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Reactions of Mono- and Bicyclic Monoterpenes with Heterocyclic Sulphenyl Chlorides

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Abstract

The reactions of (+)-limonene and (−)-β-pinene with hetarenesulphenyl chlorides (2-benzothiazolesulphenyl chloride, 3-methoxycarbonyl-2-pyridylsulphenylchloride) were studied.

Key words: monoterpenes, sulphenyl chlorination, synthesis of terpene sulphides, (+)-limonene, (−)-β-pinene

INTRODUCTION

An important field of the terpenoid chemistry is nowadays is presented by functionalizing terpene molecules in order to obtain novel compounds with a potential biological activity [1–4]. Earlier, we synthesized a wide range of sulphur-containing monoterpenoids; many of those demonstrated a high antifungal activity [5–8]. One of the main methods for obtaining biologically active compounds is based on modifying terpenes via the introduction of pharmacophore groups into the molecule. When heterocyclic compounds are used as reagents, the probability of the fact that the compounds obtained exhibit biological activity is significantly increased, because, as it is known, heterocyclic fragments are part of a variety of medications [9]. In this regard, it was interesting to combine terpene and thioheterocyclic fragments in one molecule.

The most advanced method of introducing sulphide groups in the molecules of unsaturated compounds are considered to be the reaction of olefins with sulphenyl chlorides. The interaction of olefins with different structures with heterocyclic sulphenyl chlorides was described in several papers [10, 11] where a wide range of unsaturated compounds was used. At the same time, the monoterpenes in the reactions with heterocyclic sulphenyl chlorides are still almost unexplored. Thus, in the literature we found only the works whose authors described a reaction between 3-carene and phenyltetrazolylsulphenyl chloride [12]. In this regard, we studied a series of the reactions of (+)-limonene **I** and (−)-β-pinene **II** sulphenyl chlorination using 2-benzothiazolesulphenyl chloride **III** and 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV**. The choice of these compounds is caused by the fact that these heterocyclic compounds exhibit different type biological activities [13, 14].

The sulphenyl chlorides used for the reactions were obtained immediately prior to the reactions between the corresponding disulphide with sulphuryl chloride in the environment of methylene chloride.

EXPERIMENTAL

NMR spectra were obtained with the use of a Varian Unity spectrometer with the operating frequency of 300 and 75.43 MHz for ^{1}H and ^{13}C nuclei, respectively. We used TMS as

an internal standard, $CDCl_3$ as a solvent. Electron impact gas chromatography/mass spectra were obtained by means of a Perkin-Elmer TurboMass Gold mass spectrometer, a capillary column being 30 m long with the diameter of 320 μm, V_{He} = 1.2 mL/min. For the isolation and purification of the reaction products we used the method of adsorption chromatography on silica gel L 100/160μ. As an eluent we used a mixture of *n*-hexane/methylene chloride. The monitoring of reaction the progress and the quality of reaction mixture separation was carried out by means of thin layer chromatography (TLC) on Silufol plates (developers being either I_2 or the mixture of ethanol/sulphuric acid/anisaldehyde in the ratio of 90 : 5 : 5). We used (+)-limonene **I** $[\alpha]_D^{20}$ + 115°(*c* = 10, EtOH) (Acros organics CAS: 5989-27-5); (1S)-(−)-β-pinene **II** $[\alpha]_D^{20}$ − 21° (Acros organics CAS: 18172-67-3). 2-Benzothiazolesuphenyl chloride **III** and 3-methoxy-2-carbonyl pyridylsulphenyl chloride **IV** were synthesized from the corresponding disulphides those were obtained by means of the techniques described in [15]. Purifying and drying the solvents were carried out according to the procedures described in [16].

GENERAL TECHNIQUE FOR OBTAINING SULPHENYL CHLORIDES

To 1 mmol of disulphide in 5 mL of CH_2Cl_2 was added a solution of 1 mmol of sulphuryl chloride in 5 mL of CH_2Cl_2 at a temperature of 25−30 °C with stirring for 2−5 min. The solvent was evaporated at 30−40 °C. Sulphenyl chlorides obtained were used in the reactions with terpenes within the range of 5−10 min.

Reaction between (+)-limonene I with 2-benzothiazolesulphenyl chloride III. To 2 mmol of 2-benzothiazolesulphenyl chloride **III** in 4 mL of CH_2Cl_2 was added 2 mmol (+)-limonene **I** dissolved in 4 mL of CH_2Cl_2 at a room temperature, under stirring (reactant ratio 1 : 1). The monitoring of the reaction progress was carried out by means of TLC. After completing the reaction (5 days), the solvent was evaporated using a water jet pump. Compound **V** was isolated by means of a column chromatography on silica gel (eluent *n*-hexane/methylene chloride at a ratio of 70 : 30). The yield was equal to 60 %.

