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SESQUITERPENE LACTONES OF THE EUDESMAN TYPE FROM *ARTEMISIA SEMIARIDA*: ISOLATION AND SPATIAL STRUCTURE

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As a result of studying the chemical composition of the Kazakh endemic *Artemisia semiarida* ((Krasch. Et Lavr.) Filat.), sesquiterpene γ-lactones of the eudesman type are isolated for the first time: taurine, 8α-acetoxytaurine, and 8α-hydroxytaurine. Their spatial structures are determined by X-ray diffraction (XRD). New eudesmanolide named 8α-acetoxy-2-en-taurine is also isolated. Based on the single crystal XRD data, its structure is 1-keto-8α-acetoxy-7α,6,11β(H)-eudesm-2,4-diene-6,12-olide.

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Keywords: *Artemisia semiarida*, sesquiterpene lactones, eudesmanolides, taurine, 8α-acetoxytaurine, 8α-hydroxytaurine, 8α-acetoxy-2-en-taurine, single crystal X-ray diffraction, NMR spectroscopy.

INTRODUCTION

Naturally occurring compounds, both zoogenic and phytogenic, have always attracted attention of chemists, biologists, and pharmacists, first of all, due to their biological activity. Numerous facts of using plants in folk medicine are well known. Many substances of natural origin show a broad spectrum of the biological activity together with a low toxicity and do not cause side effects compared to analogous synthetic drugs.

Interesting in this respect are sesquiterpenoids isolated from representatives of the family Asteraceae Dumort [1]. They exhibit pronounced antifeedant, attractant, antineoplastic, antibacterial, and antifungal activities. At present, a list of sesquiterpenoids and their derivatives applied in medical practice runs into the hundreds [2].

From the chloroform extract from the Kazakh endemic *Artemisia semiarida* by column chromatography four eudesman-type sesquiterpene lactones were isolated for the first time and their structures were determined from spectral data and the X-ray diffraction (XRD) analysis. *Artemisia semiarida* ((Krasch. et Lavr.) Filat., family *Asteraceae* Dumort) is an endemic species of the genus *Artemisia*. It grows on gray, light chestnut saline and solonetz soils [3].

EXPERIMENTAL

The melting point was determined on a Boetius apparatus. The IR spectrum was measured on a Thermo Nicolet Avatar 360 instrument in KBr pellets. NMR spectra were recorded on a Bruker AV-600 spectrometer.

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Extraction. 1.6 kg of the aboveground part of *Artemisia semiarida* harvested during the vegetative stage, May 17-18, 2009, in the Betpak-Dala desert on the territory of Zhanaarka District of Karaganda region were three times extracted with chloroform in the plant roughage–extracting agent (1:10) ratio. The chloroform extracts were combined and evaporated on a rotary evaporator. The resulting extract was three times treated with the ethanol–water (2:1) mixture at 70-75 °C. The deposited ballast substances were separated by decantation and the solution was filtered off. The filtrate was extracted with $CHCl_3$ (4×0.5 L). The chloroform extracts were combined and evaporated to dryness.

The sum of extractive substances of 65 g was mixed with 1200 g of the adsorbent (KSK silica gel, fraction 0.5 mL) and carried into a chromatography column in the 1:20 (sum–sorbent) ratio. The column was eluted with the petroleum ether–ethyl acetate mixture followed by an increase (from 0% to 100%) in the ethyl acetate content.

Compound 1. By eluting the chromatography column with the petroleum ether–ethyl acetate (22:3) system a colorless crystalline substance with m.p. 120-122 °C was isolated. Yield: 0.496 g (0.031% on an air-dry roughage basis).

