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Unexpected acidic transformation of allylic menthene sulfoxides into saturated sulfones

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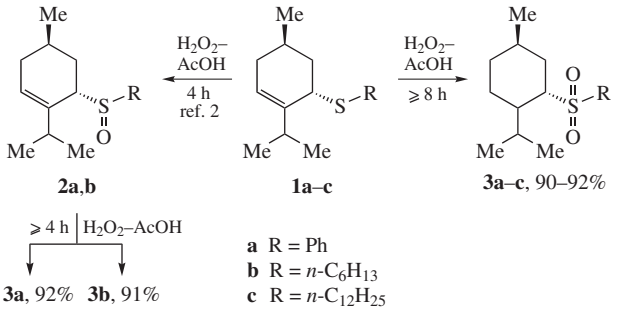
Prolonged treatment of menth-4-en-3-yl sulfides with H_2O_2 in acidic medium leads to saturated menthan-3-yl sulfones, the same products having been obtained from menth-4-en-3-yl sulfoxides in acidic medium in the absence of H_2O_2. The mechanism was evaluated by quantum chemical calculations.

Oxidation of [1,4]dithiino[2,3-*c*:5,6-*c*′]bis[1,2,5]oxadiazole di-*N*-oxide[1] and verbenone dithiolane[2] with hydrogen peroxide causes transformation of sulfide moieties into the sulfoxide ones.

Previously,[3] we found that menthene sulfides **1a**,**b** gave the corresponding sulfoxides **2a**,**b** upon oxidation with H_2O_2 in AcOH for 4 h[3,4] (Scheme 1). In this work we report that oxidation of sulfides **1a–c** with the same reagent for 8 h or more affords unusual menthane sulfones **3a–c** (method *a*).† The same products were obtained from 3-menthene sulfoxides **2a**,**b** on similar processing for 4 h or more (method *b*).†

The stereochemistry of sulfones **3a–c** was established by ^{1}H NMR spectroscopy. The small spin–spin coupling constant values of the C-1 proton (*J* 7.7 and 1.7 Hz) were indicative of the axial orientation of the S-containing substituent. Spectral parameters of isopropyl group in equatorial orientation are similar to those in L-menthol.[5,6]

It is obvious that unusual transformation of menthene sulfoxides **2a**,**b** in the presence of H_2O_2–AcOH system could be due to their structural features.



Scheme 1

Mechanism for conversion of unsaturated sulfoxides **2a**,**b** into saturated sulfones **3a**,**b** was evaluated by quantum chemical

† IR spectra were recorded in a thin layer on an IR Prestige-21 instrument (Shimadzu). NMR spectra were recorded with TMS as internal standard on Bruker Avance III 500 (500.13 MHz for ^{1}H and 125.20 MHz for ^{13}C) and Bruker AM-300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) spectrometers. The NMR resonances were assigned using two-dimensional COSY (H–H), HSQC, and HMBC correlation spectroscopy. Optical rotation was measured on a Perkin Elmer 241-MC polarimeter. Melting points were determined on a Kofler apparatus, modification S 30A/G. Column chromatography was carried out over silica gel L (60–200 μm) (Sorbfil, Russia). Sorbfil plates (Russia) were used for TLC.

Method a. Sulfide **1a–c** (0.50 mmol) dissolved in glacial AcOH (2 ml) was treated dropwise with H_2O_2 solution (0.16 ml, 30%) and stirred for 8 h at room temperature.

Method b. Sulfoxide **2a**,**b** (0.15 mmol) dissolved in glacial AcOH (1.5 ml) was treated dropwise with H_2O_2 solution (0.1 ml, 30%) and stirred for 4 h at room temperature.

