Chemistry of Natural Compounds, Vol. 29, No. 5, 1993

SYNTHESIS OF CARANOIDS WITH TWO SULFIDE FUNCTIONS FROM 3-CARENE α- AND β-SULFIDES

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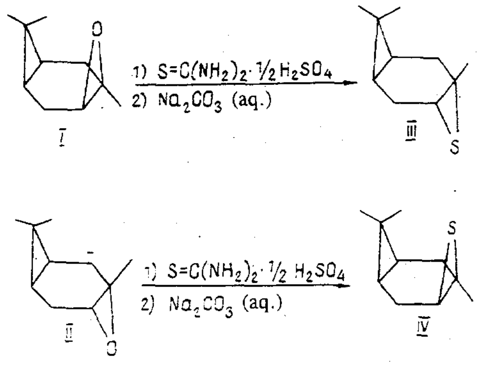
UDC 547.597.1

A convenient method has been developed for obtaining 3-carene α- and β-sulfides from which isomeric 4-RS-carane-3-thiols have been obtained by the nucleophilic addition of thiols under the conditions of base catalysis. The S-alkylation of the latter has formed the corresponding 4-RS-3-R'S-caranes. A high degree of regio- and stereoselectivity of the reactions studied has been found.

Investigations in the field of the synthesis of sulfur-containing terpene derivatives and the study of their chemical properties form one of the promising directions in the chemistry of natural compounds. Furthermore, terpene derivatives containing sulfur and, in particular, terpene thiols are scarcely found in nature [1, 2] and are one of the least studied classes of terpene compounds. It is known that thioterpenoids possess a number of interesting practical properties (they can be used as components of perfume substances and in the synthesis of drugs and pesticides) [3, 4], while having low toxicity. At the same time, the synthetic approach to this class of terpenoids and, in particular, to sulfur-containing derivatives of the carane series, is problematical, as is shown by the small number of relevant publications [5, 6].

In order to broaden the methods of obtaining terpene sulfides of the carane series and to find new effective routes to the synthesis of potentially useful substances, we have developed a convenient method of passing from 3-carene β- and α-oxides (I, II) to the isomeric α- and β-3,4-epithiocaranes (III, IV). An investigation of the possibility of synthesizing trans- and cis-sulfides of 3-carene (III, IV) by the reactions of 3-carene β- and α-oxides (I, II) with alkali-metal thiocyanates [7] and with thiourea in the presence of titanium isopropanolate in atropic solvents [8] did not lead to the desired results. In a study of the reactions of 3-carene oxides (I and II) with thiourea sulfate followed by the treatment of the isothiuronium salts with a solution of sodium carbonate, however, the isomeric α- and β-3,4-epithiocaranes (III and IV) were obtained (by analogy with the procedure of [9]). The spectral (PMR) characteristics and physicochemical constants (boiling points and n_D^{20} values) of compounds (III, IV) agreed completely with those described in the literature [10] and corresponded to a reaction scheme including the trans-opening of the oxiran ring with the formation of the trans-epithiocarane (III) from the cis-epoxide (I) and of cis-epithiocarane (IV) from thae trans-epoxide (II).



The trans- and cis-3,4-epithiocaranes (III, IV) that we had obtained were then studied in nucleophilic reactions with thiols (CH_3SH, C_2H_5SH, iso-C_3H_7SH, n-C_4H_9SH, C_6H_5SH, and prenyl-SH) under the conditions of acid and base catalysis. It was found that performing the reactions in the presence of Lewis acids (BF_3, $ZnCl_2$) led to their rapid occurrence but led

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S. V. Kurshov Kazan' State Medical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 677-684, September-October, 1993. Original article submitted April 20, 1993.

