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# Stereochemistry of Seven-Membered Heterocycles: XLV.* Highly Diastereoselective Addition of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate to 2-Substituted 1,3-Dithiacyclohept-5-enes

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**Abstract**—Conformationally heterogeneous 2-substituted 1,3-dithiacyclohept-5-enes (R = Ph, Me, *t*-Bu), which exist in solution as *chair* and *boat* conformers, react with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with high *exo*-diastereoselectivity: only the *chair* conformer is involved. The steric structure of 4-methyl-3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene was determined by X-ray analysis. Its crystal packing and supramolecular structure were also analyzed.

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Seven-membered unsaturated acetals (1,3-dioxacyclohept-5-enes) are known to give cycloaddition products with both 1,3-dipoles [2, 3] and 1,3-dienes [4–9]. We selected just Diels–Alder reactions as model processes for our systematic studies on the relations between steric structure and reactivity (selectivity) of conformationally heterogeneous substrates [6–9]. Sulfur analogs of seven-membered cyclic acetals (1,3-dithiacyclohept-5-enes) also exist as mixtures of different conformers [10, 11]; as far as we know, there are no published data on cycloaddition reactions of these compounds at the endocyclic double bond.

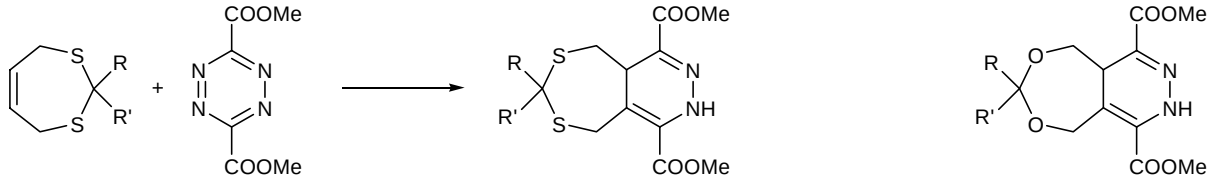
We are the first to report on reactions of 1,3-dithiacyclohept-5-enes **Ia**–**Ie** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylaye (**II**) and steric structure of adducts **IIIc**–**IIIe** thus formed. As with related acetals [6, 7], compounds **Ia**–**Ie** readily reacted with tetrazine **II** at room temperature to give in good yield bicyclic dihydropyridazines **IIIa**–**IIIe** having a 1,4-diene system (Scheme 1). The structure of the products was confirmed by their analytical data and $^{13}C$ NMR spectra and by X-ray analysis of compound **IIIc**. According to the $^{1}H$ and $^{13}C$ NMR spectra of the reaction mixtures, the addition of monosubstituted dithio acetals **Ic**–**Ie** is characterized by high selectivity, and adducts **IIIc**–**IIIe** were isolated as individual diastereoisomers.

In the $^{13}C$ NMR spectra of compounds **III**, signals from carbon atoms in the dihydropyridazine ring are similar to those observed for adducts **IV** which were synthesized previously from diene **II** and 2-substituted 1,3-dioxacyclohept-5-enes [5]. The ester groups are nonequivalent, and the methyl and carbonyl carbon atoms both gave a couple of signals in the $^{13}C$ NMR spectrum. The chemical shifts of $C^2$, $C^4$, and $C^6$ were typical of cyclic dithio acetals; the $C^4$ signal tends to shift downfield from $\delta_C$ 37 to 68 ppm in the series of substituents H < Me < Ph < *t*-Bu.

Monosubstituted diastereoisomeric products **IIIc**–**IIIe** are characterized by fairly similar chemical shifts of $C^1$, $C^2$, and $C^6$; taking into account stereochemical data for related acetals, compounds **IIIc**–**IIIe** belong to the same series. Their *exo* configuration was determined by X-ray analysis of a single crystal of compound **IIIc**. The hydrogen atoms on $C^1$ and $C^4$ in molecule **IIIc** are arranged *trans* with respect to each other (Fig. 1), and the $C^1$ and $C^4$ atoms have similar configurations.

