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Preparation and Properties of Two Polymorphic Modifications of β-Hydroxysulfoxide of the Pinane Series

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Abstract—The oxidation was performed of 2-(6,6-dimethylbicyclo[3.1.1]hept-2-ylmethylsulfanyl)ethanol **II** synthesized by adding 2-mercaptoethanol to (–)-β-pinene in the presence of a Lewis acid. The sulfoxide obtained is present in two polymorphic structures with different physical properties, spectral characteristics, and fungicidal activity.

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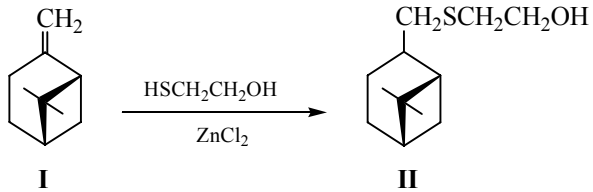
The studies on the modification of sulfur-containing biologically active compounds and the preparation of their sulfoxide analogs are nowadays extensively developed. This means that there are attempts to obtain compounds with a sulfoxide function from accessible biologically active sulfides (e.g., cephalosporin) and sulfones (various sulfonamides). It was noted that the introduction of the sulfoxide group leads to a significantly improved activity of such substances. For example, at comparing the biological activity of sulfides, sulfoxides, and sulfones of the so-called third-generation cephalosporins it was found that the activity of the sulfoxide is several times higher compared with two other derivatives [1]. Naiti et al. attributed the increased biological activity of sulfoxides to the increased membranotropic properties of the molecule and its higher hydrophilicity, while maintaining its high lipophilicity [2].

There are publications on the synthesis of the terpene series sulfoxides based on camphor, borneol, mirtenal, and menthone [3–5]. None of these studies inform on the isolation of polymorphic modifications of the sulfoxides. However, it is known that polymorphism affects the parameters of the biological activity of drugs [6].

Previously, we performed the addition of 2-mercaptoethanol to the double bond of (1*S*)-(–)-β-pinene (**I**) in the presence of zinc chloride resulting in sulfide **II** with *cis*-configuration of the sulfide group relatively to the *gem*-dimethyl fragment of the molecule [7]. It is noteworthy that the main process at the electrophilic addition to the β-pinene molecule is the isomerization to the products of bornane or menthane structure, while the above reaction proceeds with preservation of the pinane structure of the molecule [8].



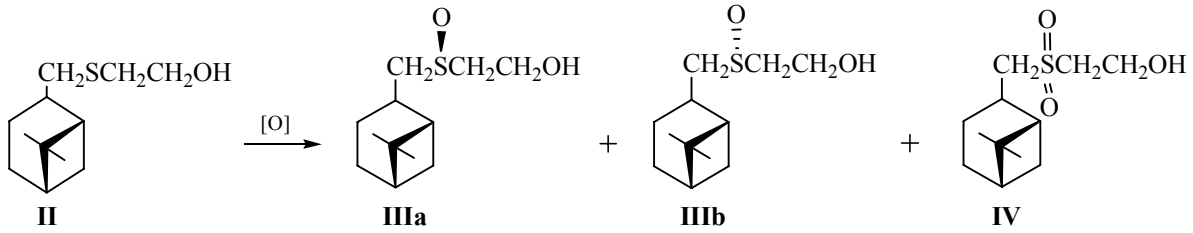
I **II**

In order to prepare a sulfur-containing derivative with new pharmacological properties we studied the oxidation of sulfide **II** to sulfoxide **III** using various oxidizing agents, including sodium periodate, peracetic and *meta*-chloroperbenzoic acids, selenium dioxide

† Deceased.

with hydrogen peroxide, and sulfuryl chloride in combination with ethyl alcohol. A significant problem at designing synthetic approach to the sulfoxide is the sulfide overoxidation to sulfone. We found that at the use of any of these oxidants formation of sulfone **IV** as a minor product occurs, which we were able to separate from the target sulfoxide by column chromatography on silica gel. The most selective oxidant was *meta*-chloroperbenzoic acid leading to minimal formanion of the sulfone (Table 1).