0009-3130/93/2905-0600$12.50

TABLE 1. PMR Spectra of Compounds (V-XXIII) (δ, ppm)

Compound	2H-1; 6	6H-8; 9	3H-10	SR	SH (SR')
V	0.5—0.7	0.93 s	1.26 s	1.93 s (CH_3)	2.23.
VI	0.6—0.9	1.13 s, 1.16 s	1.33 s	1.47 t, 2.60 q (C_2H_5)	2.26
VII	0.5—0.7	0.96 s	1.30 s	1.20 d (^3J=6.0 Hz), 2.60 m (iso-C_3H_7)	2.0
VIII	0.6—0.8	1.03 s	1.40 s	1.40—2.7 (n-C_4H_9)	2.20
IX	0.6—0.8	1.07 s	1.43 s	2.20 s (CH_3)	2.26
X	0.6—0.8	1.07 s	1.33 s	1.43 t, 2.61 q (C_2H_5)	2.46
XI	0.5—0.7	0.93 s, 1.0 s	1.27 s	1.10 d (^3J=6.0 Hz), 1.20 d (^3J=6.0 Hz), 2.86 m (iso-C_3H_7)	2.33
XII	0.6—0.8	1.07 s	1.40 s	1.4—2.63 (n-C_4H_9)	2.40
XIII	0.6—0.8	1.03 s	1.43 s	7.10 m (C_6H_5)	2.10
XIV	0.6—0.8	0.93 s, 1.0 s	1.33 s	1.70 s, 1.73 s, 3.20 d (^3J=8.7 Hz), 4.93 t (^3J=8.7 Hz), (Prenyl)	2.36
XV	0.6—0.8	1.0 s	1.23 s	1.70 s, 1.73 s, 3.0 d (^3J=8.7 Hz), 3.20 d (^3J=8.7 Hz), 4.90 t (^3J=8.7 Hz), (Prenyl)	—
XVI	0.6—0.7	0.95 s, 0.98 s	1.27 s	2.01 s (CH_3)	2.12 s (CH_3)
XVII	0.5—07	0.93 s	1.20 s	1.30 t, 2.47 q (C_2H_5)	1.90 s (CH_3)
XVIII	0.5—0.6	0.96 s, 0.98 s	1.19 s	1.07 t, 2.50 q (C_2H_5)	1.11 t, 2.50 q (C_2H_5)
XIX	0.6—0.8	1.03 s	1.23 s	1.36 t, 2.60 q (C_2H_5)	1.33 d (^3J=6.0 Hz), 2.93 m (iso-C_3H_7)
XX	0.6—08	1.03 s	1.20 s	1.30 t, 2.60 q (C_2H_5)	1.70 s, 1.73 s, 3.10 d (^3J=8.7 Hz), 5.0 t (^3J=8.7 Hz), (Prenyl)
XXI	0.5—07	1.06 s	1.33 s	1.20 d (^3J=6.0 Hz), 3.0 m (iso-C_3H_7)	1.33 t, 2.50 q (C_2H_5)
XXII	0.6—0.8	1.10 s	1.20 s	1.33 t, 2.53 q (C_2H_5)	2.03 s (CH_3)
XXIII	0.6—0.8	1.06 s	1.26 s	1.40 t, 2.53 q (C_2H_5)	1.20 d (^3J=6.0 Hz), 2.96 m (iso-C_3H_7)

to a very complex mixture of products. The use as catalysts of the corresponding sodium thiolates (in the reactions with C_2H_5SH, iso-C_7H_5SH, and n-C_4H_9SH) or sodium ethanolate (in the reactions with CH_3SH, C_6H_5SH, and prenyl-SH) the reactions took place with the formation of the products of addition to the thiirane ring. The interaction of the thiiranes (III and IV) with the alkyl mercaptans (R = CH_3, C_2H_5, iso-C_3H_7, and n-C_4H_9 (at room temperature in the presence of RSNa (or EtONa) and DMSO led to the formation of the individual products (V-XII) with good yields. The structures of the compounds (V-XII) were established with the aid of IR and ^1H and ^{13}C NMR spectroscopies and by the performance of "independent" synthesis, and their compositions were confirmed by the results of elementary analysis. The PMR spectra of the aducts (V-XII) contained the signals of the protons of a cyclopropane ring (0.5-0.8 ppm), of the gem-dimethyl fragment at C^7 (0.93-1.13 ppm), of the methyl group at C^3 (1.26-1.43 pm) of the proton of the sulfhydryl group (2.00-2.46 ppm), and the signals of the protons of the sulfide functions (1.43-2.86 ppm). The IR spectra of all the products (V-XII) contained bands characteristic for for the vibrations of the hydrocarbon fragments, including the cyclopropane fragments $\nu_{(CH)}$ 3000-3020 cm^{-1}) and of the bond of the sulfhydryl group ($\nu_{(SH)}$ 2550-2570 cm^{-1}).