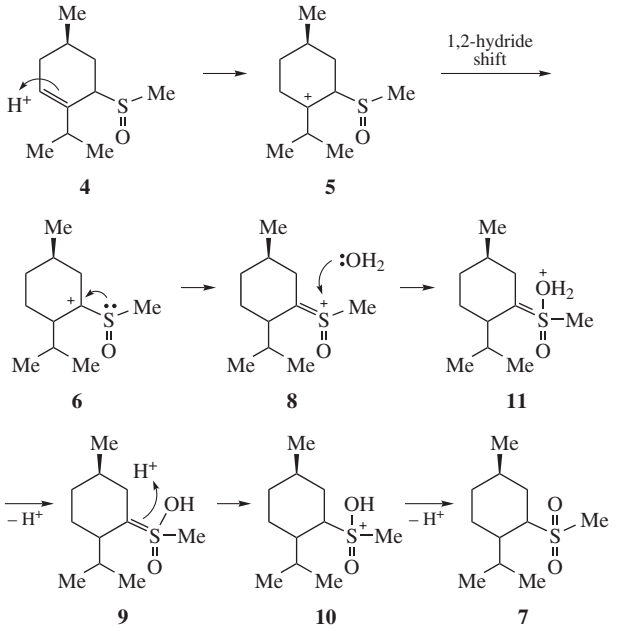
Method c. Sulfoxide **2a** (0.15 mmol) dissolved in glacial AcOH (1.0 ml) was treated dropwise with H_2SO_4 solution (0.5 ml, 93%) in H_2O (0.5 ml) and stirred for 48 h at room temperature.

Method d. Sulfoxide **2a** (0.15 mmol) dissolved in glacial AcOH (0.5 ml) was treated dropwise with H_2O (0.5 ml) and stirred for 72 h at room temperature.

Reaction mass was diluted with H_2O (5 ml) and extracted with EtOAc (3×10 ml). The combined organic extracts were washed sequentially with saturated solution of $NaHCO_3$ (1×2 ml) and H_2O (5 ml), dried over Na_2SO_4 and evaporated. The products were isolated by column chromatography [SiO_2, light petroleum–EtOAc (20:1)].

[(1R,2S,5R)-2-Isopropyl-5-methylcyclohexylsulfonyl]benzene **3a**. Yield: 0.40 g (90%) (methods *a* and *d*), 0.42 g (92%) (methods *b* and *c*). R_f 0.62 (light petroleum–EtOAc, 2:1). $[\alpha]_D^{20}$ –0.3 (*c* 1.07, CH_2Cl_2), mp 67–68 °C (hexane). IR (KBr, ν/cm^{-1}): 1447 (ν, Ar), 1306, 1132 (ν, SO_2). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 0.59 (d, 3H, 3′-H, *J* 6.8 Hz), 0.70 (d, 3H, 5-Me, *J* 6.9 Hz), 0.87 (d, 3H, 2′-H, *J* 6.8 Hz), 1.05–1.23 (m, 2H, 3-H), 1.05–1.23 (m, 1H, 6-H$_a$), 1.33–1.47 (m, 1H, 5-H), 1.73–1.90 (m, 1H, 2-H), 1.93–2.05 (m, 1H, 4-H$_a$), 1.93–2.05 (m, 1H, 6-H$_e$), 2.21–2.33 (m, 1H, 1′-H), 2.82–2.93 (m, 1H, 4-H$_e$), 3.59 (dd, 1H, 1-H$_e$, ^2J 7.7 Hz, ^3J 1.9 Hz), 7.48 (t, 2H, 5″-H, 3″-H, *J* 7.2 Hz), 7.57 (t, 1H, 4″-H, *J* 7.1 Hz), 7.94 (d, 2H, 2″-H, 6″-H, *J* 7.1 Hz). ^{13}C NMR (125.20 MHz, $CDCl_3$) δ: 19.53 (q, 3′-C), 21.01 (t, 3-C), 21.12 (q, 2′-C), 21.80 (q, 5-Me), 29.97 (d, 1′-C), 31.07 (t, 4-C), 31.32 (d, 5-C), 32.64 (t, 6-C), 52.45 (d, 2-C), 63.45 (d, 1-C), 128.75 (d, 3″-C, 5″-C), 129.65 (d, 2″-C, 6″-C), 133.73 (d, 4″-C), 139.91 (s, 1″-C). Found (%): C, 69.03; H, 8.73; S, 11.30. Calc. for $C_{16}H_{24}SO_2$ (%): C, 68.58; H, 8.57; S, 11.43.

