REACTIONS AFFECTING THE γ-LACTONE RING OF α-SANTONIN

S. M. Adekenov and N. M. Gafurov

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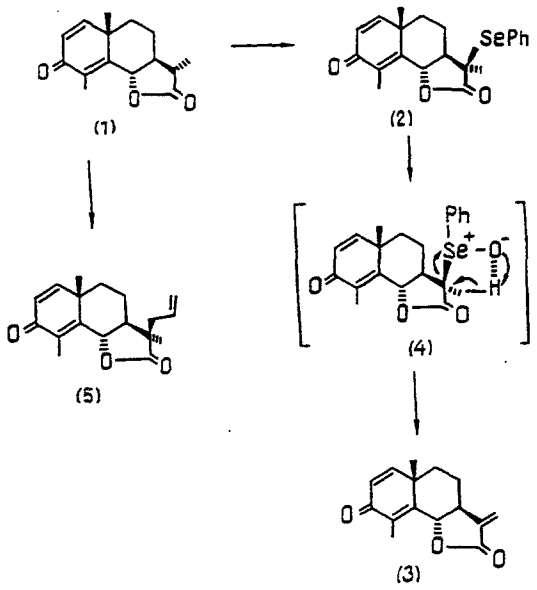
The selective dehydrogenation of the eudesmanolide α-santonin and its alkylation with the introduction of an allyl fragment into its γ-lactone ring are described. It has been established that these reactions are regio- and stereoselective. The structures of the compounds obtained were determined from their IR, UV, PMR, and mass spectra.

From its type of carbon skeleton, α-santonin (1) belongs to the eudesmanolides, in which the six-membered rings of the basic carbon skeleton are trans-condensed. The nature of the attachment of the lactone ring shows that α-santonin belongs to the nonlinear eudesmanolides with a saturated trans-γ-lactone ring in the C6—C7 position.

The presence of such types of biological activity as anthelminthic, cytotoxic, and growth-regulating for the α-santonin molecule (1) is connected with the presence of a cyclohexadiene fragment in the structure of this compound [1-3]. Chemical transformations of α-santonin have been mainly connected with this fragment of the molecule [4, 5].

Another reaction center in the α-santonin molecule is the α-carbon atom of the γ-lactone ring. In view of its potential possibility as a biologically active center, we have studied selective dehydrogenation reactions with the aim of obtaining molecules with an exomethylene group conjugated with the carbonyl of the γ-lactone system.



As the dehydrogenating agent we selected diphenyl diselenide [6, 7]. Dehydrogenation was carried out in two main stages (scheme). In the first stage, on the interaction of α-santonin (1) with lithium diisopropylamide (LDA) and then of the resulting enolate ion with diphenyl diselenide, derivative (2) was obtained in the form of a colorless crystalline substance with mp 193-195°C, $[\alpha]_D^{20}$ −60°C. Its yield amounted to 34%. The IR spectrum of (2) characterized the presence of an aromatic ring in its molecule (1530, 1480, 1450 cm^{-1}). This was confirmed by its PMR spectrum (Table 1) where the signals of the protons of an aromatic residue were observed: a multiplet (5 H) with its center at 7.36 ppm.

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TABLE 1. Chemical Shifts (ppm) and Spin-Spin Coupling Constants (in parentheses, Hz) for α-Santonin and Its Derivatives

Compound No.	Me-4	Me-10	Me-11	H-1	H-2	H-6	H-13a	H-13b	Other protons
1	2,15 br.s	1,33 s	1,28 d (6,5)	6,70 d (10)	6,28 d (10)	4,80 br.d (11)	—	—	—
2	2,12 d (1)	1,30 s	1,58 s	6,65 d (10)	6,23 d (10)	5,19 br.d (9)	—	—	Aromatic ring 7,36 m (5H)
3	2,17 br.s	1,32 s	—	6,71 d (10)	6,28 d (10)	4,73 br.d (11)	5,57 d (3)	6,24 d (3)	—
5	2,15 br.s	1,30 s	1,25 s	6,70 d (10)	6,26 d (10)	5,05 br.d (10)	—	—	H-17: 5,85 m 2H-18: 5,19—5,22

Notes: s) Singlet; d) doublet; m) multiplet; br.) broadened.

