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ADDITION OF THIOLS TO (-)-CARVONE

E. V. Sirazieva,[1] V. A. Startseva,[1] L. E. Nikitina,[1]
V. V. Plemenkov,[1] V. V. Klochkov,[2]
and B. I. Khairutdinov[2]

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Polyfunctional thioterpenoids were formed in the presence of a Lewis-acid catalyst by reaction of (-)-carvone with thiols that involved the endocyclic double bond and the carbonyl.

Key words: (-)-carvone, catalytic electrophilic addition, polyfunctional thioterpenoids.

One of the methods for introducing a sulfide into hydrocarbons is the acid-catalyzed addition of thiols and disulfides to the double bond of various alkenes [1, 2]. We studied previously the reaction of thiols with (-)-camphene, (-)-β-pinene, (+)-3-carene, α-terpinene, (±)-limonene, and alloocimene. The results depended mainly on the lability of the isoprene system of the substrate and the thiol structure [3-5]. Zinc chloride was used as catalyst in most of the reactions.

The variety of reaction pathways in the reactions of monoterpenes with thiols is evidently due to the "softness" of the three reagents (terpene, thiol, $ZnCl_2$). The terpene typically has a structurally flexible carbon skeleton; the S-containing reagent, a labile unshared pair of electrons on S; the Zn cation, easily polarized free orbitals.

In continuation of research on heterolytic addition of thiols to terpenes, we studied the reaction of (-)-carvone (**1**) with thiols of various structure [RSH, R = $-C_2H_5$, $-CH(CH_3)_2$, $-C_8H_{17}$, $-(CH_2)_2OH$, $-(CH_2)_2SH$] with $ZnCl_2$ catalyst.

It is well known that carvone is a starting material for synthesizing a large number of natural biologically active compounds [7-9].

The presence in carvone of three reactive centers that can participate in electrophilic reactions creates definite difficulties in predicting the course of reactions with various thiols.

The reactions were conducted in methylene chloride at room temperature using a two-fold excess of the mercaptan. If an equimolar ratio of reagents was used, the analogous reaction products were observed but a significant quantity of unreacted carvone remained in the mixture. This indicates indirectly that the reactions proceed by simultaneous mechanisms involving two reactive centers.

According to GCMS, the product (**3**) of the reaction of carvone and isopropylmercaptan that was preliminarily isolated by column chromatography over silica gel was a mixture of two isomers with m/z 284 in a 10:1 ratio. The identical fragmentation pattern in the mass spectra of both isomers indicates that **3** exists as a mixture of two stereoisomers. The molecular ion with m/z 284 corresponds to the addition product of carvone to two thiols minus a water molecule. The lack of a characteristic vibration band for a carbonyl in the IR spectrum of **3** suggests that the thiol added to this group; the lack of a signal for hydroxyl, dehydration of an intermediate dithioterpenol.

The PMR spectrum of **3** contains a signal for an exocyclic double bond and lacks a signal for an endocyclic double bond. The spectrum has a signal for a methine proton on C-3 as a broad singlet near 3.3 ppm in addition to singlets for methyls on double bonds near 1.73 ppm (CH_3-2) and 2.01 ppm (CH_3-8), signals for two thioisopropyls at 1.14 (d), 1.18 (d), 1.23 (d), and 1.30 (d) ($4CH_3$) and 2.93 (m) and 3.17 (m) (2H) ($J = 6.9$ Hz), and protons of an exocyclic double bond at 4.78 (s). In analogy to this, the signal for an equatorial methine proton was weakly split in the PMR spectrum of the addition product of dimethyldisulfide to (±)-limonene with a *trans*-diaxial sulfide [10]. Evidently, the principal stereoisomer is the adduct with a diaxial SR on C-3.

