Synthesis of Dihalocarbene Derivatives of Guaianolide Estafiatine

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Abstract

Guaianolide estafiatine interaction with dihalocarbenes generated from chloroform and bromoform was studied. It was established to result in the formation of corresponding halogenated derivatives whose structure has been determined using XRD technique.

It is well known that as opposed to dichlorocarbene, dibromocarbene readily interacts to form an addition product with respect to the exomethylene group of arglabine molecule [1]. Within the framework of the studies on the features of dihalocarbene addition to the molecules of natural butenolides we carried out similar reactions with another guaianolide such as estafiatine **1**.

After interaction of lacton **1** with dichlorocarbene, it was possible to isolate only one product from the reaction mixture (with the yield of 31 %) determined as $C_{17}H_{18}O_3Cl_4$ (high resolution mass spectrometry), which is corresponding to the addition of two dichlorocarbene molecules to the parent molecule **1**. Its structure established with the use of XRD technique can be presented by formula **2**, being demonstrated in Fig. 1.





Fig. 1. Spatial structure of derivative 2.

In the IR spectrum of the molecule **2** absorption bands of the carbonyl group (1781 cm^{-1}) and the C–Cl bond (757 cm^{-1}) are observed.

In the ¹H NMR spectrum of compound **2**, due to dichlorocarbene addition, the signals of the protons positioned at C-13 and C-14 are shifted in a strong field and thus they are observed at 1.82 and 2.02 ppm (H-13 a, b), 1.22 and 1.32 ppm (H-14 a, b) as doublets with an identical coupling constant J = 7.0 Hz.



Fig. 2. Spatial structure of derivative 3.



The occurrence of additional signals such as singlets at 61.13 (C-16) and 67.32 (C-17) in 13 C NMR spectra of compound **2** could be considered as the confirmation of the fact that the addition of dichlorocarbene occurs with respect to the exomrethylene bond at C-13 and C-14 atoms. Due to the effect of chlorine atoms the same signals are shifted towards the region of stronger field.

Upon the interaction of lacton **1** with bromoform under the conditions of dibromocarbene generation [3] the mixture of products is formed from those a dibromocyclopropane derivative of estafiatine was isolated with the yield of 21 %. The structure of the molecule established using an XRD technique shown in Fig. 2 may be presented by formula **3**.

In the IR spectrum of the molecule **3** absorption bands of the C–Br bond (682 cm⁻¹), the carbonyl group of γ -lacton (1768 cm⁻¹) and the double bond (1641 cm⁻¹) are observed.

There is a signal of the lacton proton at 4.17 ppm as a doublet of doublets (J = 8.0, 6.0 Hz) in the ¹H NMR spectrum molecule **3**, as well as the signals of the protons of CH₃-15 methyl group are observed as a singlet at 1.58 ppm. The H-3 proton gives rise to a signal in the

region of 3.36 ppm in the form of a broadened singlet, and the signals of the protons of exomethylene group are observed in the region of 4.79 and 4.94 ppm as two doublets. Due to dibromocarbene addition at the exomethylene bond of the lacton cycle there is a considerable shift of H-13a μ H-13b signals towards a strong field region resulting in the fact that they are observed as two doublets in the region of 2.15 and 1.95 ppm, respectively.

As opposite to the ¹³C NMR spectral data for the initial molecule **1**, the similar spectrum of the molecule **3** includes an additional signal such as a singlet at 65.67 ppm inherent to the carbon atom of the cyclopropane cycle. The signals from C-11 and C-13 atoms are shifted towards a strong field region and appear as a singlet and triplet, respectively.

According to the data of X-ray structure studies, bond lengths in the molecules 2 and 3are quite usual [4] within the limits of errors. The lacton cycle in the molecules 2 and 3 demonstrates an "envelope" conformation with C6 atom extending 0.327 (3) and 0.29 (1) Å from the plane of the other atoms of the cycle. Moreover, identical conformation of the seven-membered cycle is inherent to the molecules 2 and 3 which conformation according to the Cremer-Popple parameters may be characterized as an intermediate one between "chair" and "twistchair". According to the Cambridge Structural Database [5], almost the same conformation of a seven-membered cycle was revealed, e.g., for lacton bahia I [6] and for β -epoxyestafiatine [7]. The conformation of the five-membered cycle of the molecule 2 is close to the shape of "envelope" with C1 atom extending 0.432 (4) Å from the plane of other atoms, whereas that of the molecule 3 might be considered to be closer to the "twist" form with C1 and C2 atoms extending 0.24(2) and 0.16(2) Å, respectively.