In addition there were the signals of the protons of a methyl group at C11 in the form of a singlet shifted downfield by 0.3 ppm in comparison with that of α-santonin (1) through the influence of the geminal phenyl selenide residue. This fragment also exerted an effective descreening action on the proton at C6 (β-oriented lactone proton), shifting its PMR signal downfield by 0.39 ppm in comparison with that of molecule (1). A similar shift may take place when these two fragments have the cis- orientation, i.e., when the phenyl selenide residue has the β-conformation. Thus, according to the spectral characteristics found, compound (2) had the structure of 3-oxo-11β-phenylselenoeudesma-1,4-dien-6,12-olide.

In the following stage, by treating the phenylseleno derivative (2) with a 30% solution of hydrogen peroxide we obtained the colorless crystalline substance (3) with mp 145-147°C, $[\alpha]_D^{18}$ −10.4° (c 1.12; chloroform). The yield of (3) amounted to 80%, calculated on compound (2).

The PMR spectrum of (3) – in contrast to those of santonin (1) and derivative (2) – showed the signals of methylene protons in the form of doublets at 5.57 and 6.24 ppm (each 1 H with an SSCC of 3 Hz), which are characteristic for an exomethylene group at C11 (see Table 1). The presence of a conjugated α-methylene-γ-lactone fragment in the structure of compound (3) was also confirmed by a maximum in the UV spectrum at 230 nm (E 10017). The results obtained permitted us to propose for (3) the structure of 3-oxoeudesma-1,4,11-(13)-trien-6,12-olide.

The mechanism of the formation of the dehydro derivative (3) from (2) is shown in the scheme. As can be seen, in the oxidation of (2) by hydrogen peroxide the phenyl selenide oxide (4) is formed, the cleavage of which leads to derivative (3). The cleavage reaction is stereospecific and takes place as a syn-elimination in accordance with the Hofmann rule, forming an exomethylene group at C11.

In order to obtain an allyl derivative of α-santonin (1) at the C11 atom, its molecule was treated with LDA in THF at −78°C, and allyl bromide was added to the resulting enolate ion. This gave a crystalline substance (5), with mp 142-144°C $[\alpha]_D^{21.5}$ −25.2° (c. 0.0023; chloroform), yield 52%. The IR spectrum of (5) showed the presence in its molecule of a γ-lactone carbonyl (1790 cm^{-1}) and of a cyclodienone system (1680, 1650, 1630 cm^{-1}). Its elementary composition corresponded to the empirical formula $C_{18}H_{23}O_3$. Its PMR spectrum (see Table 1) included the signals of the protons of the methyl group at C11 in the form of a singlet at 1.25 ppm and additional signals characteristic of the protons of the allyl fragment: a multiplet at 5.85 ppm (1 H) was assigned to H17, and a broadened singlet at 5.19 ppm (1 H) and a broadened doublet at 5.22 ppm (1 H, SSCC 4 Hz) were characteristic for the protons of the methylene group, H18a and H18b. To determine the relative configuration of the allyl residue of the (5) molecule, we made use of the nuclear Overhauser effect (NOE). When the signal of the protons of the angular methyl group at C10 (1.30 ppm) was suppressed, positive nuclear Overhauser effects were observed for the protons at C2 (6.70 ppm) and C6 (5.05 ppm). Suppression of the signal of the protons of the methyl group at C11 (1.25 ppm) revealed H7 (1.95 ppm) in the form of a triplet of doublets with SSCCs of 11.5 and 5.5 Hz and also the signals of the protons of the methylene group of the allyl residue, thus showing the axial positions of the protons at C6, C7, and C8 in this molecule (5).

Consequently, compound (5) had the structure of 11β-allyl-3-oxoeudesma-1,4-dien-6,12-olide.

