NUCLEOPHILIC THIYLATION OF CARVONE

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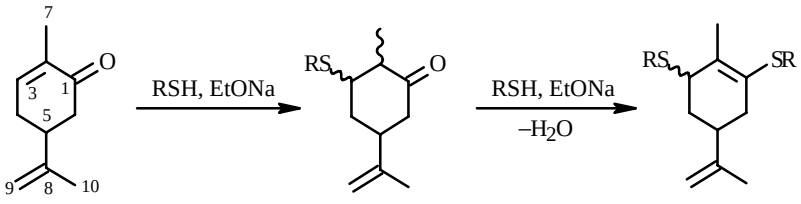
The reaction of carvone with 2-mercaptoethanol and an S-phenoxybenzylisothiuronium salt in the presence of sodium ethoxide was found to proceed exclusively at the endocyclic double bond. Under these same conditions, an S-allylisothiuronium salt reacted to produce a bis-sulfide with the menthene structure.

Key words: carvone, mercaptoethanol, isothiuronium salts.

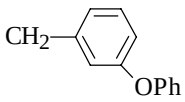
We reported previously reactions of carvone (**1**) with mono- and bifunctional thiols under Lewis-acid catalysis conditions that involve both the endocyclic double bond and the carbonyl [1]. Herein we report nucleophilic thiylation of carvone in the presence of sodium ethoxide.

The literature on the reaction of various nucleophiles with carvone teaches that nucleophilic attack can occur at the endocyclic double bond and the oxo group of the terpene [2-6].

Nucleophilic thiylation of carvone by 2-mercaptoethanol and isothiuronium salts of general formula $RSC(NH)NH_2 \cdot HX$ (R = $–CH_2–CH=CH_2$, $–C_6H_4$-*m*-O–C_6H_5, X = Br, Cl) were carried out in ethanol at 90°C in the presence of an excess of sodium ethoxide using a two-fold excess of thiol or isothiuronium salt. The products **2**-**4** were isolated by column chromatography over silica gel as oily liquids.



1 **2, 3** **4**

2: R = CH_2CH_2OH; **3:** R =  ; **4:** R = $CH_2CH=CH_2$

Our previous research indicated that the use of isothiuronium salts (ITS) as sulfiding agents of monoterpene oxides was promising although the terpenes themselves are unreactive [7-9]. Features of the carvone structure, namely the electron-accepting oxo group next to the endocyclic multiple bond, enabled us to carry out the nucleophilic thiylation on this momoterpenoid and for the first time prepare thiol adducts of it that are formed in situ from ITS in the presence of sodium ethoxide.

IR spectra of **2** and **3** contained characteristic absorption bands for carbonyl (1700 cm^{-1}) and exocyclic double bonds (1650, 890). The IR spectrum of **2** also contained stretching vibrations for hydroxyls (3560); that of **3**, characteristic aromatic C–C and C–H vibrations (695, 760, 1490, 1590).

According to GC—MS, **2** and **3** were addition products of one molecule of thiol to one molecule of carvone [*m*/*z* 228 (**2**), 366 (**3**)].

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The PMR spectra of **2** and **3** were practically identical except for regions in which protons of the SR groups resonated. A signal for protons of the exocyclic double bond (4.72 ppm, m) (values for **2** are given) and a doublet at 1.19 ppm (6.5 Hz) corresponding to the C-2 methyl protons indicated that the addition had taken place at the endocyclic double bond. The PMR spectrum of **2** also had two closely positioned triplets for the $-CH_2OH$ group at 3.69 and 3.84 ppm with identical SSCC (5.9 Hz) and a 2.5:1 ratio of integrated intensities. The ^{13}C NMR spectrum of **2** had the corresponding set of signals, in particular, at 210.3 ppm (C=O), 111.5 and 147.1 (>C=CH_2), 62.1 (OCH_2), and 46.9 (SCH_2). Each of these was two lines with similar chemical shifts.

The doubled number of lines for C atoms in the ^{13}C NMR spectrum of **2** and two peaks with *m*/*z* 366 in a 7:1 ratio in the GC—MS of **3** indicated that **2** and **3** were not pure compounds but mixtures of stereoisomers, the presence of which caused the features in the spectra of **2** and **3**.

The formation of stereoisomeric sulfides was due to the fact that the endocyclic double bond of carvone is diastereotopic, i.e., nucleophilic attack at the β-carbon atom of the conjugated system has the same probability of occurring on one side or the other but at different rates.

No conclusion about the spatial orientation of the SR group in the predominant stereoisomer can be made on the basis of existing spectral data because the signal of the corresponding proton (H-3) in PMR spectra of the products overlapped those of the methylene protons of the menthane framework or the sulfide moiety.

However, it has been reported that addition of thiols to the endocyclic double bond of carvone actually forms only two of the four theoretically possible stereoisomeric sulfides, the one with an axial sulfide and an equatorial methyl (with catalysis by sodium acetate) and the one with the diequatorial placement of both substituents (with triethylamine catalysis) [3].

Thus, it can be assumed that the C-2 methyl in stereoisomeric adducts **2** and **3** is equatorial and the SR in the principal stereoisomer is equatorial; in the minor one, axial.

