

## SYNTHESIS OF DIHALOCARBENE DERIVATIVES OF ESTAFIATIN GUAIANOLIDE

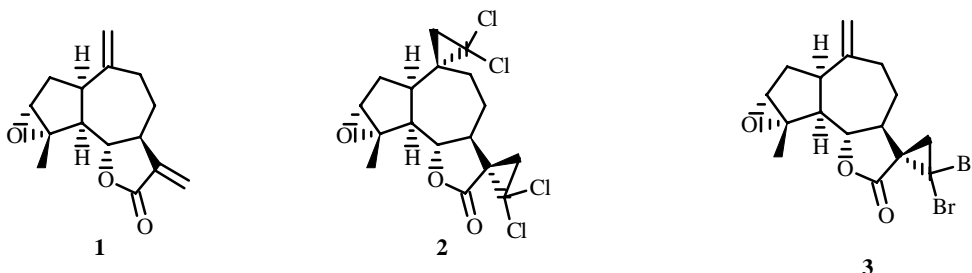
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*Adducts of dihalocarbenes generated from chloroform and bromoform were prepared by reaction with estafiatin guaianolide. Their structures were established by XSA.*

**Key words:** guaianolide, estafiatin, dihalocarbene, NMR spectroscopy, x-ray structure analysis.

It was established previously that dibromocarbene, in contrast with dichlorocarbene, gives an easily isolated product of addition to the exomethylene group of arglabin [1]. In order to understand the addition of dihalocarbenes to natural butenolides, we carried out analogous reactions with another guaianolide, estafiatin (**1**) [2].



Reaction of **1** with dichlorocarbene led to the isolation of only one product (31% yield) of formula  $C_{17}H_{18}O_3Cl_4$  (high-resolution mass spectrometry). This corresponded to addition of two dichlorocarbenes to starting **1**. Figure 1 shows the structure of the product (**2**), which was established by an x-ray structure analysis (XSA).

Reaction of **1** with bromoform under conditions where dibromocarbene is generated [3] formed a mixture of products, from which one dibromocyclopropane derivative of estafiatin was isolated in 21% yield. Figure 2 shows the structure of the product (**3**), which was also established by an XSA.

Bond lengths in **2** and **3** are normal [4] within experimental uncertainty. The lactone ring in **2** and **3** has the envelope conformation with deviations of C6 of 0.327(3) and 0.29(1) Å from the plane of the remaining ring atoms. The conformation of the seven-membered ring is also the same in **2** and **3**. According to Cremer—Pople parameters, it can be characterized as intermediate between a chair and twist-chair. According to the Cambridge Structural Database [5], practically the same conformation of a seven-membered ring is found, for example, in the lactone bahia I [6] and in  $\beta$ -epoxyestafiatin [7]. The conformation of the five-membered ring in **2** is close to an envelope with deviation of C1 by 0.432(4) Å from the plane of the other atoms; in **3**, close to a twist shape with deviations of C1 and C2 by -0.24(2) and 0.16(2) Å, respectively.

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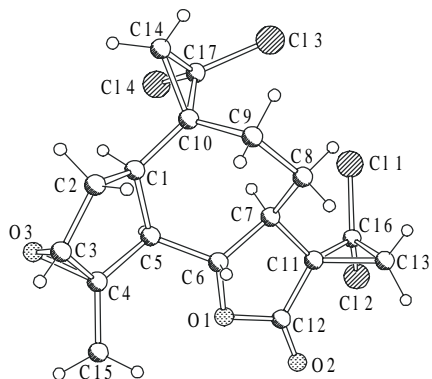


Fig. 1. Molecular structure of **2**.

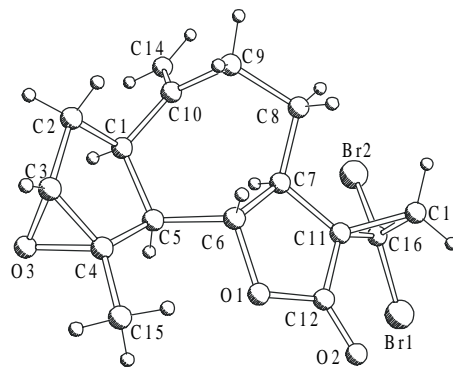


Fig. 2. Molecular structure of **3**.