All the examined methods of oxidation resulted in the formation of the hydroxysulfoxide **III** as a mixture of two diastereomers, **IIIa** + **IIIb**, in 1:1 ratio [9].



Polymorph A, [O] = $NaIO_4$, H_2O_2–SeO_2, *m*-$ClC_6H_4CO_3H$, SO_2Cl_2–C_2H_5OH, H_2O_2–CH_3COOH; polymorph B: [O] = *m*-$ClC_6H_4CO_3H$ (exess), H_2O_2–CH_3COOH (exess), O_2.

We found that sulfoxide **III** crystallizes in two polymorphic forms. The formation of the first polymorph (polymorph A) was observed at the crystallization of the product obtained in the oxidation of initial sulfide **II** with equimolar amount of any oxidant and purified by column chromatography. Another polymorph of β-hydroxysulfoxide (polymorph B) formed at the crystallization of the purified product of autoxidation of the initial sulfide by atmospheric oxygen or the product of sulfide **II** oxidation with an excess of peroxyacetic or *meta*-chloroperbenzoic acid. Both the polymorphs were isolated from reaction mixtures by column chromatography on silica gel. The polymorph B was isolated using the eluent CH_2Cl_2, whereas to isolate polymorph A a mixture of equimolar amounts of acetone and CH_2Cl_2 should be used.

The role of the synthesis methods in obtaining a certain modification is unclear. Our attempts to obtain the polymorph A by crystallization of the purified reaction mixture after oxidation by atmospheric oxygen or by an excess of a peracid failed, as well as attempts to isolate polymorph B by crystallization of the product obtained by the sulfide oxidation with the equimolar amount of any oxidant.

According to XRD data, a unit cell of the polymorph A contains the diastereomeric molecules **IIIa** and **IIIb** in 1:1 ratio (monoclinic modification, space group $P2_1$). The diastereomeric molecules in the crystals form a dimer (Fig. 1) due to the S=O···HO interactions (the hydrogen bonding parameters are listed in Table 2).

The second polymorphic modification (polymorph B) was also studied by XRD. In the crystal (triclinic modification, space group. P_1) there are also diastereomeric molecules of the sulfoxide forming a dimer through hydrogen bonds. Comparative analysis of the polymorphs structures according to the XRD data showed that the dimers formed by isomeric molecules **IIIa** and **IIIb** in both crystalline modifications are in the same conformation, but parameters of the two hydrogen bonds in the dimers differ significantly (Table 2). Thus, the parameters of two hydrogen bonds in the crystals of the polymorph A are almost the same within experimental error, while in the crystals of polymorph B one hydrogen bond is significantly shorter than the other. A significant differences are found also in the crystal packing of the polymorphs, which is associated with the difference in the crystal system. Thus, in the monoclinic crystals of polymorph A herringbone packing of the dimer

Table 1. Effect of oxidants on the selectivity of the sulfide **II** oxidation

Oxidant	**III**:**IV**[a]
H_2O_2–CH_3COOH	60/40
$NaIO_4$	67/33
SeO_2–H_2O_2	52/48
SO_2Cl_2–EtOH	68/32
m-$ClC_6H_4CO_3H$	74/26

[a] The data of chromatography–mass spectrometry.

