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trans-Diepoxy Derivative of Limonene. Synthesis, Structure, and Products of Oxirane Ring Opening with Sulfur-Containing Reagents*

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Abstract—Pure *trans*-diepoxy derivative of limonene was synthesized for the first time. Its reactions with sulfur-containing nucleophiles in basic medium resulted in formation of polyfunctional derivatives of the menthane series, 2,9-bis(R-thio)-*trans*-*p*-menthane-1,8-diols.

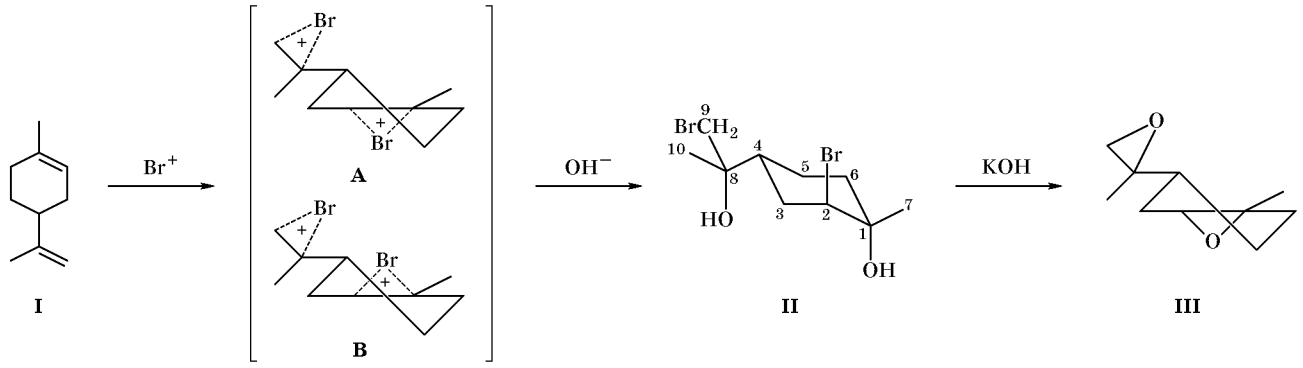
Known method of synthesis of limonene diepoxide are based on reactions of limonene with a two-fold excess of a peroxyacid [1] or oxidation of the double bond in the mono-1,2-epoxy derivative with peroxyacetic acid [2]. The resulting diepoxy derivative is isolated as an equimolar mixture of *cis* and *trans* isomers. We were the first to obtain the pure *trans*-diepoxy derivative by treatment of racemic limonene (**I**) with excess *N*-bromosuccinimide in aqueous dioxane and subsequent dehydrobromination of dihydroxy dibromide **II** with potassium hydroxide. The procedure was analogous to that described in [3] for the synthesis of 3-carene β-oxide (Scheme 1).

According to the GC–MS data, the molecular weight of product **III** (M^+, *m*/*z* 168) corresponds to the formula $C_{10}H_{16}O_2$. The purity of compound **III** was checked by GLC (we previously found that isomeric *cis*- and *trans*-1,2:9,10-diepoxy derivatives can be distinguished by GLC).

Obviously, the arrangement of the oxirane ring in **III** is determined by stereochemical structure of intermediate bromohydrin **II**. In the ^{1}H NMR spectra of the latter the 2-H signal appears as a doublet of doublets at δ 4.29 ppm with coupling constants *J* of 3.7 (*eq*–*eq*) and 7.2 Hz (*eq*–*ax*), indicating that the 2-H proton is equatorial. Hence, the configuration of the bromine atom on C^2 and hydroxy group on C^1 is *trans-diaxial*, in keeping with the general rules for addition of electrophilic reagents to olefins.

The configuration of **II** was also confirmed by chromatographic monitoring of the dehydrobromination process. Product **III** was detected in the reaction

Scheme 1.



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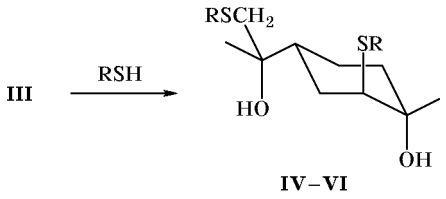
mixture 5 min after a solution of alkali was added to compound **II**. It is known [4] that oxirane ring closure in bromohydrins with diequatorial bromine atom and hydroxy group requires 76 h.

Presumably, electrophilic attack in the double bonds in limonene (**I**) by bromine cation gives rise to transition state **A**. Such stereoselectivity is most likely to be determined by electronic factors. Repulsion between bulky electronic shells of bromine atoms destabilizes transition state **B**; therefore, the corresponding *cis*-diepoxy derivative is not formed.