(1S,2R,4R)-2-Hexylsulfonyl-1-isopropyl-4-methylcyclohexane **3b**. Yield 0.41 g (91%) (methods *a* and *b*). R_f 0.53 (light petroleum–EtOAc, 2:1), $[\alpha]_D^{20}$ +231 (*c* 0.67, CH_2Cl_2). IR (KBr, ν/cm^{-1}): 1290, 1134, 1119 (ν, SO_2). ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 0.77 (d, 3H, 3′-H, *J* 6.7 Hz), 0.92 (d, 3H, 5-Me, *J* 5.7 Hz), 0.97 (t, 3H, 6″-H, *J* 6.6 Hz), 1.00 (d, 3H, 2′-H, *J* 6.7 Hz), 1.28–1.36 (m, 5H, 4″-H, 5″-H, 6-H$_a$), 1.38–1.44 (m, 2H, 4-H$_a$, 3-H$_a$), 1.40–1.48 (m, 2H, 3″-H), 1.80–1.87 (m, 3H, 2″-H, 5-H), 1.87–1.95 (m, 1H, 3″-H), 2.09 (d, 1H, 4-H$_a$, *J* 15.1 Hz), 2.17 (dd, 1H, 6-H$_e$, ^2J 15.0 Hz, ^3J 3.6 Hz), 2.78 (sept, 1H, 1′-H, *J* 6.7 Hz), 2.91 (d, 1H, 1″-H, *J* 5.4 Hz), 3.08–3.17 (m, 1H, 2-H), 3.22 (d, 1H, 1″-H, *J* 5.4 Hz), 3.51 (dd, 1H, 1-H$_e$, ^2J 7.9 Hz, ^3J 2.7 Hz). ^{13}C NMR (125.20 MHz, $CDCl_3$) δ: 13.95 (q, 6″-C), 15.22 (q, 2′-C), 19.67 (q, 3′-C), 22.41 (t, 3-C), 20.33 (t, 2″-C), 20.33 (d, 5-C), 20.81 (q, 5-Me), 22.34 (t, 5″-C), 28.45 (t, 3″-C), 30.18 (d, 1'-C), 30.72 (t, 4-C), 31.38 (t, 4″-C), 32.35 (t, 6-C), 52.56 (t, 1″-C), 52.84 (d, 2-C), 61.75 (d, 1-C). Found (%): C, 65.70; H, 11.01; S, 11.80. Calc. for $C_{16}H_{32}SO_2$ (%): C, 66.67; H, 11.11; S, 11.11.



Scheme 2

calculations (Scheme 2). For the calculations, menthyl sulfoxide **4** was chosen as a model. Calculations were carried out by the method of successive approximation[7,8] to the level of theory B3LYP/6-31G (d,p) in the gas phase using the program FireFly v.7.1 and v.8.01.[9] The key stage of the proposed mechanism is 1,2-hydride shift in primary intermediate **5** leading to carbenium ion **6**. Ion **6** is transformed into sulfone **7** as outlined in Scheme 2.

The potential energy diagram (Figure 1) shows that protonation of sulfoxide **4** occurred through an endocyclic double bond leading to a movement of positive charge on the sulfur atom (ion **8**). Ion **8** is stabilized by the addition of H_2O to form unsaturated sulfenoxide **9**. Note that exothermic transformation **9** → **10** (ΔH_r^{298} = –52.5 kJ mol^{-1}) according to the Kramm–Hemonda principle is in agreement with slow transformations of

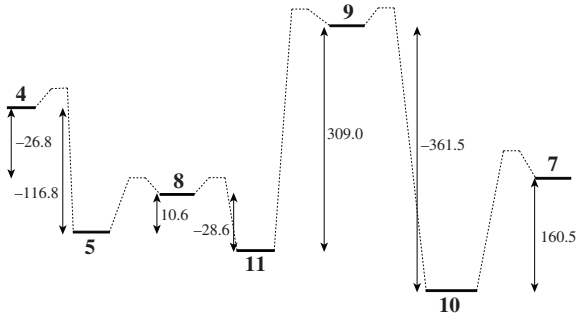


Figure 1 The surface profile of the potential energy conversion of methyl-3-(*R*)-4-menthenylsulfoxide **4** into methyl-3-(*R*)-menthanylsulfone **7**.

sulfoxide **4** into sulfone **7**. The proposed mechanism of **4** → **7** transformation involves addition of water molecule rather than hydrogen peroxide, *i.e.*, it is an intramolecular redox process.