^{1}H NMR spectrum (600 MHz, $CDCl_3$, δ, ppm. *J*, Hz): 1.19 (3H, d (*J* = 6.5), H13), 1.28 (3H, s, H14), 1.47 (1H, ddd (*J* = 4.0, 12.5, 13.0), H8a), 1.55 (3H, dddd (*J* = 3.5, 12.0, 12.0, 13.0), H9b), 1.68 (1H, ddd (*J* = 3.5, 11.0, 11.5, 12.0), H7), 1.81 (1H, m, H8a), 1.91 (3H, s, H15), 1.95 (1H, m, H9a), 2.25 (1H, dd (*J* = 6.5, 11.5), H11), 2.30 (1H, m, H2b), 2.35 (1H, m, H2a), 2.43 (1H, ddd (*J* = 1.5, 13.0, 13.0), H3b), 2.57 (1H, ddd (*J* = 1.5, 13.0, 13.0), H3a), 4.55 (1H, dd (*J* = 1.5, 11.0), H6).

^{13}C NMR spectrum (134 MHz, $CDCl_3$, δ, ppm): 12.19 (C13), 19.66 (C15), 23.30 (C14), 23.74 (C9), 32.80 (C2), 34.64 (C8), 35.84 (C3), 40.81 (C11), 48.68 (C10), 52.74 (C7), 81.60 (C6), 126.78 (C4), 129.44 (C5), 178.27 (C12), 213.25 (C1).

Compound 2. By eluting the chromatography column with the petroleum ether–ethyl acetate (17:3) system a colorless crystalline substance with m.p. 111-113 °C was isolated. Yield: 0.304 g (0.019% on an air-dry roughage basis).

^{1}H NMR spectrum (600 MHz, $CDCl_3$, δ, ppm. *J*, Hz): 1.21 (3H, d (*J* = 6.5), H13), 1.34 (3H, s, H14), 1.48 (1H, dd (*J* = 11.0, 12.5), H9b), 1.90 (1H, d (*J* = 11.0, H7), 1.92 (3H, s, H15), 2.03 (3H, s, H17), 2.14 (1H, dd (*J* = 4.0, 12.5), H9a), 2.35 (1H, m, H2b), 2.37 (1H, m, H2a), 2.41 (1H, m, H3b), 2.52 (1H, dd (*J* = 6.5, 11.0), H11), 2.66 (1H, m, H3a), 4.62 (1H, br.d (*J* = 11.0, H6), 5.14 (1H, ddd (*J* = 4.0, 10.0, 11.0), H8).

^{13}C NMR spectrum (134 MHz, $CDCl_3$, δ, ppm): 13.73 (C13), 19.54 (C15), 20.83 (C17), 24.87 (C14), 33.23 (C2), 35.18 (C3), 39.87 (C9), 40.03 (C11), 47.19 (C10), 56.11 (C7), 70.42 (C8), 78.04 (C6), 127.40 (C4), 128.27 (C5), 170.04 (C16), 177.35 (C12), 211.51 (C1).

Compound 3. By eluting the chromatography column with the petroleum ether–ethyl acetate (17:3) system a colorless crystalline substance with m.p. 153-155 °C was isolated. Yield: 0.016 g (0.001% on an air-dry roughage basis). A small amount of the isolated substance did not allow us to record NMR spectra, but was sufficient for the XRD experiment.

Compound 4. By eluting the chromatography column with the petroleum ether–ethyl acetate (13:7) system a colorless crystalline substance with m.p. 153-155 °C was isolated. Yield 0.368 g (0.023% on an air-dry roughage basis).

^{1}H NMR spectrum (600 MHz, $CDCl_3$, δ, ppm. *J*, Hz): 1.31 (3H, s, H14), 1.38 (3H, d (*J* = 6.5), H13), 1.44 (1H, dd (*J* = 10.5, 12.5), H9b), 1.55 (1H, m, 8-OH), 1.77 (1H, dd (*J* = 11.0, 13.0), H7), 1.95 (3H, s, H15), 2.11 (1H, dd (*J* = 4.0, 12.5), H9a), 2.34 (1H, m, H2b), 2.39 (1H, m, H2a), 2.44 (1H, m, H3b), 2.52 (1H, dd (*J* = 6.5, 11.0), H11), 2.64 (1H, m, H3a), 3.994 (1H, m, H8), 4.55 (1H, br.d (*J* = 11.0), H6).

