## FORMATION OF STERIC ISOMERS IN REACTION OF LIMONENE OXIDE WITH ETHANOL

L.A. Mukhamedova, M.I. Kudryavtseva, R.R. Shagidullin, and Yu.Yu. Samitov UDC 541.632:547.596.7-31:547.262

As an expansion of our studies on the reactions of unsymmetrical cyclene oxides with alcohols as a function of the nature of the catalyst [1] it was interesting to make a comparative study of the reaction of limonene oxide with ethanol in acid and alkaline media. In the literature it is only indicated that two structural isomers are formed when limonene oxide is reacted with ethanol in alkaline medium [2, 3]. Taking into consideration the fact that the limonene oxide, obtained by oxidation with peracids, consists of a mixture of the trans- and cis-isomers, and the literature data on the reaction of amines with limonene oxide [4, 5], it could be expected that the steric isomers of the addition products will also be formed in the reaction of limonene oxide with ethanol. The reactions were run by us with a mixture of the trans- and cis-limonene epoxides (I) + (II), and with the pure trans-epoxide (I). The structure of the obtained compounds was proved by chemical methods and by the IR and NMR spectra.

The reaction of a mixture of epoxides (I) + (II) with ethanol in the presence of  $C_2H_5ONa$  yields three addition products: (-)-1-hydroxy-2-ethoxy-trans-p-menth-8-ene (III), (-)-2-hydroxy-1-ethoxy-trans-pmenth-8-ene (IV) and (+)-1-hydroxy-2-ethoxy-cis-p-menth-8-ene (V) in a 5:2:1 ratio. Reaction with the trans-epoxide (I) under these conditions gives (III). Under mild conditions (III) is not oxidized by  $K_2Cr_2O_7$ , and the IR spectrum of (III) has the band of a free hydroxyl at 3617 cm<sup>-1</sup>. The structure of (IV) was proved by oxidation with  $K_2Cr_2O_7$  to ketone (VI), and by the IR spectrum (presence of the absorption of a free OH group at 3635 cm<sup>-1</sup>). The optically active 3, 5-dinitrobenzoates, and also their racemic forms, were obtained for compounds (III) and (IV). Product (V) is not oxidized by  $K_2Cr_2O_7$ , and the absorption band of the hydroxyl group is found at 3588 cm<sup>-1</sup>, which testifies to the presence of a hydrogen bond. This is possible with either a diequatorial (ee) or an equatorial-axial (ea) arrangement of the OH and OC<sub>2</sub>H<sub>5</sub> groups. The latter is less probable, since it is realized only with a cis-opening of the epoxide ring, which was not observed for similar systems [6]. The structure of the obtained compounds was also proved by the NMR method, which will be discussed below.

Starting with the obtained data, the course of the reaction in alkaline medium can be depicted by the scheme:



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Fig.1. NMR spectra of 5%  $CCl_4$  solutions of stereoisomeric derivatives of p-menth-8-enes. Upper spectrum = (+)-1-hydroxy-2-ethoxy-cis-p-menth-8-ene (V); lower spectrum = (-)-1-hydroxy-2-ethoxy-trans-p-menth-8-ene (III).

Together with the addition products, isomerization products are also formed (11.6% when based on converted oxide) in the reaction of (I) + (II) with ethanol in the presence of  $C_2H_5ONa$ , and specifically: dihydrocarvone (VII), trans-carveol (VIII) and trans-isocarveol (IX) in a 1:4:7 ratio. The physicochemical constants, the crystalline derivatives, and the IR and NMR spectra of these compounds are identical with the literature data [7-9].



The reaction products of the (I) + (II) mixture with ethanol in acid medium are (III), (IV) and (+)-2hydroxy-1-ethoxy-cis-p-menth-8-ene in a 4:6:1 ratio. The structure of (X) was confirmed by the IR spectrum, which contains the absorption of a bound hydroxyl at 3590 cm<sup>-1</sup>, by the NMR spectrum, and by oxidation with  $K_2Cr_2O_7$  to ketone (XI). Compounds (III) and (X) are formed from the trans-epoxide under these conditions, and consequently compound (IV) can be formed only from the cis-epoxide (see Scheme 1).

Among the reaction products of limonene oxide with ethanol was also detected (-)-trans-1, 2-dihydroxy-trans-p-menth-8-ene: 3% in alkaline medium, and  $\sim 25\%$  in acid medium. This amount of diol in acid medium could be formed via the water that is liberated in the dehydration of the ethanol under the reaction conditions.



