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Synthesis of Sulfur-Containing Polyfunctional Terpenoids from (–)-Carvone

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Abstract — Reactions of (–)-carvone with aliphatic, aromatic, heterocyclic, and functional thiols, catalyzed with potassium carbonate, gave the corresponding derivatives in high yields. Isopropyl mercaptan, 2-mercaptoethanol, furfuryl mercaptan, and *N*-acetylcysteine add across the endocyclic double bond of (–)-carvone with the predominant formation of the isomers with the *S* configuration of C^3, whereas addition of hexadecyl mercaptan and 1,2-ethanedithiol mainly yields the *R* isomers.

Monoterpenes and terpenoids of the menthane series, in particular, carvone, are convenient precursors in syntheses of natural and synthetic biologically active compounds [1–3]. The availability of the starting compound, carcinostatic activity of limonene sulfides [4], diverse medicobiological activity of other polyfunctional terpenoids, and insufficiency of published data on synthesis of various functional sulfur-containing carvone derivatives stimulated us to study addition of thiols to carvone.

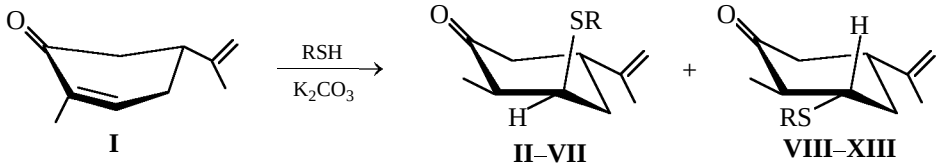
Although addition of thiols to terpene double bonds was studied in numerous works, available data concerning (–)-carvone are limited only to synthesis of dicarvone sulfide, ethylthiocarvone, and phenylthiocarvone under catalysis with sodium acetate and trimethylamine [5].

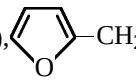
We have studied the reactions of (–)-carvone with isopropyl, hexadecyl, and furfuryl mercaptans, 2-mercaptoethanol, *N*-acetylcysteine, and 1,2-ethanedithiol under catalysis with potassium carbonate, and also the reaction with mercaptoacetic acid without a catalyst. Previously we showed that various thiols add to both endocyclic and exocyclic double bonds in limonene in the presence of Lewis acids to give the corresponding sulfides [6].

The reactions of (–)-carvone with the above reagents, performed at room temperature in the presence of K_2CO_3, in all the cases resulted in addition to the endocyclic double bond only. Among four possible stereoisomers, only two formed in appreciable amounts. Addition of mercaptoacetic acid without K_2CO_3 at 60°C occurred at both double bonds, with the exocyclic C=C bond being involved predominantly (Scheme 1).

The ^{1}H NMR (Table 1), IR, analytical, and mass-spectrometric data for compounds **II**–**XVI** isolated

Scheme 1.



R = *i*-Pr (**II**, **VIII**), $C_{16}H_{33}$ (**III, IX**), CH_2CH_2OH (**IV, X**),  (**V, XI**), CH_2CH_2SH (**VI, XII**), $CH_2CH(NHCOCH_3)COOH$ (**VII, XIII**).

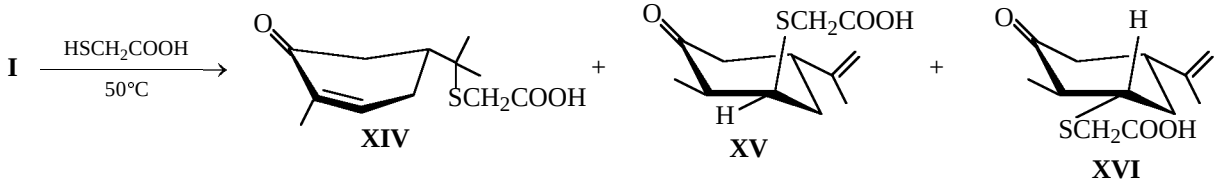


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Table 1. Chemical shifts δ (ppm) and coupling constants *J* (Hz) in the ^{1}H NMR spectra of **II**–**XVIII**