* For communication XLIV, see [1].

**Scheme 1.**




R = R' = H (**a**), Me (**b**); R = H, R' = Me (**c**), Ph (**d**), *t*-Bu (**e**).

The bond lengths and bond angles in the dihydropyridazine fragment of molecule **IIIc** coincided within experimental error with the corresponding parameters of related *exo*-acetal **IVc** [7]. The dihydropyridazine ring in **IIIc** adopts a *flattened boat* conformation. The $C^7C^8N^{10}C^{11}$ fragment is planar within 0.005(7) Å, and the $C^1$ and $N^9$ atoms deviate from that plane by –0.31(1) and –0.18(1) Å, respectively (i.e., in the same direction). The seven-membered heteroring in molecule **IIIc** has an asymmetric *twist–chair* conformation, which slightly differs from that found for molecule **IVc**. The four-atom $O^5C^6C^7C^1$ fragment in **IVc** is planar (the heteroring has an approximate $C_s$ symmetry), whereas the corresponding fragment in molecule **IIIc** is not planar. On the other hand, the five-atom $C^1C^2C^4S^5C^6$ fragment is almost planar [within 0.09(1) Å] with the $S^3$ and $C^7$ atoms deviating from that plane by –1.124(3) and 0.818(8) Å, respectively (i.e., in the opposite directions); the heteroring in **IIIc** has an approximate $C_2$ symmetry. The methoxycarbonyl groups in both molecules (**IIIc** and **IVc**) lie almost in the plane of the dihydropyridazine ring base. The ester groups on $C^8$ and $C^{11}$ in acetal **IVc** are turned apart in opposite directions so that the carbonyl group on $C^8$ is faced opposite to the N–H group, making intramolecular hydrogen bonding in this fragment impossible. The ester groups in the molecule of sulfur analog **IIIc** are turned in one direction. Another structural specificity of molecule **IIIc** is that the bond angles at the sulfur atoms differ by about 5°, which underscores asymmetry of the heteroring.

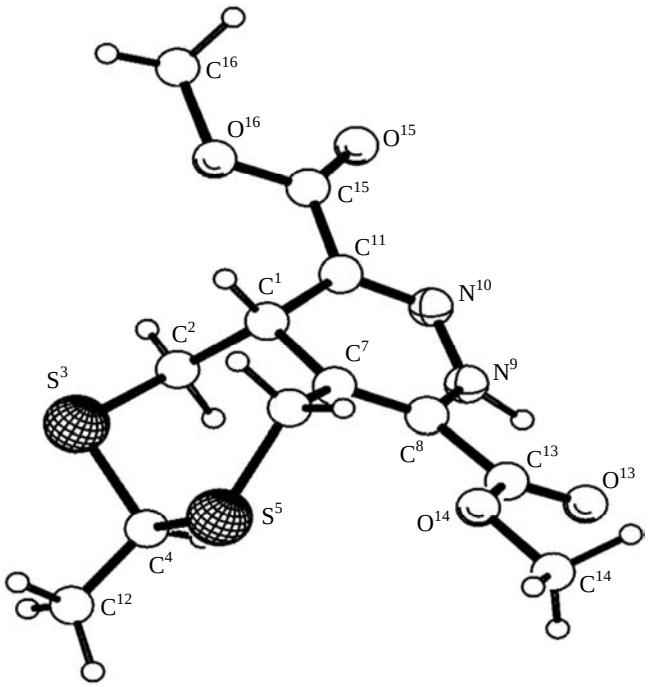
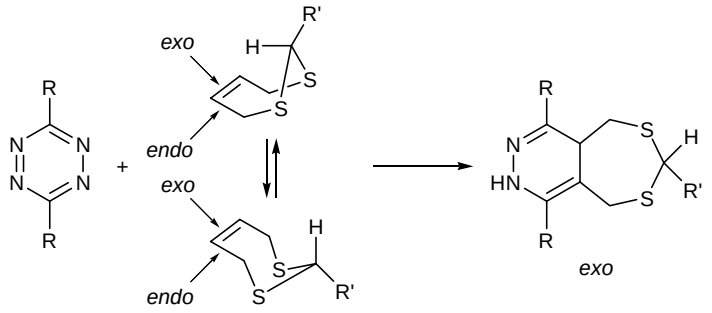



