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SYNTHESIS OF SULFIDE DERIVATIVES OF THE CARANE SERIES BY THE REACTIONS OF 3-CARENE EPISULFIDE WITH FUNCTIONAL DERIVATIVES OF MERCAPTANS

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Reactions of α- and β-epithiocaranes with 2-mercaptoethanol under basic conditions have given the isomeric 4-hydroxyethylthiocarane-3-thiols and 4-hydroxyethylthio-3-hydroxyethyldithiocaranes. A high degree of regio- and stereoselectivity of the addition of mercaptoethanol has been found. The interaction of 3-carane β-episulfide with mercaptoacetic acid has yielded a terpene sulfide with a trithiepane fragment.*

We have previously proposed a convenient method for the synthesis of isomeric 3,4-epithiocaranes by the reactions of 3-carene α- and β-epoxides with thiourea sulfate and have also shown the possibility of using the episulfides so obtained as synthons in the synthesis of bifunctional terpenoids [1].

In an expansion of the synthetic possibilities of thiiranes with a carane structure, we have studied the reactions of α- and β-3,4-epithiocaranes (**1, 2**) with functional derivatives of mercaptans – 2-mercaptoethanol and mercaptoacetic acid – in the presence of sodium ethanolate. The reactions of episulfides (**1**) and (**2**) with mercaptoethanol were carried out at room temperature for 4-8 h and led to the formation of two products in each case, which were isolated by column chromatography on silica gel in the form of individual compounds in ratios of 1:2 and 2:1, respectively.

The reactions of episulfides (**1**) and (**2**) with mercaptoethanol as the bifunctional reagent could, in theory, take place with the participation of either the mercapto or the hydroxy group. The IR spectra of the adducts with the larger R_f values (**3, 5**) contained bands of the characteristic vibrations both of SH groups (ν 2560 cm^{-1}) and of OH groups (ν 3410 cm^{-1} (O—H) and 1040 (C–O), cm^{-1} infl), which showed an attack of the thiirane ring by the SH function of the mercaptoethanol.

This fact was confirmed by the PMR spectra of compounds (**3 and 5**), which contained – in addition to the signals of cyclopropane protons, of a gem-dimethyl fragment, and of a methyl group at C^5 – the signals of the protons of an SH group (2.20 ppm (**3**) and 2.30 ppm (**5**)) and of a hydroxy group (2.73 ppm (**3**) and 2.76 ppm (**5**)) (Table 1). The S-chemoselectivity of the addition of mercaptoethanol is obvously explained by the greater nucleophilicity of the S atom than of the oxygen atom, which most probably favors reaction in the form of an alkanol anion.

The regio- and stereochemistry of the opening of the thiirane ring of episulfides (**1**) and (**2**) by mercaptoethanol corresponded to the results of the reactions of these episulfides with alkanethiols and of α- and β-3,4-epoxycaranes with mercaptoethanol [2], in which it was established that in all cases without exception adducts are obtained of the *trans*-opening of the thiirane and oxirane rings the regiodirectivity of which obeys Kraskuskii's rule.

In the IR spectra of the products with the smaller R_f vales (**4 and 6**) there were no bands of the characteristic vibrations of a mercapto group and, at the same time, the PMR spectra of compounds (**4**) and (**6**) showed the presence of two β-thioethanol fragments per carane skeleton (2.5-3.0 ppm, $-SCH_2$, t, 4H; 3.5-4.0, $-O-CH_2$, t, 4H). The elementary analyses

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*The equivalent of "trithiane" is given in the original here and throughout this paper. The formulae show trithiepane fragments – Translator.

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TABLE 1. PMR Spectra of Compounds (**3-7**), δ, ppm

