SYNTHESIS OF SULFIDE DERIVATIVES OF THE CARANE SERIES BY REACTIONS OF 3-CARENE OXIDES WITH FUNCTIONAL MERCAPTANS

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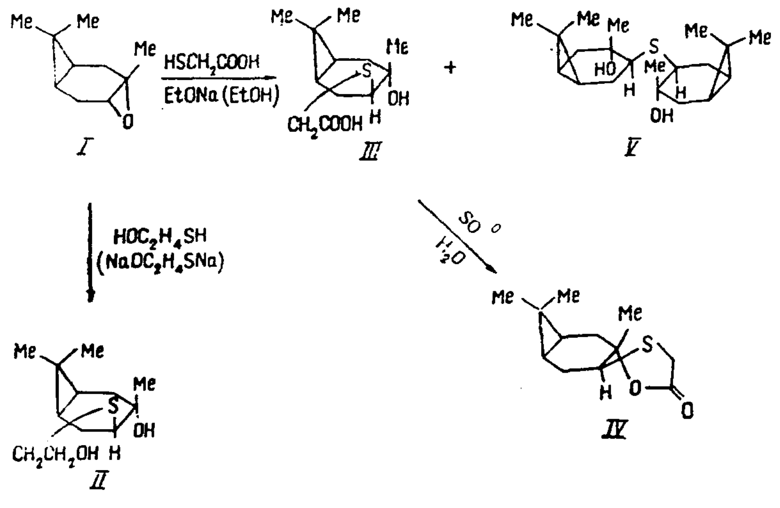
The reaction of 3-carene oxides with functional mercaptans under the conditions of basic catalysis takes place regio- and stereoselectively and is a convenient method of obtaining polyfunctional derivatives of 3-carene and the products of their chemical transformations (hydroxyethvlthiocaranols, carboxyalkylthiocarenols, carane thiolactones). Together with the products mentioned, a new type of bicyclic, terpenes — bis-hvdroxvcaranvl) sulfides — is formed in th3ese reactions.

The high level of monoterpene hydrocarbons, includign 3-carene, in the oleoresins of coniferous plants of the family Pinaceae [1], and also existing information [2] on the possibility of synthesizing biologically active compounds from them has led to the necessity for developing new pathways for the rational utilization of a widely available natural raw material.

We have previously shown the possibility of the S-alkylation of trans-3,4-epoxycarane (I) with alkanethiols under the conditions of basic catalysis [3]. Continuing the development of regio- and stereoselective methods of synthesizing new derivatives of the cerane series with presumed biological activity [4], we have studied the reaction of the isomeric 3,4-epoxycaranes (I and VI) with bifunctional nucleophiles in the presence of bases.



Scheme 1

We have investigated the interaction of the 3-carene oxides (I and VI) with mercaptoethanol (schemes 1 and 2). It must be mentioned that, in contrast to alkanethiols [3], the reaction with mercaptoethanol took place fairly readily and, in the case of the α-oxide (I), went to completion on heating (80°C), while in the case of the β-oxide (VI) it did so at room temperature, forming individual compounds in each case, according to PMR and TLC — the isomeric 4-hvdroxyethvlthiocaran-3-ols (II and VII). The structures of the adducts (II and VII) were

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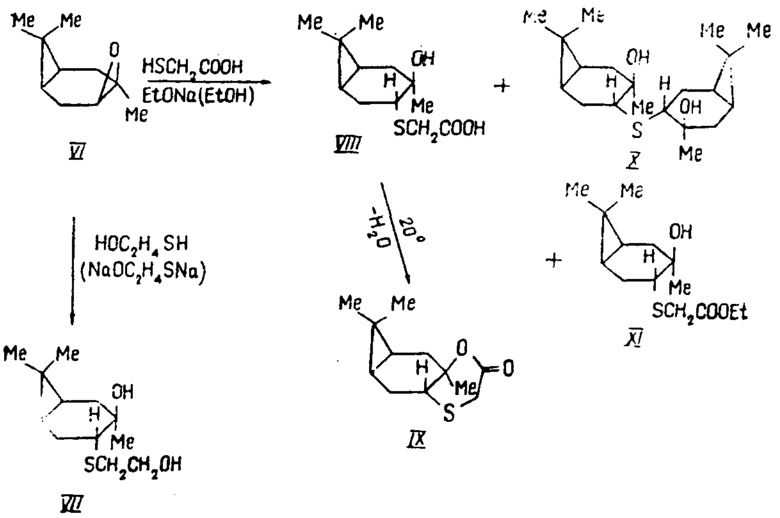
confirmed by PMR results (Table 1) and IR spectroscopy. The presence in the IR spectra of compounds (II and VII) of strong absorption bands of the stretching vibrations of a primary C–O bond (1045-1060 cm^{-1}) showed the presence of a primary alcohol group and the selective nature of the opening of the epoxides (I and VI) with the formation of a sulfide bond. The direction and stereochemistry of the opening of the oxirane ring were assumed to be in agreemetn with the results of previous wrok [3, 5].