2-[2-Chloro-2-(4-methylcyclohexyl-3-enyl)propylthio]benzo[*d*]thiazole V. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.65 s, 1.69 s (6H, H-7, H-10), 1.40−2.30 m (7H, H-3, H-4, H-5, H-6), 4.00 dd (1H, $-SCH_2-$, $^2J_{H\text{-}9\alpha H\text{-}9\beta}$ = 13.4 Hz, $^4J_{H\text{-}9\alpha H\text{-}4}$ = 14.9 Hz), 4.02 dd (1H, $-SCH_2-$, $^2J_{H\text{-}9\alpha H\text{-}9\beta}$ = 13.4 Hz, $^4J_{H\text{-}9\beta H\text{-}4}$ = 48 Hz), 5.39 br. s (1H, H-2), 7.29 м (1H, H_{arom}), 7.41 m (1H, H_{arom}), 7.75 m (1H, H_{arom}), 7.86 m (1H, H_{arom}). ^{13}C NMR spectrum, δ, ppm, 23 (C-5), 24.5, 24.6 (C-7), 26.3, 26.8 (C-3), 27.0, 27.1 (C-6), 30.6, 30.7 (C-10), 43.7, 43.9 (C-9), 45, 45.3 (C-4), 75.7, 75.8 (C-8), 119.6, 119.9 (C-2), 120.9 (C-13), 121.4 (C-16), 124.2 (C-15), 125.9 (C-14), 133.8, 134.1 (C-1), 135.4 (C-11),152.9, 153.0 (C-12), 166.2, 166.3 (C-17). GC-MS: *m/z* (I_{rel}, %): 302 [M^+−Cl] (1), 268 (100), 218(8), 232 (72), 218 (20), 206 (80), 200 (68), 186 (16), 167 (69), 149 (20), 136 (88), 119 (62), 108 (60), 91 (100), 77 (78), 67 (81), 53 (62). $C_{17}H_{20}ClNS_2$. Calculated, %: C 60.42, H 5.97, Cl 10.49, N 4.14, S 18.98. Found, %: C 60.51, H 6.01, Cl 10.45, N 4.12, S 18.91.

Reaction between (+)-limonene I and 3-metoxycarbonyl-2-pyridylsulphenyl chloride IV. To 2 mmol of 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV** in 4 mL of CH_2Cl_2 at a room temperature under stirring, was added 2 mmol of (+)-limonene **I** dissolved in 4 mL of CH_2Cl_2 (reactant ratio 1 : 1). The monitoring of the reaction progress was carried out by means of TLC. After completing the reaction (5 days), the solvent was evaporated with the use of a water jet pump. Compound **VI** was isolated by means of column chromatography on silica gel (eluent *n*-hexane/methylene chloride at a ratio of 70 : 30). The yield was equal to 72 %.

Methyl 2-[(1S,2S)-2-chloro-1-methyl-4-(prop-1-en-2-yl)cyclohexylthio] nicotinate (VI). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.25 s, 1.36 s (6H, H-7, H-10), 1.61−2.40 m (7H, H-3, H-4, H-5, H-6), 3.93 s (3H, $-OCH_3$), 4.47 dd (1H, H-2, $^3J_{H\text{-}2H\text{-}3\alpha}$ = 6.3 Hz, $^3J_{H\text{-}2H\text{-}3\beta}$ = 39 Hz), 4.81 d (2H, H-9, $^2J_{H\text{-}9\alpha H\text{-}9\beta}$ = 13 Hz), 7.06 dd (1H, H_{arom}, ^3J = 7.8 Hz, *J* = 4.76 Hz), 8.21 dd (1H, H_{arom}, ^3J = 7.8 Hz, *J* = 1.89 Hz), 8.52 dd (1H, H_{arom}, ^3J = 4.76 Hz, *J* = 1.89 Hz). GC-MS: *m/z* (I_{rel}, %): 303 [M^+−HCl] (2), 288 (14), 270 (12), 234 (18), 220 (10), 208 (45), 202 (8), 170 (50), 138 (84), 119 (95), 107 (57), 91 (100), 82 (20), 77 (70), 67 (30), 65 (28), 55 (46). $C_{17}H_{22}ClNO_2S$. Calculated, %: C 60.07, H 6.52,

Cl 10.43, N 4.12, S 9.43. Found, %: C 60.12, H 6.58, Cl 10.45, N 4.13, S 9.51.