**Fig. 1.** Structure of the molecule of dimethyl 4-methyl-3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylate (**IIIc**) according to the X-ray diffraction data.

The above differences in the structure of molecules **IIIc** and **IVc** determine differences in the crystalline structure of these compounds. Molecules **IVc** in crystal give rise to centrosymmetric dimers via N–H···N intermolecular hydrogen bonds. Centrosymmetric dimers are also formed in the crystalline structure of compound **IIIc**, but through NH···O hydrogen bonds with the following parameters: $N^9$–$H^9\cdots O^{13'}$ [$-x, -1-y, -z$], $d(H^9\cdots O^{13'})$ = 2.09, $d(H^9\cdots O^{13'})$ = 2.973(8) Å, $\angle N^9H^9O^{13'}$ = 147°. The $H^9$ atom is also involved in intramolecular hydrogen bonding with $O^{13}$ in the ester group [$d(H^9\cdots O^{13})$ = 2.29, $d(H^9\cdots O^{13})$ = 2.644(7) Å, $\angle N^9H^9O^{13}$ = 100°], which is likely to fix the methoxycarbonyl group in the heteroring plane [the torsion angle $N^9C^8C^{13}O^{13}$ is –4(1)°]. Hydrogen bonds C–H···O between the methyl hydrogen atoms $H^{141}$ and $H^{161}$ in one molecule and $O^{15}$ oxygen atoms in the neighboring molecules (related to the former through a symmetry center and translation along the 0*b* axis, respectively) connect the dimers to skewed stacks along the crystallographic 0*b* axis (Fig. 2). These interactions are characterized by the following parameters: $C^{14}$–$H^{141}\cdots O^{15'}$ [$-x, -y, -z$], $d(H^{141}\cdots O^{15'})$ = 2.31, $d(C^{14}\cdots O^{15'})$ = 3.326(7) Å, $\angle C^{14}H^{141}\cdots O^{15'}$ = 149°; $C^{16}H^{161}O^{15''}$ [$x, 1+y, z$], $d(H^{161}\cdots O^{15''})$ = 2.57, $d(C^{16}\cdots O^{15''})$ = 3.440(9) Å, $\angle C^{16}H^{161}O^{15''}$ = 140°. On

**Scheme 2.**




the whole, the crystal packing may be represented by stacking of the above supramolecular structures (Fig. 3) with a fairly high packing coefficient (71.7%).

We also tried to verify a model based on localization of hydrophilic and hydrophobic domains in crystals of organic compounds [12–14] using compound **IIIc** as an example. It was found that, like microphase separation in liquid crystals and polymeric systems [15–17], analogous separation is observed in crystals of organic compounds with the difference that hydrophilic and hydrophobic domains are formed by the corresponding molecular fragments. The degree of separation of hydrophilic and hydrophobic domains in crystal may be characterized by the volume ratio of the hydrophilic and hydrophobic constituents corresponding to the symmetry-independent part of a unit cell. Change of this ratio in crystal leads to change of the type of morphological structure.

As follows from the structure of molecule **IIIc** and calculation data, the hydrophobic fragment therein is $C^4H–C^{12}H_3$, while the other part of the molecule (excluding neutral $C^2H_2$ and $C^6H_2$ methylene groups) is essentially hydrophilic. The calculated volume fraction of the hydrophobic component is 0.24; as shown by us previously [18], this value corresponds to formation of cylindrical hydrophobic associates in a matrix consisting mainly of hydrophilic fragments. In fact, graphical representation of the distribution of hydrophobic and hydrophilic regions (Fig. 3) indicates just that morphological type of supramolecular structures formed by molecules **IIIc** in crystal, in support of our previous assumptions.