The structure of the obtained addition products was also confirmed by the NMR spectra. The spectra of the stereoisomeric (III) and (V) are given in Fig.1. The lines of the H<sub>a</sub> and H<sub>e</sub> protons at C<sub>2</sub> serve as the key to the proof of the configuration and conformation of the substituents at C<sub>1</sub>, C<sub>2</sub>, and C<sub>4</sub> of the ring. If the configuration of the substituents at C<sub>1</sub> was the same in (III) and (V), then the chemical shifts of the H<sub>a</sub> and H<sub>e</sub> protons at C<sub>2</sub> would differ by at least 0.48 ppm [10], which actually is not the case. Consequently, in the stereoisomeric (III) and (V) the configuration of the substituents with respect to the C<sub>1</sub> -C<sub>2</sub> bond is different. In addition, a stronger temperature dependence is observed for the OH line in (V) than in (III), which proves the equatorial position of the OH in (V). From the scheme of the multiplet splitting of the  $\alpha$ -CH<sub>2</sub> group of the ethoxyl radical it can be seen that the methylene protons are anisochrones (diastereotopes) due to the asymmetry of C<sub>1</sub>\* and C<sub>2</sub>\*. The chair conformation is confirmed by the values of the vicinal constants  ${}^{3}J_{aa} = 11.3$ ,  ${}^{3}J_{ae} = 4.3$  and  ${}^{3}J_{ea} = 2.8$  Hz.

The spectra of the stereoisomeric (IV) and (X) are given in Fig.2. Here the spectra of these isomers are shown containing added tris(dipivalomethanato)europium (III), which causes paramagnetic pseudo-contact shifts [11]. The same as in the previous cases, the proof of the configuration and preferred conformations was based on the character of the multiplet splitting of the H<sub>a</sub> and H<sub>e</sub> protons. In the case of (IV) the configuration of the substituents with respect to C<sub>2</sub> and C<sub>4</sub> can be judged on the basis of the triplet at  $\delta$  1.90 ppm, with the vicinal constants  ${}^{3}J_{3a4a} = 12.0$  and  ${}^{3}J_{3a2e} = 2.6$  Hz, which indicate that the isopropenyl group has an equatorial configuration.

The numerical values of the  ${}^{3}J_{HH}{}^{11}$  constants can be used to judge the distortion of the chair conformation by the "R-factor" method [12]: R =  $J_{trans}/J_{cis}$ , where  $J_{trans} = 1/2({}^{3}J_{aa} + {}^{3}J_{ee})$ , and  $J_{cis} = 1/2$  ( ${}^{3}J_{ae} + {}^{3}J_{ea}$ ), in which connection the R factor is independent of the electronegativity of the adjacent heteroatoms. From the value of R it is possible to estimate the torsion angle  $\psi$ ; if  $\psi$  is smaller than the angle  $\psi_{0} = 56-58^{\circ}$ , which is typical for cyclohexane, then the analyzed ring is more planar; if it is greater than  $\psi_{0}$  then it is curved more. For menthenes (IV) and (X), R = 1.92;  $\psi = 56^{\circ}45^{\circ}$ , while for menthenes (III) and (V), R = 1.931;  $\psi = 56^{\circ}43^{\circ}$ , i.e., the ring has a nearly cyclohexane conformation in the studied stereo-isomers.

## METHOD

The melting points were determined on a "Boetius" heating stand. The IR spectra were taken on UR-10 and UR-20 spectrophotometers in  $CCl_4$  solutions. The NMR spectra were taken on an HA-100D instrument in  $CCl_4$  solution, using TMS as the internal standard. The TLC was run on plates covered with a mixture of ASK silica gel and 5% gypsum. The GLC was run on a "Khrom-2" chromatograph, using a 267 × 0.2 cm column filled with 15% of 1, 4-butanediol succinate deposited on Celite 545, a flame-ionization detector and a temperature of 128°C (A conditions), and a 292 × 0.2 cm column filled with 15% of poly(ethylene glycol adipate) deposited on Chromosorb W and a temperature of 200° (B conditions).

(-)-1,2-Epoxy-p-menth-8-ene, a mixture of the trans- and cis-isomers (I) + (II), was obtained by the oxidation of p-mentha-1,8-diene with acetyl hydroperoxide in ether. After fractional distillation through a column with an efficiency of 90 theoretical plates the epoxide had bp 62.7-62.8° (5.3 mm);  $n_D^{20}$  1.4460;  $d_4^{20}$  0.9279;  $[\alpha]_D^{20} - 44.9^\circ$ .