Reaction between (1S)-(−)-β-pinene II with 2-benzothiazolesulphenyl chloride III. To 2 mmol of 2-benzothiazolesulphenyl chloride **III** in 4 mL of CH_2Cl_2 was added 2 mM of (1S)-(−)-β-pinene **II**, dissolved in 4 mL of CH_2Cl_2 at a room temperature under stirring (reactant ratio 1 : 1). The monitoring of the reaction progress was carried out by means of TLC. After completing the reaction (10 days), the solvent was evaporated using a water jet pump. Compound **VII** was isolated by means of column chromatography on silica gel (eluent *n*-hexane/methylene chloride at a ratio of 70 : 30). The yield was equal to 70 %.

2-[(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methylthio]benzo[*d*]thiazole VII. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.80 s, 1.28 s (6H, H-8, H-9), 2.04−2.45 m (6H, H-1, H-4, H-5, H-6), 3.97 br. s (2H, $-SCH_2-$), 5.65 br. s (1H, H-3), 7.27 m (1H, H_{arom}), 7.40 m (1H, H_{arom}), 7.74 d (1H, H_{arom}), 7.85 m (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.80 s, 1.28 s (6H, H-8, H-9), 2.04−2.45 m (6H, H-1, H-4, H-5, H-6), 3.97 br. s (2H, $-SCH_2-$), 5.65 br. s (1H, H-3), 7.27 m (1H, H_{arom}), 7.40 m (1H, H_{arom}), 7.74 d (1H, H_{arom}), 7.85 m (1H, H_{arom}). GC-MS: *m/z* (I_{rel}, %): 301 [M^+] (12), 286 (4), 268 (14), 232 (24), 200 (4), 167 (25), 13 (27), 119 (53), 108 (21), 91 (100), 77 (34), 65 (17), 53 (18). $C_{17}H_{19}NS_2$. Calculated, %: C 67.73, H 6.35, N 4.65, S 21.27. Found, %: C 67.74, H 6.36, N 4.61, S 21.29.

Reaction between (1S)-(−)-β-pinene II with 3-methoxycarbonyl-2-pyridylsulphenyl chloride IV. To 2 mmol of 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV** in 4 mL of CH_2Cl_2 was added 2 mM of (1S)-(−)-β-pinene **II** dissolved in 4 mL of CH_2Cl_2 at a room temperature under stirring (reactant ratio 1 : 1). The monitoring of the reaction progress was carried out by means of TLC. After completing the reaction (2 days), the solvent was evaporated using a water jet pump. Compounds **VIII** and **IX** were characterized in the reaction mixture.

Methyl 2-[(2-chloro-6,6-dimethylbicyclo-[3.1.1]heptane-2-yl)methylthio] nicotinate VIII. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.03 s, 1.12 s (6H, H-8, H-9), 1.72−3.0 m (8H, H-1, H-3, H-4, H-5, H-7), 3.41−3.82 m (2H, $-SCH_2-$), 3.63 s (3H, $-OCH_3$), 6.85 m (1H, H_{arom}), 7.95 m (1H, H_{arom}), 8.22 m (1H, H_{arom}). GC-MS: *m/z* (I_{rel}, %): 303 [M^+−HCl] (8), 288 (4), 270 (14), 260 (4), 234 (32), 220 (7), 202 (6), 188 (4), 170 (14), 138 (24), 119 (52), 111 (19), 91 (100), 79 (37), 65 (18), 53 (18).

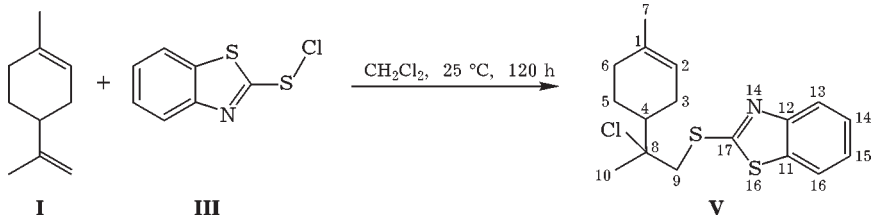
8′-(Methoxycarbonyl)-2′H-spiro[6,6-dimethylbicyclo[3.1.1]heptane-2,3′-thiazole[3,2-a]-pyridin]-4′-ium chloride IX. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.95 s, 1.12 s (6H, H-8, H-9), 1.72−3.0 m (8H, H-1, H-3, H-4, H-5, H-7), 3.41−3.82 m (2H, $-SCH_2-$), 3.78 s (3H, $-OCH_3$), 7.96 m (1H, H_{arom}), 8.51 m (1H, H_{arom}), 10.00 m (1H, H_{arom}). GC-MS: *m/z* (I_{rel}, %): 304 [M^+−Cl] (7), 288 (18), 270 (30), 248 (11), 234 (73), 220 (70), 202 (18), 170 (9), 138 (42), 119 (21), 111 (30), 97 (38), 91 (100), 79 (96), 69 (30), 65 (30), 53 (24).