Taking into account the ability of epoxy compounds to selectively take up nucleophilic reagents under conditions of base catalysis, product **III** was brought into reactions with some thiols: 2-propanethiol, 1-butanethiol, and *m*-phenoxyphenylmethanethiol (Scheme 2). Compounds **IV** and **V** were obtained by reaction of **III** with excess 2-propanethiol and 1-butanethiol which were preliminarily converted into the corresponding sodium thiolates. In the synthesis of **VI**, *m*-phenoxyphenylmethanethiol was generated *in situ* from isothiuronium salt in ethanol in the presence of sodium ethoxide [5]. Products **IV**–**VI** were isolated from the reaction mixtures by column chromatography on silica gel.

Scheme 2.



IV–**VI**

IV, R = *i*-Pr; **V**, R = Bu; **VI**, R = *m*-$PhOC_6H_4CH_2$.

Compounds **IV** and **V** give the molecular ion peaks in the mass spectra; in the mass spectrum of **VI** the maximal *m*/*z* value corresponds to the ion formed by elimination of one RS group from the molecular ion. The IR spectra of **IV**–**VI** contain bands belonging to stretching vibrations of the hydroxy groups (3560 cm^{-1}) and bending and stretching vibrations of the C–O bonds (1015 cm^{-1}); their position was typical for compounds with a tertiary hydroxy group. In the IR spectrum of **VI** we also observed bands typical of benzene ring vibrations (695, 760, 1490, and 1590 cm^{-1}).

The ^1H NMR spectra of adducts **IV**–**VI** contained signals from two methyl groups, two alkylthio groups, methylene group attached to sulfur (C^9H_2), and proton on C^2. The latter appeared as a doublet of doublets at δ 2.48–2.73 ppm ($J_{eq,eq}$ = 3.0 Hz and $J_{eq,eq}$ = 6.0 Hz), indicating axial orientation of the alkylthio group on C^2. Taking into account general relations holding in oxirane ring opening (*trans*-nucleophilic attack [6, 7]), we can conclude that the RS and OH groups both occupy axial positions in the cyclohexane ring. The regioselectivity of cleavage of the 8,9-epoxy ring in **III** was derived from the chemical shift of protons at C^9 (δ 2.4–2.6 ppm, *AB* system), which is characteristic of a methylene group attached to sulfide sulfur atom (CH_2SR). Some specific features of the ^1H NMR spectra of compounds **IV**–**VI** should be noted. Superposition of signals belonging to two *AB* systems gives rise to appearance of 6 to 8 lines instead of 4 lines characterizing a classical *AB* system. Protons of the methyl group on C^8 give two nearby singlets with equal intensities. This suggests that, like initial diepoxy derivative **III** which possesses two asymmetric carbon atoms (C^4 and C^8), adducts **IV**–**VI** are mixtures of four stereoisomers, including two isomers with 8*R* and 8*S* configuration (ratio ~1 : 1) and their enantiomers (4*R*,8*S* and 4*S*,8*R*).

A conclusion can be drawn that products **IV**–**VI** are formed by opening of both oxirane rings in diepoxy derivative **III** at the O–C bond with the least substituted carbon atom; therefore, they have the structure of 2,9-bis(alkylthio)-*trans*-*p*-menthane-1,8-diols.

EXPERIMENTAL

The ^1H NMR spectra were recorded in $CDCl_3$ on a Varian Unity-300 spectrometer (300 MHz) using TMS as internal reference. The mass spectra were obtained on an Incos-50B mass spectrometer coupled with a Varian-3400 chromatograph (SE-30 capillary column 0.25 mm i.d.; energy of ionizing electrons 70 eV; injector temperature 250°C; ion source temperature 150°C).

***trans*-1,2 : 8,9-Bis(epoxy)-*p*-menthane (III).** A flask equipped with a stirrer and a dropping funnel was charged with 0.2 mol of *N*-bromosuccinimide, 100 ml of 1,4-dioxane, 50 ml of water, and 10 g of calcium carbonate. (±)-Limonene (**I**), 0.1 mol, was added under stirring, and the mixture was stirred for 6 h, poured into water, and filtered. The filtrate was extracted with ether, and the combined extracts were washed with water and a 5% solution of $Na_2S_2O_3$, dried over $MgSO_4$, and evaporated to obtain bromohydrin **II** as a yellow oily substance. It was treated with a solution of 15.0 g of KOH in 15 ml of water and 150 ml of ethanol (the solution was added dropwise), and the mixture was stirred for 1 h at room

temperature, diluted with water, and extracted with ether. The ether extracts were washed with water until neutral reaction and dried over Na_2SO_4. By vacuum distillation we isolated a fraction with bp 91–92°C (5 mm), n_D^{20} 1.4670.