Fig.2. NMR spectra of 5%  $CCl_4$  solutions of (+)-2-hydroxy-1-ethoxy-cis-p-menth-8-ene (X) (upper) and (-)-2-hydroxy-1-ethoxy-trans-p-menth-8-ene (IV).

(-)-1,2-Epoxy-trans-trans-p-menth-8-ene (I) was obtained by the Kuvzynski method [13] and had bp 86-87° (8 mm);  $n_D^{20}$  1.4712;  $[\alpha]_D^{20}$  - 72.3°.

Reaction of (I) + (II) Mixture with Ethanol in the Presence of  $C_2H_5ONa$ . To a solution of  $C_2H_5ONa$  from 1.04 g-atoms of Na and 8.24 M of ethanol was added 1.05 M of a (I) + (II) mixture and the whole was heated at 80° for 25 h. After workup the reaction mixture was analyzed by GLC (A conditions) and then fractionally distilled through a column with an efficiency of 90 theoretical plates. The pure compounds were obtained either by the decomposition of the crystalline 3,5-dinitrobenzoates or by the preparative chromatography of the narrow fractions using a fractionation column. The purity of the products was checked by TLC and GLC.

Dihydrocarvone (VII) was isolated as the semicarbazone with mp 189-190.5° (from aqueous methanol) (in a capillary) [6].

(+)-Mentha-6,8-diene-trans-2-ol (trans-carveol) (VIII) was obtained by the saponification of the 3,5-dinitrobenzoate with mp 110-111.2° (from MeOH);  $[\alpha]_D^{21} + 236.7°$  (C 4.3; benzene) [7]. We also isolated the 3,5-dinitrobenzoate of dl-carveol with mp 118.5-119.5° (from MeOH);  $[\alpha]_D^{21}0°$  (C 4.0; benzene) [7].

(-)-p-Mentha-1(7),8-diene-trans-2-ol (trans-isocarveol) (IX) was obtained as a fraction that contained 76% of (IX). NMR spectrum ( $\delta$ , ppm): 4.26 (1H, proton at C<sub>2</sub>); 4.66-4.76 (4H, multiplet, vinyl protons) [8].

 $(-)-1-Hydroxy-2-ethoxy-trans-p-menth-8-ene (III). The 3,5-dinitrobenzoate with mp 95° (from EtOH) was obtained: <math>[\alpha]_D^{20} - 25.9°$  (C 4.08; benzene). Found: C 58.18; H 6.26; N 7.58%. C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>. Calculated:

C 58.16; H 6.17; N 7.14%. Saponification of the 3,5-dinitrobenzoate gave (III) with bp 86-87° (4 mm);  $n_D^{20}$  1.4676;  $d_4^{20}$  0.9471;  $[\alpha]_D^{20} - 53.9^\circ$ . Found: C 72.41; H 11.19%. C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>. Calculated: C 72.68; H 11.19%. The 3,5-dinitrobenzoate of dl-(III) had mp 75-76° (from EtOH);  $[\alpha]_D^{20}$  0° (C 4.1; benzene). Found: C 57.85; H 6.40; N 7.24%. C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>. Calculated: C 58.16; H 6.17; N 7.14%.

We also obtained the 3, 5-dinitrobenzoate of dl-(IV) with mp 104-106° (from EtOH);  $[\alpha]_D^{21} 0^\circ$  (C 5.0; benzene). Found: C 58.21; H 6.30; N 7.14%. C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>. Calculated: C 58.16; H 6.17; N 7.14%.

(+)-1-Hydroxy-2-ethoxy-cis-p-menth-8-ene (V) was obtained from the fraction containing 65% of (V) by preparative chromatography on silica gel, with elution using a 1:1 petroleum ether-ethyl acetate mixture; bp 98-99° (5 mm);  $n_D^{20}$  1.4695;  $d_4^{20}$  0.9567;  $[\alpha]_D^{20}$  + 30.9°. Found: C 72.36; H 11.09%. C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>. Calculated: C 72.68; H 11.19%. 3,5-Dinitrobenzoate, mp 127.0-127.5° (from petroleum ether);  $[\alpha]_D^{20.5}$  + 94.6° (C 4.2; benzene). Found: C 58.06; H 6.20%. C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>. Calculated: C 58.16; H 6.17%.