RESULTS AND DISCUSSION

The reaction between (+)-limonene **I** and 2-benzothiazolsulphenyl chloride **III** was finished by the formation of a product *via* the addition at exocyclic double bond of (+)-limonene **I** according to the extended Markovnikov's rule (Scheme 1).

The chromatographic profile of the GC-MS spectrum of compound **V** exhibits a peak at *m/z* 302 [M^+−Cl].

Beilstein test demonstrated the presence of chlorine atom in the product **V**. The ^{1}H NMR spectrum of this product exhibits the signals of four protons from thiazole fragment in the



Scheme 1.

form of multiplets (7.29,7.44, 7.75, 7.86 ppm), two protons from the methyl groups (1.65 s, 1.69 s (6H, H-7, H-10)), a multiplet of seven protons from cyclohexene fragment within the range of 1.40–2.30 ppm, and the proton signal from the endocyclic double bond as a broad singlet at 5.38 ppm. The absence of a signal within the range of 4.8 ppm indicates the fact that the reaction occurs exclusively with the exocyclic double bond of (+)-limonene **I**. The protons of $-SCH_2-$ fragment are magnetically nonequivalent and "feel" the influence of methine proton at C-4, there for they are presented as ABX system. This is consistent with the data available from the literature concerning such a type of compounds [17]. The signal from corresponding methine proton at C-4 (X-proton) is exhibited within the range of 1.40–2.30 ppm. The ^{13}C NMR data for compound **III** are also consistent with the proposed structure of adduct **V**.

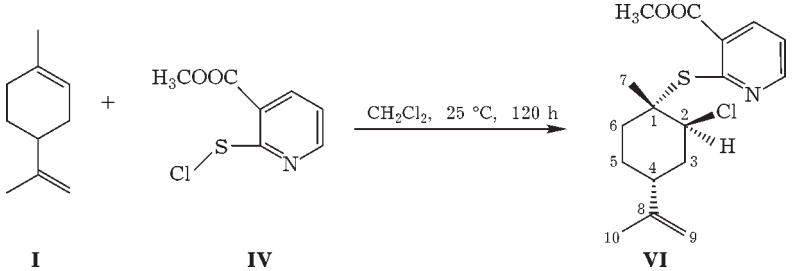
The reaction between (+)-limonene **I** and 3-metoxycarbonyl-2-pyridylsulphenyl chloride **IV** was completed with the formation of the product of sulphenyl chloride addition at the endocyclic double bond of (+)-limonene **I** against the extended Markovnikov's rule **VI** (Scheme 2).

The chromatographic profile in the GC-MS spectrum exhibits a peak at m/z 303 [M^+–HCl].

The ^1H NMR spectrum of the product **VI** demonstrates proton signals from the pyridine moiety as a doublet of doublets within the range of 7.06, 8.20, 8.52 ppm, protons of two methyl groups (1.25 s, 1.36 s (6H, H-7, H-10)), a multiplet of seven protons from cyclohexene fragment within the range of 1.30–2.40 ppm, a singlet of $-OCH_3$ group at 3.93 ppm, as well as the proton signal from exocyclic double bond as a doublet (4.82 ppm). Methine proton signal at C-2 atom is in the form of the doublet of doublets with coupling constants 3.9 (*ee*) and 6.3 (*ae*) Hz within the range of 4.47 ppm, which indicates its equatorial position. Thus, the sulphapyridine fragment also occupies the equatorial position, which is consistent with the known rules concerning the addition of sulphenyl chlorides to cycloolefines [15]. The regioselectivity of the addition reaction was established basing one of the chemical shift of the signal inherent in the methine proton at C-2 (4.47 ppm), which shift indicates the addition of 3-methoxycarbonyl-2-pyridylsulphenyl chloride to occur against the extended Markovnikov's rule, with the formation of an adduct with chlorine atom at the second carbon atom. In the case of addition in accordance with the rule the signal from corresponding proton should be exhibited within the range up to 4 ppm [18].