Molecules of **2** in the crystal are bonded through weak H-bonds C14–H...O3 (H...O, 2.40 Å; C–H...O, 152°) into zigzag chains along the *a* axis. H-bonds C6–H...O2 (H...O2, 2.54 Å; C–H...O, 116°) and C=O2...C12 [O...C, 2.921(4) Å] join the chains into layers parallel to the *ab* plane. Interlayer H-bonds C15–H...C11 with H...C1 of 2.81 Å and C–H...O of 163° are noteworthy. Molecules of **3** in the crystal do not form layers. Shortened [8] intermolecular contacts C3–H...C12 with H...C2 of 2.76 Å and Br2...O3 of 3.25 (1) Å are noteworthy.

## EXPERIMENTAL

The course of reaction and purity of products were monitored by TLC using Silufol plates and development by spraying with aqueous KMnO<sub>4</sub> (2%). Column chromatography used Armsorb silica gel. Melting points were determined on a Boetius instrument. IR spectra in KBr were obtained on an Avatar 360 ESP instrument. NMR spectra were recorded on a Bruker DRX-500 spectrometer (operating frequency 500.13 MHz for <sup>1</sup>H; 125.76 MHz, <sup>13</sup>C; δ-scale). Mass spectra (EI, 70 eV) were obtained in a Finnigan MAT 8200 instrument. Estafiatin (**1**) used for the reactions was isolated from the aerial part of *Achillea nobilis* L. [9].

**3,4α-Epoxy-10(14);11(13)-bis-(1',1'-dichloromethano)-5,7α,6β(H)-guai-12,6-olide (2)**. A solution of crown ether (30 mg) in CHCl<sub>3</sub> (3 mL) and aqueous NaOH (2 mL, 50%) was stirred at room temperature and treated with estafiatin (**1**, 100 mg, 0.0004 mol). After the reaction was complete, the CHCl<sub>3</sub> layer was dried over MgSO<sub>4</sub>. The solid (0.21 g) was chromatographed over a column of SiO<sub>2</sub> (eluent petroleum ether and ethylacetate) to afford **2** (0.052 g, 31%), mp 194–196°C, *R<sub>f</sub>* 0.44 (petroleum ether:EtOAc, 3:2).

Mass spectrum (*m/z*, *I<sub>rel</sub>*, %): 410 (2) [M]<sup>+</sup>, 397 (9), 327 (13), 199 (6), 115 (14), 95 (34), 66 (16), 65 (16), 43 (100). C<sub>17</sub>H<sub>18</sub>O<sub>3</sub>Cl<sub>4</sub>.

PMR spectrum (500 MHz, CDCl<sub>3</sub>, δ, ppm, J/Hz): 3.34 (1H, s, H-3), 4.10 (1H, dd, J = 8.6, H-6), 2.02 (1H, d, J = 7.0, H-13a), 1.82 (1H, d, J = 7.0, H-13b), 1.32 (1H, d, J = 7.0, H-14a), 1.22 (1H, J = 7.0, H-14b), 1.58 (3H, s, CH<sub>3</sub>-15).

<sup>13</sup>C NMR spectrum (125.75 MHz, CDCl<sub>3</sub>): 40.58 (d, C-1), 30.39 (t, C-2), 42.72 (d, C-3), 37.42 (s, C-4), 60.75 (d, C-5), 80.07 (d, C-6), 48.38 (d, C-7), 25.39 (t, C-8), 29.29 (t, C-9), 35.18 (s, C-10), 31.87 (s, C-11), 171.43 (s, C-12), 26.36 (t, C-13), 65.42 (q, C-14), 18.50 (q, C-15), 61.13 (s, C-16), 67.32 (s, C-17).

