

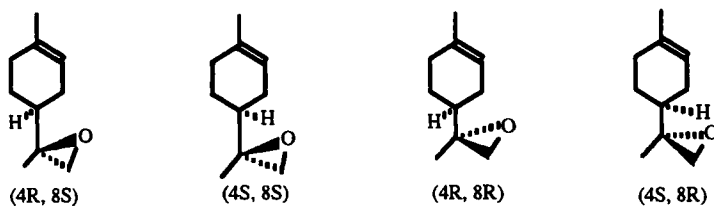
NUCLEOPHILIC THIYLATION OF LIMONENE 8,9-OXIDE

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Thioterpenols of the menthane series have been obtained by reactions of limonene 8,9-oxide with thiols and with isothiuronium salts.

We have previously developed regio- and stereoselective methods of synthesizing sulfur-containing derivatives of the menthane series from (\pm)-limonene and its 1,2-oxide [1, 2]. With the aim of obtaining new potentially biologically active terpene sulfides we have now studied the reactions of limonene 8,9-oxide (1) with thiols and isothiuronium salts. We synthesized the initial oxide (1) by a known procedure [3] involving the action of peroxybenzimidic acid, obtained in situ, on racemic limonene. According to chromato-mass spectroscopy, a chromatogram of the oxide obtained contained two signals of equal intensity with close retention times, while the mass spectra of the compounds corresponding to these signals were practically identical and each had a molecular ion with m/z 152. The oxide synthesized obviously consisted of a mixture of four diastereomers, and the pair of optical isomers with the 8S and 8R configurations differing by the spatial arrangement of the oxide ring in relation to the cyclohexene fragment of the molecule were responsible for the observed pattern of the chromato-mass spectrum (Fig. 1).



Diastereomers of limonene 8,9-oxide (1)

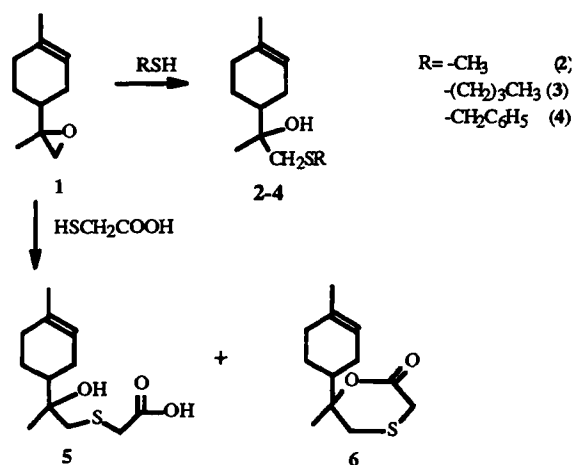
We also studied the reaction of oxide (1) with thiols (n -BuSH and HSCH₂COOH) and with methyl- and benzylisothiuronium salts under conditions of base catalysis. The reactions were conducted with heating to 80°C in ethanol in the presence of the sodium thiolates (in the reactions with thiols) or sodium ethanolate (in the reactions with isothiuronium salts) and led to the formation of the addition products (2—5), which were isolated by column chromatography on silica gel (scheme).

In the ¹H NMR spectra of the adducts (2—5) signals of the protons of the methylene group at the C-8 atom were observed in the 2.5 ppm region, which indicated an opening of the oxide ring in accordance with Krasuskii's rule [4] and led to the formation of products with the hydroxy group located on the most highly substituted carbon atom. The ¹H NMR spectra of the adducts (2—5) had a characteristic feature, observed previously in the spectra of related compounds that are products of the addition of thiols and disulfides to (\pm)-limonene [1] — namely, the signals of the protons of the methyl group at the C-8 atom consisted of two singlets of equal intensity, their combined intensity corresponding to one methyl group, and the signals of the protons of the methylene group at the C-8 atom were in the form of two AB systems of equal intensity with the same SSCC (12.7—14.2 Hz). When the ¹H NMR spectra were measured at different temperatures the ratio of the intensities of these signals

TABLE 1. Yields, and Details of the IR and ¹H NMR (300 MHz) Spectra of Compounds (2—6)

Compound	Yield, %	IR, cm ⁻¹	¹ H NMR (CDCl ₃), δ (J, Hz)
2	34	845, 1665, 3470	1.16 s, 1.21 s (3H, CH ₃ -C-8), 1.69 s (3H, CH ₃ -C-1), 2.71 d 2.72 d (2H, H-C-9, 13.1), 2.75 d 2.80 d (2H, H-C-9, 13.1), 2.19 s (3H, H-C-11), 2.60 s (OH), 5.36 s, 5.42 s (1H, H-C-2)
3	38	840, 1645, 3500	0.94 s (3H, CH ₃ -C-14), 0.97 (2H, H-C-13), 1.14 s 1.16 s (3H, CH ₃ -C-8), 1.65 s (3H, CH ₃ -C-1), 2.45 m (4H, H-C-11,12), 2.60 d, 2.65 d (2H, H-C-9, 12.7), 2.48 d (2H, H-C-9, 12.7), 2.75 s (OH), 5.37 s, 5.43 s (1H-C-2)
4	42	840, 1650, 3480, 700, 1500, 1600	1.15 s, 1.19 s (3H, CH ₃ -C-8), 1.67 s (3H, CH ₃ -C-1), 2.55 d (2H, H-C-9, 1.31), 2.74 s (OH), 3.76 s (2H, H-C-11), 5.36 s, 5.42 s (1H, H-C-2), 7.32 m (C ₆ H ₅)
5	28	850, 1650, 1715-1725, 2500-2710, 3450	1.38 s (6H, CH ₃ -C-8), 1.71 s (3H, CH ₃ -C-1), 2.67 d, 2.78 d (2H, H-C-9, 14.2), 2.82 d, 2.91 d (2H, H-C-9, 14.2), 3.30 s (2H, H-C-11), 5.35 s, 5.41 s (1H, H-C-2), 5.88 s (1H, COOH)
6	14	840, 1650, 1720, 1230-1250	1.38 s (6H, CH ₃ -C-8), 1.67 s (3H, CH ₃ -C-1), 2.63 d (2H, H-C-9, 13.3), 2.89 d, 2.97 d (2H, H-C-9, 13.3), 3.36 s (2H, H-C-11), 5.36 s, 5.43 s (1H, H-C-2)