^{13}C NMR spectrum (134 MHz, $CDCl_3$, δ, ppm): 14.19 (C13), 19.62 (C15), 24.78 (C14), 33.05 (C2), 35.42 (C3), 40.71 (C11), 44.36 (C9), 47.55 (C10), 58.64 (C7), 69.60 (C8), 78.31 (C6), 127.90 (C4), 127.99 (C5), 178.06 (C12), 212.08 (C1).

Single crystal XRD experiment. The unit cell parameters and reflection intensities from the crystals of **2**, **3**, and **4** were measured on a Bruker KAPPA Apex2 CCD diffractometer (MoK_α, graphite monochromator, φ,ω-scanning) at 299 K. The initial dataset of the measured intensities were processed and the absorption correction was applied using the SAINT and SADABS programs (multiscan, *T*(min) and *T*(max): 0.949 and 0.989 for **2**, 0.950 and 0.960 for **3**, 0.959 and 0.989 for **4**) from the Apex2 software [4].

TABLE 1. Crystallographic Data and Details of the XRD Experiment for Compounds **2**, **3**, and **4**

Parameter	**2**	**3**	**4**
Chemical formula	$C_{17}H_{22}O_5$	$C_{17}H_{20}O_5$	$C_{15}H_{20}O_4$
M	306.34	304.33	264.31
Crystal symmetry	Orthorhombic	Orthorhombic	Monoclinic
T, K	299	299	299
a, *b*, *c*, Å	7.2037(3), 7.3859(3), 30.916(1)	9.7481(5), 11.7803(5), 14.4458(7)	5.6170(3), 17.3218(8), 7.0913(3)
β, deg	90	90	99.926(2)
V, Å^3; *Z*	1644.9(1); 4	1658.9(1); 4	679.6(1); 2
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
d_{calc}, g/cm^3	1.237	1.219	1.292
μ, mm^{-1}	0.090	0.089	0.093
Measured / independent reflections (R_{int})	12510 / 4036 (0.0203)	18656 / 4050 (0.0299)	10918 / 3217 (0.0161)
Observed reflections ($I \geq 2\sigma(I)$)	3459	2984	3070
Refined parameters	204	224	180
F(000)	656	648	284
θ range, deg	1.317 ≤ θ ≤ 28.344	2.231 ≤ θ ≤ 28.306	2.916 ≤ θ ≤ 27.934
R_1, wR_2 ($I \geq 2\sigma(I)$)	0.0429, 0.1070	0.0533, 0.145	0.0345, 0.0952
R_1, wR_2 (all dataset)	0.0519, 0.1178	0.0753, 0.1676	0.0365, 0.0970
GOOF	1.070	1.054	1.069
$\Delta\rho_{max}$ / $\Delta\rho_{min}$, e/Å^3	0.192 / –0.174	0.199 / –0.233	0.193 / –0.153

The structures were solved by a direct method. The positions on non-hydrogen atoms were refined in the anisotropic approximation by full-matrix LSM. The acetyl group in the structure of **3** is disordered over two positions in an approximately 1:1 ratio.

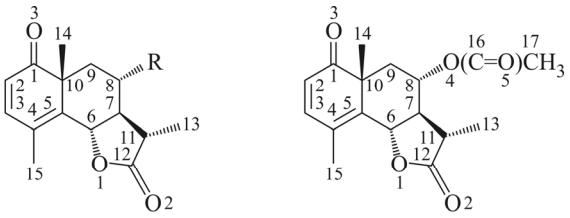
The hydrogen atom of the hydroxyl group in compound **4** was located from difference maps. Its position was refined in the isotropic approximation. The positions of the other hydrogen atoms were calculated geometrically and with a riding model.

The structures were solved by a direct method using the SHELXS-97 software [5]. The positions of non-hydrogen atoms were refined in the anisotropic approximation by full-matrix LSM using the SHELXL-2018/3 software [6]. The main crystallographic data and details of the XRD experiment are given in Table 1. The single crystal XRD data in the form of a CIF file have been deposited with the Cambridge Crystallographic Data Center (CCDC 875024 for **2**, 875025 for **3**, and 875023 for **4**).