TABLE 2. Physicochemical Constants of Compound (V-XXIII)

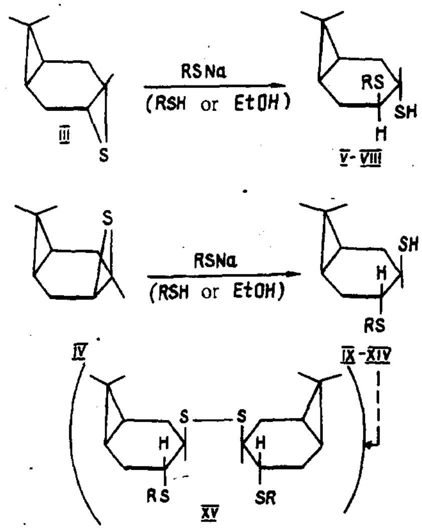
Compound	Empirical formula	T. bp, °C (mm Hg); mp °C *	n_D^{20}	$[\alpha]_D$, deg	R_f in hexane—ether (30:1)	Yield, %
V	$C_{11}H_{20}S_2$	—	1.5184	+69.79	0.47	60
VI	$C_{12}H_{22}S_2$	—	1.4308	+64.0	0.43	73
VII	$C_{13}H_{24}S_2$	—	1.4331	+16.07	0.41	21
VIII	$C_{14}H_{26}S_2$	—	1.4961	+67.3	0.47	40
IX	$C_{11}H_{20}S_2$	—	1.5176	-88.38	0.54	47
X	$C_{12}H_{22}S_2$	—	1.5214	-55.7	0.52	75
XI	$C_{13}H_{24}S_2$	—	1.4329	-49.05	0.41	73
XII	$C_{14}H_{26}S_2$	—	1.5192	-72.62	0.52	40
XIII	$C_{16}H_{22}S_2$	113—114*	—	—	0.43	40
XIV	$C_{15}H_{26}S_2$	—	—	—	0.14	42
XV	$C_{30}H_{50}S_4$	—	—	—	0.1	36
XVI	$C_{12}H_{22}S_2$	83(2)	1.5382	—	0.4	76
XVII	$C_{13}H_{24}S_2$	120(2)	1.5207	—	0.26	71
XVIII	$C_{14}H_{26}S_2$	90(2)	1.5251	—	0.4	71
XIX	$C_{15}H_{28}S_2$	122(2)	1.4319	-74.66	0.32	76
XX	$C_{17}H_{28}S_2$	—	1.4972	—	0.32	94
XXI	$C_{15}H_{28}S_2$	125(2)	1.5182	-79.05	0.32	63
XXII	$C_{13}H_{24}S_2$	115(2)	1.5165	—	0.3	76
XXIII	$C_{15}H_{28}S_2$	—	1.4300	—	0.29	42

In an attempt to establish the regiodirectivity of the process we measured the ^{13}C NMR spectrum of compound (V). The nuclei of the carbon atom connected with the sulfhydride function and the carbon atom connected with the SC_2H_5 group resonated in the 49.59-56.09 ppm region, while when the "off-resonance" spectrum was recorded, a contraction of the singlet nature of the signal of one carbon atom (49.59 ppm) and an expansion into a doublet of the other signal (56.09 ppm) was observed, which showed the presence of the SH and the SC_2H_5 groups at tertiary and secondary atoms. However, this was insufficient to determine at precisely which carbon atom the SH was present (C^3 or C^4) and at which the SC_2H_5 group (C^4 or C^3).

