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SYNTHESIS OF NEOMENTHYLSULFANYLIMIDAZOLES

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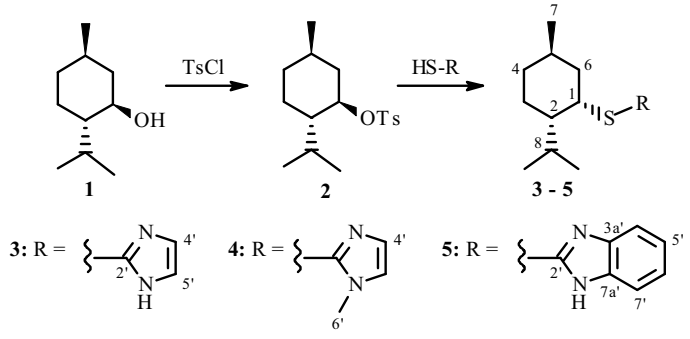
*2-Neomenthylsulfanyl-1*H-*imidazole, 1-methyl-2-neomenthylsulfanyl-1*H-*imidazole, and 2-neomenthylsulfanyl-1H-benzimidazole were synthesized.*

Keywords: L-menthol tosylate, imidazole, benzimidazoleneomenthyl sulfides, synthesis.

Heterocyclic sulfides and compounds including imidazole and benzimidazole groups possess antiviral, antibacterial, antiulcer, anti-inflammatory, and anticancer activity. Furthermore, imidazole-containing sulfides are used as herbicides and fungicides [1]. (–)-Menthol and its derivatives find applications in the pharmaceutical industry and the production of cosmetics [2] and are inductors of chirality, which enables them to be used in asymmetric synthesis [3]. Therefore, the introduction of the chiral menthane structure into a molecule with an imidazole-containing fragment raises expectations, on one hand, of the appearance of new pharmacological properties and, on the other, of performing further asymmetric transformations with optically active compounds.

We synthesized for the first time imidazole- and benzimidazole-containing neomenthylsulfides.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-*p*-toluenesulfonate (**2**), which was prepared from *l*-menthol (**1**) and *p*-toluenesulfonylchloride by the literature method [4] in 98% yield, reacted with the heterocyclic thiols 2-mercaptoimidazole, 2-mercapto-1-methylimidazole, and 2-mercaptobenzimidazole to produce the corresponding sulfides 2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-imidazole (**3**); 1-methyl-2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-imidazole (**4**); and 2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-benzimidazole (**5**). Sulfides **3** and **4** were obtained from the corresponding thiols and menthol tosylate **2** in an alcohol solution of KOH in yields of 47 and 48%, respectively [5]. Sulfide **5** could be produced using Cs_2CO_3/tetrabutylammonium iodide (TBAI) in 68% yield [6].



The reactions occurred by a bimolecular nucleophilic substitution mechanism with total inversion of configuration at C-1. This was proved using NMR spectroscopy, HPLC, and an x-ray structure analysis (XSA). Two-dimensional H^1–H^1 NOESY spectra of **3**–**5** showed correlations characteristic of the interaction of an isopropyl methyl and the C-1 proton and lacked an NOE interaction for the C-1 and C-8 protons. This was characteristic of the neomenthane structure in which the sulfanyl group is situated in the axial position. HPLC did not show impurities of diastereomeric menthyl-containing sulfides with a sulfanyl group in the equatorial position.

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TABLE 1. H-Bonds D–H…A According to XSA Data

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
			3		
N3-H3	0.74 (3)	2.150 (3)	176 (3)	2.891 (3)	N3A [x + 1, y, z]
N1A-H1	1.09 (4)	1.807 (4)	164 (3)	2.871 (3)	N1
			5		
N1-H1B	0.860	1.975 (3)	158.9 (3)	2.795 (3)	N2A [x – 1/2, -y + 3/2, –z]
N1A-H1A	0.855 (14)	1.982 (14)	163 (1)	2.810 (3)	N2 [x – 1/2, –y + 3/2, –z]