remained unchanged, which was evidence in favor of the existence of the reaction products (just like the initial oxide) in the form of a mixture of diastereomers and not of hindered conformers [5].



A chromatogram from the chromato-mass spectrum of compound (3) had a single, but considerably broadened, signal, and the mass spectrum contained a molecular ion with *m/z* 242 corresponding to an adduct with the empirical formula C₁₄H₂₆OS. The observed broadening of the signal confirmed the existence of adduct (3) in the form of a mixture of isomers.

In the isolation of the product of the addition of mercaptoacetic acid to limonene 8,9-oxide (compound 5) by column chromatography on silica gel, it was found that it underwent partial dehydration with the formation of the lactone (6). Heating the adduct (5) at 90°C led to its complete conversion into lactone (6). The IR spectrum of lactone (6) showed characteristic bands of vibrations of an ester function (1230—1250 and 1720 cm⁻¹). In the ¹H NMR spectrum of lactone (6) a regular downfield shift of the signal of the methyl group at C-8 in comparison with the chemical shift of the analogous group in the initial compound (5) is observed. We have observed the formation of the corresponding lactones previously in all thioterpenols containing vicinally located hydroxy and thiocarboxy functions [2, 6].

Thus, the regioselective opening of the oxide ring in reactions of limonene 8,9-oxide with thiols and isothiuronium salts under conditions of base catalysis and the fairly high yields of adducts permit this reaction to be used as a preparatively convenient method of synthesizing thioterpenols of the menthane series.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of compounds (2—6) in CCl_4 or CDCl_3 were measured on a Varian UNITY spectrometer (working frequencies 300 and 75.43 MHz) with TMS as internal standard, and refractive indices were measured on an IRF-454 BM refractometer. The mass spectrum of adduct (3) was obtained on an Incos 50 B spectrometer in combination with a Varian 3400 gas chromatograph using a capillary column with a diameter of 0.25 mm, and the phase SE-30; the energy of the ionizing electrons was 70 eV, the temperature of the injector 250°C , and that of the ion source 150°C . Silica gel 100/160 μ was used to purify the reaction products.

Limonene 8,9-oxide was obtained by the method of [3]. bp $120\text{--}124^\circ\text{C}$ (52 mm Hg), n_{D}^{20} 1.4722. Mass spectrum, m/z (%): 152 (M^+ , 2), 137 (18), 121 (80), 105 (40), 93 (78), 84 (31), 79 (100), 67 (47), 53 (27), 43 (57), 28 (44).

Isothiuronium salts of the general formula $\text{RSC}(\text{NH})\text{NH}_2\cdot\text{HCl}$ were obtained by the procedure of [7].

Interaction of (\pm)-Limonene 8,9-Oxide with Isothiuronium Salts. A mixture of 0.456 g (0.003 mole) of the 8,9-oxide (1) and 0.0045 mole of a methyl- or benzylisothiuronium salt in an EtONa solution obtained from 0.138 g (0.006 g-atom) of Na and 30 ml of absolute EtOH was stirred at 80°C for 2—2.5 h, after which it was cooled to 20°C , washed with water, and treated with diethyl ether. The organic layer was washed with NH_4Cl solution and with water, and was dried with MgSO_4 . After elimination of the solvent, reaction products (2—4) were isolated by column chromatography on silica gel with hexane—ether mixtures containing from 20 to 50% of the latter, n_{D}^{20} (2) 1.5180, (4) 1.5612. Mass spectrum of compound (3), m/z (%): 242 (M^+ , 5), 224 (9), 138 (52), 121 (43), 104 (25), 95 (61), 79 (11), 71 (20), 55 (19), 43 (100), 29 (23).

Interaction of (\pm)-Limonene 8,9-Oxide with Thiols. To a solution of the sodium thiolate obtained from 0.39 g (0.017 g-atom) of Na and 0.008 mole of a thiol having the general formula RSH ($\text{R} = n\text{-Bu}$ or $-\text{CH}_2\text{COOH}$) was added, in drops, 0.91 g (0.006 mole) of (\pm)-limonene 8,9-oxide in 40 ml of absolute EtOH, and the mixture was heated with stirring for 4—5 h and was then cooled and worked up as described above. After elimination of the solvent the residue was chromatographed on silica gel with mixtures of hexane and ether containing from 50 to 100% of the latter. n_{D}^{20} (3) 1.4971.

The elementary analyses corresponded to the calculated figures.

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