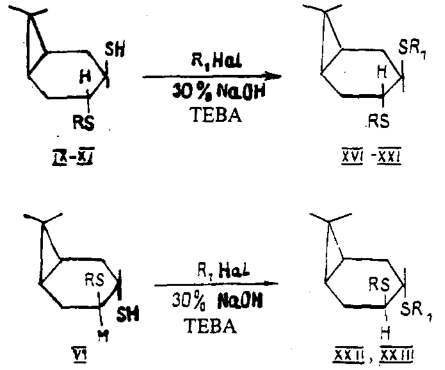
The direction and stereochemistry of the opening of the thiirane ring in the reactions of the isomeric 3-carene sulfides (III, IV) with mercaptans were determined with the aid of the "independent" synthesis of 3β,4α-di(methylthio)carane, which has been obtained [11] by the electrophilic addition of dimethyl disulfide to 3-carene in the presence of catalytic amounts of zinc chloride. The structure of this compound was shown by the authors concerned [11] with the aid of x-ray structural analysis of the oxidized form 3β,4α-di(methylthio)carane disulfone. The product of the interaction of 3-carene β-sulfide (IV) with methyl mercaptan (IX) was treated with methyl iodide in the presence of alkali and a phase-transfer catalyst and led to 3,4-di(methylthio)carane, identical according to its physicochemical constants and spectral characteristics with the 3β,4α-di(methylthio) carane described in [11]. Thus, it may be concluded that the reactions of the isomeric α- and β-3,4-epithiocaranes (III, IV) with alkanethiols under the conditions of base catalysis proceed with the formation of the products of trans-addition (V-XII) according to Krasuskii's rule (nucleophilic attack of the least substituted carbon atom) — 4-alkylthiocarane-3-thiols.

The reactions of of the isomeric 3-carene α- and β-sulfides (III, IV) with thiophenol took place in the presence of EtONa and DMSO. The reaction of β-3,4-epithiocarane (IV) with PhSH was conducted at room temperature and led to the formation of the addition product (XIV), the structure of which was determined from the results of IR and PMR spectroscopies and elementary analysis. The PMR spectrum of compound (XIII) contained the signals of the protons of the carane fragment

(Table 1), of the protons of a sulfhydryl group (2.10 ppm), and of the protons of a benzene ring (7.10 ppm). The IR spectrum of adduct (XIII) had the characteristic absorption band in the 2560 cm^{-1} region that corresponds to the stretching vibrations of a sulfhydryl group. The 3-carene trans-sulfide (III) did not form an addition product with thiophenol (even at an elevated temperature and with a long reaction time), obviously because of the steric hindrance to the approach of the SPh group from the side of the gem-dimethylcyclopropane fragment.



R = CH_3(V, IX), C_2H_5 (VI, X), iso-C_3H_7 (VII, XI), n-C_4H_9 (VIII, XII, C_6H_5 (XIII), Prenyl (XIV, XV).



XVI. R=CH_3, R′=CH_3
XVII. R=C_2H_5, R′=CH_3
XVIII. R=C_2H_5, R′=C_2H_5
XIX. R=C_2H_5, R′= iso-C_3H_7
XX. R=C_2H_5, R′= Prenyl
XXI. R= iso-C_3H_7, R′=C_2H_5
XXII. R=C_2H_5, R′=CH_3
XXIII. R=C_2H_5, R′= iso-C_3H_7

The reaction of β-3,4-epithiocarane (IV) with prenyl mercaptan under the conditions of base catalysis (in the presence of EtONa) led to the formation of two products (according to TLC), (XIV) and (XV), with good yields, and these were isolated by column chromatography on silica gel in a ratio of 1:2, respectively. The structures of compounds (IV) and (V) were established from the results of IR and PMR spectroscopies and elementary analysis. The PMR spectrum of adduct (XIV) contained the signals of the protons of the carane fragment and of the gem-dimethyl group of the prenyl fragment at the C=C bond (1.70, 1,73 ppm) and the signals of the protons of the sulfhydryl group (2.36 ppm), of the methylene group of the prenyl fragment (3.20 ppm), and of an olefinic proton (4.93 ppm). The IR spectrum of product (XIV) contained characteristic absorption bands of the stretching vibrations of a sulfhydryl group ($\nu_{(SH)}$ 2560 cm^{-1} and of the double bond of a prenyl group ($\nu_{(C=C)}$ 1670 cm^{-1}). On the basis of the totality of the results of IR and PMR spectroscopy, compound (XIV) was assigned the structure of 4α-prenylthiocarane-3β-thiol.

