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 (±)-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 chromatomass spectrum (Fig. 1).

\[
\begin{align*}
(4R, 8S) & \quad (4S, 8S) & \quad (4R, 8R) & \quad (4S, 8R) \\
\text{Diastereomers of limonene 8,9-oxide (1)}
\end{align*}
\]

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 \(^1\)H 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 \(^1\)H 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 (±)-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 \(^1\)H NMR spectra were measured at different temperatures the ratio of the intensities of these signals...
TABLE 1. Yields, and Details of the IR and $^1$H NMR (300 MHz) Spectra of Compounds (2—6)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield, %</th>
<th>IR, cm$^{-1}$</th>
<th>$^1$H NMR (CDCl$_3$), $\delta$ (J, Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>34</td>
<td>845, 1665, 3470</td>
<td>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)</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>840, 1645, 3500</td>
<td>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)</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>840, 1650, 3480, 700, 1500, 1600</td>
<td>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, 13.1), 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$_5$)</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>850, 1650, 1715-1725, 2500-2710, 3450</td>
<td>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)</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>840, 1650, 1720, 1230-1250</td>
<td>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)</td>
</tr>
</tbody>
</table>

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 C$_{14}$H$_{26}$O$_8$. 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 $^1$H 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.