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NEW THIOTERPENOIDS BASED ON CARVONE

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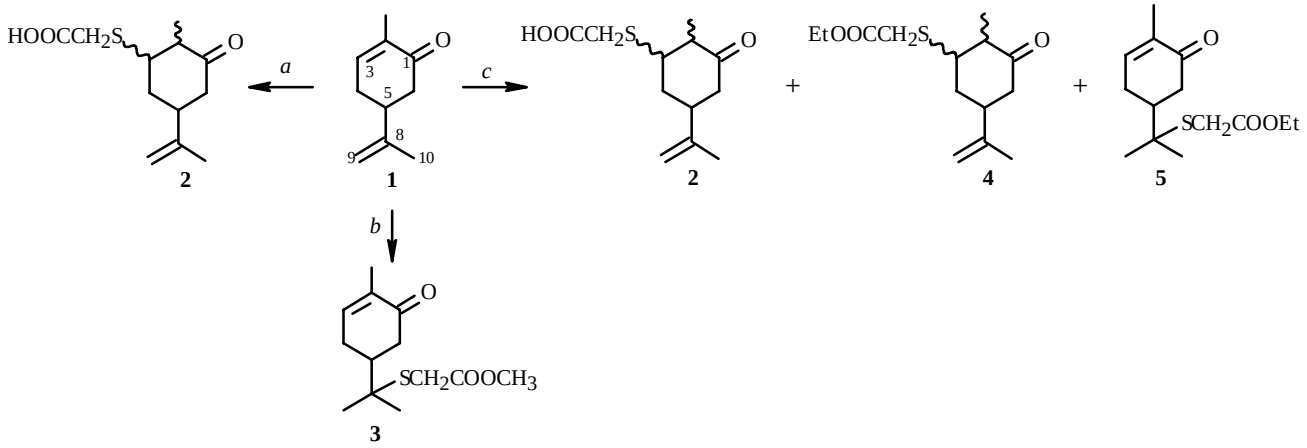
Reactions of carvone with mercaptoacetic acid and its esters in the presence of $ZnCl_2$ were studied. New menthane-type thioterpenoids were produced.

Key words: carvone, thiols, $ZnCl_2$ catalysis, thioterpenoids.

In continuation of research on the addition of thiols to monoterpenes under acid-catalysis conditions [1-3], we studied the reaction of optically active (-)-carvone with mercaptoacetic acid and its esters in the presence of $ZnCl_2$.

We have previously reported on catalytic addition of mono- and bifunctional thiols to carvone in the presence of $ZnCl_2$ and the dependence of the reaction pathways on the thiol structure. All reactions involved the endocyclic double bond and the carbonyl [4]. It is also known that carvone reacts with mercaptoacetic acid with heating without a catalyst to form an inseparable mixture of addition products at the exo- and endocyclic double bonds [5].

The reaction of carvone (**1**) with mercaptoacetic acid was carried out at room temperature in CH_2Cl_2 in the presence of a two-fold excess of mercaptan and catalytic amounts of $ZnCl_2$. The reaction formed a single product **2**, which was isolated as an oily liquid using column chromatography over silica gel. Spectral data indicated that **2** had the structure 2-methyl-3-carboxymethylthio-5-methyl(ethenyl)cyclohexanone.



a. $HSCH_2COOH$, $ZnCl_2$, CH_2Cl_2; *b*. $HSCH_2COOCH_3$, $ZnCl_2$, CH_2Cl_2 ; *c*. $HSCH_2COOH$, EtOH, $ZnCl_2$

The IR spectrum of **2** contained characteristic absorption bands for carbonyl (1700 cm^{-1}) and hydroxyl (3500). GC—MS data were consistent with the addition to carvone of one molecule of mercaptoactic acid (*m*/*z* 242).

The ^{13}C NMR spectrum of **2** had signals for carbonyl C atoms (210.1 ppm), carboxyl (176.0), and an exocyclic double bond (112.0, 146.2). The PMR spectrum of **2** exhibited signals for protons of an exocyclic double bond (4.74), a multiplet for the SCH_2 protons (3.17-3.38), and a singlet for the carboxylic proton at 11.4 ppm in addition to signals for protons of the menthane framework.

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A feature of the PMR spectrum of **2** was the shape of the signal for the protons of the C-2 methyl group, which appeared as two doublets of identical intensity at 1.10 and 1.17 ppm (overall intensity of 3H) with the same SSCC (J = 6.9 Hz). The duplicity of the CH_3 signals was explained by splitting by the methine proton (H-2); the doubling of the number of lines, to the existence of acid **2** as a mixture of diastereomers with the 2*R*,3*S*- and 2*S*,3*R*-configurations in a nearly 1:1 ratio.

Carvone was reacted with methylmercaptoacetate under conditions analogous to the reaction of mercaptoacetic acid in CH_2Cl_2. According to GC—MS, the product with *m*/*z* 256 that was isolated using column chromatography over silica gel was a mixture of three isomers in a 5:1:1 ratio.

The ^{13}C NMR spectrum of the three isomers contained signals for C atoms of endo- (120, 131 ppm) and exocyclic bonds (115, 146), three CH_3O groups (55, 56, 57), $-SCH_2-$ (41, 42, 44), and menthane framework C atoms (17-32 ppm).

According to PMR spectroscopy, the predominant isomer was the addition product of methylmercaptoacetate to the exocyclic double bond of carvone (**3**).

The PMR spectrum of the mixture of isomers of **3** contained signals from protons of an endocyclic double bond (6.6 s) and a methyl group on a double bond (1.6 ppm), singlets for hydroxymethyl protons (3.55) and a thiomethylene group (3.2), and a 6H singlet at 1.1 ppm from two CH_3 groups on C-8.