EXPERIMENTAL

For column chromatography we used silica gel (100-160 μm) of type LL (Chemapol), the ratio of the total material to the support being 1:30, and the eluent hexane with increasing concentrations (from 0 to 100%) of ethyl acetate. The individuality of the compounds was checked by thin-layer chromatography (TLC) on Silufol plates. The chromatograms were visualized with a saturated solution of $KMnO_4$.

PMR spectra were taken on a Bruker WP-200 SY (100.13 MHz) instrument for solutions in $CDCl_3$, the chemical shifts being given in ppm (δ scale) relative to TMS, and SSCCs in Hz. IR spectra were taken on a UR-20 instrument for solutions of the compounds in $CHCl_3$ and for tablets with KBr; and UV spectra on an SF-26 instrument in ethanol. The elementary compositions of the compounds obtained were determined with the aid of calculation on a computer (Nairi-S) from the accurate values of the mass numbers of the molecular ions, which were determined by high-resolution mass spectrometry on a Finnigan MAT-8200 (direct introduction at 120°C, at an energy of the ionizing electrons of 70 eV). The mass spectra of the compounds obtained were taken on the same instrument.

Angles of optical rotation were determined on a SM-2 polarimeter for solutions in $CHCl_3$. Melting points were determined on a Boëtius instrument.

α-Santonin (1) – colorless crystalline substance with the composition $C_{15}H_{18}O_3$, mp 171-173°C (from alcohol), $[\alpha]_D^{20}$ −173° (c 0.2; methanol). It has been isolated from more than 20 species of wormwood (Artemisia L.) [8-10].

3-Oxo-11-phenylselenoeudesma-1,4-dien-6,12-olide (2). A solution of 500 mg (2 mmole) of santonin (1) in 15 ml of THF was added dropwise in an atmosphere of argon at −78°C to a stirred solution of lithium diisopropylamide (LDA, 8 mmole; prepared from 0.6 ml of diisopropylamine and 2.7 ml of a 1.47 molar solution of BuLi in hexane). After the resulting mixture had been stirred for 20 min at the same temperature, a solution of 1.3 g (4 mmole) of diphenyl selenide in 10 ml of THF containing 0.67 ml of hexamethylphosphoramide (HMPA) was added. The reaction mixture was stirred for 1 h and then its temperature was raised to 0°C and 3 ml of a 10% solution of HCl and, after that, 25 ml of a saturated aqueous solution of $NaHCO_3$ were added, and the product was extracted with diethyl ether (3 × 100 ml). The extract was dried over $MgSO_4$, and the solvent was eliminated. The total residue (750 mg) was chromatographed on a column containing 22.5 g of silica gel. Elution with hexane–ethyl acetate (2:3) led to the isolation of a colorless crystalline substance (2) with the composition $C_{21}H_{22}O_3Se$, mp 193-195°C (from ether) $[\alpha]_D^{20}$ −60° (c 0.01), R_f 0.63 (ether). The yield was 270 mg (34%). IR spectrum (ν_{max}, cm^{-1}): 3030, 2945, 2870, 1780, 1665, 1635, 1620, 1530, 1480, 1450.

3-Oxoeudesma-1,4,11(13)-trien-6,12-olide (3). With stirring at 0°C, a solution of 270 mg (0.67 mmole) of derivative (2) and 0.1 ml of AcOH in 10 ml of THF was treated with 0.5 ml of a 30% solution of hydrogen peroxide. The mixture was kept at the same temperature for 30 min, and then 10 ml of a saturated aqueous solution of sodium carbonate was added, and the product was extracted with chloroform (3 × 50 ml). The extract was dried with $MgSO_4$, the solvent was evaporated off in vacuum, and the residue (200 mg) was chromatographed on a column containing 6 g of silica gel. Elution of the column with hexane–ethyl acetate (1:4) led to the isolation of a colorless crystalline substance (3), with the composition $C_{15}H_{16}O_3$, mp 145-147°C (from ethyl acetate), $[\alpha]_D^{18}$ −10.4° (c 1.12), R_f 0.49 (ether). Yield 133 mg (80%). UV spectrum: λ_{max} 230 nm (E 10017). IR spectrum (ν_{max}, cm^{-1}): 3030, 2945, 2870, 1780, 1665, 1635, 1619, 1460, 1400, 1310, 1300, 1260, 1210, 1190, 1140, 1010, 990, 910.