The ^{13}C NMR spectrum of **4** prepared by reaction of carvone with allylmercaptan, which was formed *in situ* from an S-allylisothiuronium salt in basic medium, lacked a signal for a carbonyl carbon. It had signals for a C atom of an endocyclic double bond (124.1, 127.5 ppm) in addition to signals for C atoms of an exocyclic double bond (111.5, 145.6) and allyl double bonds (112.1, 125.5). The PMR contained two singlets for protons of methyls on double bonds (1.69, 1.71 ppm), two signals for protons of $-SCH_2$ groups (3.68, 3.70), and multiplets for eight protons of triple bonds at weak field (5.4-6.02).

The ^{13}C NMR and PMR spectra of **4** indicated that both the endocyclic double bond and the carbonyl group of carvone were involved in the reaction with allylmercaptan. A peak at *m*/*z* 278 in the GC—MS indicated that two thiols added to one terpene and one water molecule was lost to form a *bis*-sulfide menthene structure.

We have previously prepared menthene *bis*-sulfides similar to **4** in reactions of carvone with ethyl- and isopropylmercaptan in acidic medium. However, reactions with bifunctional thiols (2-mercaptoethanol, ethanedithiol) formed thiolanes [1].

The question of the lack of formation of the *bis*-adduct in the reaction of carvone with 2-mercaptoethanol remains unanswered. The lack of the *bis*-adduct in the reaction with phenoxybenzylmercaptan in the presence of sodium ethoxide is apparently explained by steric factors that affect the reactions of this bulky nucleophile with other terpenoids, as we have previously noted [10].

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ were measured on a Varian Unity spectrometer (400, 300, and 75.43 MHz) with TMS internal standard. IR spectra were obtained for samples in mineral oil on a 75-IR spectrometer; mass spectra, in a Turbo Mass Gold (Perkin—Elmer) with a capillary column 30 m in length and 320 μm in diameter with ν_{He} = 1.2 mL/min. (-)-Carvone (Fluka), $[\alpha]_D^{20}$ -61.5 ± 2° was used. Isothiuronium salts were prepared by the literature method [11].

Synthesis of *S*-containing Carvone Derivatives (2-4). Sodium ethoxide was prepared from Na (1.5 g, 0.065 mol) and ethanol (50 mL) in a flask equipped with a reflux condenser and a $CaCl_2$ tube. The solution was stirred and treated with mercaptoethanol (0.016 mol) (or the corresponding isothiuronium salt, 0.016 mol) and carvone (0.008 mol), stirred at 90°C until the reaction was complete, diluted with water, and extracted with ether. The combined ether extracts were washed with saturated NH_4Cl solution, with water until neutral, and dried over $MgSO_4$. Ether was removed. The products were purified by column chromatography over silica gel [PE:DE, 1:1 (**2**, **4**); PE:DE, 10:1 (**3**)]. Yields were calculated after isolation by column chromatography over silica gel.

2-Methyl-5-isopropenyl-3-(2′-hydroxyethylthio)cyclohexanone (2). Yield 58%. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19 (3H, d, J = 6.5, H-7), 1.70 (3H, s, H-10), 2.26 (5H, m, H-4, H-5, H-6), 2.78 (3H, m, SCH_2, H-3), 3.69 (2H, t, J = 5.9, CH_2OH), 3.84 (2H, t, J = 5.9, CH_2OH), 4.72 (2H, m, H-9).

^{13}C NMR spectrum (75.43 MHz, $CDCl_3$, δ, ppm): 210.3 (C-1), 111.5, 147.1 (C-8, C-9), 62.1 (CH_2OH), 46.9 (SCH_2), 44.8-13.1 (C-2—C-7,10).

Mass spectrum (*m*/*z*, I_{rel}, %): 228 (1) $[M]^+$, 183 (15), 150 (10), 109 (30), 107 (26.25), 97 (31), 81 (42), 67 (42), 55 (100), 41 (50).

2-Methyl-5-isopropenyl-3-(3′-phenoxybenzylthio)cyclohexanone (3). Yield 51%. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.23 (3H, d, J = 6.6, H-7), 1.75 (3H, s, H-10), 3.3-3.5 (3H, m, H-3, SCH_2), 4.77 (2H, m, H-9), 7.20 (9H, m, $C_6H_4OC_6H_5$).

Mass spectrum (*m*/*z*, I_{rel}, %): 366 (20) $[M]^+$, 216 (18), 184 (32), 183 (100), 150 (25), 107 (9), 93 (19), 82 (7), 81 (10), 77 (18), 67 (13), 55 (30).

2-Methyl-5-isopropenyl-1,3-*bis*-(allylthio)cyclohex-1-ene (4). Yield 55%. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.69 (3H, s, H-10), 1.71 (3H, s, H-7), 3.68, 3.70 (4H, each s, $2SCH_2$), 4.78 (2H, m, H-9), 5.41, 5.89 (6H, each m, $2CH=CH_2$).

^{13}C NMR spectrum (75.43 MHz, $CDCl_3$): 145.6, 111.5 (C-8, C-9), 127.5, 124.1 (C-1, C-2), 112.1, 125.5 (C-12,13,15,16), 48.1, 46.2 (C-11,14), 40.3-16.2 (C-3—C-7,10).

Mass spectrum (*m*/*z*, I_{rel}, %): 278 (2) $[M]^+$, 263 (1), 167 (22), 150 (10), 139 (19), 121 (19), 107 (27), 97 (40), 7 (48), 67 (33), 55 (30), 41 (100), 29 (30).

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