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1) Kazan′ State Medical University, 420012, Kazan′, ul. Butlerova, 49, e-mail: nikit@mi.ru; 2) Kazan′ State University.
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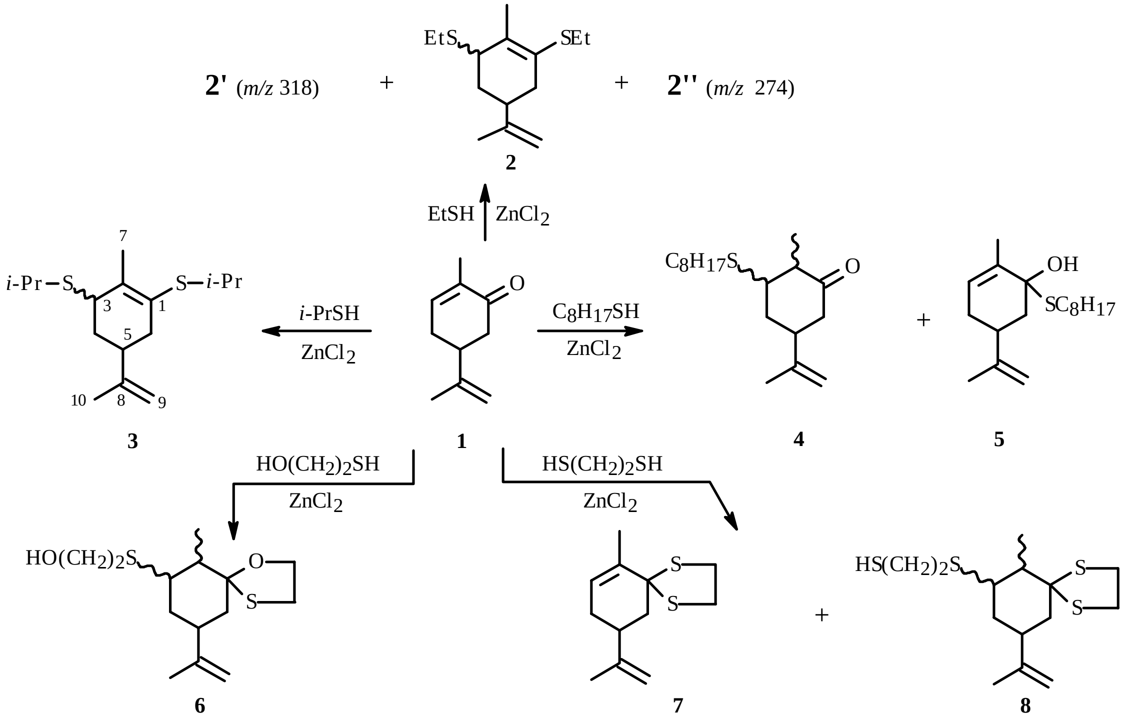

The reaction of (-)-carvone and ethanethiol formed **2**, **2′**, and **2″**. Column chromatography over silica gel isolated **2″** whereas **2** and **2′** were not separated. According to GCMS, products with *m*/*z* 256 (**2**), 318 (**2′**), and 274 (**2″**) were isolated in ratios of 9:4 [(**2** + **2′**):**2″**] and 3:1 (**2**:**2′**). According to spectral data (PMR, ^{13}C NMR, and IR), **2** has a structure analogous to that of **3**. Evidently, **2′** (*m*/*z* 318) is the product from reaction of a third EtSH molecule with one of the double bonds of **2**.

The minor product from the reaction of (-)-carvone and ethanethiol (**2″**) gives an IR spectrum with characteristic vibrations for hydroxyl (3200-3600 cm^{-1}) and ketone (1700 cm^{-1}); the GCMS, two pairs of peaks with similar retention times and *m*/*z* 274. Sulfide **2″** is probably a mixture of two regioisomers that form by addition of one of the ethanethiols to the endocyclic double bond whereas the second RSH adds to the carbonyl or the exocyclic double bond.

The products (**4** and **5**) of reacting (-)-carvone and octylmercaptan form a mixture of two regioisomers with *m*/*z* 296 that are formed by addition of thiol to either the endocyclic double bond (**4**) or the carbonyl (**5**) in a 1:1 ratio. The PMR spectrum of the mixture contains signals for endo (6.8, s) and exocyclic (4.78, m) double bonds. The signal for the methine proton on C-3 (for **4**) appears as a doublet of doublets near 3.3 ppm (J = 3.1, 8.6 Hz). This indicates that **4** exists primarily as the sterioisomer with an axial SR.

The ratio of stereoisomers for **2-4** was established using GCMS as 6:1 (**2**), 10:1 (**3**), and 10:1 (**4**) in favor of stereoisomers with an axial sulfide on C-3.

The PMR of the product (**6**) of reacting (-)-carvone and 2-mercaptoethanol contains a multiplet for protons of an exocyclic double bond near 4.6 ppm. Signals for each C atom in the ^{13}C NMR spectrum consist of three lines with similar chemical shifts. According to GCMS, the ratio of the three stereoisomers of **6** is 6:4:3. It can be assumed that **6** is a mixture of compounds with different positions for the functional groups (SR on C-3, CH_3 on C-2): *aa*, *ae*, and *ee*.

The product from reaction of (-)-carvone and ethanedithiol is a mixture of compounds (**7** and **8**) in ~6:1 ratio according to spectral data.

