OXIDATION OF MENTHONE OXOTHIOLANE

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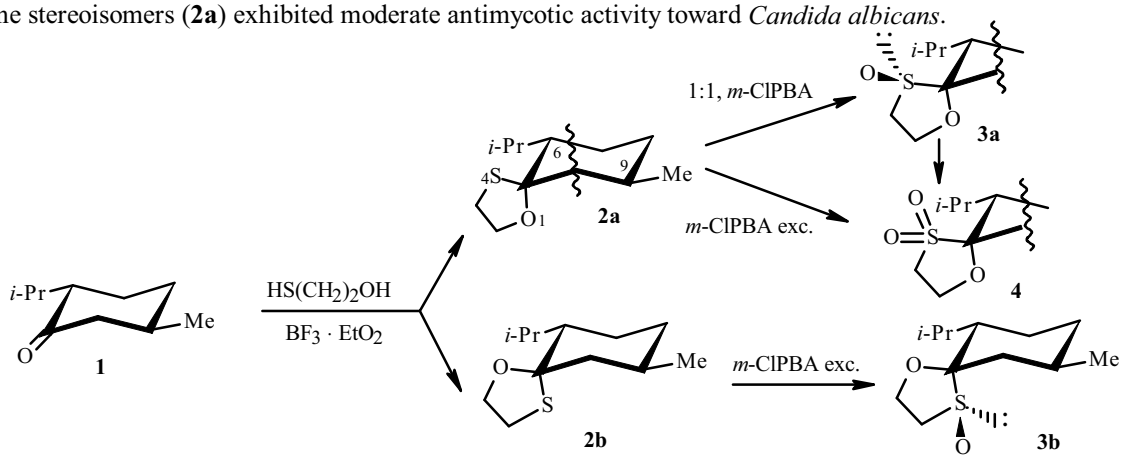
meta-*Chloroperoxybenzoic acid (*m-*ClPBA) was shown to be an oxidant for two stereoisomers of menthone oxothiolane. The effect of steric factors on the ability to oxidize the sulfide group was found. Oxidation of (5*S*,6*S*,9*R*)-6-isopropyl-9-methyl-1-oxo-4-thiaspiro[4.5]-decane to the sulfone was prevented by the steric proximity of an isopropyl group to the S atom in the oxothiolane ring.*

Key words: menthone oxothiolane, stereoisomers, sulfoxide, oxidation of menthone oxothiolane.

We have previously reported the oxidation of (-)-menthone dithiolane [1]. In continuation of research on asymmetric synthesis of sulfenyl- and sulfonyl derivatives of terpene di- and oxothiolanes, which are potentially physiologically active compounds, we now report the oxidation of menthone oxothiolane. It is known that dithiolane and oxothiolane rings are found in nucleosides with antiviral activity [2]. These nucleoside analogs that contain more than one heteroatom in the ring are very interesting because of their pronounced anti-HIV activity [3]. Introduction of a chiral sulfoxide group and the presence of the terpene moiety are expected to produce new physiologically active properties.

One of the most convenient methods for preparing thiolanes is the reaction of a ketone [(-)-menthone, **1**] and 1,2-mercaptoethanol in the presence of BF_3·etherate [4-7]. A similar reaction that is often used in organic chemistry to protect ketones was used previously to prepare menthone oxothiolane (**2**) as a mixture of two stereoisomers **2a** and **2b** in a 1:1 ratio. However, the structures of each of them were not determined [8, 9]. We separated **2a** and **2b** by column chromatography and determined the structures of both during the course of oxidation by *m*-ClPBA. We also established that one of the menthone oxothiolane stereoisomers (**2a**) exhibited moderate antimycotic activity toward *Candida albicans*.



Steric factors were found to play an important role in oxidation of **2**. Oxidation of **2a** and **2b** with a 1:1 substrate:oxidant ratio formed monosulfoxides **3a** and **3b**, one of which (**3b**) was a liquid; the other, a crystalline compound. The IR spectra of **3a** and **3b** exhibited characteristic bands for sulfoxide stretching vibrations at 1054 cm^{-1}. Recrystallization from MeOH of **3a** produced crystals that were suitable for x-ray structure analysis (XSA). This enabled the structure of **3a** and its configuration as 4*R*,5*R*,6*S*,9*R* to be determined (Fig. 1).