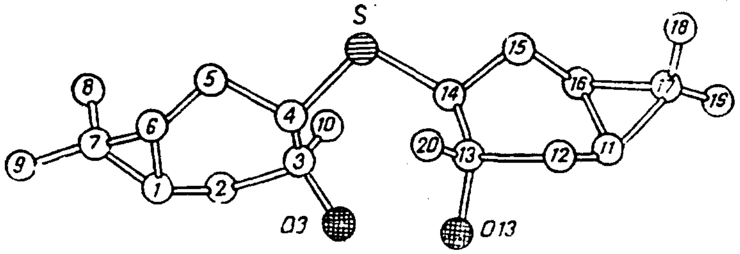


Scheme 2

In view of a report [4] on the biological activity of derivatives of thioalkanoic acids, the study of the reactions of the 3-carene oxides (I) and (VI) with mercaptoacetic acid appear to us to be of interest. As shown in schemes 1 and 2, the interaction of the 3,4-epoxycaranes (I) and (VI) with mercaptoacetic acid in the presence of an excess of sodium ethanolate led in both cases to a mixture of addition products. Thus, as the result of the reaction of α-3,4-epoxycarane (I) with the above-mentioned reagent (III) and (V) were isolated in a ratio of 2.5:1. The analogous reaction of the β-epoxide (VI) led to compounds (VIII), (IX), (X), and (XI) in a ratio of 4.5:1:1:0.5, respectively.

On the basis of their spectral characteristics, we assigned the structures of the isomeric hydroxycaranylthioacetic acids (III) and (VIII) to the predominating reaction products. The PMR spectra (see Table 1) of compounds (III and VIII) had the signals of the protons of all the structural fragments in the expected regions, a signal of the protons of the hydroxy and carboxy groups being observed in the form of a two-proton singlet at 7.83 ppm. We found that, at room temperature, the hydroxycaranylthioacetic acid (VIII) changed spontaneously into the corresponding carnae thiolactone (IX). It was possible to achieve the analogous conversion of (III) into the lactone (IV) by heat (90°C). The structures of (IV) and (IX) were confirmed by PMR and IR spectroscopies.

The results of a comparison of the PMR spectra (Table 1) of the hydroxycaranylthioacetic acids (III and VIII) and the corresponding carane thiolactones (IV and IX) showed an appreciable downfield shift of the signals of the protons at C-10 in the PMR spectra of the cyclization products (IV and IX), which is probably connected with the close position of the carbonyl group.



Structure of the bis (3α-hydroxy-4β-caranyl) sulfide molecule (V). Hydrogen atoms are not shown.

TABLE 1. PMR Spectra of Compounds (II-V and VII-XI), δ, ppm

Compound	2H-1,6	6H-8,9	3H-10	1H-4	S—R	OH
II	0,74 m	0,96s, 1,05s	1,20 s		2,66 t, 3,70 t (SCH_2CH_2)	4,26 s
III	0,80 m	0,96s, 1,03s	1,23 s	2 90 m	3,43 m (SCH_2)	7,83 s
IV	0,75 m	1,03s, 1,10s	1,56 s	3,05 dd (J=10 Hz, J=4 Hz)	3,41 d (SCH_2)	
V	0,75 m	0,96s, 1,00s	1,12 s	2,60 dd (J=10 Hz J=5 Hz)		2,00 s
VII	0 80 m	1,00s, 1,03 s	1,20 s		2,70t, 3,66 t (SCH_2CH_2)	3,36 s
VIII	0,75 m	1,16 br.s	1,36 s	2,65m	3,40 s (SCH_2)	7,83 s
IX	0,70 m	1,00s, 1,06s	1,59 s	2,65 dd (J=12 Hz, J=7 Hz)	3,23 d (SCH_2)	
X	0,75 m	1,00s, 1,03s	1,13 s	2,00 дд (J=12 Hz, J=8 Hz)		2,30 s
XI	0,75 m	1,06s, 1,10 s	1 30 s	2,66 m	1,33 t. 3,40 d. 4,23 q (SCH_2COOEt)	3,70 s