Comp. no.	H_3C^7	H_3C^{10}	HC^2	HC^3	HC^5	H_2C^9	SR
II	1.00 d (6.7)	1.62 s	2.75 d (4.8)	3.30 d.d (3.5, 4.8)	2.88 t.d (12.0, 15.0)	4.65 d.d (14.0, 17.0)	1.12 d (CH_3, 7.0), 1.45 m (CH)
III	1.16 d (6.9)	1.76 s	2.81 d.d (4.8, 12.0)	3.40 d.d (3.2, 4.8)	2.95 t.d (3.5, 12.0, 15.0)	4.80 d.d (15.0)	0.88 t (CH), 1.20–1.50 $(CH_2)_n$, 2.50 t (SCH_2CH_2)
IV	1.01 d (6.7)	1.70 s	2.84 d.d (4.7, 12.0)	3.36 d.d (3.6, 4.7)	3.02 m	4.66 d.d	2.88 s (OH), 3.62 d.d (CH_2OH)
V	1.02 d (6.7)	1.65 s	2.76 d.d (4.9, 12.0)	3.34 d.d (3.4, 4.9)	2.82 m	4.70 d.d	7.3 s, 6.25 m, 6.14 d (Ar), 3.64 d (CH_2Ar)
VI	1.14 d (6.7)	1.74 s	2.70 d (4.9, 12.0)	3.43 d.d (3.4, 4.9)	2.88 m	4.78 d.d (15.0)	2.68 m ($2CH_2$)
VII	1.20 d (6.7)	1.78 s	2.99 d (12.0)	3.10 d.d (5.0, 12.0)	2.82 m	4.80 d	2.62–2.70 m ($2CH_2$)
VIII	1.12 d (6.7)	1.62 s	2.70 d.d (12.0)	2.80 t.d (12.3, 12.0)	1.70 m	4.65 d.d (14.0)	1.12 d ($2CH_3$, 7.0)
IX	1.18 d (6.7)	1.70 s	2.52 t.d (12.0, 12.3)	2.42 d.d (12.0, 12.0)	1.73 m	4.71 d (12.0)	0.80 t (CH_3), 1.2–1.4 s $(CH_2)_n$, 1.50 m (SCH_2CH_2)
X	1.10 d (6.4)	1.70 s	2.33 d (12.0, 3.5)	2.45 d.d (12.0, 3.5)	1.70 m	4.66 d (12.0)	2.88 s (OH), 3.62 d.d (CH_2OH), 2.70 d.d (SCH_2)
XI	1.15 d.d (6.4)	1.65 s	3.68 d.d (12.0, 3.5)	3.73 d.d (12.0, 3.5)	1.70 m	4.70 d	7.36, 6.25 m, 6.14 d (Ar), 3.64 d (CH_2Ar)
XII	1.24 d (6.4)	1.74 s	2.40 d (12.0)	2.48 d (12.0)	1.75 m	4.78 d	2.62–2.70 m ($2CH_2$)
XIII	1.25 d.d (6.4)	1.74 s	2.4 d.d (12.0)	2.45 t.d (12.0, 12.3)	1.65 m	4.80 d	7.35 d.t (NH), 9.35 s (COOH), 4.10 m (CH_2), 3.60 m (CH)
XIV	1.76 s	1.00 s	–	6.60 d	2.78 m	1.01 s (H_3C^9)	3.25 s (CH_2), 10.8 s (COOH)
XV	1.00 d (6.7)	1.62 s	3.10 d (12.0)	3.50 (5.0)	2.70 m	4.60 d	3.08 s (CH_2), 8.6 s (COOH)
XVI	1.10 d (6.4)	1.62 s	3.05 d (12.0)	3.15 d.d (12.0)	1.68 m	4.60 d	3.08 s (CH_2), 8.6 s (COOH)
XVII	1.28 d (6.4) ($2CH_3$)	1.78 s ($2CH_3$)	2.47 d (2H, 12.0)	2.60 t.d (2H, 12.0, 12.3)	1.85 m (2H)	4.82 d (4H, 14.0)	2.83 m ($2CH_2$)
XVIII	1.28 d (6.4) 1.20 d (6.7)	1.78 s (3H), 1.80 s (3H)	2.47 d.d (1H, 12.0), 2.82 d (1H, 12.0, 3.5)	2.60 t.d (1H, 12.0, 12.3), 3.5 d.d (1H, 5.0)	1.85 m (1H), 2.94 m (1H)	4.82 d (2H, 14.0), 4.84 d (2H, 14.0)	2.70–2.83 m ($2CH_2$)

pure by column chromatography on silica gel showed that the adducts were pairs of stereoisomers differing in the configuration of C^3. The stereoisomer ratio differs for different mercaptans (Table 2). (2*S*,5*S*,3*R*)-2-Methyl-5-isopropenyl-3-thiohexadecylcyclohexanone **III** and (2*S*,5*S*,3*S*)-2-methyl-5-isopropenyl-3-thiohexadecylcyclohexanone **IX** were isolated as pure isomers.