In summarizing the results for reactions of thiols and (-)-carvone with $ZnCl_2$ catalyst, it should be emphasized that various reaction pathways are possible. This is an effect of the actual thiol. In reactions with alkanethiols (ethanethiol, isopropylmercaptan), it is difficult to say exactly which group of (-)-carvone (carbonyl or endocyclic double bond) will add the thiol in the first step. Moreover, it can be confirmed that dehydration of the initially formed adduct occurs in the next step or else formation of the *bis*-sulfides (**2** and **3**) is impossible.

As the length of the carbon chain increases in octanethiol, the *bis*-sulfide is not formed. The reaction stops at formation of two single adducts at the carbonyl (**5**) or the double bond (**4**).

The structure of the principal product (**7**) from reaction of (-)-carvone and ethanedithiol is consistent with the reaction of thiol with carbonyl (with loss of water under acid-catalysis conditions) and then with the endocyclic double bond of the terpene. An analogous mechanism can be proposed for the reaction of (-)-carvone and 2-mercaptoethanol.

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ were measured on a Varian Unity spectrometer (300 and 75.43 MHz) with TMS internal standard. IR spectra were obtained from samples in mineral oil on a 75-IR spectrometer; mass spectra, in a Turbo Mass Gold (Perkin—Elmer) mass spectrometer using a capillary column, 30 m length, 320 μm diameter, and He flow rate 1.2 mL/min.

Synthesis of S-containing Derivatives of (-)-Carvone (2-8). (-)-Carvone (**1**, 0.02 mol) was treated at room temperature with stirring with the appropriate thiol (0.04 mol) in CH_2Cl_2 (30 mL) and $ZnCl_2$ in catalytic amounts. For **2-6**, the reaction was complete after 1-3 h; for **7** and **8**, after one week. After the reaction was complete, the reaction mixture was treated with water (200 mL). The products were extracted with CH_2Cl_2 and dried over $MgSO_4$. After solvent was removed, the adducts were purified using column chromatography over silica gel [petroleum ether (**2-5**), petroleum ether:diethylether (20:1, **6-8**)].

5-Isopropenyl-2-methyl-1,3-di(ethylthio)-cyclohex-1-ene (2). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.16-1.32 (m, 6H, $2CH_3$), 1.96 (s, 3H, H-10), 1.73 (s, 3H, H-7), 2.53 and 2.63 (both m, 4H, $2SCH_2$), 4.68 and 4.71 (both s, 2H, H-9).

^{13}C NMR spectrum (δ, ppm): 150 (C-8), 132, 129 (C-2,3), 110 (C-9), 50 (C-3), 38 (C-5), 34.5, 36.1 (C-11,13), 26, 27 (C-4,6), 22 (C-10), 20.5 (C-7), 15.9, 16.1 (C-12,14).

IR spectrum (ν, cm^{-1}): 890, 1650 ($>C=CH_2$).

Mass spectrum (m/z, I_{rel}, %): 256 (1) $[M]^+$, 195 (100), 167 (24), 153 (58), 139 (16), 133 (47), 125 (41), 117 (20), 111 (12) 105 (52), 91 (59), 77 (26), 65 (17), 59 (19), 53 (14), 47 (5).

5-Isopropenyl-2-methyl-3-octylthiocyclohex-1-ene (3). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.17, 1.26 (both m, 6H, $2CH_3$, J = 6.9), 1.73 (s, 3H, H-7), 2.01 (s, 3H, H-10), 2.93, 3.17 (both m, 2H, J = 6.9), 3.3 (s, 1H, H-3), 4.78 (s, 2H, H-9).

IR spectrum (ν, cm^{-1}): 890, 1650 ($>C=CH_2$).

Mass spectrum (m/z, I_{rel}, %): 284 (1) $[M]^+$, 209 (100), 181 (10), 167 (29), 151 (4), 139 (29), 133 (32), 125 (79), 105 (21), 91 (32), 77 (14), 59 (14), 43 (2).

5-Isopropenyl-2-methyl-3-octylthiocyclohexan-1-one (4) + 5-Isopropenyl-2-methyl-3-hydroxy-3-octylthiocyclohex-1-ene (5). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.8, 1.2 (both s, 6H, $2CH_3$), 1.68 (s, 3H, H-7), 1.0-1.6 (m, 28H, $14CH_2$), 2.0-2.9 (m, 4H, $2SCH_2$), 3.3 (dd, 1H, H-3, J = 3.1, 8.6), 4.78 (m, 4H, H-9), 6.8 (s, 1H, H-1).

