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SYNTHESIS OF SULFUR-CONTAINING BIS-TERPENOIDS BASED ON MONOTERPENE OXIDES

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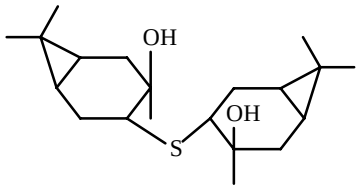
Ethanedithiol and di(mercaptoethyl)sulfide react regio- and stereoselectively with (+)-3-carene and α-hydroxy(-)-β-pinene β-oxides in the presence of sodium ethoxide to give the corresponding bis- and tris-sulfides with two terpene fragments.

Key words: monoterpene oxides, ethandithiol, di(mercaptoethyl)sulfide.

Natural monoterpenoids exhibit various biological activity, including antitumor [1]. Chemical modification of these compounds can effectively increase the biological activity. On the other hand, various mono-, di-, and polysulfides exhibit significant antitumor activity [2].

A series of terpenylsulfides synthesized by us was tested at the National Cancer Institute (NCI, USA) for antitumor activity. These included **1**, obtained from the reaction of (+)-3-carene β-oxide (**2**) with thiourea in the presence of sodium ethoxide [3]:



1

The antitumor effect was evaluated in percent effectiveness of inhibiting the growth of 60 cell lines for 8 tumor types (Leukemia, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Colon Cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer). The experiment was carried out using a series of concentrations (from 10^{-9} to 10^{-4} mol/L) of the studied compound. Sulfide **1** acted as a growth inhibitor (34%) for leukemia and melanoma cell lines at 10^{-4} mol/L concentration.

The literature indicates that the biological activity tends to increase on going from mono- to bis- and polysulfides [2]. Thus, we hypothesized that increasing the number of sulfide groups in **1** could positively affect the biological activity of the modified compound.

A synthetic approach to the new potentially biologically active terpenoids was developed by synthesizing bis- and tris-sulfides using (+)-3-carene β-oxide (**2**) and β-pinene α-oxide (**3**) as starting materials. The literature method was used to synthesize **2** [4]. Reaction of (-)-β-pinene and peroxybenzimidic acid using a method analogous to that in the literature [5] gave β-pinene α-oxide (**3**).

Reaction of **2** and **3** with ethanedithiol and di(mercaptoethyl)sulfide in the presence of sodium ethoxide gives in each instance a single product (**4**-**7**), which is isolated by column chromatography on silica gel. The purity of the compounds was confirmed by GLC; the composition of **4** and **5**, by elemental analysis; adducts **6** and **7**, by mass spectrometry. The structure was established using IR and ^{1}H NMR spectroscopies. The reactions typically have good yields of the target compounds (62-64%).

Apparently the reactions follow the general mechanism (described previously by us for reactions of 3-carene α- and

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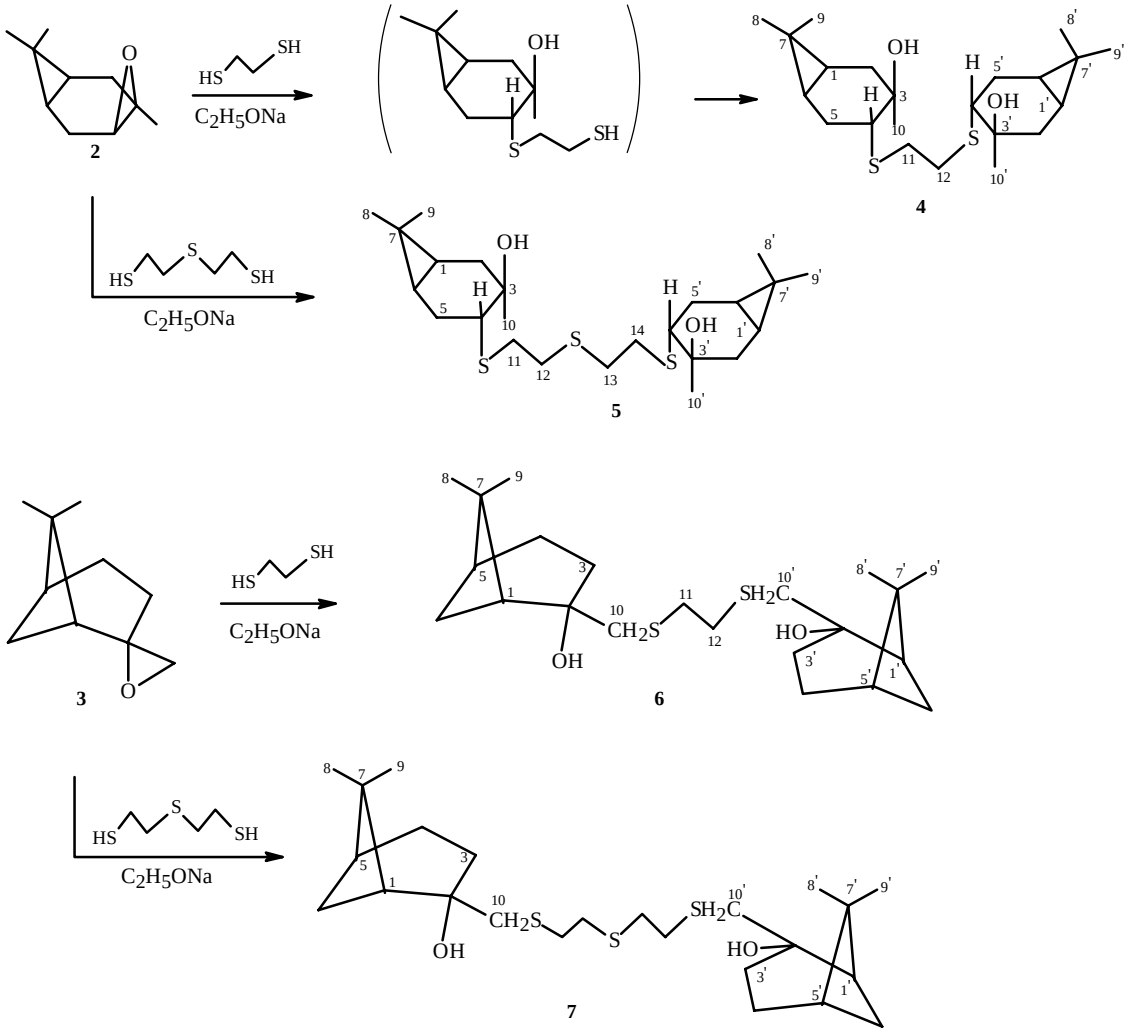
β -oxides with thiourea in the presence of sodium ethoxide [3]). Thus, the thiol formed in the first step attacks a second oxide molecule. This produces the corresponding bis- and tris-sulfides **4-7**.