Let us consider stereochemical features of the reaction of tetrazine **II** with monosubstituted dithioacetals **Ic**–**Ie**, which lead exclusively to the corresponding *exo* adducts. According to the dynamic $^1H$ NMR data, compounds **Ia** and **Ic**–**Ie** in carbon disulfide at –105°C exist as equilibrium mixtures of *chair* and *boat* conformers with equatorial orientation of the 2-substituent (in monosubstituted derivatives) [10, 11]. In the present work we supplemented the NMR data by AM1 calculations of the energies of formation of the *chair*, *boat*, and *twist* conformers of compounds **Ic**–**Ie**. In all cases, the *chair* conformer turned out to be the most stable; the energy of the *boat* conformer is higher by 1.1 kcal/mol, and that of *twist*, by 1.75–2.1 kcal/mol.

Clearly, the stereochemical result of the reaction of diene **II** with compounds **Ic**–**Ie** rules out both directions of attack by the reagent at the *endo* side of the double bond in the conformers involved in equilibrium. *exo* Attack on the *boat* conformer is less probable since the reaction center is sterically shielded. Thus the high stereoselectivity in the reaction of tetrazine **II** with seven-membered cyclic dithioacetals **Ic**–**Ie** originates from attack by the reagent on the spatially accessible *exo* side of the *chair* conformer.

Stereochemical aspects of the reverse Diels–Alder reactions (where diene acts as acceptor, and dienophile, as donor) will be analyzed in terms of orbital interactions in a separate communication.

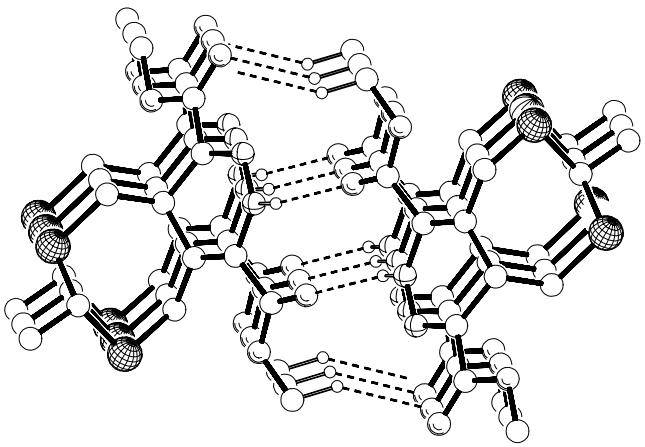


**Fig. 2.** Formation of skewed stacks from centrosymmetric dimers of molecules **IIIc** via hydrogen bonds C–H···O. Hydrogen atoms involved in hydrogen bonding are shown. Hydrogen bonds are denoted with dashed lines.

## EXPERIMENTAL

The $^{13}C$ NMR spectra were recorded on a Varian Unity-300 spectrometer at 25°C using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference. Initial dithioacetals **Ia**–**Id** were synthesized by the procedures described in [10, 11].

**2-*tert*-Butyl-1,3-dithiacyclohept-5-ene (Ie).** A mixture of 0.75 g (6.6 mmol) of *cis*-but-2-ene-1,4-dithiol [10, 11] and 0.47 g (5.5 mmol) of 2-methylpropanal in 30 ml of benzene containing a catalytic amount of *p*-toluenesulfonic acid was heated for 1 h under reflux in a flask equippd with a Dean–Stark trap. The mixture was washed with a 10% aqueous solution of sodium hydroxide (2×50 ml) and water (2×50 ml) and dried over $MgSO_4$. Yield 0.73 g (72%), mp 26–28°C (from ethanol). Found, %: C 57.51; H 8.75. $C_9H_{16}S_2$. Calculated, %: C 57.45; H 8.51.