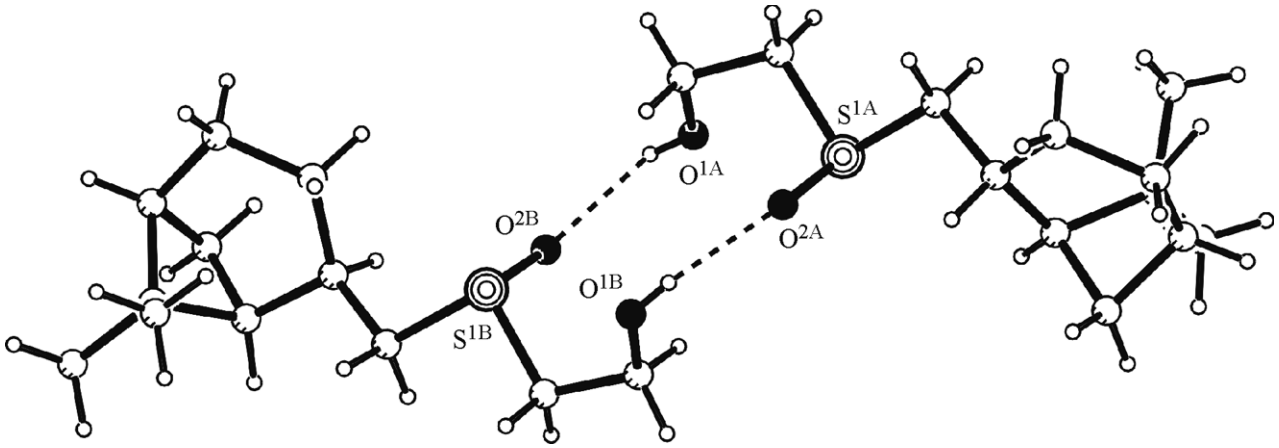


Fig. 1. H-bonded dimer of diastereomeric molecules **IIIA** and **IIIB** by an example of the polymorph A. The dotted lines show hydrogen bonds.

molecules was observed, which is consistent with the presence of the second order rotational axis (Fig. 2a). In contrast, in the crystals of triclinic polymorph (polymorph B) parallel packing of the dimer molecules occurs (Fig. 2b).

The polymorphs obtained differ by the shape of crystal, melting point, solubility, and IR spectra of the solutions (Table 3). The NMR spectra of both polymorphs were identical.

As a parameter characterizing distinct polymorphic dimers we used the stretching vibration frequencies of free and bound hydroxy groups in the IR spectra. In the IR spectrum of crystalline sulfoxide (polymorph A) the stretching vibrations of OH groups $\nu(OH)_{ass}$ give rise to a rather broad band of moderate intensity in the region of 3050–3450 cm^{-1} centered at 3230 cm^{-1}. In the IR spectrum of crystalline sulfoxide in another polymorphic modification (polymorph B) this band is less intense and more broad, 3050–3550 cm^{-1}, with clearly seen two peaks at 3185 and 3346 cm^{-1}. The broadening of the bands of OH stretching vibrations in a sample of polymorph B is consistent with the difference in the characteristics of the two hydrogen bonds of the dimer in the molecules **IIIa** and **IIIb** detected by XRD of this modification. The IR spectra

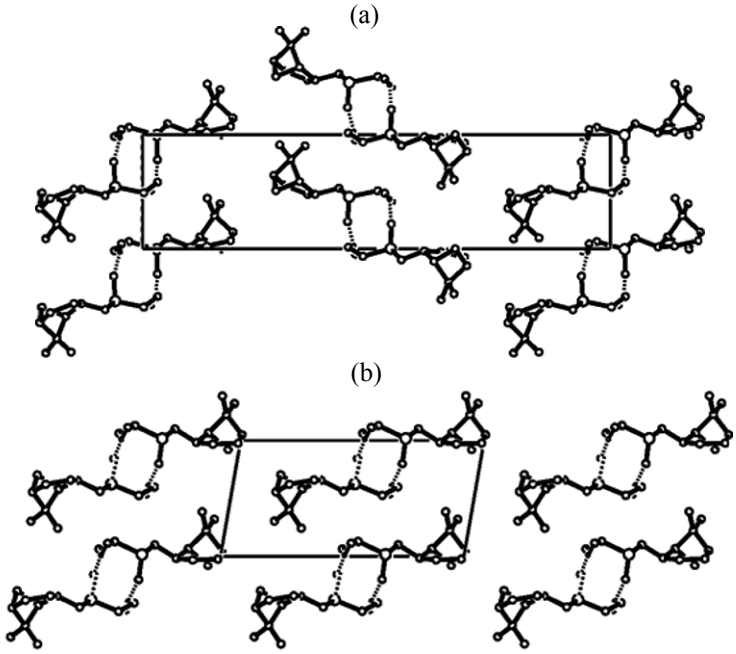


Fig. 2. Fragments of herringbone packing of dimers in the crystals (a) of the polymorph A and (b) parallel packing of dimers in the crystals of the polymorph B, projections on the 0*x* plane.

of melts and dilute solutions of two polymorphic modifications of the sulfoxide **III** are identical.