The PMR spectra of the second product (XV) of the reaction of prenyl mercaptan with 3-carene β-sulfide (IV)) was characterized by the presence of the signals of the protons of the carane and prenyl fragments, as in the case of the first product (XIV) and by the absence of a signal from the proton from a sulfhydryl group. There was no band of the characteristic vibrations of the bond of a sulfhydryl group in the IR spectrum of this substance either. A comparison of the spectral characteristics, and also the results of elementary analysis, which corresponded to the empirical formuula $C_{30}H_{50}S_4$ permitted the conclusion that in the reaction of 3-carene β-sulfide (IV) with prenyl mercaptan, in addition to the "normal" addition product, a disulfide with the structure (XV) had been formed.

Thus, it was found that the reactions of 3-carene α- and β-sulfides (III, IV) with mercaptans is a convenient synthetic route to the corresponding carane derivatives of sulfide and sulfhydryl functions which, in their turn, can be synthons for carane derivatives with two different sulfide groups. The S-alkylation of the carane thiols (VI, IX-XI) under alkaline conditions by alkyl halides led to the corresponding isomeric 4-RS-3R'S-carane derivatives (XVI-XXIII). The structures (XVI-XXIII) were confirmed by PMR spectroscopy (Table 1) and elementary analysis.

It must be mentioned that the S-alkylation reactions of the carane thiols with structures (VI, IX-XI) that have been studied permit bifunctional sulfides with controlled regio- and stereoisomerism having a wide range of SR groups to be obtained.

EXPERIMENTAL

The PMR spectra of compounds (V-XXIII) were measured in CCl_4 solution on a Tesla BS-457 (60 MHz) spectrometer and a Bruker WM-250 spectrometer with a resonance frequency for ^{13}C nuclei of 62.9 MHz, using HMDS as internal standard. Refractive indices n_D^{20} were measured on a IRF-454 BM refractometer, and α_D values on a Polarmat A instrument. IR spectra were recorded in CCl_4 solutions on a UR-20 spectrometer. The melting point of compound (XIII) was determined on a Kofler instrument. The results of the elementary analysis of compounds (V-XXIII) corresponded to the calculated figures.

β-3,4-Epoxycarane (I) was obtained by the procedure described in [12], with bp 69-70°C (10 mm Hg), $[\alpha]_D{}^{20}$ — 1.5°, $n_D{}^{20}$ 1.4680. α-3,4-Epoxycarane (II) was obtained by the procedure of [13], with bp 75-80°C (10 mm Hg), $[\alpha]_D{}^{20}$ + 14.2°, $n_D{}^{20}$ 1.4660.

Synthesis of α- and β-3,4-Epithiocaranes (III, IV). To a solution of 3 ml (0.1 equiv.) of H_2SO_4 in 35 ml of water was added 8.0 g (0.1 mole) of thiourea. With stirring, 16.0 g (0.1 mole) of β- or α-3,4-epoxycarane (I or II) was added dropwise over 1.5-2 h to the reaction mixture at 0-5°C. After the end of addition, the temperature of the bath was raised to 60-70°C, and 10.6 g (0.1 mole) of Na_2CO_3 in 50 ml of water was added to the reaction mixture. The resulting oil was separated off, and the aqueous solution was extracted with ether (4 × 50 ml), dried with Na_2SO_4, and distilled in vacuum. The yield of compound (III) was 12.9 g (73.6%), bp 40-41°C (0.1 mm Hg), $n_D{}^{20}$ 1.5175. The yield of compound (IV) was 11.0 g (62.3%), bp 37-39°C (0.1mm Hg), $n_D{}^{20}$ 1.5151.

