

MOLECULAR AND CRYSTAL STRUCTURES OF ARGOLIDE EPOXIDE

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The sesquiterpene lactone argolide has been converted into its 1(10)-epoxide. The structure of the latter has been investigated by NMR, x-ray structural analysis, and molecular mechanics.

The sesquiterpene lactone argolide (1) has been isolated previously from *Artemisia glabella*, an endemic plant of Kazakhstan [1]. We have performed the epoxidation of this germacranolide with trifluoroperacetic acid to give an 85% yield of the epoxide (2).



The ¹H NMR spectrum (Table 1) of compound (2) showed groups of signals superposed upon one another in the 1.20-1.30 and 2.00-2.20 ppm regions. Therefore, for a complete assignment of all the protons in the molecule we used two-dimensional ¹H-¹H NMR spectroscopy (COSY).

With the aim of establishing the spatial structure of argolide epoxide (2) and, in particular, the conformations of the rings, we made an x-ray structural analysis of it. The structure of the (2) molecule is shown in Fig. 1. The bond lengths and valence angles have the usual values to within the experimental error [2].

As follows from the values of the torsional angles C2C1C10C9 (151.4°) and C3C4C5C6 (-53.9°), compound (2) belongs to the class of E,Z-germacranolides. A comparison of the intracyclic torsional angles in ring A (Table 2) with the corresponding angles in the argolide (1) [1] molecule shows that in the C1...C5...C7 section their difference does not exceed ±7°. However, the presence in (2) of an epoxide group at the C1 and C10 atoms leads to considerable differences in other torsional angles (Δφ): Δφ_{7,8} = 10.7°, Δφ_{10,1} = 13.2°. The conformation of ring A in the (2) molecule is the same as in argolide (1) — a ₁D¹⁴, ₅D¹⁵ boat-chair (the torsional angles are given in Table 2). Analysis of literature reports on the crystal structures of E,Z-germacranolides showed that in the heliangolidin molecule investigated previously a similar conformation is observed [3]. The germacrane skeleton is linked to the γ-lactone ring (B) in the *trans*-manner (the torsional angle H6C6C7H7 is -102.2°). In the ten-membered ring the methyl groups at the C4 and C10 atoms have the β-orientation. On the basis of the facts given above, epoxyargolide (2) is 3-oxo-1β,10α-epoxy-1,4,7α,6β(H)-germacr-11(13)-en-6,12-olide.

It must be mentioned that the γ-lactone ring assumes a conformation inverted in relation to the usual one — a 6α,7β-half-chair (ΔC₂¹² = 1.2°) (see Table 2). Under these conditions the SSCC between the H6 and H7 protons has a small value, comparable with a broad line, and appears only in the form of a weak interaction in the two-dimensional ¹H-¹H NMR (COSY) spectrum. According to the results of various authors [4, 5] ³J_{6,7} should amount to 1.67-2.10 Hz, depending on the H6C6C7H7 torsional angle. This is probably connected with the fact that the constant of vicinal interaction also depends on the length of

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TABLE 1. ^{13}C (100 MHz) and ^1H (400 MHz) NMR Spectra of Argolide Epoxide (2), δ , CDCl_3

Atom	δ (C)	δ (H)
1	58.74 d	3.28dd (10.0; 5.5)
2	43.79 t	3.21dd (14.5; 5.5; H2a) 2.16dd (14.5; 10.0; H2b)
3	209.82 s	-
4	39.79 d	2.91m(1H)
5	39.66t †	2.15ddd (13.0; 13.0; 3.0; H5a) 1.40ddd (13.0; 11.5; 4.0; H5b)
6	80.69 d	4.02dd (11.5; 3.0)
7	43.97 d	2.74 br.d. (10.5)
8	33.55 d	1.87m(1H) 1.63m(1H)
9	39.29t †	2.25ddd (14.0; 3.7; 3.7) 1.25*ddd (14.0; 14.0; 4.5)
10	58.66 s	-
11	140.06 s	-
12	166.90 s	-
13	123.29 t	6.21d (1.0) 5.66d (1.3)
14	17.89 q	1.25s (3H)
15	15.40 q	1.10d (3H; 7.0)

*Signal superposed on the signal of the $\text{H}_3\text{C}(14)$ group.

†The assignments may be reversed.

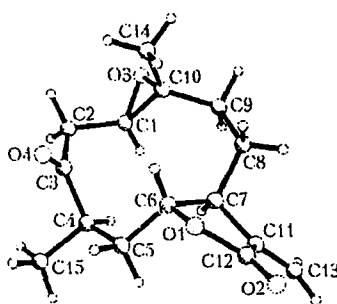


Fig. 1. Structure of the argolide epoxide (2) molecule.

the bond between the interacting atoms and their valence angles [5]. An analogous absence of $^3J_{6,7}$ is observed in the ketopelenolide B molecule [6].

A comparison of the conformation of the (2) molecule calculated by the method of molecular mechanics (using the MMX-86 program) with the x-ray structural results showed that the corresponding intracyclic torsional angles differed by not more than 10° . The H6C6C7H7 torsional angle for the free molecule assumed practically the same value (-102.1°).

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were taken on a UR-20 instrument. Optical rotations were determined for solutions in CHCl_3 on a Polamat A polarimeter (at 580 nm). NMR spectra were recorded on a Bruker WP-400SY spectrometer (working frequency for ^1H 400 MHz, and for ^{13}C 100 MHz) using the standard Bruker programs for recording COSY two-dimensional spectra. Mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument.