EXPERIMENTAL

^{1}H NMR spectra of **4-7** in $CDCl_3$ were measured on a Varian Unity-300 (300 MHz) spectrometer with TMS internal standard; IR spectra, in mineral oil on a spectrometer-75 IR. Mass spectra of **6** and **7** were obtained on an Incos-50B mass spectrometer in combination with a Varian-3400 gas chromatograph, capillary column, SE-30 phase, and 0.25 mm diameter. The ionizing-electron energy was 70 eV. The injector temperature was 250°C; ion-source temperature, 150°C. Elemental analyses of **4** and **5** correspond with those calculated.

Synthesis of 1,2-bis(4,4′-(3-Hydroxycaranyl))dithioethane (4), 2,2′-bis(4,4′-(3-Hydroxycaranyl))di(thioethyl) sulfide (5), 1,2-bis(10,10′-(2-Hydroxypinanyl)dithioethane (6), and 2,2′bis(10,10′-(2-Hydroxypinanyl)di(thioethyl)sulfide (7). A solution of sodium ethoxide (0.76 g Na, 0.033 mol) in absolute C_2H_5OH (30 mL) was treated upon stirring with thiol (3.3 mmol) and oxide (**2**, **3**, 6.6 mmol). The reaction mixture was heated at 90°C for 1.5-2.5 h. Water (100 mL) was added. The mixture was extracted with ether. The ether was dried over $MgSO_4$. Solvent was distilled off. Products were separated by column chromatography on silica gel (hexane—ether) as oily liquids. Yield, %: **4**, 62; **5**, 64; **6**, 68; **7**, 74.

Compound 4: ^{1}H NMR (δ, ppm, J, Hz): 0.44, 0.63 (m, m, H-1, H-1′, H-6, H-6′), 0.84, 0.86 (s, s, 6H-7, 6H-7′), 1.042, 1.052 (s, s, 3H-10, H-10′), 1.74, 1.92 (m, m, 2H-5, 2H-5′, 2H-2, 2H-2′), 2.09, 2.22 (m, m, H-4, H-4′), 2.70 (m, 2H-11, 2H-12). IR spectrum (ν, cm^{-1}): 3500 (OH).

Compound 5: ^{1}H NMR (δ, ppm, J, Hz): 0.59, 0.78 (m, m, H-1, H-1′, H-6, H-6′), 0.99, 1.02 (s, s, 6H-7, 6H-7′), 1.20 (s, 3H-10, 3H-10′), 1.89, 2.07 (m, m, 2H-5, 2H-5′, 2H-2, 2H-2′), 2.22, 2.38 (dd, dd, J = 6.0, J = 10.0, H-4, H-4′), 2.75 (m, 2H-

12, 2H-13), 2.86 (m, 2H-11, 2H-14).

IR spectrum (ν, cm^{-1}): 3520 (OH).

Compound 6: $[\alpha]_D^{20}$ -17.8° (0.16 M, ethanol), ^1H NMR (δ, ppm, J, Hz): 0.93, 1.24 (s, s, 6H-7, 6H-7′), 1.53 (d, H-1, H-1′), 1.75-2.25 (m, 2H-3, 2H-3′, 2H-4, 2H-4′, 2H-6, 2H-6′), 2.77, 2.86 (2H-10, 2H-10′, AB centers, J = 13.36), 2.02 (t, J = 5.4, 2H-11, 2H-12).

IR spectrum (ν, cm^{-1}): 3500 (OH). Mass spectrum, *m*/*z* (I_{rel}, %): [M^+] 398 (0.2), 380 (1), 260 (8), 139 (90), 122 (100), 69 (89), 55 (83), 41 (80).

Compound 7: $[\alpha]_D^{20}$ -10.3° (0.5 M, ethanol), ^1H NMR (δ, ppm, J, Hz): 0.94, 1.24 (s, s, 6H-7, 6H-7′), 1.52 (d, H-1, H-1′), 1.75-2.25 (m, 2H-3, 2H-3′, 2H-4, 2H-4′, 2H-6, 2H-6′), 2.76, 2.85 (2H-10, 2H-10′, AB centers, J = 13 Hz), 2.01 (t, J = 5.4, 2H-11, 2H-12, 2H-13, 2H-14).

IR spectrum (ν, cm^{-1}): 3500 (OH). Mass spectrum, *m*/*z* (I_{rel}, %): [M^+] 458 (0.2), 440 (5), 320 (10), 182 (28), 167 (37), 134 (79), 93 (62), 81 (27), 75 (59), 69 (100), 41 (83).

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