RESULTS AND DISCUSSION

Based on the ^{1}H and ^{13}C NMR spectral data the isolated substances were identified as taurine (**1**), 8α-acetoxytaurine (**2**), 8α-acetoxy-2-en-taurine (**3**), and 8α-hydroxytaurine (**4**). Compounds **1**, **2**, and **4** from *Artemisia semiarida* were isolated for the first time and compound **3** is new (Fig. 1).

For the crystals of **1** the unit cell parameters were determined. As a result, they were found to agree with the previously published values for the structure of taurine [7]. It should also be noted that the crystal structure of taurine was previously solved as another polymorph [8]. Interestingly that taurine was isolated for the first time from *Artemisia taurica* Willd. [9].



1 (R–H), **2** (R–O(C=O)CH_3), **4** (R–OH) **3**

Fig. 1. Structural formulas of compounds **1**-**4**.

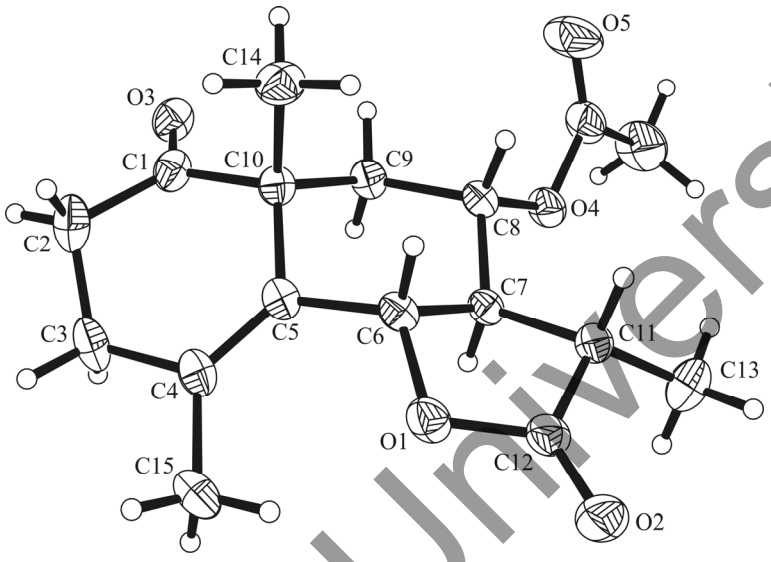


Fig. 2. Structure of 8α-acetoxytaurine (**2**) (thermal vibration ellipsoids are shown at the 30% probability level).

To determine the spatial structure of compound **2** the single crystal XRD study was performed. The general view of the molecule is depicted in Fig. 2. Earlier, 8α-acetoxytaurine (**2**) was isolated from *Artemisia santonicum* [10].

Upon further elution of the column with the same system, colorless crystalline substance (**3**) was isolated. A small amount of the isolated substance did not allow us to record NMR spectra, but was sufficient for the XRD experiment. The single crystal XRD analysis reveals that compound **3** is new; it was named 8α-acetoxy-2-en-taurine. The general view of the molecule of **3** is depicted in Fig. 3.

To determine the spatial structure of compound **4** the single crystal XRD study was also performed. The general view of the molecule is depicted in Fig. 4. 8α-Hydroxytaurine (**4**) was previously isolated from *Artemisia santonicum* [10] and *Artemisia pontica* [11].

From the analysis of the geometry of compounds **2**-**4** it follows that the bond lengths and bond angles in them are close to normal [12].

The six-membered C1C2C3C4C5C10 cycle (A) in compound **1** takes different conformations creating a semblance of partial pseudo-rotation. Thus, in one polymorph (monoclinic crystal system, space group $P2_1$ [11]), cycle A takes the conformation of a distorted 1α,2β-*half-chair* ($\Delta C_2^{4,5} = 3.1°$) [13]. This conformation is the most stable for cyclohexene [14]. In another polymorph (orthorhombic crystal system, space group $P2_12_12_1$ [10]) in two crystallographically independent molecules of **1** cycles A are in the conformation of a strongly distorted 2β-*sofa* ($\Delta C_S^5 = 8.5°$) and the intermediate conformation between 2β-*sofa* and 2β,3α-*half-chair* ($\Delta C_S^5 = 13.1°$; $\Delta C_2^{5,10} = 16.3°$) respectively.