In the crystal of compound **2** the molecules are bound via weak interactions C14–H...O3 (H...O distance being 2.40 Å, C–H...O angle amounting to 152°) to form zigzag-shaped chains along the *a* axis. Upon interaction C6–H...O2 (H...O 2.54 Å, C–H...O 116°) and C=O2...C12 (O...C 2.921(4) Å) the chains can combine to form layers parallel to plane *ab*. We may point out interlayer interactions C15-H ... Cl1 with H ... Cl distance equal to 2.81 Å, and C–H...O angle equal to 163° . In the case of the crystal of compound **3** the layers of molecules are not looked through it is possible to point out reduced intermolecular contacts [8] such as C3-H...C12 with H...C distance equal to 2.76 Å and Br2 ... O3 distance equal to 3.25(1) Å.

The reaction process as well as the purity of the derivatives obtained were monitored by means of a TLC technique using Silufol plates those were developed through the spraying with 2 % aqueous solution of $KMnO_4$. For the column chromatography technique an Armsorb silica gel was used. Melting point was determined by means of a Boetius device. IR absorption spectra were registered in KBr with the use of an Avatar 360 ESP spectrometer; UV absorption spectra were obtained for solutions in ethanol using a Helios в spectrophotometer. NMR spectra were registered with the help of a Bruker DRX-500 spectrometer (operation frequency amounted to 500.13 and 125.76 MHz for ¹H and ¹³C, respectively, δ -scaling). Mass spectra (electron impact, 70 eV) were obtained using a Finnigan MAT 8200 mass spectrometer. Estafiatine 1 used for the reaction was isolated from the plant aerial part of Achillea nobilis L. [9]. The isolated compound represented a colorless crystal substance with gross formula $C_{15}H_{18}O_3$, m.p. being at 102–104 °C, $[\alpha]_D^{20}$ –10° (chloroform).

3,4α-epoxy-10(14),11(13)-bis-(1',1'dichloromethano-)-5,7β,6β(H)-guai-12,6-olide (2). To a mixture of 3 mL CHCl₃, 2 mL of 50 % NaOH aqueous solution and 30 mg of crown ether was added 100 mg (0.0004 mol) of estafiatine 1, upon stirring. After the reaction completion, the mixture was poured into water and then extracted with chloroform. The organic extract was dried over MgSO₄. A residue (0.21 g) was chromatographed on a column packed with SiO₂ (a mixture of petroleum-ether with ethylacetate being used as an eluent). Product 2 was isolated with the yield of 0.052 g (31 %), m.p. being at 194–196 °C, $R_f = 0.44$ (petroleum ether/EtOAc = 3 : 2).

Mass spectrum $(m/z, I_{\rm rel}, \%)$ 410 $(M^+, 2)$, 397 (9), 327 (13), 199 (6), 115(14), 95 (34), 66 (16), 65 (16), 43 (100). High Resolution Mass Spectrometry (m/z): Found: 410.00259. Calculated for $C_{17}H_{18}O_3Cl_4$: 410.001.

¹H NMR spectrum (500 MHz, CDCl₃, 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, CH₃-15).

¹³C NMR spectrum (125.75 MHz, CDCl₃):
(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, δ , cm⁻¹): 3088, 3011, 2978, 2938, 2896, 2869, 1781 (C=O γ -lacton), 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.

UV absorption spectrum (λ , nm, log ϵ , EtOH): 202 (0.367).

3,4α-epoxy-11,13-(1',1'-dibromomethano-)-1α,5α,7α,6β(H)-guai-10(14)-ene-12,6-olide (3). To a mixture of 3 mL CHBr₃, 2 mL of 50 %NaOH aqueous solution and 30 mg of crown ether was added 100 mg (0.0004 mol) of estafiatine 1, upon stirring. After the reaction completion, the mixture was poured into water and then extracted with chloroform. An organic layer was dried over MgSO₄. A residue was chromatographed on a column packed with SiO₂ (a mixture of petroleum-ether with ethylacetate being used as an eluent). Colorless crystal substance 3 was isolated, m.p. being at 204-206 °C, gross formula being presented as $C_{16}H_{18}O_3Br_2$, $R_f = 0.66$ (petroleum ether/EtOAc = 1 : 1). The yield amounted to 0.035 g (21 %).

IR spectrum (KBr, v, cm⁻¹): 3096, 3043, 2954, 2929, 2870, 1768 (C=O γ -lacton), 1641 (C=C), 1451, 1405, 1385, 1352, 1329, 1311, 1278, 1240, 1217, 1205, 1146, 1087, 1040, 1021, 1003, 986, 932, 891, 864, 827, 757, 699, 682 (C-Br), 601, 563, 523, 491, 444.

¹H NMR spectrum (500 MHz, CDCl₃, δ , ppm, J, Hz): 2.99 (1H, m, H-1), 3.36 (1H, s, H-3), 2.42 (1H, dd, J = 8.0; 6.0, H-5), 4.17 (1H, dd, J = 8.0; 6.0, H-6), 2.15 (1H, d, J = 8.0, H-13a), 1.95 (1H, d, J = 8.0, H-13b), 4.79 (1H, s, H-14b), 4.94 (1H, s, H-14a), 1.58 (3H, s, 15-Me).