**Dimethyl 3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylates IIIa–IIIe (*general procedure*).** Compound **Ia**–**Ie**, 1.2 mmol, was added at room temperature to a suspension of 1 mmol of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**II**) [19] in 5 ml of anhydrous chloroform. The progress of the reaction was monitored by TLC on Silufol UV-254 plates (petroleum ether–ethyl acetate, 4:1). When the reaction was complete, the solvent was removed, and the residue was recrystallized from ethanol (yield 75–85%).

**Dimethyl 3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylate (IIIa).** mp 164–165°C. $^{13}C$ NMR spectrum, $\delta_C$, ppm: 33.73 and 33.91 ($C^2$, $C^6$); 36.92 ($C^4$); 43.50 ($C^1$); 53.52 and 53.67 ($OCH_3$); 119.48, 127.22, and 132.62 ($C^7$, $C^8$, $C^{11}$); 161.73 and 164.19 (C=O). Found, %: C 45.14; H 5.09; N 9.27; S 21.59. $C_{11}H_{14}N_2O_4S_2$. Calculated, %: C 43.69; H 4.67; N 9.26; S 21.21.

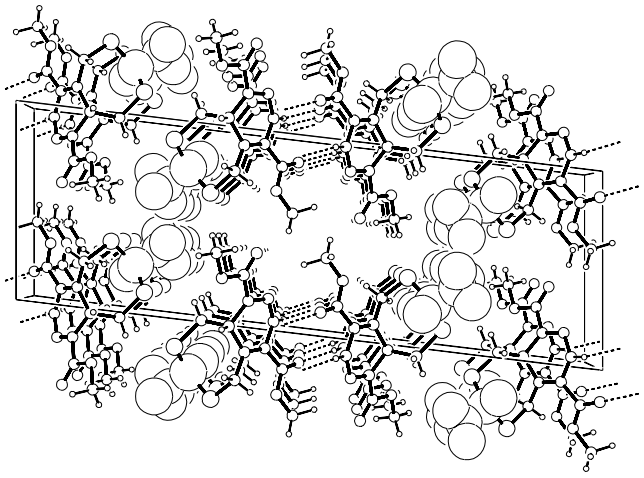


**Fig. 3.** Fragment of crystal packing of compound **IIIc**. Hydrophobic molecular fragments are denoted with large circles. Projection along the crystallographic 0*b* axis is shown.

**Dimethyl 4,4-dimethyl-3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylate (IIIb).** mp 102–103°C. $^{13}C$ NMR spectrum, $\delta_C$, ppm: 32.18 and 32.64 ($CH_3$); 33.06 and 34.94 ($C^2$, $C^6$); 37.61 ($C^1$); 52.61 and 52.81 ($OCH_3$); 54.29 ($C^4$); 124.12, 124.24, and 132.80 ($C^7$, $C^8$, $C^{11}$); 161.84 and 164.67 (C=O). Found, %: C 47.06; H 5.34; N 8.51; S 19.73. $C_{13}H_{18}N_2O_4S_2$. Calculated, %: C 47.26; H 5.49; N 8.48; S 19.41.

**Dimethyl 4-methyl-3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylate (IIIc).** mp 140–141°C. $^{13}C$ NMR spectrum, $\delta_C$, ppm: 22.81 ($CH_3$); 34.21 and 34.78 ($C^2$, $C^6$); 44.18 ($C^1$); 49.12 ($C^4$); 53.34 and 53.45 ($OCH_3$); 120.99, 126.97, and 131.98 ($C^7$, $C^8$, $C^{11}$); 161.67 and 164.26 (C=O). Found, %: C 45.99; H 4.95; N 8.76; S 20.44. $C_{12}H_{16}N_2O_4S_2$. Calculated, %: C 45.55; H 5.10; N 8.85; S 20.27.