3	0.6—0.8 m (2H, H-$C^{1(6)}$), 1.0 s (6H, $(CH_3)_2$-C^7), 1.36 s (3H, CH_3-C^3, 2.20 s (1H, SH), 2,56 t, 7.0 Hz (2H, CH_2S), 2.73 s (1H, OH), 3.50 s, 7.0 Hz (2H, CH_2O).
4	0.6–0,8 m (2H, $H_2C^{1(6)}$), 1.03 s (6H, $(CH_3)_2$-C^7), 1.36 s (3H, CH_3-C^3), 2.70 t 7.0 Hz (4H, $(CH_2S)_2$), 3.20 s (1H, OH), 3.30 s (1H, OH), 3.63 t, 7.0 Hz (4H, $(CH_2O)_2$)
5	0.6—0.8 m (2H, H-$C^{1(6)}$), 1.0 s (6H, $(CH_3)_2$-C^7), 1.40 s (3H, CH_3-C^3, 2,30 s (1H, SH), 2,60 t, 7.0 Hz (2H, CH_2S), 2.76 s (1H, OH), 3.50 t, 7.0 Hz (2H, CH_2O).
6	0,6—0,8 m (2H, H-$C^{1(6)}$), 1.10 s (3H, $(CH_3)_2$-C^7), 1.33 s (3H, CH_3-C^3), 2.66 t, 2.93 t, 7.0 Hz (4H, $(CH_2\ _2)$, 3.60 t, 3.83 t, 7.0 Hz (4H, $(CH_2O)_2$). 4.26 s, 4.36 s (2H, OH)
7	0.5–0.7 m (4H, H-$C^{1(6)}$, $C^{1'(6')}$), 1.00 s (12H, (CH_3)-C^7-$C^{7'}$), 1.30 s (6H, CH_3-C^3, $C^{3'}$), 1.30–3.0 m (2H, H-C^4, $C^{4'}$)

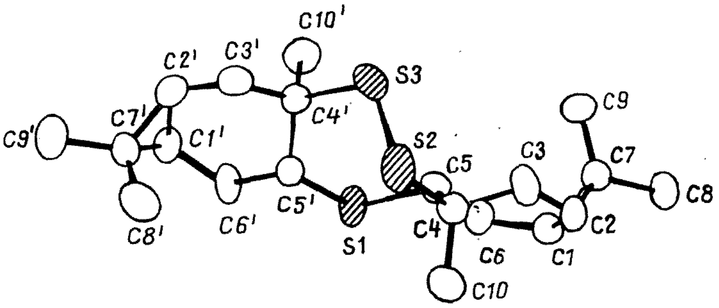
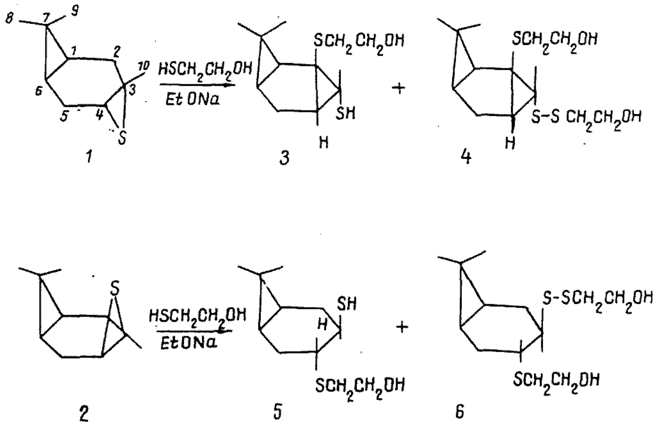


Fig. 1. Geometry of the (7) molecule. The hydrogen atoms are not shown.

of products (**4**) and (**6**) also correponded to structures with two thioethanol fragments and three sulfur atoms. This gives grounds for assuming that compounds (**4**) and (**6**) are the result of an interaction of the 3-carene episulfides (**1**) and (**2**) successively with two molecules of mercaptoethanol – compounds (**3**) and (**5**) formed during the reactions then enter into reaction with additional mercaptoethanol molecules to form the disulfides (**4**) and (**6**). It was observed here that compound (**3**) takes part in such a reaction more readily and, on reacting with mercaptoethanol, forms (**4**) as the main product. The ease of formation of compound (**4**) is most probably due to the smaller steric hindrance from the α-side of the (**3**) molecule in comparison with (**5**), where the approach of the mercaptoethanol molecule from the β-side is hindered by the presence of the gem-dimethylcyclopropane fragment, and compound (**6**) is formed as a minor product.