IR spectrum (ν, cm^{-1}): 1700 ($>C=O$), 3200-3600 (OH).

Mass spectrum (m/z, I_{rel}, %): 296 (4) $[M]^+$, 225 (18), 184 (39), 149 (23), 127 (5), 113 (28), 109 (40), 97 (31), 93 (23), 81 (77), 67 (40), 55 (100).

2-Spiro[5′-(isopropenyl)-2′-methyl-3′-(2″-hydroxyethyl)thiocyclohexyl]-1,3-oxothiolane (6). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 108, 1.11, 1.15, 1.18 (all d, 3H, H-7, J = 7.7), 1.67 (s, 3H, H-10), 2.64, 2.86 (both m, 4H, $2SCH_2$), 3.60 (s, 2H, OCH_2), 3.80-4.30 (m, 2H, CH_2OH), 4.61 (br.s, 2H, H-9).

^{13}C DEPT NMR spectrum (75.43 MHz, $CDCl_3$): 148 (C-8), 110 (C-9), 71, 62 (C-12,14), 50, 38 (C-2,3,5), 46, 40 (C-11,13), 34, 31 (C-4,6), 22 (C-10), 14 (C-7).

Mass spectrum (m/z, I_{rel}, %): 288 (4) $[M]^+$, 243 (39), 228 (5), 211 (45), 183 (14), 151 (38), 133 (41), 109 (57), 93 (37), 81 (59), 67 (71), 55 (100).

2-Spiro[5′-(isopropenyl)-2′-methylcyclohexen-2′-yl]-1,3-dithiolane (7) + 2-Spiro[5′-(isopropenyl)-2′-methyl-3′-(2″-mercaptoethyl)thiocyclohexyl]-1,3-dithiolane (8). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.82, 0.86, 0.91 (**8**: all d, 3H, H-7, J = 6.9), 1.95 (**7**: s, 3H, H-7), 1.74 (s, 6H, H-10), 2.36, 2.71 (**8**: both m, 4H, SCH_2 + CH_2SH), 3.16-3.40 [m, 8H, $2(SCH_2)_2$], 4.73 (s, 4H, H-9), 5.29, 5.31 (**7**: both s, 1H, H-1).

^{13}C DEPT NMR spectrum (75.43 MHz, $CDCl_3$): 160, 150, 138, 123 [C-1,2 (**7**), C-8,9], 60.5-26.5 (**7**: C-3,4,5,6,7,10,11,12; **8**: C-1,2,3,4,5,6,7,10,11,12,13,14).

IR spectrum (ν, cm^{-1}): 890, 1650 ($>C=CH_2$), 790, 1670 ($>C=CH$).

Mass spectrum (**7**, *m*/*z*, I_{rel}, %): 226 (67) $[\mathrm{M}]^+$, 198 (9), 183 (8), 165 (67), 151 (40), 133 (100), 125 (18), 119 (26), 105 (64), 91 (79), 77 (40), 61 (41), 53 (27).

Mass spectrum (**8**, *m*/*z*, I_{rel}, %): 320 (4) $[\mathrm{M}]^+$, 292 (44), 259 (63), 227 (35), 199 (17), 171 (51), 133 (100), 105 (74), 91 (48), 79 (38), 67 (81), 61 (83), 55 (45), 47 (12).

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REFERENCES

1. C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, **44**, 713 (1979).
2. T. Mukaiyama, T. Izawa, and K. Saigo, *Chem. Lett.*, 355 (1973).
3. L. E. Nikitina, A. V. Pashagin, and V. V. Plemenkov, *Zh. Org. Khim.*, **34**, 525 (1998).
4. L. E. Nikitina, A. V. Pashagin, and V. V. Plemenkov, *Zh. Org. Khim.*, **29**, 1794 (1993).
5. V. A. Morgunova, L. E. Nikitina, and V. V. Plemenkov, *Zh. Org. Khim.*, **36**, 512 (2001).
6. P. J. Kraulis, *J. Appl. Crystallogr.*, **24**, 946 (1991).
7. H. Chen, F. Nan, and S. Shao, *Indian J. Chem., Sect. B*, **32**, 772 (1993).
8. A. Srikrishna and S. Gharpure, *Tetrahedron Lett.*, **40**, 1035 (1999).
9. A. Daniewski and L. Garofalo, *J. Org. Chem.*, **67**, 1580 (2002).
10. L. E. Nikitina, V. V. Plemenkov, R. A. Shaikhutdinov, and V. V. Klochkov, *Zh. Org. Khim.*, **32**, 1007 (1996).