**Dimethyl 4-phenyl-3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylate (IIId).** mp 149–150°C. $^{13}C$ NMR spectrum, $\delta_C$, ppm: 34.87 and 36.06 ($C^2$, $C^6$); 44.06 ($C^1$); 53.29 and 53.47 ($OCH_3$); 57.82 ($C^4$); 120.94, 127.14, and 132.00 ($C^7$, $C^8$, $C^{11}$); 127.40, 128.86, 129.29, and 139.87 ($C_{arom}$); 162.07 and 164.60 (C=O). Found, %: C 53.29; H 4.63; N 7.26; S 16.72. $C_{17}H_{18}N_2O_4S_2$. Calculated, %: C 53.95; H 4.79; N 7.40; S 16.94.

**Dimethyl 4-*tert*-butyl-3,5-dithia-9,10-diazabicyclo[5.4.0]undeca-7,10-diene-8,11-dicarboxylate (IIIe).** mp 88–89°C. $^{13}C$ NMR spectrum, $\delta_C$, ppm: 28.54 ($CH_3$); 33.17 and 35.55 ($C^2$, $C^6$); 37.39 (C); 43.12 ($C^1$); 53.05 and 53.18 ($OCH_3$); 67.55 ($C^4$); 121.89, 126.32, and 131.92 ($C^7$, $C^8$, $C^{11}$); 161.81 and 164.45 (C=O). Found, %: C 50.46; H 6.06; N 7.90; S 17.55. $C_{15}H_{22}N_2O_4S_2$. Calculated, %: C 50.26; H 6.19; N 7.81; S 17.89.

**X-Ray analysis** of a single crystal of compound **IIIc** was performed at the Diffraction Methods Laboratory, Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences. The X-ray diffraction data were acquired at 20°C on a CAD-4 automatic diffractometer (NONIUS B.V.; $\lambda Mo K_\alpha$ irradiation, graphite monochromator, $\omega/2\theta$ scanning, $\theta \le 24.47°$). $C_{12}H_{14}N_2O_4S_2$. Monoclinic crystals with the following unit cell parameters (20°C): $a$ = 9.915(5), $b$ = 4.894(3), $c$ = 29.39(1) Å; $\beta$ = 96.89(4)°; $V$ = 1416(1) Å$^3$; $d_{calc}$ = 1.47 g/cm$^3$; $Z$ = 4;

space group $P2_1/c$. Intensities of 3304 reflections were measured, 930 of which were with $I \geq 3\sigma(I)$. No drop in intensity of three control reflections was observed during data acquisition; correction for absorption was not introduced ($\mu$Mo = 3.73 $cm^{-1}$). The structure was solved by the direct method using SIR program [20] and was refined first in isotropic and then in anisotropic approximation. All hydrogen atoms were visualized from the difference electron density series, and their contributions to structural amplitudes were taken into account with fixed positional and isotropic temperature factors. The final divergence factors were $R$ = 0.050 and $R_w$ = 0.049 (from 930 independent reflections with $F^2 \geq 3\sigma$). All calculations were performed using MolEN software package [21]; intermolecular interactions were analyzed and the structures were plotted using PLATON program [22]. The hydrophilic–hydrophobic distribution in molecule **IIIc** was calculated using MMP program, and the molecular volumes were calculated using MMP and XSEED programs [23]. The complete set of crystallographic data for compound **IIIc** was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 268917)