TABLE 2. Coordinates of Nonhydrogen Atoms Molecular Bonds

Atom	x	y	z	Atom	x	y	z
S	—0.0064(2)	0.8756(2)	0,32546(6)	C9	0,3051(7)	0,2406(8)	0,2976(3)
O3	0,1154(4)	0,7383(4)	0,4427(2)	C10	0,3099(7)	0,8694(8)	0,3738(3)
O13	—0,1201(4)	0,8288(4)	0,4748(2)	C11	—0,2108(7)	1.1457(6)	0,4703(3)
C1	0,2663(7)	0,4640(7)	0,3516(3)	C12	—0,2894(7)	1,0135(7)	0,4488(3)
C2	0,3335(7)	0,6057(7)	0,3802(3)	C13	—0,1824(6)	0,8456(7)	0,4257(2)
C3	0,2247(6)	0,7337(6)	0,3857(2)	C14	—0,0640(6)	0,9676(6)	0,3902(2)
C4	0.0882(6)	0,7119(6)	0,3492(2)	C15	—0,0969(6)	1,1229(8)	0,3732(3)
C5	0,1221(6)	0,6261(7)	0,2946(2)	C16	—0,1048(7)	1.2090(7)	0,4279(3)
C6	0,1546(6)	0,4739(7)	0,3125(3)	C17	—0.2411(8)	1,2949(7)	0,4450(3)
C7	0.3050(7)	0,4024(7)	0,3032(3)	C18	—0,3662(8)	1,3231(8)	0,4052(3)
C8	0,4142(8)	0,4686(8)	0,2648(3)	C19	—0.2085(9)	1,4171(8)	0,4843(4)
				C20	—0,2777(6)	0,7852(8)	0,3938(3)

As follows from schemes 1 and 2, the reactions of both epoxides (I and VI) were accompanied by the formation of small amounts of isomeric bis(hydroxycaranyl) sulfides (V and X), the structures of which were established from the results of the PMR and IR spectroscopies. The bis(hydroxycaranyl) sulfide structure of compound (V) and, consequently, the stereochemistry of the addition of the reagent to the 3-carene oxides (I and VI) and were shown by x-ray structural analysis (Fig. 1). It was established that the bicyclic fragments of the molecule (V) has a skew anti-boat conformation with torsional angles of −32 and −17° along the C3—C4 and C13—C14 bonds, respectively. In the crystal, the molecules of compound (V) are linked into infinite chains with the aid of the intramolecular hydrogen bonds O3—H(O3)···O13' (x + 1/2, y + 3/2, z + 1) with the parameters O3—H(O3) 1.028 Å, H(O3)···O13' 1.18 Å, <O3—H(O3)···O13' 171.5°. A O13—H(O13)···O3 hydrogen bond is also formed, with the parameters O13—H(O13) 1.030 Å, H(O13)···O3 1.86 Å, <O13—H(O13)··· 160.2°.

Thus, the results of x-ray structural analysis confirmed the bis(hydroxycaranyl) sulfide structure of compound (V) in which the hydroxylic functions of the two terpene moieties are located in the trans position to the sulfide group.

On the basis of spectral characteristics (Table 1), the minor product (XI) was ascribed the structure of ethyl 3β-hydroxycaran-4α-ylthioacetate.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-467 spectrometer wtih a working frequency of 60 MHz. TMS was used as the internal standard and CCl_4 as the solvent. IR spectra were recorded on a Specord 75-IR spectrometer in a thin layer or in paraffin oil. $[\alpha]_D$ values were measured on a Polamat A instrument. The products of synthesis were separated by column chromatography on silica gel L 100/160 μ (Czechoslovakia) with hexane—ether as the eluent. Thin-layer chromatography was conducted on Silufol UV-254 plates with detection by the action of a mixture of anisaldehvde, ethanol, and sulfuric acid (5:90:5) followed by heating at 70-80°C.

