 241-242°C.

2-Methyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-methoxychromone (Ia). A sample of 1.38 ml (15 mmoles) acetic anhydride and 1.68 g (12 mmoles) triethylamine was added to 1.03 g (3 mmoles) ketone III. The mixture was heated at 125-130°C for 10 h. The reaction mixture was added to ice water containing 0.5 ml (21 mmoles) hydrochloric acid. The precipitate was filtered off and washed with water until there was no further odor to give 0.4 g (36.8%) Ia as colorless, shiny plates, mp 225-226°C (from 60% ethanol).

2-Trifluoromethyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-hydroxychromone (Id). A sample of 0.28 ml (2 mmoles) trifluoroacetic acid was added dropwise to a solution of 0.32 g (1 mmole) ketone II in 1 ml absolute pyridine at 0°C. The mixture was left for 48 h and then heated for 1.5 h at 60°C and poured into ice water containing 0.3 ml hydrochloric acid. The precipitate was filtered off and washed on the filter until there was no further odor to give 0.25 g (62.5%) as colorless needles, mp 236-237°C (from 50% ethanol).

2-Trifluoromethyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-methoxychromone (Ie). A sample of 0.28 ml (2 mmoles) trifluoroacetic acid was added to a solution of 0.68 g (2 mmoles) ketone III in 4 ml absolute pyridine at 0°C. The mixture was maintained at room temperature for 48 h and then heated for 2 h at 60°C and left for an additional 12 h at room temperature. The mixture was poured into ice water containing 0.3 ml 1 N hydrochloric acid. The precipitate was filtered off and washed on the filter until there was no further odor to give 0.49 g (60.9%) Ie as colorless needles, mp 207-208°C (dec., from 50% methanol).

2-Trifluoromethyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-acetoxychromone (Ib). A sample of 0.16 ml (1.85 mmole) acetic anhydride was added to a solution of 0.15 g (0.37 mmole) 7-hydroxychromone Id in 0.5 ml absolute pyridine and left for 48 h at room temperature. The reaction mixture was poured into ice water and the precipitate was crystallized from 1:3 ethyl acetate:hexane to give 0.1 g (60%) Ib as colorless, shiny needles, mp 185-186°C.

2-Ethyl-3-(7-methyl-6-benzodioxan-1,4-yl)-6-ethyl-7-methoxychromone (Ic). A mixture of 1.03 g (3 mmoles) ketone III, 1.68 ml (12 mmoles) triethylamine, and 1.93 ml (15 mmoles) propionic anhydride was heated for 30 h at 125-130°C. The reaction mixture was poured into ice water containing 0.5 ml (21 mmoles) hydrochloric acid. The precipitated oil was crystallized from ethanol to give 0.25 g (22%) Ic as colorless plates, mp 217-218°C.

The authors express their gratitude to the INTAS program and ISSEP International Soros Program (Grant No. SPU063069) for financial support of this work.

REFERENCES

1. N. V. Gorbulenko and V. P. Khilya, Ukr. Khim. Zh., **60**, No. 1, 709 (1994).
2. A. L. Kazakov, V. P. Khilya, V. V. Mezheritskii, and D. Litkei, Natural and Modified Isoflavonoids [in Russian], Izd. Rostovsk. Univ., Rostov-on-the-Don (1985).
3. L. Carollini and G. Lucchetti, Gazz. Med. Ital., **135**, Nos. 7-8, 365 (1976).
4. A. V. Turov, I. V. Komarov, V. P. Khilya, and M. Yu. Kornilov, Teor. Éksperim. Khim., No. 5, 629 (1989).
5. A. V. Turov and V. P. Khilya, Khim. Geterotsikl. Soedin., No. 6, 723 (1996).
6. B. Bleany, J. Magn. Reson., **8**, 91 (1972).
7. M. Yu. Kornilov, A. V. Turov, and V. I. Zamkovoi, Ukr. Khim. Zh., **41**, No. 7, 769 (1975).
8. H. M. McConnel and R. E. Robertson, J. Chem. Phys., **29**, No. 12, 1361 (1958).
9. M. Yu. Kornilov, V. V. Plakhotnik, A. V. Turov, and V. P. Khilya, Ukr. Khim. Zh., **58**, No. 11, 1026 (1992).