(-)-2-Oxo-1-ethoxy-trans-p-menth-8-ene (VI) was obtained by the oxidation of (IV) with  $K_2Cr_2O_7$  in ether as described in [14]; bp 99-100° (7 mm);  $n_D^{20}$  1,4612;  $d_4^{20}$  0.9474;  $[\alpha]_D^{20} - 46.3°$ . Found: C 73.31; H10.35%.  $C_{12}H_{20}O_2$ . Calculated: C 73.42; H 10.27%. Infrared spectrum: 1715 cm<sup>-1</sup> (C = O). 2,4-Dinitrophenylhydrazone, mp 152.0-152.8° (from MeOH). Found: N 14.92%.  $C_{18}H_{24}N_4O_5$ . Calculated: N 14.89%.

(-)-trans-1, 2-Dihydroxy-trans-p-menth-8-ene (XII) was detected by GLC (B conditions) in the residue from the fractional distillation of the reaction mixture.

Reaction of (I) with Ethanol in the Presence of  $C_2H_5ONa$ . The reaction with 2.2 g of (I) was run under the above described conditions. The formation of product (III) was established by GLC (A conditions).

Reaction of (I) + (II) Mixture with Ethanol in the Presence of  $BF_3 \cdot O(C_2H_5)_2$ . A mixture of 0.33 M of the (I) + (II) mixture, 3.3 M of ethanol and 0.24 ml of  $BF_3 \cdot O(C_2H_5)_2$  was heated at 80° for 20 min. After removal of the ethanol the reaction mixture was analyzed by GLC and then fractionally distilled through a column with an efficiency of 36 theoretical plates. Compounds (III) and (IV) were identified by GLC and by the 3,5-dinitrobenzoates.

(+)-2-Hydroxy-1-ethoxy-cis-p-menth-8-ene (X); from the fraction, containing a mixture of (IV) + (X), was isolated the 3, 5-dinitrobenzoate with mp 112-113° (from EtOH);  $[\alpha]_D^{20.5}$  + 70.9° (C 5.3; benzene). Found: C 58.32; H 6.13; N 6.86%.  $C_{19}H_{24}N_2O_7$ . Calculated: C 58.16; H 6.17; N 7.14%. Saponification of the 3,5-dinitrobenzoate gave (X) with bp 121-122° (3.8 mm);  $n_D^{20}$  1.4765;  $d_4^{20}$  0.9648;  $[\alpha]_D^{20}$  + 12.2°. Found: C 72.71; H 11.30%.  $C_{12}H_{22}O_2$ . Calculated: C 72.68; H 11.19%.

(+)-2-Oxo-1-ethoxy-cis-p-menth-8-ene (XI) was obtained by the oxidation of (X) with  $K_2CR_2O_7$ ; bp 100° (9 mm);  $n_D^{20}$  1.4680;  $d_4^{20}$  0.9745;  $[\alpha]_D^{20}$  + 8.7°. Found: C 73.08; H 10.26%.  $C_{12}H_{20}O_2$ . Calculated: C 73.42; H 10.27%. Infrared spectrum: 1718 cm<sup>-1</sup> (C=O). 2,4-Dinitrophenylhydrazone, mp 96.5-98.0° (from MeOH). Found: C 57.44; H 6.43%.  $C_{16}H_{24}N_4O_5$ . Calculated: C 57.43; H 6.43%.

Diol (XII) was isolated from the residue from the fractional distillation of the reaction mixture; mp 69.5-71° (from aqueous EtOH);  $[\alpha]_D^{20.5} - 50^\circ$  (C 4.0; acetone) [15].

Reaction of (I) with Ethanol in the Presence of  $BF_3 \cdot O(C_2H_5)_2$ . The reaction with 1.76 g of epoxide (I) was run under analogous conditions. The formation of (III) and (X) in a 6:1 ratio was established by GLC (A conditions).

The GLC analysis was run by A. A. Martynov, for which the authors express their gratitude to him.

## CONCLUSIONS

1. The reaction of limonene oxide with ethanol in both alkaline and acid media proceeds stereospecifically with the formation: a) in alkaline medium of (-)-2-hydroxy-1-ethoxy-trans-p-menth-8-ene and the steric isomers of (-)-1-hydroxy-2-ethoxy-trans-p-menth-8-ene and (+)-1-hydroxy-2-ethoxy-cisp-menth-8-ene; b) in acid medium of (-)-1-hydroxy-2-ethoxy-trans-p-menth-8-ene and the steric isomers of (-)-2-hydroxy-1-ethoxy-trans-p-menth-8-ene and (+)-2-hydroxy-1-ethoxy-cis-p-menth-8-ene. The isomerization products of limonene oxide: dihydrocarvone, trans-carveol and trans-isocarveol, are also formed in alkaline medium.

2. The NMR method was used to study the conformation of the obtained addition products of ethanol to limonene oxide.

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