X-Ray Structural Analysis of Compound (V). The crystals of compound (V) were rhombic; at 20°C, a = 9.129(3), b = 9.287(2), c = 23,607(7) Å, z = 4 d_{calc} = 1.124 g/cm³, space group $P2_12_12_1$. The cell parameters and the intensities of 1393 reflections with $F^2 \geq 5\sigma$ were measured on an automatic ENRAF-NONIUS CAD-4 K-diffractometer (λ MoK_α, graphite monochromator, ω/2θ scanning, $\theta \leq 25°$). The structure was interpreted by the direct method using the MULTAN program and was refined in the isotropic approximation. The hydrogen atoms were revealed from a difference series and were not refined in the concluding stage. In order to establish the absolute configuration, the refinement was made of the "direct" and "inverted" structures with allowance for corrections for anomalous scattering of the nonhydrogen atoms. The divergence factors for the "direct" structure were $R = 0.04725$ and $R_w = 0.05951$, and for the "inverted" structure $R = 0.04765$ and $R_w = 0.6007$. According to Hamilton's test [6], the "direct" structure corresponds to the absolute structure with a probability exceeding 95%. The final values of the divergence factors were $R = 0.042$ and $R_w = 0.057$. All the calculations were made on a PDP 11/23 computer by the SDP programs. The coordinates of the nonhydrogen atoms of compound (V) are given in Table 2.

α-3,4-Epoxycarane (I) was obtained by the procedure described in [7]; bp 75-80°C (10 mm), $[\alpha]_D + 14.2°$, n_D^{20} 1.4660. β-3,4-Epoxycarane (VI) was obtained in accordance with [8]; b.p. 69-70°C (10 mm), $[\alpha]_D - 1.5°$, n_D^{20} 1.4680.

4-Hydroxyethylthiocaran-3-ols (II and VII). With stirring at 20°C, 1 g (0.066 mole) of a 3-carene oxide (I) or (VI) was added dropwise to a solution of the disodium salt of thioethanol obtained from 0.3 g (0.013 g-atom) of Na and 3.1 g (0.039 mole) of 2-mercaptoethanol. Then the reaction mixture was stirred until the reaction was complete: in the case of α-3,4-epoxycarane (I) at 90°C for 5 h, adn in the case of β-3,4-epoxycarane (VI) at room temperature for 7 h, and in the case of β-3,4-epoxycarane (VI) at room temperature for 7 h, after which the mixture was diluted with water and was extracted wtih ether. The combined extracts were washed with saturated NH_4Cl solution and with water and were dried over Na_2SO_4. The solvent was distilled off and the residue was chromatographed on a column with hexane—ether (1:3) as eluent. The yield of compound (II) was 51.6%, R_f 0.22; the yield of the crystalline sulfide (VII) was 82.7%, mp 79-80°C. IR spectrum (cm^{-1}): 1045-1060 (primary C—O), 3320-3350 (OH). Calculated, %: C 62.61; H 9.56; S 13.91. $C_{12}H_{22}O_2S$. Found, %: C 62.77; H 9.51; S 13.91 (II); C 62.59; H 9.76; S 14.23 (VII).

3α-Hydroxycaran-4β-ylthioacetic acid (III) and Bis(3α-hydroxycaran-4β-yl) Sulfide (V). To a solution of the disodium derivative of mercaptoacetic acid obtained from 1.80 g (0.0195 mole) of $HSCH_2COOH$ and EtONa (0.049 g-atom of Na + 20 ml of absolute EtOH) were added 2.97 g (0.0195 mole) of the 3-carene oxide (I) and 8 ml of DMSO. The reaction mixture was stirred at 80°C for 100 h and was then diluted with water, acidified with 3% HCl solution to pH 3, and extracted with ether. The combined ethereal extracts were washed with water and dried with Na_2SO_4. After elimination of the solvent, the residue was chromatographed on a column with elution by hexane—ether mixtures in which the concentration of the latter increased from 10 to 100%. The yield of compound (III) was 16%, R_f 0.39 (hexane—ether (1:5)); the yield of (VII) was 9%, mp 124-125°C. IR spectrum of compound (III) (cm^{-1}): 1710-1720, 2500-2700 (COOH); 3450 (OH). IR spectrum of compound (V) (cm^{-1}): 3400 (OH). Calculated, %: C 59.01; H 8.19; S 13.11. $C_{12}H_{20}O_3S$. Found, %: C 58.66; H 8.10; S 13.18 (III). Calculated, %: C 71.00; H 10.05; S 9.46; $C_{20}H_{34}O_2S$. Found, %: C 71.36; H 10.62; S 9.41 (V).

Lactone of 3α-Hydroxycaran-4β-ylthioacetic Acid (IV). When 0.8 g (0.0033 mole) of 3α-hydroxycaran-4β-ylthioacetic acid (III) was heated at 90°C for 8 h and the proudcts were subjected to column chromatography on silica gel (with hexane—ether (1:1) as the eluent), the lactone (IV) was isolated, with R_f 0.55 (hexane—ether (1:5)), yield 20.5%. IR spectrum (cm^{-1}): 1720 (C=O), 1230-1250 (C—O—C), Calculated, %: C 63.75; H 7.96; S 14.11. $C_{12}H_{18}O_2S$. Found, %: C 63.31; H 8.39; S 14.56.