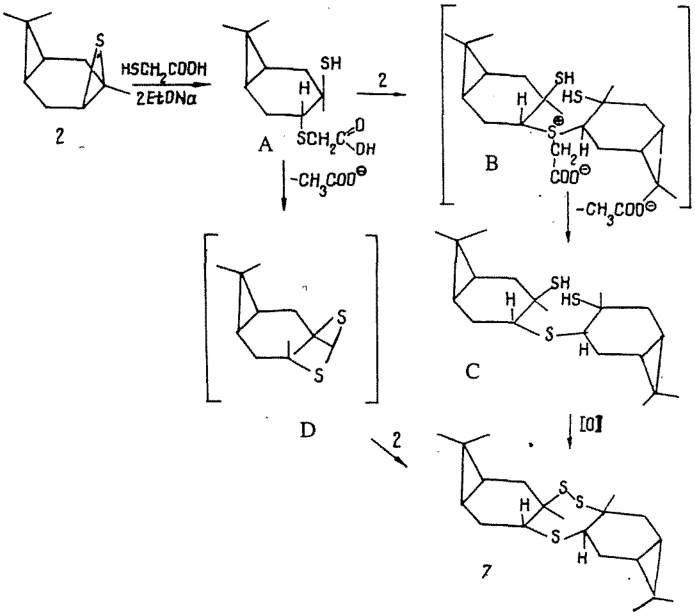
The reactions of the epithiocaranes (**1** and **2**) with meraptoacetic acid under the conditions of base catalysis at 90°C are concluded by the formation of an addition product only in the case of the β-episulfide (**2**) and do not give a positive result with the α-episulfide (**1**).

TABLE 2. Coordinates of the Nonhydrogen Atoms of Compound (7)

Atom	x	y	z
S^1	0.6274 (1)	0.7795 (1)	0.58689 (3)
S^2	0.4258 (1)	0.7651 (1)	0.58689 (3)
S^3	0.2646 (1)	0.8643 (1)	0.65104 (3)
C^1	0.8736 (4)	1.0874 (3)	0.66480 (1)
$C^{1'}$	0.1241 (5)	0.5461 (4)	0.55370 (1)
C^2	0.8026 (4)	0.9996 (4)	0.62450 (1)
$C^{2'}$	0.1359 (4)	0.6405 (4)	0.59720 (1)
C^3	0.6247 (4)	0.8612 (3)	0.68380 (1)
$C^{3'}$	0.2559 (4)	0.7570 (3)	0.59500 (1)
C^4	0.6383 (4)	0.9174 (3)	0.63379 (9)
$C^{4'}$	04367 (4)	0.6718 (3)	0.59010 (9)
C^5	0.6325 (5)	0.9979 (4)	0.71640 (1)
$C^{5'}$	0.4398 (5)	0.5778 (4)	0.54460 (1)
C^6	0.7886 (4)	1.0865 (4)	0.71160 (1)
$C^{6'}$	0.2804 (5)	0.5139 (4)	0.52720 (1)
C^7	0.8006 (4)	1.2297 (3)	0.68420 (1)
$C^{7'}$	0.1880 (5)	0.3876 (4)	0.55050 (1)
C^8	0.9215 (5)	1.3466 (4)	0.70250 (1)
$C^{8'}$	0.2592 (6)	0.3115 (4)	0.59280 (1)
C^9	0.6512 (1)	1.2988 (4)	0.66220 (1)
$C^{9'}$	0.0956 (6)	0.2818 (5)	0.51900 (2)
C^{10}	0.7568 (6)	0.7449 (4)	0.69630 (1)
$C^{10'}$	0.2461 (5)	0.8729 (4)	0.55700 (1)

The question of the structure of compound (7) was solved on the basis of the results of x-ray structural analysis. It was established that the (7) molecule has a condensed system of five rings: two carane fragments linked through three sulfur atoms forming a central trithiepane ring. The $C^1C^2C^5C^6$ and $C^{1'}C^{2'}C^{5'}C^{6'}$ fragments are practically planar, the dihedral angles between them being 27.1° and between each of them and the corresponding cyclopropane ring 65.3 and 66.6°. The dihedral angle between the planar fragments $S^2S^3C^3C^4$ and $S^1C^5C^4$ amounts to 120.3°, the trithiepane ring having a *twist* conformation. The orientations of the methyl substituents at C^3 and $C^{3'}$ and also of the sulfide groups at the C^4 and $C^{4'}$ atoms are axial while the orientation of the disulfide group is equatorial. Thus compound (7) has the structure of 4,4'-thiodicaranyl 3,3'-epidisulfide.