These spectral data lead to the conclusion that the minor isomers are addition products of methylmercaptoacetate to the endocyclic bond of carvone, i.e., stereoisomers of the methyl ester of acid **2**.

The reaction of carvone with mercaptoacetic acid was also performed using ethanol as solvent because we previously demonstrated for reactions with other terpenes in ethanol that esterification of mercaptoacetic carboxylic acid and addition to the double bond of the terpene are possible [6].

Based on GC—MS data, we established that carvone reacts with mercaptoacetic acid in ethanol (in the presence of $ZnCl_2$) to form **2**, **4**, and **5** in a 4:5:1 ratio. Column chromatography over silica gel isolated pure **2** whereas **4** and **5** were characterized as a mixture of isomers.

The PMR spectrum of the mixture of isomers **4** and **5** exhibited signals for protons of multiple bonds (4.7 m and 6.6 s), thiomethylene groups (3.02-3.62 m), multiplets of $-OCH_2-$ groups (4.0 ppm), and two triplets corresponding to CH_3 protons of the oxyethyl fragment (1.16).

Apparently mercaptoacetic acid forms in the first reaction step an addition product involving the endocyclic double bond of **2**, after which most of **2** in an excess of alcohol is esterified to form sulfide **4** and only about 10% of the mercaptoacetic acid is esterified to form ethylmercaptoacetate, which as a result attacks the carvone exocyclic double bond.

Thus, mercaptoacetic acid reacts with carvone in the presence of $ZnCl_2$ catalyst to form sulfides at the endocyclic double bond whereas the primary site of attack of mercaptoacetic acid esters is the sterically more accessible exocyclic bond.

EXPERIMENTAL

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

Synthesis of Carvone Derivatives Containing S (2-5). Carvone (**1**, 0.02 mol) at room temperature was stirred, treated with the appropriate thiol (0.04 mol) in CH_2Cl_2 (30 mL) and $ZnCl_2$ (catalytic amounts). The completion of the reaction was judged by the disappearance of carvone from the reaction mixture according to TLC. After the reaction was finished, water (200 mL) was added to the flask. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. Solvent was removed. Adducts were isolated using column chromatography over silica gel.

2-Methyl-3-carboxymethylthio-5-(methylethenyl)cyclohexanone (2). Yield 58%. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.10, 1.17 (each 3H, d, J = 6.9, H-7), 1.70 (3H, s, H-10), 3.17-3.38 (2H, m, SCH_2), 4.74(2H, m, H-9), 11.40 (1H, s, COOH). IR spectrum (ν, cm^{-1}): 1700 (>C=O), 3500 (OH).

^{13}C NMR spectrum (75.43 MHz, $CDCl_3$, δ, ppm): 210.1 (C-1), 176.0 (C-12), 146.2 (C-8), 112.0 (C-9), 54.5-15.0 (C-2,3,4,5,6,7,10,11).

Mass spectrum (*m*/*z*, I_{rel}, %): 242 (1) $[M]^+$, 224 (0.2), 183 (59), 149 (15), 127 (4), 111 (13), 109 (38), 107 (26), 97 (46), 81 (37), 67 (43), 55 (100), 53 (26), 47 (8).

Methyl((1-oxo-2,8,8-trimethylcyclohexen-3-yl)-8-methylthio)ethanoate (3). Yield 55%. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.1(6H, s, H-9,10), 1.6 (3H, s, H-7), 3.1 (2H, s, $SC\underline{H}_2$), 3.55 (3H, s, $OC\underline{H}_3$), 6.6 (1H, s, H-3).

^{13}C DEPT NMR spectrum (75.43 MHz, $CDCl_3$): 210.1 (C=O), 171.2 ($\underline{C}OCH_3$), 146.1 (C-8), 131.0 (C-2), 120.0 (C-3), 114.8 (C-9), 55.0, 54.5, 54.0 (OCH_3), 39.5, 39.0, 38.5 (SCH_2). Mass spectrum (*m*/*z*, I_{rel}, %): 256 (1) $[M]^+$, 150 (17), 135 (14), 115 (26), 109 (65), 108 (100), 95 (28), 87 (32), 81 (18), 75 (26), 67 (12), 53 (17).

Ethyl((1-oxo-2,8,8-trimethylcyclohexen-3-yl)-2-methylthio)ethanoate (4) + Ethyl((1-oxo-2,8,8-trimethyl-cyclohexen-3-yl)-8-methylthio)ethanoate (5). Yield 41% (yield of **2**, 16%). PMR spectrum (**4** + **5**) (300 MHz, $CDCl_3$, δ, ppm): 1.16 (6H, m, 2 $OCH_2C\underline{H}_3$), 3.02-3.62 (4H, m, 2 SCH_2), 4.00 (4H, m, 2 $OC\underline{H}_2CH_3$), 4.64 (**4**:2H, m, H-9), 6.6 (**5**:1H, s, H-3).

Mass spectrum (**4**) (*m*/*z*, I_{rel}, %): 270 (1) $[M]^+$, 225 (5), 197 (6), 183 (2), 150 (31), 135 (12), 121 (41), 109 (100), 81 (20), 67 (13), 53 (25), 41 (30).

Mass spectrum (**5**) (*m*/*z*, I_{rel}, %): 270 (3) $[M]^+$, 227 (0.5), 197 (4), 183 (2), 150 (100), 135 (28), 122 (17), 107 (63), 93 (74), 81 (27), 67 (32), 55 (51), 41 (32).

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