Synthesis of the 4-Alkylthiocarane-3-thiols (VI-VIII) and (X-XII). With stirring, 0.0089 mole of a 3-carene sulfide (III) or (IV) and 2 ml of DMSO were added to a solution of the sodium thiolate obtained from 0.0086 g-atom of Na and 0.089 mole of a mercaptan (C_2H_5SH, iso-C_3H_7SH or n-C_4N_9SH). The reaction mixture was stirred at room temperature for 9-15 h, after which the mixture was diluted with 100 ml of water and was extracted with ether (5 × 50 ml), and the ethereal extract was washed with NH_4Cl and dried with Na_2SO_4. Compounds (VI-VIII), (X-XII) were isolated by column chromatography on silica gel (with hexane as the eluent). The yields of adducts were: (VI) — 1.0 g (73%), (VII) 0.3 g (20.6%), (VIII) — 0.9 g (40%), (X) — 1.5 g (75%), (XI) — 1.6 (73.4%), (XII) — 0.9 g (40%).

Synthesis of the 4-Methylthiocarane-3-thiols (V and IX). With stirring 2.0 g (0.212 mole) of a 3-carene sulfide (III) or (IV) and 2 ml of DMSO were added to a solution of the sodium ethanolate obtained from 0.3 g (0.013 g-atom) of Na and 20 ml of absolute ethanol. Over 0.5 h, 0.208 mole of CH_3SH was passed through the reaction mixture, and this was stirred at room temperature for 4-8 h and was then diluted with water (100 ml) and extracted with ether (5 × 50 ml), and the extract was washed with NH_4Cl and dried with Na_2SO_4. The product was isolated by chromatography on silica gel (with hexane as eluent). The yield of compound (V) was 0.8 g (31.7%), and that of compound (IX) 1.2 g (46.7%).

Synthesis of 4α-Phenylthiocarane-3β-thiol (XIII). With stirring at room temperature, 1.68 g (1.015 mole) of PhSH, 2.0 g (0.012 mole) of 3-carene sulfide (IV), and 2 ml of DMSO were added to a solution of sodium ethanolate obtained from 0.28 g (0.012 g-atom) of Na and 10 ml of absolute ethanol. After being stirred at room temperature for 40 h, the reaction mixture was diluted with 100 ml of water and extracted with ether (5 × 50 ml), and the extract was washed with NH_4Cl and dried with Na_2SO_4. Compound (XIII) was isolated by column chromatography on silica gel (with hexane as eluent) and was additionally purified by recrystallization from acetone. The yield of compound (XIII) was 1.32 g (40%).

Synthesis of Compounds (XIV) and (XV). With stirring at room temperature, 2.44 g (0.024 mole) of prenyl mercaptan 2.0 g (0.021 mole) of β-3,4-epithiocarane (IV) and 2 ml of DMSO were added to solution of sodium ethanolate obtained from 0.28 g (0.012 g-atom) of Na and 10 ml of absolute ethanol. The reaction mixture was stirred at room temperature for 15 h, after which it was diluted with water (100 ml) and extracted with ether (5 × 50 ml), and the extract was washed with NH_4Cl and dried with Na_2SO_4. Compounds (XIV) and (XV) were separated by column chromatography on silica gel (with hexane as eluent). The yield of compound (XIV) was 1.16 g (42%) and that of compound (XV) 2.32 g (36%).

Synthesis of Compounds (XVI)-(XXIII). To 1 ml of a 30% aqueous solution of NaOH was added 0.005 mole of compound (VI), (IX), (X), or (XI) in 5 ml of ether and 0.1 g of TEBA. Wih vigorous stirring at room temperature, 0.01 mole of R'Hal (CH_3I, C_2H_5I, iso-C_3H_7Br, or prenyl-Cl) was added. After being stirred at room temperature for 1 h, the reaction mixture was poured into water (100 ml) and was repeatedly extracted with ether, and the extract was washed with NH_4Cl and dried with Na_2SO_4. Compounds (XVI-XXIII) were isolated by column chromatography on silica gel (with hexane as eluent). Yields of products: (XVI) — 0.8 g (75%), (XVII) — 0.75 g (70.8%), (XVIII) — 0.8 g (71.4%), (XIX) — 0.9 g (76.3%), (XX) — 1.2 g (93.7%), (XXI) — 0.7 g (63%), (XXII) — 0.8 g (75.5%), (XXIII) — 0.5 g (42.4%).

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