It may be assumed that the formation of the adduct (7) takes place through the intermediate compound A, which is the product of the *trans*-addition of mercaptoacetic acid to the thiirane ring of the epithiocarane (**2**). As it is formed, intermediate A attacks another (**2**) molecule with the simultaneous protonation of the episulfide, leading to intermediate B. The process is accompanied by the splitting out of a methylenecarboxy group, with the formation of intermediate compound C and its subsequent oxidation, leading to the disulfide (7).



In addition to the proposed mechanism, we do not exclude the possibility of the existence of other intermediates in the formation of compound (7). For example, in the presence of sodium ethanolate the intermediate compound A may be converted into the cyclic disulfide D, the hypothesis of the formation of which was based on literature information on 1,2-dithietanes [3].

EXPERIMENTAL

The PMR spectra of compounds (3-7) in CCl_4 were measured on a Bruker spectrometer (300 MHz) with TMS as internal standard, and IR spectra in thin layer and in CCl_4 on a Specord 75 IR spectrometer. The elementary analyses of compounds (3-7) corresponded to the calculated figures. The epithiocaranes (**1** and **2**) were obtained as described in [1]: bp's: (**1**) 40-41°C/0.1 mm Hg; (**2**) 37-39°C/0.1 mm Hg; (**1**) (+14.5); (**2**) (−44.3) [sic]; n_d^{20} (**1**) 1.5175; (**2**) 1.5151.

X-Ray Structural Analysis of Compound (7). The crystals of compound (7) were rhombic; at 20°C, $a = 8.121(1)$; $b = 8.913(1)$, $c = 28.617(6)$ Å; Z = 4; $d_{calc} = 1.18$ g/cm^3; space group $P2_12_12_1$. The cell parameters and the intensities of 1730 reflections with $F_2 \geq 3\sigma$ were measured on an ENRAF-NONIUS CAD-4 K-diffractometer with a graphite monochromator, ω-scanning, $\theta \leq 27°$. The structure was interpreted by the direct method using the MULTAN program and was refined in the anisotropic approximation.

The hydrogen atoms were revealed from a difference series and were refined in the isotropic approximation in the concluding stage. In order to establish the absolute configuration, a refinement of the "direct" and "inverted" structures was carried out taking anomalous scattering corrections for nonhydrogen atoms into account. The divergence factors for the "direct" structure were R = 0.03136, $R_w = 0.04285$, while for the "inverted structure" R = 0.03169, $R_w = 0.04360$. According to the Hamilton test, the direct structure corresponded to the absolute structure with a probability of more than 95%. All the calculations were conducted on a PDP 11/23 computer by the SDP program. The coordinates of the nonhydrogen atoms are given in Table 2.

Synthesis of 4β(α)-Hydroxyethylthiocarane-3α(β)-thiols (3, 5) and 3α(β)-Hydroxyethyldithio-4β(α)-hydroxyethylthiocaranes (4, 6). To 4.6 g (0.06 M) of 2-mercaptoethanol were successively added 0.56 g (0.24 g-atom) of Na, 2 ml of DMSO, and 2.0 g (0.012 mole) of an episulfide (**1** or **2**); the mixture was stirred at room temperature (8 h in the reaction with (**1**); 4 h with (**2**)) and was extracted with ether, and products (**3-6**) were isolated by column chromatography on silica gel (hexane – diethyl ether). Yields: (**3**) ($C_{12}H_{22}S_2O$) 22%; (**4**) ($C_{14}H_{26}S_3O_2$) 40%; (**5**) ($C_{12}H_{22}S_2O$) 38%; (**6**) ($C_{14}H_{26}S_3O_2$) 32%; R_f values: (**3**) 0.55; (**4**) 0.33; (**5**) 0.53: (**6**) 0.24 (diethyl ether): n_d^{20} (**5**) 1.5049.

Synthesis of 4,4′-Thiodicaran-3,3′-diyl Epidisulfide. At room temperature, with stirring, 1.1 g (0.012 mole) of mercaptoacetic acid and 2.0 g (0.012 mole) of the episulfide (**2**) in 2 ml of DMSO were added to the sodium ethanolate obtained from 0.56 g (0.024 g-atom) of Na and 20 ml of ethanol (abs.). After being heated at 90°C for 60 h, the reaction mixture was poured into 200 ml of water and extracted with ether; the extract was dried with Na_2SO_4, and the crystals that deposited after evaporation of the solvent were recrystallized from ethanol. The yield of (7) ($C_{20}H_{32}S_3$) was 27%, mp 147-148°C.

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