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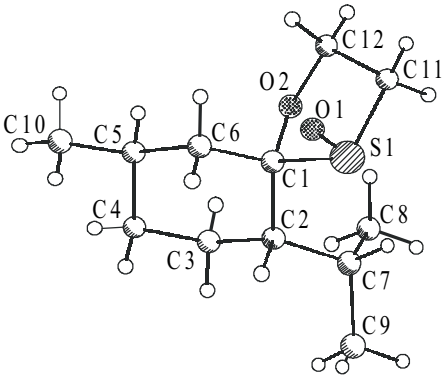

Fig. 1. X-ray structure of **3a**.

According to the XSA of monosulfoxide **3a**, stereoisomer **2a** that was used for the oxidation had the 5*R*,6*S*,9*R*-configuration. Therefore, the isolated stereoisomer **2b** should have had the 5*S*,6*S*,9*R*-configuration.

Oxidation of both stereoisomers **2a** and **2b** by an excess of oxidant (1:3 substrate:oxidant ratio) resulted in formation of the sulfone (**4**) only for **2a**, which was sterically less hindered and in which the isopropyl group and S atoms of the spiro-ring were located on different sides of the plane of the cyclohexane ring. Thus, the structure of the second stereoisomer **2b** led to the conclusion that the S atom in the spiro-ring was situated next to the isopropyl group and in the same plane with it. As a result, the isopropyl group shielded the S atom of the spirane ring and made it impossible to form the sulfone.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on Bruker Avance-II-300 (operating frequency 300.17, 75.42 MHz, respectively, $CDCl_3$) and Bruker DRX-400 (400.13, 100.62 MHz, respectively, $CDCl_3$, C_6D_6). Compounds **3a** and **3b** were unstable in $CDCl_3$. Therefore, spectra of these compounds were recorded in C_6D_6. Resonances were assigned using ^{13}C NMR spectra in JMOD mode and 2D NMR spectroscopy (^1H—^1H COSY, ^{13}C—^1H HETCOR, ^1H—^{13}C HMBC). IR spectra in thin layers and KBr disks were recorded on a Shimadzu IR Prestige 21 IR-Fourier spectrometer. Mass spectra were obtained in a Finnigan Trace DSQ spectrometer. The course of reactions was monitored by TLC on Sorbfil plates. Compounds were developed using $KMnO_4$ solution (5%) and alcoholic vanillin.

Dichloromethane was dried over $CaCl_2$ and distilled. Column chromatography used silica gel (70/230 μm, wet-packing method). We used *l*-menthone (97%) and *meta*-chloroperoxybenzoic acid (70-75%, Alfa Aesar) for the synthesis and oxidation of menthone oxothiolane.

X-ray structure analysis of **3a** was performed on a chip of a colorless single crystal of prismatic habit (0.51 × 0.42 × 0.31 mm). The XSA was carried out by the standard method on an Xcalibur 3 x-ray diffractometer with a CCD detector [λ(Mo Kα) = 0.71073, graphite monochromator, ω- and φ-scanning, T = 295(2) K]. A total of 6811 reflections of which 3376 were independent (R_{int} = 0.0401), 1812 of which had $I > 2\sigma(I)$, was collected. The scan range was $2.87° < \theta < 32.42°$. The scan completeness at $\theta < 27.0°$ was 98.8%. Crystals were monoclinic, space group $P2_1$, unit-cell constants a = 8.4833(8) Å, b = 6.1452(4), c = 12.5331(10), β = 91.238(7)°, V = 653.22(9) Å^3, Z = 2, d_{calc} = 1.171 g/cm^3. The structures were solved by direct methods using the SHELXS-97 program and refined using the SHELXL-97 program. Absorption corrections were not made because of the small value (μ = 0.229 mm^{-1}). Positions and thermal parameters of nonhydrogen atoms were refined first isotropically and then anisotropically using full-matrix least-squares methods. H atoms were found from maxima in an electron density map and were included in the refinement using the rider model. The final agreement factors were R_1 = 0.0498, wR_2 = 0.0969 [$I > 2\sigma(I)$], R_1 = 0.0996, wR_2 = 0.1053 (over all reflections) with a GooF = 1.000. The range of residual electron-density peaks was Δe = 0.357 and –0.159 eÅ^{-3}.