¹³C NMR spectrum (125.75 MHz, CDCl₃):
40.13 (d, C-1), 31.70 (t, C-2), 44.71 (d, C-3),
35.70 (s, C-4), 63.08 (d, C-5), 79.53 (d, C-6),

50.59 (d, C-7), 27.31 (t, C-8), 29.16 (t, C-9), 144.98 (s, C-10), 32.98 (s, C-11), 171.79 (s, C-12), 27.53 (t, C-13), 115.55 (t, C-14), 18.34 (q, C-15), 65.67 (s, C-16).

The XRD experiments were carried out with the use of Bruker P4 and Syntex P21 diffractometers (a graphite monochromator, $\lambda(MoK_{\alpha})$ = 0.71073 Å, room temperature, $\theta/2\theta$ scanning mode) for compounds 2 and 3, respectively. The accounting of the absorption was carried out according to experimental curves of azimuthal scanning $(T_{\min}/T_{\max} = 0.925/0.981)$ for **2** and according the crystal facetting $(T_{\min}/T_{\max} =$ 0.311/0.656) for **3**. The structures were identified by means of a direct method. The positions and temperature parameters of non-hydrogen atoms were adjusted in isotropic, and then in anisotropic approximation by means of a full-matrix least-squares method. Hydrogen atoms were placed into geometrically determined positions and included then in the justification of the «equestrian» model. All the calculations were performed by means of SHELX-97 software. The geometrical analysis was performed with the use of PLATON software.

Crystallographic data and parameters of the XRD experiment for lacton **2** are as it follows: $C_{17}H_{18}Cl_4O_3$, M = 410.11, rhombic syngony, space group $P2_12_12_1$, a = 6.4539(5), b = 15.009(1), c = 19.453(2) Å, V = 1884.3(3) Å³, Z = 4, $d_{calc} = 1.449$ g/cm³, $\mu = 0.640$ mm⁻¹, scanning range $2\theta < 54^{\circ}$, 2374 measured reflections, 2077 reflections with $I \ge 2\sigma(I)$ ", 217 adjustable parameters, $R_1(I \ge 2\sigma(I)) = 0.0425$, $wR_2 = 0.1228$ (for all the reflections), the Flack's absolute structure parameter being 0.0(1).

Crystallographic data and parameters of the XRD experiment for lacton **3** are as it follows: $C_{16}H_{18}Br_2O_3$, M = 418.12, rhombic syngony, space group $P2_12_12_1$, a = 8.039(4), b = 11.255(5), c = 17.546(8) Å, V = 1588(1) Å³, Z = 4, $d_{calc} = 1.749$ g/cm³, $\mu = 5.113$ mm⁻¹, scanning range $2\theta < 50^{\circ}$, 1620 measured reflections, 1046 reflections with $I \ge 2\sigma(I)$ ", 190 adjustable parameters, $R_1(I \ge 2\sigma(I)) = 0.0579$, $wR_2 = 0.1335$ (for all the reflections), the Flack's absolute structure parameter being -0.05(5).

The crystallographic data and atomic coordinates for compounds **2** and **3** have been deposited in the Cambridge Structural Database (deposition numbers being CCDC651580 and CCDC651581, respectively).

REFERENCES

- 1 R. I. Jalmakhanbetova, A. T. Kulyjasov, V. A. Raldugin et al., 2nd Int. Conf. on Natural Products and Physiologically Active Substances (Book of Abstracts), Novosibirsk, 2004, p. 64.
- 2 F. Sánchez-Viesca, J. Romo, Tetrahedron, 19 (1963) 1285.
- 3 R. R. Kostikov, A. P. Molchanov, Zh. Org. Khim., 11 (1975) 1767.
- 4 F. H. Allen, O. Kennard, D. G. Watson et al., J. Chem. Soc. Perkin Trans. II, 12 (1987) 1.
- 5 F. H. Allen, Acta Cryst., B57, 380 (2002). Version 5-28.
- 6 W. Herz, S. V. Govindan, J. F. Blount, J. Org. Chem., 45 (1980) 3163.
- 7 C. S. de Heluani, M. P. de Lampasona, C. A. N. Catalan et al., Phytochem., 28 (1989) 1931.
- 8 R. S. Rowland, R. Taylor, J. Phys. Chem., 100 (1996) 7384.
 9 S. M. Adekenov, M. N. Mukhametzhanov, A. D. Kagar-
- litskiy, A. Zh. Turmukhambetov, *Khim. Prirod. Soyed.*, 603 (1984) [*Chem. Nat. Comp.*, 1984, (Engl. Transl.)].