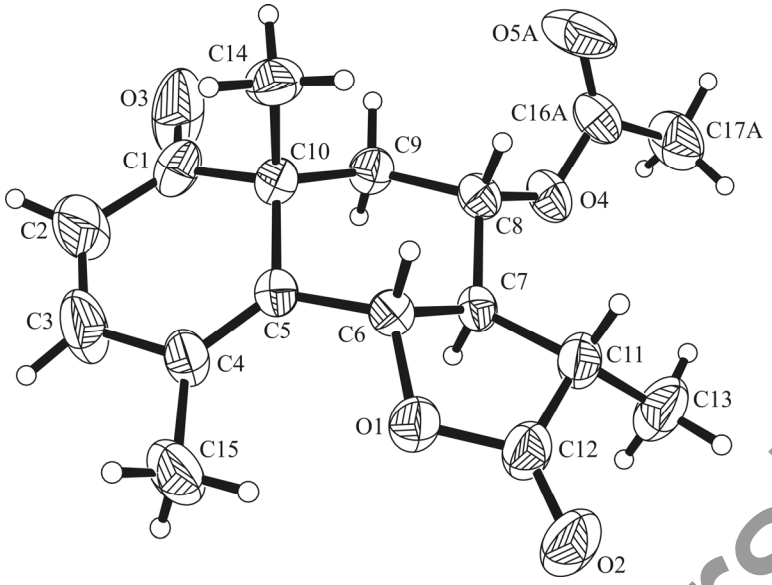


Fig. 3. Structure of 8α-acetoxy-2-en-taurine (**3**) (thermal vibration ellipsoids are shown at the 30% probability level). The minor part of the disordered acetoxy group is omitted.

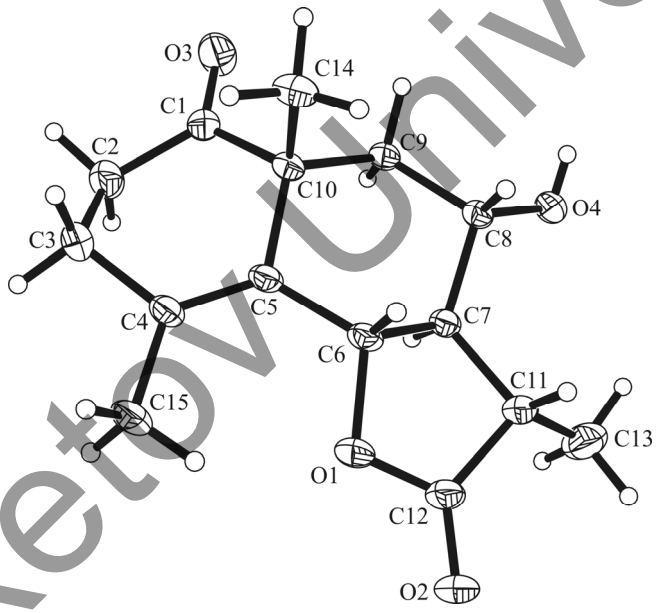


Fig. 4. Structure of 8α-hydroxytaurine (**4**) (thermal vibration ellipsoids are shown at the 30% probability level).

In compound **2**, cyclohexene cycle A takes the quite expected conformation of a distorted 2β-*sofa* ($\Delta C_S^5 = 6.7°$). In compound **4**, the intracyclic torsion angle C4C5C10C1 (at the cycle conjugation) is increased to 32.8° against the maximum of 12.2° in **1**. As a result, cyclohexene cycle A takes a distorted 3,10β-*twist* conformation ($\Delta C_2^{5,10} = 5.2°$). In compound **3**, the presence of two conjugated double bonds in 2,4-diene cycle A largely flattens them. Here the C1–C2=C3–C4 torsion angle abnormally (21.0°) deviates from perfect zero, hence, cycle A takes the conformation of a distorted 1α,2β-*g-half-chair* ($\Delta C_2^{4,5} = 4.5°$). The intracyclic torsion angles in compounds **2**-**4** are given in Table 2.