Synthesis of Menthone Oxothiolane Stereoisomers 2a and 2b. *l*-Menthone (6.48 mmol) was dissolved in diethylether (50 mL) at room temperature, treated with 1,2-mercaptoethanol (6.48 mmol) and BF_3·etherate (4.35 mmol), stirred for 24 h at room temperature, and extracted with ether after the reaction was finished. The organic extracts were washed with $NaHCO_3$

solution, water, and saturated NaCl solution and dried over anhydrous Na_2SO_4. The excess of solvent was removed at reduced pressure. The reaction mixture was separated over a column (silica gel 70/230 μm, eluent heptane:ether, 50:1).

(5*R*,6*S*,9*R*)-6-Isopropyl-9-methyl-1-oxo-4-thiaspiro[4.5]-decane (2a). Oil, yield 48%, $[\alpha]_D^{20}$ −72.4° (*c* 1.1, EtOH). IR spectrum (thin layer, ν, cm^{-1}): 880 (C–S), 1256 (C–O–C). $C_{12}H_{22}SO$. $[M]^+$ 214.00.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.86 (d, 6H, H-13,14, J = 7.0), 0.91 (d, 3H, H-12, J = 7.0), 0.93 (m, 1H, H-8″), 1.30 (dd, 1H, H-10″, J = 14.0, 12.1), 1.35 (ddd, 1H, H-6, J = 12.6, 3.7, 1.3), 1.49 (tdd, 1H, H-7″, J = 12.8, 12.6, 3.3), 1.60 (ddt, 1H, H-7′, J = 12.8, 3.7, 3.5), 1.70 (m, 1H, H-9), 1.75 (dddd, 1H, H-8′, J = 12.9, 6.3, 3.5, 3.3), 2.21 (ddd, 1H, H-10′, J = 14.0, 3.4, 2.4), 2.45 (sept.d, 1H, H-11, J = 7.0, 1.3), 2.93 (td, 1H, H-3″, J = 10.1, 5.8), 3.00 (ddd, 1H, H-3′, J = 10.1, 5.0, 2.0), 3.91 (ddd, 1H, H-2″, J = 10.1, 9.2, 5.0), 4.31 (ddd, 1H, H-2′, J = 9.2, 5.8, 2.0).

^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 18.45 (C-13), 21.99 (C-14), 23.14 (C-7), 23.72 (C-12), 27.19 (C-11), 30.32 (C-9), 33.76 (C-3), 34.69 (C-8), 50.35 (C-10), 50.63 (C-6), 70.49 (C-2), 100.46 (C-5).

(5*S*,6*S*,9*R*)-6-Isopropyl-9-methyl-1-oxo-4-thiaspiro[4.5]-decane (2b). Oil, yield 45%, $[\alpha]_D^{20}$ +5.2° (*c* 1.1, EtOH). IR spectrum (thin layer, ν, cm^{-1}): 880 (C–S), 1256 (C–O–C). $C_{12}H_{22}SO$. $[M]^+$ 214.00.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87 (m, 1H, H-8″), 0.92 and 0.94 (both d, 9H, H-12, H-13, H-14, J = 7.0), 1.11 (dddd, 1H, H-7″, J = 13.3, 13.1, 12.8, 3.0), 1.29 (dd, 1H, H-10″, J = 12.2, 12.1), 1.48 (ddd, 1H, H-6, J = 12.8, 3.3, 3.2), 1.57 (m, 1H, H-9), 1.70 (dddd, 1H, H-8′, J = 12.7, 6.5, 3.4, 3.0), 1.78 (dtd, 1H, H-7′, J = 13.3, 3.4, 3.3), 2.02 (ddd, 1H, H-10′, J = 12.2, 3.3, 2.1), 2.04 (sept.d, 1H, H-11, J = 6.9, 3.2), 2.94 (m, 2H, H-3), 4.03 (m, 1H, H-2″), 4.35 (m, 1H, H-2′).