TABLE 2. Crystallographic Data and X-ray Structure Parameters

Parameter	**3**	**5**
Formula	$C_{13}H_{22}N_2S$	$C_{17}H_{24}N_2S$
MW, g/mol	238.39	288.44
System	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a, Å	9.9805 (5)	9.8198 (6)
b, Å	14.2791 (12)	17.230 (2)
c, Å	19.5503 (16)	20.1887 (9)
α, deg	90	90
β, deg	90	90
γ, deg	90	90
V, Å^3	2786.2 (4)	3415.9 (5)
Z	8	8
d_{calc}, g/cm^{-3}	1.137	1.122
μ/mm^{-1}	0.211	0.183
Scan range, θ/°	From 2.70 to 26.39	From 2.89 to 26.38
Reflections collected	10180	11583
Independent reflections (R_{int})	3169 (0.0529)	6821 (0.0364)
Reflections with $I \geq 2\sigma(I)$	1579	3434
Completeness (for θ/°)	98.3 % (26.39)	98.9 % (26.38)
Number of refined parameters	297	369
R_1 ($I \geq 2\sigma(I)$)	0.0397	0.0407
wR_2 ($I \geq 2\sigma(I)$)	0.0536	0.0380
R_1 (over all reflections)	0.1083	0.1047
wR_2 (over all reflections)	0.0596	0.0415
S over F^2	1.000	0.959
Flack parameter	–	0.10(6)
$\Delta\rho_{min/max}$, ē/Å^3	0.181/–0.146	0.312/–0.179

PMR and ^{13}C NMR spectra of **3**–**5** exhibited resonances for both the neomenthyl component and the heterocyclic fragment.

The structures of **3** and **5** were established by XSA (Table 1). According to the XSA, the crystal packings of **3** and **5** were highly similar. Thus, both sulfides crystallized in a chiral space group of the orthorhombic system and the crystals were formed by two crystallographically independent molecules with similar stereometric parameters. The molecules in the crystal were packed in chains formed through a system of intermolecular H-bonds (IMHB) of the N–H…N type between the heterocyclic fragments (Table 2). The direction of these chains coincided with the *a* axis of the unit cell. As a result, the similarity of the N…N distances in the IMHB (Table 1) of **3** and **5** caused the *a* axes of the unit cells of these compounds to have similar lengths (Table 2). Figure 1 shows general views of **3** and **5** and the atomic numbering.

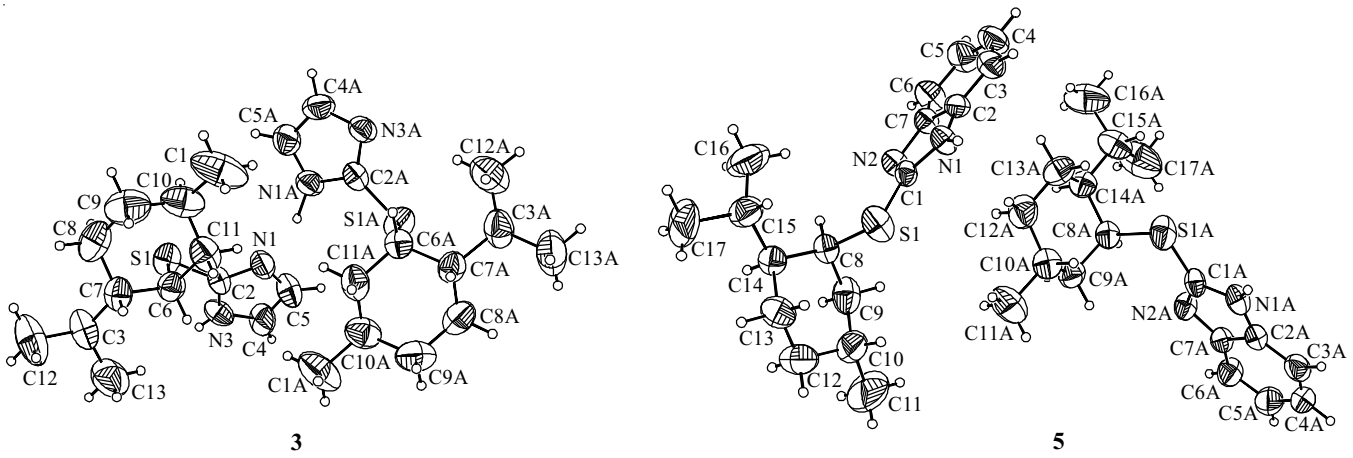

Fig. 1. X-ray molecular structures of **3** and **5** (50% probability ellipsoids).