TABLE 2. Intracyclic Torsion Angles (deg) in Compounds **2**, **3**, and **4**

Angle	**2**	**3**	**4**
	A cycle		
C3–C1–C2–C10	–54.7(3)	–30.2(9)	26.6(3)
C1–C2–C3–C4	48.8(3)	21.0(1)	–50.0(3)
C2–C3–C4–C5	–21.6(4)	–8.3(9)	33.1(3)
C3–C4–C5–C10	–2.5(4)	5.4(6)	9.4(3)
C4–C5–C10–C1	–1.7(3)	–13.6(4)	–32.8(3)
C2–C1–C10–C5	31.0(3)	24.4(5)	12.9(3)
	B cycle		
C10–C5–C6–C7	–61.9(2)	–58.9(3)	–48.6(2)
C5–C6–C7–C8	62.6(2)	65.8(3)	64.3(2)
C6–C7–C8–C9	–55.2(2)	–60.8(3)	–64.1(2)
C7–C8–C9–C10	53.6(3)	54.9(3)	55.5(2)
C8–C9–C10–C5	–53.9(2)	–49.8(3)	–42.7(2)
C6–C5–C10–C9	55.5(2)	49.6(3)	36.9(2)
	C cycle		
O1–C6–C7–C11	–41.6(2)	–38.4(3)	–40.2(2)
C12–O1–C6–C7	30.9(2)	27.4(3)	27.1(2)
C6–O1–C12–C11	–7.0(2)	–4.7(4)	–2.4(2)
C7–C11–C12–O1	–19.6(2)	–19.8(4)	–23.0(2)
C6–C7–C11–C12	36.2(2)	34.5(3)	37.5(2)

The C5C6C7C8C9C10 (B) cycle in compounds **2**-**4** is in the *chair* conformation, with different degrees of distortion, as in the structure of **1**. The conformation varies from an almost ideal *chair* ($\Delta C_S^6 = 0.5°$) in **2** to a distorted *chair* in **3** ($\Delta C_S^7 = 3.7°$) and a strongly distorted *chair* in **4** ($\Delta C_S^7 = 5.2°$). The C6C7C11C12O1 (C) lactone cycle in compounds **2**-**4**, the same as in **1**, takes the conformation of a distorted 7α-*envelope* ($\Delta C_S^7 = 3.5°$) in **4**, a strongly distorted *envelope* in **3** ($\Delta C_S^7 = 6.0°$), and an intermediate conformation between 7α-*envelope* and 6β,7α-*half-chair* ($\Delta C_S^7 = 8.9°$; $\Delta C_2^{12} = 9.7°$).

In compounds **2**-**4**, cycles A and B are pseudo-*trans* conjugated (torsion angles C1C10C5C4 and C6C5C10C9 in Table 2). The lactone cycle and the carbocycle are *trans* conjugated (the torsion angle H6C6C7H7 = –174°, –170°, and –173° in **2**-**4** respectively). The hydroxyl group in **4** and the acetoxy group in **3** and **4** at the C8 atom are equatorially oriented, and the methyl group in the γ-lactone cycle is pseudo-equatorially oriented.

In the crystal, the molecules of **4** are linked by the intermolecular O4–H…O2 hydrogen bond (–1+*x*, *y*, –1+*z*) (O–H distances of 0.77(3) Å, O…O of 2.881(2) Å, H…O of 2.14(3) Å, the O–H…O angle of 162(3)°) forming infinite chains along the [1 0 1] direction.

Thus, as a result of the chemical study of *Artemisia semiarida,* the known sesquiterpene γ-lactones of the eudesman type **(**taurine, 8α-acetoxytaurine, and 8α-hydroxytaurine) were isolated for the first time. Their spatial structure is determined by XRD. Also, new eudesmanolide named α-acetoxy-2-en-taurine was isolated. Based on the single crystal XRD data, its structure is 1-keto-8α-acetoxy-7α,6,11β(H)-eudesm-2,4-diene-6,12-olide.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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