3-Oxo-1 β ,10 α -epoxy-1 α ,4 α ,6 β ,7 α (H)-germacr-11(13)-en-6,12-olide (2). This was synthesized as in [7]. Colorless acicular crystals with mp 203-205 $^\circ\text{C}$ (ethyl acetate-petroleum ether). Yield 87%, $[\alpha]_{580}^{23} +40.3^\circ$ (c 1.19; CHCl_3). IR spectrum (KBr, ν , cm^{-1}): 1760, 1710, 1450, 1280, 1200, 1100. Mass spectrum (m/z , I (%)): 264 [M^+] (0.5), [$\text{M}^+ - \text{H}_2\text{O}$] (5.0), 221 (2.6), 220 (5.2), 203 (8.6), 176 (5.0), 175 (12.9), 167 (15.4), 166 (97.4), 165 (14.6), 151 (12.6), 149 (12.7), 147 (23.4), 124 (47.9), 123 (26.7), 109 (26.9), 107 (16.5), 99 (38.7), 97 (85.3), 95 (36.9), 81 (27.0), 79 (25.0), 71 (42.9), 69

TABLE 2. Intracyclic Torsional Angles φ (deg) in the (2) Molecule from the XSA and MM Results

Angle	φ (XSA)	φ (MM)
C10C1C2C3	-75.0	-75.8
C1C2C3C4	-60.6	-54.8
C2C3C4C5	135.6	129.3
C3C4C5C6	-53.9	-54.3
C4C5C6C7	-74.1	-72.5
C5C6C7C8	150.8	152.9
C6C7C8C9	-93.4	-93.5
C7C8C9C10	63.1	58.5
C8C9C10C1	-94.1	-96.9
C9C10C1C2	151.4	158.4
O1C6C7C11	27.3	26.4
C12O1C6C7	-23.3	-21.9
C6O1C12C11	8.5	6.1
C7C11C12O1	10.1	13.1
C6C7C11C12	-22.9	-24.3

TABLE 3. Coordinates ($\times 10^4$; for H atoms, $\times 10^3$) for the Atoms of the (2) Molecule

Atom	X	Y	Z
C1	60(4)	22(2)	1536(1)
C2	669(5)	6808(2)	2239(1)
C3	2614(4)	6148(2)	2530(1)
C4	2189(4)	4932(2)	2655(1)
C5	4190(5)	4258(2)	2393(1)
C6	4817(4)	4479(2)	1636(1)
C7	3217(4)	4009(2)	1076(1)
C8	3178(5)	4698(2)	398(1)
C9	1303(5)	5566(2)	357(1)
C10	1404(4)	6470(2)	897(1)
C11	4307(4)	2917(2)	942(1)
C12	6719(4)	3000(2)	1157(1)
C13	3458(4)	2016(2)	668(1)
C14	3368(5)	7245(2)	854(2)
C15	1803(7)	4755(2)	3441(1)
O1	7017(3)	3953(1)	1505(1)
O2	8273(3)	2385(1)	1054(1)
O3	-782(3)	7017(1)	993(1)
O4	4467(3)	6539(1)	2639(1)
H1	-67(4)	566(2)	155(1)
H2a	108(5)	759(2)	220(1)
H2b	-51(6)	685(2)	252(2)
H4	64(5)	470(2)	240(1)
H5a	559(5)	449(2)	268(1)
H5b	384(4)	345(2)	244(1)
H6	501(4)	522(2)	155(1)
H7	167(5)	391(2)	127(1)
H8a	465(5)	503(2)	33(1)
H8b	293(4)	418(2)	-3(1)
H9a	134(5)	600(2)	-12(1)
H9b	-16(5)	518(2)	41(1)
H13a	439(5)	136(2)	65(1)
H13b	199(5)	199(2)	54(1)
H14a	335(6)	755(3)	38(2)
H14b	338(5)	782(2)	123(1)
H14c	493(8)	688(3)	87(2)
H15a	160(5)	397(2)	355(1)
H15b	310(5)	502(2)	370(1)
H15c	49(7)	521(3)	360(2)

(43.4), 55 (36.7), 53 (38.0), 43 (100.0), 41 (64.4). Elementary analysis. Found % C 67.98; H 7.78. Calculation %: C 68.18; H 7.58.

X-Ray Structural Assay of (2). The cell parameters and the intensities of 1973 independent reflections were measured on a Siemens P3/PC automatic four-circle diffractometer with monochromatized Mo-K α radiation, $\theta/2\theta$ scanning, $2\theta \leq 50^\circ$. Crystals orthorhombic, $a = 5.9032(1)$, $b = 12.2730(3)$, $c = 19.2140(4)$ Å, $V = 1392.1$ Å 3 , $M = 263.3$, $Z = 4$ (C $_{15}$ H $_{19}$ O $_4$), sp.gr. P2 $_1$ 2 $_1$ 2 $_1$.

In the calculations we used 1764 reflections with $I \geq 3\sigma$. The structure was interpreted by the direct method and was refined by full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms. The H atoms were revealed in a difference synthesis and their positions were refined isotropically.

The final divergence factors were $R = 0.0380$ and $R_w = 0.0380$.

The coordinates of the atoms are given in Table 3. All the calculations were made on an IBM PC/AT by the Siemens SHELXTL package of programs (PC version).

The calculations by the method of molecular mechanics were made by the MMX program adapted for the IBM PC/AT.

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