^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 18.88, 21.89, 24.65 (C-12, C-13, C-14), 26.10 (C-11), 26.94 (C-7), 31.16 (C-9), 32.96 (C-3), 34.57 (C-8), 50.70 (C-10), 51.61 (C-6), 69.68 (C-2), 100.80 (C-5).

Synthesis of Sulfoxides of Menthone Oxothiolane 3a and 3b, Sulfone of Menthone Oxothiolane 4. Compounds **2a** and **2b** (4.67 mmol) were dissolved in dry CH_2Cl_2 (50 mL) at −10°C, treated dropwise with *m*-ClPBA in CH_2Cl_2 (1:1 substrate:oxidant ratio for **3a** and **3b**; 1:3 ratio, **4**), stirred for 5 h, and purged with dry NH_3 gas prepared by heating an aqueous solution of NH_4OH and passage through a drying tube ($CaCl_2$). Reaction of NH_3 and *m*-ClPBA produced the ammonium salt of *m*-chloroperoxybenzoic acid as a gummy precipitate that was filtered off. The excess of solvent was removed at reduced pressure. The reaction mixture was separated by column chromatography over SiO_2 (silica gel 70/230 μm, eluent diethylether:heptane, 25:1).

(4*R*,5*R*,6*S*,9*R*)-6-Isopropyl-9-methyl-1-oxo-4-thiaspiro[4.5]-decane-4-sulfoxide (3a). Colorless crystals, 90% yield, $[\alpha]_D^{20}$ −129.8° (*c* 3.0, EtOH), mp 111-112°C. IR spectrum (thin layer, ν, cm^{-1}): 1051 (SO). $C_{12}H_{22}SO_2$. $[M]^+$ 230.00.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.73, 0.82 (d, 6H, H-12, H-13, J = 6.8), 0.87 (d, 3H, H-14, J = 6.4), 0.92 (m, 1H, H-8″), 0.97 (dd, 1H, H-10″, J = 14.2, 12.2), 1.38-1.50 (m, 2H, H-7″, H-11), 1.53 (m, 1H, H-7′), 1.60-1.80 (m, 3H, H-6, H-8′, H-9), 1.92 (ddd, 1H, H-10′, J = 14.2, 3.0, 2.4), 2.65 (ddd, 1H, H-3″, J = 13.0, 11.7, 6.9), 2.80 (dd, 1H, H-3′, J = 13.1, 3.9), 4.16 (ddd, 1H, H-2″, J = 11.7, 10.0, 3.9), 4.35 (ddd, 1H, H-2′, J = 10.0, 6.9, 3.0).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 17.98 (C-13), 22.19 (C-14), 22.60 (C-7), 23.36 (C-12), 27.55 (C-11), 29.42 (C-9), 34.11 (C-8), 35.61 (C-10), 47.59 (C-6), 52.84 (C-3), 66.50 (C-2), 108.94 (C-5).

PMR spectrum (300 MHz, C_6D_6, δ, ppm, J/Hz): 0.75, 0.77 (d, 6H, H-12, H-13, J = 4.8), 0.87 (d, 3H, H-14, J = 6.6), 0.72 (m, 1H, H-8″), 1.12 (dd, 1H, H-10″, J = 14.4, 12.4), 1.29 (m, 1H, H-11), 1.35-1.45 (m, 2H, H-7″, H-7′), 1.48-1.60 (m, 2H, H-6, H-8′), 1.70 (m, 1H, H-9), 1.95 (ddd, 1H, H-3″, J = 13.1, 7.0, 11.9), 2.10 (ddd, 1H, H-10′, J = 14.4, 3.4, 2.1), 2.30 (dd, 1H, H-3′, J = 13.1, 3.5), 3.74 (ddd, 1H, H-2″, J = 9.8, 7.0, 2.9), 3.90 (dddd, 1H, H-2′, J = 11.9, 9.9, 3.8, 2.0).