IR spectrum (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3088, 3011, 2978, 2938, 2896, 2869, 1781 (γ-lactone C=O); 1464, 1451, 1433, 1412, 1380, 1351, 1330, 1319, 1301, 1287, 1257, 1217, 1207, 1184, 1152, 1102, 1077, 1055, 1035, 1019, 1000, 986, 961, 954, 933, 920, 897, 875, 867, 828, 815, 777, 757 (C–Cl); 700, 681, 625, 591, 582, 510, 504, 487, 477, 461, 440.

**3,4α-Epoxy-11,13-(1',1'-dibromomethano)-1α,5α,7α,6β(H)-guai-10(14)-en-12,6-olide (3)**. Colorless crystals, mp 204–206°C, *R<sub>f</sub>* 0.66 (petroleum ether:EtOAc, 1:1), yield 21%. IR spectrum (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 682 (C–Br), 1641 (C=C), 1768 (C=O).

PMR spectrum (500 MHz, CDCl<sub>3</sub>, δ, ppm, J/Hz): 1.58 (3H, s, 15-Me), 3.36 (1H, s, H-3), 4.17 (1H, dd, J = 8 and 6, H-6), 4.79 (1H, s), 4.94 (1H, s).

The x-ray diffraction experiment was performed on Bruker P4 and Syntex P2<sub>1</sub> diffractometers [graphite monochromator,  $\lambda(\text{Mo-K}\alpha) = 0.71073 \text{ \AA}$ , room temperature,  $\theta/2\theta$ -scanning] for **2** and **3**, respectively. Absorption corrections for **2** were applied from experimental azimuthal scanning curves ( $T_{\text{min}}/T_{\text{max}} = 0.925/0.981$ ) and for **3** from the crystal faces ( $T_{\text{min}}/T_{\text{max}} = 0.311/0.656$ ). Structures were solved by direct methods. Positions and thermal parameters of nonhydrogen atoms were refined isotropically and then anisotropically using full-matrix least-squares methods. H atoms were located in geometrically calculated positions and included in the refinement as "rider" atoms. All calculations were carried out using SHELX-97 programs. Geometric analysis used the Platon program.

Crystallographic data and parameters of the XSA for **2**: C<sub>17</sub>H<sub>18</sub>Cl<sub>4</sub>O<sub>3</sub>, MW = 411.11, orthorhombic system, space group  $P2_12_12_1$ ,  $a = 6.4539(5)$ ,  $b = 15.009(1)$ ,  $c = 19.453(2) \text{ \AA}$ ,  $V = 1884.3(3) \text{ \AA}^3$ ,  $Z = 4$ ,  $d_{\text{calc}} = 1.449 \text{ g/cm}^3$ ,  $\mu = 0.640 \text{ mm}^{-1}$ , scanning range  $2\theta < 54^\circ$ , 2374 measured reflections, 2077 reflections with  $I \geq 2\sigma(I)$ , 217 refined parameters,  $R_1 [I \geq 2\sigma(I)] = 0.0425$ ,  $wR_2 = 0.1228$  (all reflections), absolute structure parameter (Flack) 0.0(1).

Crystallographic data and parameters of the XSA for **3**: C<sub>16</sub>H<sub>18</sub>Br<sub>2</sub>O<sub>3</sub>, MW = 418.12, orthorhombic system, space group  $P2_12_12_1$ ,  $a = 8.039(4)$ ,  $b = 11.255(5)$ ,  $c = 17.546(8) \text{ \AA}$ ,  $V = 1588(1) \text{ \AA}^3$ ,  $Z = 4$ ,  $d_{\text{calc}} = 1.749 \text{ g/cm}^3$ ,  $\mu = 5.113 \text{ mm}^{-1}$ , scanning range  $2\theta < 50^\circ$ , 1620 measured reflections, 1046 reflections with  $I \geq 2\sigma(I)$ , 190 refined parameters,  $R_1 [I \geq 2\sigma(I)] = 0.0579$ ,  $wR_2 = 0.1335$  (all reflections), absolute structure parameter (Flack) -0.05(5).

Crystallographic data and atomic coordinates for **2** and **3** were deposited in the Cambridge Structural Database (Nos. CCDC651580 and CCDC651581).

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