In the ^{1}H NMR spectrum of **III**, the signal of the methine proton at C^3 (3.4 ppm) is a doublet of doublets (J_{ae} 3.2, J_{ee} 4.8 Hz), which suggests the axial orientation of the sulfide group. The signal of the similar proton in the spectrum of **IX** (2.52 ppm) is a triplet of doublets (J_{ae} 3.5, J_{aa} 12.0 Hz), which is characteristic of cyclohexane with the equatorial sulfide

Table 2. Ratios of stereoisomers of (–)-carvone sulfides **II**–**XVIII**

Thiol added	Isomers	Ratio of *R* and *S* stereoisomers
Isopropyl mercaptan	**II/VIII**	1 : 2
Hexadecyl mercaptan	**III/IX**	2 : 1
2-Mercaptoethanol	**IV/X**	1 : 3
Furfuryl mercaptan	**V/XI**	2 : 3
1,2-Ethanedithiol	**VI/XII**	2 : 1
N-Acetylcysteine	**VII/XIII**	1 : 4
Thioglycolic acid	**XIV/XV/XVI**	20 : 1 : 1
1,2-Ethanedithiol	**XVII/XVIII** (bis-adducts)	1 : 2

group. The signal of the methine proton at C^3 in the stereoisomers with the *S* configuration is considerably shifted upfield as compared to the *R* isomers ($\Delta\delta$ 0.8–1.2 ppm). This fact allows easy determination of the stereoisomer ratio using ^{1}H NMR data only. The chemical shifts of the signal of the methine proton at C^5 also differ in the *S* and *R* isomers. In the spectra of the *R* isomers, this signal is shifted downfield relative to the starting (–)-carvone owing to the deshielding effect of the closely located sulfur atom. In the spectra of the *S* isomers in which the sulfide group occupies the equatorial position and is remote from the axial methine proton at C^5, this signal is shifted upfield relative to (–)-carvone, probably owing to the effect of the sulfur lone electron pair.

Mercaptoacetic acid at 50°C in the absence of catalyst adds to (–)-carvone mainly at the exocyclic C=C bond to form adduct **XIV** according to the Markownikoff rule. Compounds **XV** and **XVI** formed by addition across the endocyclic double bond (*S* and *R* isomers) are formed as minor products in a ratio of about 1 : 1.

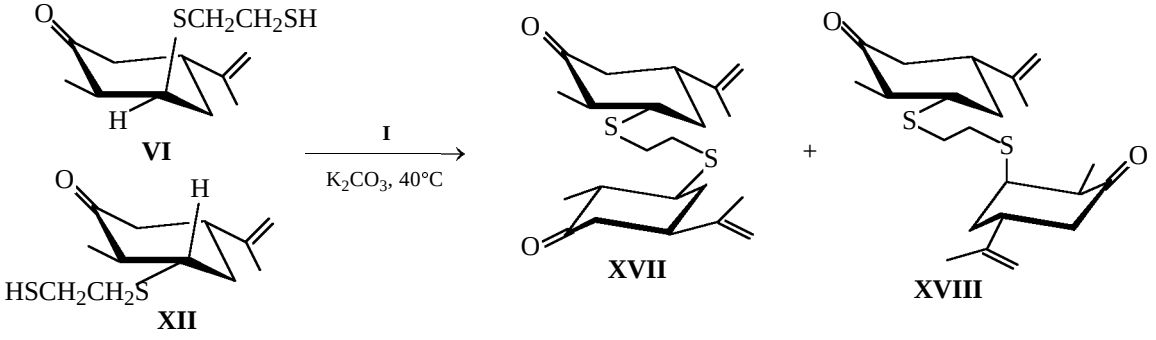
The reaction of (–)-carvone with 1,2-ethanedithiol in the equimolar ratio under catalysis with K_2CO_3 at room temperature yielded an unseparable mixture of monoadducts with almost equal content of **VI** and **XII**. Subsequent addition of an equimolar amount of (–)-carvone to these terpenethiols gave two stereoisomers, **XVII** and **XVIII**, which were separated by column chromatography on silica gel (Scheme 2). In the ^{1}H NMR spectrum of **XVII**, which is the *S* isomer with respect to all the asymmetric centers and has a symmetry plane, the proton signals of the two carvone fragments fully coincide. The spectrum of **XVII** differs from that of monoadduct **XII** in that the number of signals from methylene protons at the sulfur atom in **XVII** is two times smaller. Stereoisomer **XVIII** is an *S* isomer with respect to one center and an *R* isomer with respect to the other center. Its ^{1}H NMR spectrum is a set of proton signals of equal intensities, characteristic of monoadducts **VI** and **XII**, with the number of signals of methylene protons at the sulfur atoms decreased by half. The mass spectra of **XVII** and **XVIII** contain a molecular peak at *m/z* 394. The fragmentation pattern also confirms the presence of two carvone sulfide fragments.