^{13}C NMR spectrum (75 MHz, C_6D_6, δ, ppm): 17.93, 23.12 (C-12, C-13), 22.21 (C-14), 22.63 (C-7), 27.40 (C-11), 29.48 (C-9), 34.16 (C-8), 36.01 (C-10), 47.43 (C-6), 52.58 (C-3), 66.34 (C-2), 108.39 (C-5).

(5*R*,6*S*,9*R*)-6-Isopropyl-9-methyl-1-oxo-4-thiaspiro[4.5]-decane-4-sulfoxide (3b). Oil, yield 65-70%, $[\alpha]_D^{20}$ −13.5° (*c* 5.5, EtOH). IR spectrum (thin layer, ν, cm^{-1}): 1051 (SO). $C_{12}H_{22}SO_2$. $[M]^+$ 230.00.

PMR spectrum (300 MHz, C_6D_6, δ, ppm, J/Hz): 0.68, 0.90 (d, 6H, H-12, H-13, J = 7.0), 0.81 (m, 1H, H-8″), 0.97 (d, 3H, H-14, J = 6.5), 1.07 (dd, 1H, H-10″, J = 13.0, 12.7), 1.34 (ddd, 1H, H-7″, J = 13.0, 6.0, 2.5), 1.65-1.70 (m, 3H, H-6, H-7′, H-8′), 1.80 (m, 1H, H-11), 1.85 (m, 1H, H-9), 2.04 (ddd, 1H, H-3″, J = 12.7, 6.7, 6.0), 2.50 (dd, 1H, H-3′, J = 12.7, 2.8), 2.82 (ddd, 1H, H-10′, J = 13.0, 3.1, 1.6), 4.00 (dd, 1H, H-2″, J = 9.7, 6.7), 4.23 (ddd, 1H, H-2′, J = 9.7, 6.0, 2.8).

^{13}C NMR spectrum (75 MHz, C_6D_6, δ, ppm): 18.83, 22.26 (C-12, C-13), 24.03 (C-14), 24.79 (C-11), 25.52 (C-7), 30.96 (C-9), 34.09 (C-8), 39.17 (C-10), 50.09 (C-6), 52.57 (C-3), 66.17 (C-2), 110.46 (C-5).

(5*R*,6*S*,9*R*)-6-Isopropyl-9-methyl-1-oxo-4-thiaspiro[4.5]-decane-4-sulfone (4). Colorless crystals, yield 73%, $[\alpha]_D^{20}$ –151.2° (*c* 1.8, EtOH), mp 63-64°C. IR spectrum (thin layer, ν, cm^{-1}): 1301 [$\nu_{as}(SO_2)$], 1141 [$\nu_s(SO_2)$]. $C_{12}H_{22}SO_3$. $[M]^+$ 246.00.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81, 0.87 (d, 6H, H-12, H-13, J = 6.9), 0.91 (d, 3H, H-14, J = 6.5), 0.90 (m, 1H, H-8″), 1.14 (ddd, 1H, H-7″, J = 14.1, 4.2, 3.3), 1.50 (dd, 1H, H-10″, J = 13.4, 12.0), 1.61-1.73 (m, 3H, H-7′, H-8′, H-10′), 1.75-1.92 (m, 3H, H-6, H-9, H-11), 2.92-3.02 (m, 2H, H-2″, H-3″), 3.18-3.37 (m, 2H, H-2′, H-3′).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 18.86, 24.09 (C-12, C-13), 22.04 (C-14), 25.39 (C-7), 26.73 (C-3), 27.41 (C-11), 29.62 (C-9), 35.26 (C-8), 38.22 (C-10), 46.52 (C-6), 52.53 (C-2), 79.50 (C-5).

The data from the XSA of **3a** were deposited in the Cambridge Crystallographic Data Center under number CCDC 705659.

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