3β-Hydroxycaran-4α-ylthioacetic Acid (VIII), the Lactone of 3β-Hydroxycaran-4α-ylthioacetic Acid (IX), Bis(3β-hydroxycaran-4α-yl) Sulfide (X), and Ethyl 3β-Hydroxycaran-4α-ylthioacetate (XI). To a solution of the disodium derivative of mercaptoacetic acid obtained from 1.21 (0.013 mole) of $HSCH_2COOH$ and EtONa (0.022 g-atom of Na + 10 ml of absolute EtOH) were added 2 g (0.013 mole) of the 3-carene oxide (VI) and 3 ml of DMSO. The reaction mixture was stirred at 80°C for 39 h and was then diluted with water, acidified with 3% HCl solution to pH 3, and extracted with ether. The combined ethereal extracts were washed with water and dried with Na_2SO_4. The solvent was distilled off and the residue was chromatographed on a column with, as eluent, hexane—ether mixtures in which the concentration of the latter rose from 10 to 100%. The yield of compound (VIII) was 40.6%; that of the lactone (IX) 8.6%, mp 105-106°C; that of product (X), 9% 92-93°C; and that of compound (XI) 4.5%, IR spectrum (cm^{-1}): 1230-1280 (C—O—C), 1710-1725 (C=O), 2500-2700 (OH(COOH)), 3400-3600 (OH). Calculated, %: C 63.75; H 7.96; S 14.11, $C_{12}H_{18}O_2S$. Found, %: C 63.58; 8.57; S 14.47 (IX). Calculated, %: C 71.00; H 10.05; S 9.46. $C_{20}H_{34}O_2S$. Found %: C 71.24; H 10.19; S 9.71 (X). Calculated %: C 61.76; H 8.82; S 11.76. $C_{14}H_{24}O_3S$. Found %: C 62.22; H 8.73; S 11.63 (XI).

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POSSIBLE CONFORMATIONS OF THE SEVEN-MEMBERED RINGS AND RELATIVE STABILITIES OF 1β,5α,6β,7α(H)- AND 1α,5α,6β,7α(H)-GUAI-11(13)-EN-6,12-OLIDES

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A calculation has been made by the method of molecular mechanics, using the MM2 program, of a number of stereomeres of 1β,5α,6β,7α(H)- and 1α,5α,6β,7α(H)-guai-il(13)-en-6,12-olides. The possibilities of the adoption by the seven-membered ring of particular conformations according to the type of its linkage with the 5-membered carbocycle have been considered. Questions of the influence of the orientation of the Me groups on the degree of distortion of the conformation of the seven-membered ring from the ideal and the relative stabilities of the various conformers are discussed.

We have previously reported on the analysis by the method of molecular mechanics (MMM) of the spatial structures and conformations of 6,7- and 7.8-linked eudesmanolides [1, 2]. Continuing conformational studies of sesquiterpene lactones, in the present paper we give the results of a MMM calculation for some trans,trans- and cis,trans-linked nonlinear guaianolides with the aim of elucidating the possibility of the realization of particular conformations of their seven-membered carbocycles and relative stabilities of these conformers for different (α or β) orientations of the methyl groups at the C4 and C10 atoms.

For calculation we selected eight model compounds (I-VIII) with different configurations of the chiral centers – the C1, C4, and C10 atoms – and the trans-linkage of rings B and C.

The choice of just these compounds as models was due to the fact that nonlinear guaianolides with such types of skeletons are found most frequently in nature [3, 4].

A preliminary consideration of the conformations of the molecules (I-VIII) using Dreiding molecular models showed that the seven-membered ring B in the molecules (I-IV), having the trans-linkage of rings A/B can assume four chair (C) conformations: 7α,1,10β-C (a), 9,10α,6β-C (b), 5α,8,9β-C (c), and 7,8α-1β-C (d). In the molecules (V-VIII), having the cis-linkage of rings A/B, ring B can assume three chair conformations: 1,5α,8β-C (e), 5α,8,9β-C (f), and 7,8α,1β-C (g) and three boat (B) conformations: 1,7,8α-B (h), 6,9,10β-B (i), and 5,6,9β-B (j).

After optimization of the geometry of the four initial idealized conformers a-d of molecules (I-IV) (Table 1) it was found that only three conformers of (I) were stable: conformer a is only slightly distorted relative to the ideal transition into form IA; ($\Delta C_s^7 =$ and

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