The proposed mechanism was confirmed by a series of experiments, in which the conversion of sulfoxide **2a** into sulfone **3a** does not require the presence of H_2O_2. Thus, keeping menthene sulfoxide **2a** in H_2SO_4–H_2O–AcOH or AcOH–H_2O systems affords menthane sulfone **3a** in 92% yield (TLC data, method *c*).†

Conversion of sulfoxide **2a** into sulfone **3a** in AcOH–H_2O system (90% yield, TLC data, method *d*)† proceeds much more slowly because acetic acid is a weak electrolyte. It is obvious that the increase in acidity (addition of H_2SO_4, in the method *c*) accelerates the reaction. However, the effect of H_2O_2 additives on the reaction rate is not quite clear.

In conclusion, the easiness of migration of positive charge in the cyclohexane ring and the structural features of (*R*)-4-menthen-3-one caused isomerization of menthene sulfoxide into menthane sulfone. The process is slow because of high activation energy of the last stage and can be accelerated by raising acidity of the medium.

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(1S,2R,4R)-2-Dodecylsulfonyl-1-isopropyl-4-methylcyclohexane **3c**. Yield 0.51 g (92%) (method *a*), mp 80–81 °C (hexane). R_f 0.74 (light petroleum–EtOAc, 2:1), $[\alpha]_D^{20}$ +316.1 (*c* 1.26, CH_2Cl_2). IR (KBr, ν/cm^{-1}): 1312, 1134, 1119 (v, SO_2). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 0.69 (d, 3H, 5-Me, *J* 6.8 Hz), 0.82 (t, 3H, 12″-H, *J* 6.3 Hz), 0.87 (d, 3H, 3′-H, *J* 6.6 Hz), 0.93 (d, 3H, 2′-H, *J* 6.6 Hz), 1.14–1.33 (m, 16H, 3″-H, 4″-H, 5″-H, 6″-H, 7″-H, 8″-H, 9″-H, 10″-H), 1.25–1.40 (m, 2H, 11″-H), 1.38–1.47 [m, 2H, 2″-H), 1.70–1.88 (m, 1H, 6-H), 1.70–1.88 (m, 2H, 3-H), 1.71–1.89 (m, 1H, 2-H), 2.03–2.14 (m, 1H, 4-H), 2.64–2.76 (m, 1H, 1′-H), 2.64–2.76 (m, 1H, 6-H), 2.83 (dt, 1H, 1″-H, ^2J 14.2 Hz, ^3J 5.7 Hz), 3.05–3.10 (m, 1H, 4-H), 3.15 (dt, 1H, 1″-H, ^2J 14.2 Hz, ^3J 6.4 Hz), 3.42 (dd, 1H, 1-H$_e$, ^2J 7.9 Hz, ^3J 2.8 Hz]. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 14.10 (q, 12″-C), 19.55 (q, 3′-C), 20.34 (t, 3-C), 20.68 (q, 2′-C), 22.57 (t, 11″-C), 28.67 (t, 2″-C), 29.12 (t, 8″-C, 9″-C), 29.21 (t, 6″-C, 7″-C), 29.40 (t, 3″-C), 29.41 (d, 1′-C), 29.49 (t, 4″-C, 5″-C), 30.12 (d, 5-C), 31.80 (t, 10″-C), 32.28 (t, 4-C), 32.31 (q, 5-Me), 33.17 (t, 6-C), 52.39 (d, 2-C), 52.52 (t, 1″-C), 61.67 (d, 1-C). Found (%): C, 69.98; H, 11.23; S, 8.23. Calc. for $C_{22}H_{44}SO_2$ (%): C, 70.96; H, 11.83; S, 8.60.