Both the polymorphic forms were tested for fungicidal activity against nine strains of yeast and filamentous fungi by the disco-diffusion method in the agar-based medium: *Candida albicans, Candida parapsilosis*, *Rhodoto-rula rubra*, *Penicillium tardum*, *Penicillium chrysogenum*, *Epidermophyton floccosum*, *Aspergillus niger*, *Aspergillus fumigatus*.

It is noteworthy that the polymorph B practically shows no fungicidal activity, except for weak activity against the strains of *Candida albicans* (nonpatogenic), whereas polymorph A showed activity against all studied species of fungi.

Thus, we for the first time have discovered the phenomenon of polymorphism in a series of β-hydroxysulfoxides of terpene series. For further study of the phenomenon of polymorphism in this class of compounds we plan to investigate a possibility of occurrence of polymorphic forms of the sulfoxides based on camphene, as well as camphene and β-pinene oxides.

EXPERIMENTAL

NMR spectra were obtained on a Bruker Avance instrument (Germany) with the operating frequencies 400.13 and 100.61 MHz for ^{1}H and ^{13}C nuclei respectively, internal reference TMS. IR spectra were registered in the Laboratory of optical studies of the Federal Center of joint use on a Fourier spectrometer Tensor-27 Bruker in the wavenumber range 4000–400 cm^{-1} (KBr tablets). Melting points of substances were determined on a Koeffler apparatus.

The XRD study of crystalline samples of polymorphs A and B was performed on a Bruker SMART Apex II diffractometer [graphite monochromator, $\lambda Mo K_{\alpha}$ = 0.71073 Å]. The extinction was accounted for semiempirically using the SADABS software [10]. The structures were solved by the direct method with the SHELXS software [11]. The non-hydrogen atoms were refined in the isotropic and then anisotropic approximations with the SHELXL-97 software [12]. The hydrogen atoms not involved in hydrogen bonding were placed in the calculated position and refined using the *rider* model. Hydroxy hydrogen atoms were revealed from the difference Fourier series. At the final stage of refinement the position of the atom H^{1A} in the structure of polymorph A, as well as H^{1A} and H^{1B} in the structure of the polymorph B were not refined, while the H^{1B} position in the structure of polymorph A was refined in the isotropic approximation. All calculations were performed using the WinGX [13] and APEX2 [14] software. The images were prepared using the PLATON software [15]. The XRD data of structures **III** and **IV** are deposited in the Cambridge Structural Database (registration numbers CDD817380 and CDD817381, respectively).

For isolation and purification of the reaction products the method of adsorption chromatography on silica gel L (100/160 μ) was applied. As eluents methylene chloride and a methylene chloride–acetone mixture were used. The reaction progress and the quality of the separation of reaction mixtures were monitored by TLC on Silufol plates, developers I_2 and ethanol–sulfuric acid–anisaldehyde mixture 90:5:5. To remove water and purify the solvents we used known techniques described in [16].

Table 2. Hydrogen bonds in the crystals of polymorphs A and B by the XRD data for the mixture of diastereomeric sulfoxides **IIIA** + **IIIB**

Bond	O–H, Å	H···O, Å	O···O, Å	Angle, O–H···O
Polymorph A				
O^{1A}–H^{1A}···O^{2B}	0.8800	1.8100	2.671(7)	167.00
O^{1B}–H^{1B}···O^{2A}	0.84(7)	1.81(7)	2.650(7)	178(1)
Polymorph B				
O^{1A}–H^{1A}···O^{2B}	0.87	1.82	2.69(1)	175.00
O^{1B}–H^{1B}···O^{2A}	0.85	1.78	2.62(1)	179.00

Table 3. Physical properties and spectral characteristics of the polymorphic structures of sulfoxide **III** of pinane series

Polymorph	Crystal shape	Solubility	Melting point, °C	IR spectra (KBr), ν, cm^{-1} (OH)
A	Thin narrow plates	$(CH_3)_2CO$–CH_2Cl_2 1:1	112–118	3050–3450 m
B	Thin square plates	CH_2Cl_2	95–106	3050–3550 br

The antimycotic activity was studied according to the procedure described in [17].