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## REFERENCES

1. Fedorenko, V.Yu., Baryshnikov, R.N., Khairutdinov, B.I., Vafina, R.M., Shtyrlin, Yu.G., Klochkov, V.V., and Klimovitskii, E.N., *Russ. J. Org. Chem*., 2005, vol. 41, p. 293.
2. Fisera, L., Stibranyi, Z., and Oremus, V., *Chem. Zvesti*, 1984, vol. 38, p. 557.
3. Camilleri, P., Munro, D., Weaver, K., Williams, D.J., Rzepa, H.S., and Slawin, A.M.Z., *J. Chem. Soc., Perkin Trans. 2*, 1985, p. 1265.
4. Hausweiler, A., Schwarzer, K., Wollweber, H., and Hiltmann, R., FRG Patent no. 1088066, 1958; *Chem. Abstr*., 1962, vol. 56, p. 3498.
5. Hausweiler, A., Schwarzer, K., Wollweber, H., Hiltmann, R., and Unterstenhofer, G., FRG Patent no. 1075373, 1960; *Chem. Abstr*., 1961, vol. 55, p. 18003.
6. Klimovitskii, E.N., Shtyrlin, Yu.G., Kashaeva, E.A., Kiselev, V.D., Vafina, R.M., and Khotinen, A.V., *Russ. J. Gen. Chem*., 1996, vol. 66, p. 477.
7. Klimovitskii, E.N., Shtyrlin, Yu.G., Shaikhutdinova, G.R., Vafina, R.M., Kashaeva, E.A., Kataeva, O.N., and Litvinov, I.A., *Russ. J. Gen. Chem*., 2000, vol. 70, p. 788.
8. Shtyrlin, Yu.G., Fedorenko, V.Yu., Kataeva, O.N., Litvinov, I.A., Gubaidullin, A.T., Krivolapov, D.B., and Klimovitskii, E.N., *Russ. J. Gen. Chem*., 1998, vol. 68, p. 1793.
9. Shtyrlin, Yu.G., Fedorenko, V.Yu., and Klimovitskii, E.N., *Russ. J. Gen. Chem*., 2001, vol. 71, p. 819.
10. Klimovitskii, E.N., Strel'nik, D.Yu., Il'yasov, K.A., and Klochkov, V.V., *Zh. Org. Khim*., 1991, vol. 27, p. 1065.
11. Strel'nik, D.Yu., *Cand. Sci. (Chem.) Dissertation*, Kazan, 1991.
12. Gubaidullin, A.T. and Litvinov, I.A., *Acta Crystallogr., Sect. A*, 2000, vol. 56, p. 318.
13. Gubaidullin, A.T. and Litvinov, I.A., *XVII Mendeleevskii s"ezd po obshchei i prikladnoi khimii. T1. Plenarnye doklady* (XVIIth Mendeleev Congr. on General and Applied Chemistry. Vol. 1. Plenary Lectures), Kazan, 2003, p. 252.
14. Gubaidullin, A.T., Mamedov, V.A., and Litvinov, I.A., *ARKIVOC*, 2004, part XII, p. 80.
15. Grosberg, A.Yu. and Khokhlov, A.R., *Fizika v mire polimerov* (Physics in the Polymer World), Moscow: Nauka, 1989.
16. Frenkel, S., *J. Polym. Sci., Polym. Symp*., 1977, vol. 61, p. 327.
17. Goldacker, T. and Abetz, V., *Macromolecules*, 1999, vol. 32, p. 5165.
18. Gubaidullin, A.T., Beskrovnyi, D.V., and Litvinov, I.A., *Zh, Strukt. Khim*., 2005, vol. 46, p. 193.
19. Boger, D.L., Coleman, R.S., Panek, J.S., Huber, F.X., and Sauer, J., *J. Org. Chem*., 1985, vol. 50, p. 5377.
20. Altomare, A., Cascarano, G., Giacovazzo, C., and Viterbo, D., *Acta Crystallogr., Sect. A*, 1991, vol. 47, p. 744.
21. Straver, L.H. and Schierbeek, A.J., *MOLEN. Structure Determination System. Vol. 1. Program Description*, Nonius B.V., 1994.
22. Spek, A.L., *Acta Crystallogr., Sect. A*, 1990, vol. 46, p. 34.
23. Barbour, L.J., *J. Supramol. Chem*., 2001, vol. 1, p. 189.