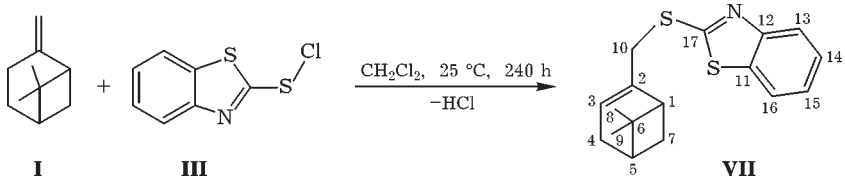
The reaction between (–)-β-pinene **II** with 2-benzothiazolesulphenyl chloride **III** results in forming the product of addition-abstraction **VII** (Scheme 3).

The Beilstein test for compound **VII** demonstrated the absence of chlorine atom in the reaction product. The ^1H NMR spectrum ex-



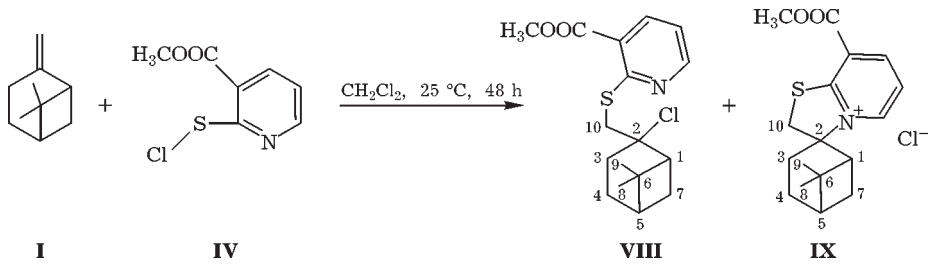
I **IV** **VI**

Scheme 2.



I **III** **VII**

Scheme 3.



I **IV** **VIII** **IX**

Scheme 4.

hibits a signal of the proton from the endocyclic double bond at 5.65 ppm. The ^{1}H NMR spectrum also demonstrates proton signals from the pinene core and the hetaryl fragment. The $-SCH_2-$ fragment is presented in the form of a singlet within the range of 3.97 ppm. The ^{13}C NMR spectrum also exhibits the signals of carbon atoms C-2 and C-3 involved in the endocyclic double bond (122.3 ppm (C-3), 141.8 ppm (C-2)). Thus, the reaction between (−)-β-pinene **II** and 2-benzothiazolesulphenyl chloride **III** results in forming the adduct with the further abstraction of hydrogen chloride molecule.

The reaction between (−)-β-pinene **II** and 3-methoxy-2-carbonyl pyridylsulphenyl chloride **IV** results in forming a mixture of the two products such as **VIII**, **IX**, as indicated by the presence of peaks corresponding to the two compounds **VIII** (*m/z* 303 [M^+−HCl]) and **IX** (*m/z* 304 [M^+−Cl]) in the chromatographic profile of the GC-MS spectrum at a ratio of 1 : 3, respectively. When tried to separate the mixture using column chromatography on silica the reaction mixture underwent decomposition followed by resinification, therefore the products **VIII** and **IX** were characterized in the reaction mixture. Compound **VIII** represents the product of adding at the terpene double bond in accordance with the Markovnikov's rule, whereas compound **IX** is the product of its subsequent cyclization (Scheme 4).

The formation of the cyclization product **IX** is indicated by additional proton signals from the pyridine moiety in the ^{1}H NMR spectrum within the range of 7.96, 8.51 and 10.00 ppm those undergo a low-field shift as compared to the corresponding signals of the protons from adduct **VIII** (6.85, 7.95 and 8.22 ppm).

The differences in the chemoselectivity inherent in the reaction between (+)-limonene **I** and 2- benzothiazolesulphenyl chloride **III** and the reaction between 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV**, to all appearance, could be caused by both electronic and steric factors. So, more bulky 2- benzothiazolesulphenyl chloride **III** is added at the sterically most accessible exocyclic double bond, whereas the more electrophilic 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV** interacts with the nucleophilic endocyclic double bond of the molecule. The formation of the kinetically controlled anti-Markovnikov adduct in the case of 3-metoxycarbopnyl-2-pyridylsulphenyl chloride **IV** is in a good agreement with the data from the literature concerning the sulphenyl chlorination of this terpene by methyl- and phenylsulphenyl chlorides [18, 19].

The formation of an intramolecular cyclization product only in the reaction between (−)-β-pinene **II** with 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV** could be caused, above all, by the features of chemical behaviour of the 3-methoxycarbonyl-2-pyridylsulphenyl chloride **IV** itself, whose tendency to cyclization reactions with alkenes is typical [10, 11]. The absence of such a cyclization product in the reaction with (+)-limonene **I** is caused by the structure of the reaction adduct formed with endocyclic double bond in the molecule, which prevents the formation of such a strained condensed ring system.

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