The XRD investigation of the samples of polymorphs A and B was carried out in the Federal collective spectro-analytical center of physico-chemical studies of structure, composition and properties of substances and materials (Kazan).

Crystals of polymorph A, $C_{12}H_{22}O_2S$, are monoclinic. At 20°C a = 6.648(2), b = 28.381(8), c = 7.148(2) Å, β = 104.106(4) Å, V = 1307.9(6) Å3, Z = 4, d_{calc} = 1.170 g cm^{-3}, space group $P2_1$, μ(Mo) = 2.29 cm^{-1}. Intensities of 5322 independent reflections were measured, of which 2052 had $I \geq 2\sigma(I)$. The absolute configuration was established precisely on the basis of the value of Flack parameter –0.05(14), it corresponds to the (–)-β-pinene configuration. The final values of divergence factors R = 0.0795, R_W = 0.1930.

Crystals of polymorph B, $C_{12}H_{22}O_2S$, are triclinic. At 20°C a = 6.658(8), b = 7.172(8), c = 14.85(2) Å, α = 96.28(1), β = 102.562(13), γ = 104.29(1)°, V = 661(1) Å^3, Z = 2, d_{calc} = 1.158 g cm^{-3}, space group P_1, μ(Mo) = 2.27 cm^{-1}. The absolute configuration is given in accordance with the Flack parameter 0.2 (2) and corresponds to the configuration of (–)-β-pinene. Intensities of 10302 independent reflections were measured, of which 3324 had $I \geq 2\sigma(I)$. The final values of divergence factors R = 0.0938, R_W = 0.2916.

2-{[(1*S*,2*R*,5*S*,*S*$_S$)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl]methylsulfinyl}ethanol and 2-{[(1*S*,2*R*,5*S*,*R*$_S$)-6,6-dimethylbicyclo[3.1.1]hept-2-yl] methylsulfinyl} ethanol. Polymorph A. The oxidation of pinanyl sulfide **II** was carried out according to described procedures [18–22]. The reaction mixture was concentrated in a vacuum and purified by column chromatography on silica gel, eluent methylene chloride–acetone, 1:1. White crystals, mp 112–118ºC. Below are listed the oxidant, reference, yield: $NaIO_4$ [18], 69.5%; H_2O_2/CH_3COOH [19], 60%; *m*-ClC6H4COOOH [20], 74%; SeO_2/H_2O_2 [21], 52%; SO_2Cl_2/EtOH [22], 68%.

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J, Hz): 1.00 s (3H, H^9), 1.20 s (3H, H^8), 1.21 m (1H, H^7), 1.46–1.58 m (1H, H^3), 1.82–2.08 m (4H, H^1, H^2, 2H^4), 2.21 m (1H, H^3), 2.36 m (1H, H^7), 2.42 m (1H, H^5), 2.54–2.66 m (2H, H^{10}), 2.70 m (2H, $SOCH_2$), 3.70 t (2H, C$\underline{H_2}$OH). ^{13}C NMR spectrun (100 MHz, $CDCl_3$), δ_C, ppm: 22.85 (C^3), 23.91, 23.93 (C^9), 26.53, 26.65 (C^4), 28.42, 28.46 (C^8), 33.58, 33.77 (C^7), 35.46, 35.87 (C^5), 39.26, 39.34 (C^6), 41.54, 41.57 (C^1), 45.60, 47.31 (C^2), 54.34, 54.70 (C^{10}), 57.27 (CH_2OH), 61.48, 62.19 ($SOCH_2$).