Thus, we prepared and characterized for the first time 2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-imidazole; 1-methyl-2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-imidazole; and 2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-benzimidazole in 50–70% yields.

EXPERIMENTAL

Melting points were determined on a Gallencamp-Sanyo instrument. HPLC analyses were performed on a Thermo Finnigan Surveyor chromatograph using BDS Hypersil C18, Hypersil Gold, and Hypercarb columns and solvent systems CH_3CN:H_2O (30:70 and 40:60, 1% HCOOH) and MeOH:H_2O (20:80). PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-300 spectrometer (300.17 MHz for ^1H and 75.48 MHz for ^{13}C). Resonances of $CDCl_3$ were used as internal standards. Resonances of ^1H and ^{13}C were fully assigned using two-dimensional homo- (^1H–H^1 COSY, ^1H–H^1 NOESY) and heteronuclear experiments (^1H–^{13}C HSQC, ^1H–^{13}C HMBC). Optical rotation angles were measured on a Kruss P3002RS automated digital polarimeter. TLC was performed on Sorbfil plates using heptane:Et_2O solvents and phosphomolybdic acid in EtOH and $KMnO_4$ solution as detectors. Elemental analysis was carried out using an EA 1110CHNS–O automated analyzer. All reactions were carried out using freshly distilled solvents. Commercially available reagents were used without further purification. Column chromatography was performed over Alfa Aesar silica gel (0.06–0.2 mm) using $CHCl_3$:Et_2O solvent systems.

X-ray structure analyses (XSA) of the compounds were performed on an Xcalibur 3 automated four-circle diffractometer equipped with a CCD detector at 295(2) K using Mo Kα-radiation (0.71073 Å). Datasets were collected and processed using the standard procedure [7]. Absorption corrections were not applied. The structures were solved and refined using the SHELX programs [8] with refinement by full-matrix anisotropic least-squares methods over F^2 for all non-hydrogen atoms. The H atoms of C–H bonds were placed in geometrically calculated positions and refined isotropically with dependent thermal parameters using a rider model. Those of N–H groups were solved by direct methods and refined independently (Table 1). Table 2 presents the principal structural parameters of the experiments.

Data from the XSA were deposited in the Cambridge Crystallographic Data Centre under numbers CCDC 818566 and 818567. These data have free access and can be requested at the address www.ccdc.cam.ac.uk/data_request/cif.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-*p*-toluenesulfonate (menthol tosylate) (2) was prepared by the literature method [4].

Preparation of Sulfides: 2-[((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-imidazole (3) and 1-Methyl-2-[((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-imidazole (4). A solution of the appropriate thiol (1 mmol) in EtOH (5 mL) at room temperature was treated with KOH solution (0.07 g, 1.2 mmol) in EtOH (3 mL), stirred for 10 min, heated to 60°C, treated with a solution of **2** tosylate (0.37 g, 1.2 mmol) in alcohol, stirred for 24 h, evaporated *in vacuo*, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4. The solvent was distilled. Reaction products **3** and **4** were isolated by column chromatography ($CHCl_3$ eluent).

Compound 3. Transparent light-yellow crystals, 47% yield, mp 149.3°C, $[\alpha]_D^{22}$ +97.06° (*c* 0.85, EtOH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, d, J = 6.3, Me-7), 0.83–0.99 (1H, m, H-4*a*), 0.93 (6H, d, J = 6.6, Me-9, Me-10), 1.11–1.25 (1H, m, H-2), 1.13–1.23 (1H, m, H-3*a*), 1.18–1.33 (1H, m, H-6*a*), 1.61–1.75 (1H, m, H-8), 1.70–1.83 (1H, m, H-4*e*), 1.74–1.85 (1H, m, H-3*e*), 1.86–2.03 (1H, m, H-6*e*), 1.87–2.02 (1H, m, H-5), 3.96–4.06 (1H, m, H-1), 7.13 (2H, br.s, H-4′, H-5′), 10.18 (1H, br.s, NH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 20.57 (C-9), 21.04 (C-10), 22.05 (C-7), 26.09 (C-3), 26.70 (C-5), 30.31 (C-8), 35.19 (C-4), 41.38 (C-6), 48.56 (C-2), 51.33 (C-1), 123.66 (C-4′,5′), 140.63 (C-2′). $C_{13}H_{22}N_2S$.