EXPERIMENTAL

The IR spectra (mulls in mineral oil) were recorded on an IR-75 spectrophotometer. The ^{1}H NMR spectra of **II**–**XVII** ($CDCl_3$, reference TMS) were recorded on a Varian Unity-300 spectrometer (300 MHz). The mass spectra were taken on an MKh-1321A mass spectrometer; ionizing electron energy 70 eV, injector temperature 250°C, and ion source temperature 150°C.

(2*S*,5*S*)-3-(Alkylthio)-5-isopropenyl-2-methylcyclohexanones II–XIII. To a suspension of 0.003 mol of K_2CO_3 in 5 ml of a mixture of diethyl ether with acetone, we added in an argon flow 0.033 mol of appropriate mercaptan RSH and 0.033 mol of (–)-carvone. The mixture was stirred at room temperature for 10–24 h and poured into water; the reaction products were extracted with methylene chloride, and the ex-

Scheme 2.



tract was washed with an NH_4Cl solution and dried over $MgSO_4$. After distillation of the solvent, products **II**–**IV**, **VII**–**X**, and **XIII** were isolated by column chromatography on silica gel [eluents hexane (**II** + **VIII**, **III** + **IX**); hexane–ether, 1 : 1 (**IV** + **X**, **VII** + **XIII**)]. Isomers **VI** and **XII** were recrystallized from hexane–ether, 1 : 1. Compounds **V** and **XI** formed in a quantitative yield and did not require additional purification according to TLC data. Yields, %: 70 (**III** + **IX**), 75 (**VII** + **XIII**), 85 (**II** + **VIII**), 87 (**IV** + **X**), 90 (**VI** + **XII**), 99 (**V** + **XI**). IR spectrum of **II** + **VIII**, ν, cm^{-1}: 890, 1640 ($C=CH_2$), 1705 (C=O), 2650 (C–S–C). IR spectrum of **V** + **XI**, ν, cm^{-1}: 880, 1630 ($C=CH_2$), 1705 (C=O), 2650 (C–S–C). IR spectrum of **VI** + **XII**, ν, cm^{-1}: 880, 1630 ($C=CH_2$), 1695 (C=O), 3400 (SH). IR spectrum of **VII** + **XIII**, ν, cm^{-1}: 880, 1630 ($C=CH_2$), 1645, 1705 (C=O), 2600 (C–S–C), 3330 (NH), 3500 (OH). Mass spectrum of **VI** + **XII**, *m/z* (I_{rel}, %): 244 (64) [M^+], 211 (1), 184 (4), 150 (85), 108 (51), 93 (57), 82 (100). The analytical data were consistent.

Compounds XIV–XVI. To a solution of 0.033 mol of (–)-carvone in 20 ml of methylene chloride, we added dropwise in an argon flow 0.033 mol of thioglycolic acid. The mixture was stirred at 50°C for 24 h and then poured into water acidified with 3% HCl to pH 3. The products were extracted with methylene chloride, and the extract was dried over $MgSO_4$. After distillation of the solvent, products **XIV**–**XVI** were isolated by column chromatography on silica gel (eluent ether). Yield 85%. IR spectrum of **XIV**, ν, cm^{-1}: 890, 1640 ($C=CH_2$), 1670, 1720 (C=O), 2650 (C–S–C), 3400–3500 (OH). The analytical data were consistent.

Compounds XVII and XVIII. To a suspension of 0.003 mol of potassium carbonate in 5 ml of a mixture of diethyl ether with acetone, we added in an argon flow 0.033 mol of a 2 : 3 mixture of stereoisomers **VI** + **XII** and 0.033 mol of (–)-carvone. The mixture was stirred for 24 h at 40°C and poured into water, the products were extracted with methylene chloride, and the extract was washed with an NH_4Cl solution and dried over $MgSO_4$. After distillation of the solvent, the products were isolated by column chromatography on silica gel (eluent hexane). **Compound XVII.** Yield 35%, mp 78–79°C. Mass spectrum, *m/z* (I_{rel}, %): 394 (1) [M^+], 244 (47), 183 (20), 150 (48), 107 (46), 93 (68), 82 (40), 55 (100). **Compound XVIII.** Yield 60%, mp 92–93°C. Mass spectrum, *m/z* (I_{rel}, %): 394 (1) [M^+], 245 (34), 183 (25), 150 (42), 107 (42), 93 (66), 82 (67), 55 (100). The analytical data were consistent.

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