Compound **II**. Yield 70%. ^{1}H NMR spectrum, δ, ppm: 1.20 s and 1.24 s (3H, 10-H); 2.27 s (3H, 7-H), 3.80 and 3.85 (*AB* system), 3.96 and 4.04 (*A′B′*) (2H, 9-H, J = 21 Hz); 4.29 d.d (1H, 2-H, J = 3.7, 7.2 Hz).

Compound **III**. Yield 57%. ^{1}H NMR spectrum, δ, ppm: 1.15 s (3H, 10-H), 1.23 s (3H, 7-H), 2.35 s (2H, 9-H), 2.75 m (1H, 2-H). Mass spectrum, *m*/*z* (I_{rel}, %): 153 $[M-15]^+$ (2), 137 (10), 123 (7), 107 (18), 93 (40), 79 (36), 67 (18), 54 (9), 43 (100), 27 (14).

2,9-Bis(alkylthio)-*trans*-*p*-menthane-1,8-diols IV and V. To a solution of sodium ethoxide in anhydrous ethanol, prepared from 1.5 g (0.065 mol) of metallic sodium and 50 ml of ethanol, we added 0.021 mol of 2-propanethiol or 1-butanethiol and 1 g (0.0065 mol) of diepoxy derivative **III**. The mixture was heated for 3–5 h at 80°C under stirring, cooled, diluted with water, treated with a solution of NH_4Cl, and extracted with ether. The extract was dried over $MgSO_4$ and evaporated, and the product was isolated by column chromatography on silica gel using hexane–ether (20 to 50% of the latter) as eluent.

Comnpound **IV**. Yield 56%. ^{1}H NMR spectrum, δ, ppm: 0.90 s and 0.95 s (3H, 10-H); 1.15 s (3H, 7-H); 1.25 s, 1.26 s, 2.75 m [14H, $SCH(CH_3)_2$]; 2.40, 2.52 (*AB* system), 2.41, 2.52 (*A′B′*) (2H, 9-H, J = 12.4 Hz); 2.57 d.d (1H, 2-H, J = 3.1, 5.8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 320 M^+ (2), 302 (10), 230 (15), 213 (27), 169 (8), 155 (8), 137 (73), 128 (100), 98 (44), 71 (17), 55 (5), 43 (94).

Compound **V**. Yield 60%. ^{1}H NMR spectrum, δ, ppm: 1.21 s and 1.22 s (3H, 10-H); 1.30 s (3H, 7-H); 1.08 s, 1.11 s, 2.49 m (18H, $SCH_2CH_2CH_2CH_3$); 2.63, 2.74 (*AB*), 2.67, 2.74 (*A′B′*) (2H, 9-H, J = 14.2 Hz); 2.56 d.d (1H, 2-H, J = 3.2, 6.1 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 348 M^+ (6), 330 (4), 245 (31), 227 (35), 183 (4), 155 (10), 137 (77), 128 (100), 98 (54), 85 (7), 71 (15), 57 (38), 43 (69), 28 (15).

2,9-Bis(*m*-phenoxybenzylthio)-*trans*-*p*-menthane-1,8-diol (VI). A mixture of 0.228 g (0.0015 mol) of compound **III**, 0.0045 mol of *S*-(*m*-phenoxybenzyl)-isothiuronium salt, and a solution prepared from 0.138 g (0.006 mol) of metallic sodium and 30 ml of anhydrous ethanol was stirred for 2 h at 80°C, cooled to 2 h, washed with water, and extracted with ether. The organic phase was washed with a solution of NH_4Cl and with water, dried over $MgSO_4$, and evaporated. The product was isolated by column chromatography on silica gel using ether as eluent. Yield 60%. ^{1}H NMR spectrum, δ, ppm: 1.15 s and 1.17 s (3H, 10-H); 1.31 s (3H, 7-H); 2.56 d.d (1H, 2-H, J = 3.0, 6.0 Hz); 2.52, 2.68 (*AB*), 2.55, 2.68 (*A′B′*) (2H, 9-H, J = 13.2 Hz); 3.72 s, 3.73 s (4H, SCH_2), 7.21 m (18H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 384 $[M-216]^+$ (15), 214 (31), 183 (38), 168 (13), 155 (100), 137 (10), 109 (15), 93 (30), 71 (8), 55 (6).

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