Polymorph B. *a*. To 0.4 mmol of sulfide **II** was added dropwise while stirring a solution of 0.8 mol of *m*-ClC_6H_4COOOH and the mixture was left for 24 h at room temperature. The precipitate was separated, the solution was saturated with gaseous ammonia to bind the remained *m*-ClC_6H_4COOOH. Crystalline mass was filtered off, the residue was concentrated in a vacuum and purified by column chromatography on silica gel, eluent dichloromethane. Yield 73%, white crystals, mp 95–106ºC.

b. To 0.4 mmol of sulfide **II** while stirring was added dropwise a solution of 1.6 mol of H_2O_2/CH_3COOH. After 48 h the crystalline mass was filtered off, the residue was concentrated in a vacuum and purified by column chromatography on silica gel, eluent dichloromethane. The product yield 69%. The crystalline product obtained by autooxidation in atmospheric oxygen is identical by spectral data to the crystalline product obtained by oxidation of β-hydroxysulfide **II** with a peracid excess.

The ^{1}H and ^{13}C NMR spectra of polymorphs A and B are identical.

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REFERENCES

1. Naiti, C.N., Lee, M., and Singh, R., *J. Antibiot*., 1988, no. 3, p. 673.
2. Eugene, L.W., *Tetrahedron Lett*., 1988, vol. 29, no. 67, p. 6055.
3. Vargas, D.A., Tamariz, J., and Joseph-Nathan, P., *Tetrahedron Lett*., 2005, vol. 46, p. 3297.
4. Aversa, M.C., Barattucci, A., and Bonaccorsi, P., *ARKIVOC*, 2002, vol. 17, p. 79.
5. Timshina, A.V., Rubtsova, S.A., Alekseev, I.N., Kodess, M.I., Matochkina, P.A., Slepukhin, P.A., and Kuchin, A.V., *Khim. Prirod. Soedin*., 2008, no. 6, p. 1053.
6. McMahon, J.A., Vishweshwar, P., and Oliveira, M., *J. Am. Chem. Soc*., 2005, vol. 127, p. 16802.
7. Startseva, V.A., Gavrilov, V., Nikitina, L., Lodochnikova, O., Gnezdilov, O., Lisovskaya, S., Glushko, N., and Klimovitskii, E., *Khim. Fiz. Zh*., 2010, vol. 44, no. 3. p. 17.

8. Nikitina, L.E., Startseva, V., and Dieva, S.A., *Khim. Prirod. Soedin*., 2006, vol. 42, no. 2, p. 17.
9. Startseva, V.A., Nikitina, L.E., and Lodochnikova, O.A., Abstract of Papers, *23 Int. Symp. Org. Chem. of Sulfur ISOCS-23*, Moscow, 2008, p. 142.
10. Sheldrick, GM. *SADABS*, University of Göttingen, Germany, 2004.
11. Sheldrick, G.M., *Acta Cryst.,* 2008, no. 64, p. 112.
12. Sheldrick, G.M*., SHELXL-97 Program for Crystal Structure Refinement*, University of Goettingen, Germany, 1997.
13. Farrugia, L.J., *J. Appl. Crystal*., 1999, no. 32, p. 837.
14. *APEX2 (Version 2.1), SAINTPlus. Data Reduction and Correction Program. Version 7.31A, Bruker Advansed X-ray Solutions*, BrukerAXS Inc., Madison, Wisconsin, USA, 2006.
15. Spek, A.L., *Acta Crystallogr*., 1990, vol. 46, p. 34.
16. Weisberger, A., and Proskauer, E., *Organic Solvents*, Moscow: Inostrannaya Literatura, 1958.
17. Gradova, N.B., Babusenko, E.S., and Gornova, I.B., *Laboratornyi praktikum po obshchei mikrobiologii* (Laboratory Manual on General Microbiology), Moscow: DeLi Print, 2004, p.111.
18. Leonard, N.J. and Johnson, C., *J. Am. Chem. Soc*., 1962, vol. 27, p. 282.
19. Siegfried, H.V. and Boes, O*., Liebigs Ann. Chem*., Weinbeim, 1953, vol. 79, p. 23.
20. Johnson, C.R. and McCants, D., *J. Am. Chem. Soc*., 1965, vol. 5, p. 348.
21. Mikolajczyk, M., *Synth. Commun*., 1978, vol. 8, p. 758.
22. Traynelis, V.J., Yoshikawa, Y., and Tarka, S., *J. Org. Chem*., 1973, vol. 38, no. 23, p. 3987.