11β-Allyl-3-Oxoeudesma-1,4-dien-6,12-olide (5). With stirring in an atmosphere of argon at −78°C, a solution of 500 mg (2 mmole) of santonin (1) in 7 ml of THF was added to a solution of LDA (6 mmole, prepared from 0.4 ml of diisopropylamine and 1.6 ml of a 1.8-molar solution of BuLi in hexane) in 10 ml of THF. After the resulting mixture had been stirred at the same temperature for 30 min, a solution of 0.34 ml (4 mmole) of allyl bromide in 5 ml of THF was added. The reaction mixture was stirred for 1 h, and then, after the temperature had been raised to 0°C, it was treated with 5 ml of a 10% aqueous solution of HCl. After this, 10 ml of a saturated solution of $NaHCO_3$ was added, and the product was

extracted with diethyl ether (3 × 100 ml). The extract was dried over $MgSO_4$, the solvent was evaporated off in vacuum, and the residue (700 mg) was chromatographed on a column containing 21 g of silica gel. Elution of the column with hexane–ethyl acetate (2:3) yielded the colorless crystalline substance (5), with the composition $C_{18}H_{22}O_3$, mp 142-144°C (from ether), $[\alpha]_D^{21.5}$ −25.2°, (c 0.003), R_f 0.65 (ether). Yield 300 mg (52%). IR spectrum (ν_{max}, cm^{-1}): 3030, 2945, 2870, 1790, 1680, 1650, 1630, 1470, 1420, 1390, 1310, 1230, 1200, 1180, 1120, 1050, 1005, 980, 920. Mass spectrum (m/z, %): 286 (M^+, 72), 271(76), 245(100), 215(13.8), 201(18), 189(47), 173(48), 161(16.6), 149(43), 135(86), 128(13.8), 122(36), 115-(13.8), 107 (16.6), 91(55.5), 77(36), 67(57), 55(57), 42(80.5).

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TRITERPENE GLYCOSIDES OF Hedera taurica

IX. STRUCTURES OF TAUROSIDES G_1, G_2, T_3, H_1, AND H_2 FROM THE LEAVES OF CRIMEAN IVY

V. I. Grishkovets, N. V. Tolkacheva, A. S. Shashkov, and V. Ya. Chirva

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From the leaves of Crimean ivy we have isolated the previously known glycosides 3-O-α-L-Ara_p-28-O-[O-α-L-Rha_p-(1→4)-O-β-D-Glc_p-(1→6)-β-D-Glc_p]hederagenin, 3-O-[O-α-L-Rha_p-(1→2)-α-L-Ara_p]-28-O-[O-α-L-Rha_p-(1→4)-O-β-D-Glc_p-(1→6)-β-D-Glc_p]oleanic acid and -hederagenin, and 3-O-[O-α-L-Rha_p-(1→2)-α-L-Ara_p]-28-O-[O-β-D-Glc_p-(1→6)-β-D-Glc_p]hederagenin and a new one: tauroside H_1 – 3-O-[O-α-L-Rha_p-(1→2)-O-α-L-Ara_p]-28-O-[O-α-L-Rha_p-(1→4)-O-β-D-Glc_p-(1→6)-β-D-Glc_p]echinocystic acid.

Continuing a study of the leaves of Crimean ivy Hedera taurica Carr., family Araliaceae, we have isolated glycosides of medium polarity, which have been called tauroside G_1–G_3 and H_1 and H_2. For their isolation, the plant raw material, after enzyme inactivation by boiling, was dried and was extracted successfully with chloroform and with mixtures of chloroform and ethanol (6:1 and 3:2). The chloroform extract contained chlorophyll, carotenoids, resins, and other substances of low polarity; the following extract contained low-polarity glycosides; and the last extract a mixture of medium-polarity glycosides.

M. V. Frunze Simferopol' State University.

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