Compound 4. Light-yellow oily liquid, 48% yield, $[\alpha]_D^{22}$ +60.06° (*c* 0.93, EtOH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85–1.01 (1H, m, H-4*a*), 0.89 (3H, d, J = 6.5, Me-7), 0.95 (3H, d, J = 6.6, Me-10), 0.97 (3H, d, J = 6.6, Me-9), 1.12–1.26 (1H, m, H-2), 1.14–1.25 (1H, m, H-3*a*), 1.21–1.37 (1H, m, H-6*a*), 1.60–1.75 (1H, m, H-8), 1.73–1.85 (1H, m, H-4*e*), 1.78–1.88 (1H, m, H-3*e*), 1.87–2.01 (1H, m, H-6*e*), 3.63 (3H, m, H-6′), 4.06–4.15 (1H, m, H-1), 6.92 (1H, s, H-5′), 7.08 (1H, s, H-4′).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 20.63 (C-9), 21.06 (C-10), 22.04 (C-7), 26.42 (C-3), 27.07 (C-5), 30.46 (C-8), 33.13 (C-6′), 35.23 (C-4), 41.37 (C-6), 48.53 (C-2), 51.19 (C-1), 121.71 (C-5′), 129.24 (C-4′), 142.41 (C-2′). $C_{14}H_{24}N_2S$.

2-[((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)sulfanyl]-1*H*-benzimidazole (5). A solution of 2-mercaptobenzimidazole (0.15 g, 1 mmol), Cs_2CO_3 (0.33 g, 1 mmol), and TBAI (0.37 g, 1 mmol) in EtOH (5 mL) was stirred at 20°C for 1 h, treated with **2** (0.34 g, 1.1 mmol), and refluxed for 24 h. The course of the reaction was followed by TLC (heptane:Et_2O eluent, 1:2). The solvent was distilled in vacuo. The mixture was extracted with Et_2O (3 × 30 mL). The extracts were dried over Na_2SO_4. The solvent was distilled. The reaction product **5** was isolated by column chromatography over silica gel ($CHCl_3$ eluent).

Colorless transparent crystals, 68% yield, mp 229.8°C, $[\alpha]_D^{22}$ +56.08° (*c* 0.51, EtOH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83 (3H, d, J = 6.5, Me-7), 0.85–1.00 (1H, m, H-4*a*), 0.90 (3H, d, J = 6.5, Me-9), 0.92 (3H, d, J = 6.4, Me-10), 1.02–1.19 (1H, m, H-3*a*), 1.19–1.32 (1H, m, H-2), 1.31–1.44 (1H, m, H-6*a*), 1.56–1.70 (1H, m, H-8), 1.70–1.82 (1H, m, H-4*e*), 1.78–1.88 (1H, m, H-3*e*), 1.86–2.03 (1H, m, H-6*e*), 1.83–1.97 (1H, m, H-5), 4.41–4.48 (1H, m, H-1), 7.11–7.19 (2H, m, H-5′,6′), 7.43–7.50 (2H, m, H-4′,7′), 12.25 (1H, br.s, NH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 20.50 (C-10), 20.92 (C-9), 21.89 (C-7), 26.60 (C-3), 27.22 (C-5), 30.55 (C-8), 35.09 (C-4), 41.45 (C-6), 48.27 (C-2), 49.12 (C-1), 121.84 (C-4′,5′,6′,7′) (assigned using ^1H–^{13}C HSQC), 135.34 (C-3a′,7a′) (assigned using ^1H–^{13}C HMBC), 151.11 (C-22). $C_{17}H_{24}N_2S$.

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