Synthesis of two new chloro derivatives of the guaianolide grossmisin and the crystal structure of one derivative

O. V. Alebastrov,[a] S. A. Pigiltsova,[a] G. A. Atazhanova,[a] V. A. Raldugin,[b] M. M. Shakirov,[b] I. Yu. Bagryanskaya,[b] Yu. V. Gatilov,[b] A. T. Kulyjiasov,[a] S. M. Adekenov,[a] and G. A. Tolstikov[b]*

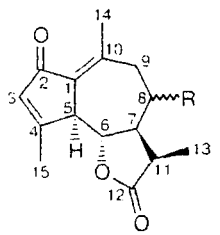
[a]*Institute of Phytochemistry, Ministry of Sciences and High Education of the Kazakhstan Republic, 4 ul. Gazalieva, 470032 Karaganda, Kazakhstan. Fax: +7 (321 2) 43 3773. E-mail: arglabin@phyto.karaganda.su*

[b]*Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent'eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383 2) 35 4752. E-mail: raldugin@nioch.nsc.ru*

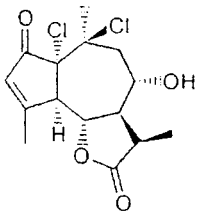
The reaction of grossmisin (8α-hydroxyachillin, **1**) with chlorine in benzene afforded a mixture of products. The less polar product readily crystallized after chromatography. According to the X-ray diffraction data, this product has the structure of 1α,10β-dichloro-1,10-dihydrogrossmisin. The second chloro derivative of grossmisin, *viz.*, 8β-chloroachillin, was prepared in good yield by the reaction of lactone **1** with PCl_5 in $CHCl_3$ in the presence of Py.

Key words: sesquiterpenoids; guaianolides; grossmisin; chlorination; X-ray diffraction analysis; two-dimensional NMR spectroscopy.

Natural chloro derivatives of sesquiterpene lactones are rather widespread in plants[1] and often exhibit pronounced biological activity. As part of continuing studies of natural[2] and semisynthetic[3] chloroguaianolides, we prepared two new chloro derivatives based on the well-known and readily accessible guaianolide grossmisin (8α-hydroxyachillin) (**1**). The latter is a component of the above-ground part of milfoil (*Achillea micrantha* Willd.),[4] which is a typical plant of Central Kazakhstan.[5]



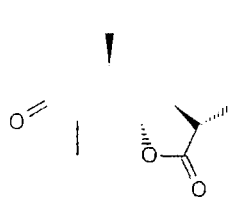
1: R = α-OH
5: R = β-Cl



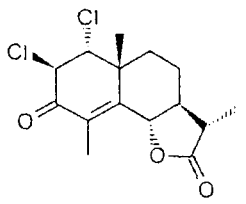
2

One of these derivatives, *viz.*, dichloride **2**, was prepared by the reaction of lactone **1** with chlorine in benzene. It should be noted that cross-conjugated dienone α-santonin **3** under analogous conditions (but in chloroform) also gave *trans*-dichloride **4**.[6] However, the latter compound is the product of addition at the carbon—carbon double bond, which is the less substituted of the two bonds.

Product **2** was obtained in low yield (~18%). After chromatography, this compound readily crystallized and



3



4

was separated from more polar admixtures of unidentified products. The molecular structure of **2** was established by X-ray diffraction analysis (Fig. 1). The bond lengths in molecule **2** are close to the average standard values.[7] The seven-membered ring of the molecule adopts a chair conformation, which is one of the most stable conformations for cycloheptanes. The lactone ring and the cyclopentenone fragment adopt envelope conformations with the C(7) and C(1) atoms, respectively, deviating from the corresponding planes through the remaining four atoms (the average deviation from the plane is 0.002 Å) by −0.546(8) and 0.325(8) Å, respectively. The following shortened[8] intermolecular contacts in the crystal of compound **2** are worthy of note: O(1)...H(O(4)), 2.41(10) Å; O(3)...H(C(11)), 2.37(5) Å; and Cl(2)...H(14), 2.89(9) Å.

The ^{13}C (Table 1) and ^{1}H NMR spectra (see the Experimental section) were interpreted with the use of the two-dimensional $^{1}H-^{1}H$ (COSY) and $^{13}C-^{1}H$ (COSY and COLOC (7 Hz)) spectra. The singlet signal at δ 74.56 in the ^{13}C NMR spectrum was assigned to the C(1) atom based on the fact that the two-dimensional COLOC NMR spectrum has a cross-peak caused by the corresponding carbon atom and the H(3) atom.

Published in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 1932—1934, November, 2000.

1066-5285/00/4911-1902 $25.00

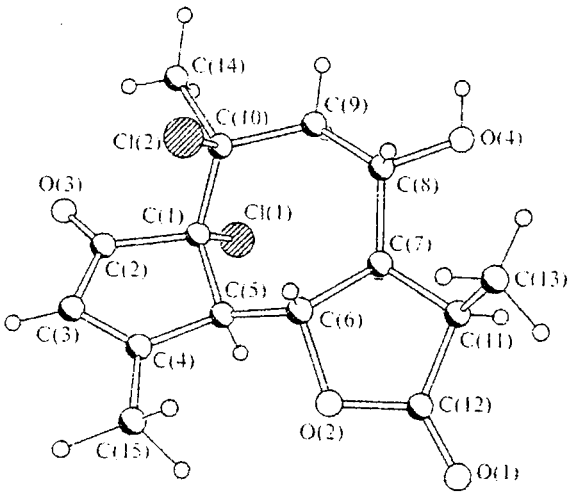


Fig. 1. Molecular structure of dichlorolactone **2**.

Chloride **5**, which is a product of replacement of the hydroxy group by the chlorine atom, was smoothly formed upon treatment of lactone **1** with phosphorus pentachloride in $CHCl_3$ in the presence of pyridine at room temperature. As expected,[9] the asymmetric center at the C(8) atom adopts a configuration reversed with respect to the initial configuration, which is evident from a comparison of the vicinal spin-spin coupling constants $J_{8,9A}$ and $J_{8,9B}$ in the ^1H NMR spectrum of product **5** with the analogous spin-spin coupling constants for 8α-hydroxy derivative **2** (see the Experimental section).

Experimental

The melting points were determined on a Boetius instrument. The IR spectra were recorded on a Vector 22 instrument in $CHCl_3$. The UV spectra (solutions in EtOH) were obtained on a Specord UV VIZ instrument. The NMR spectra were measured on a Bruker DRX-500 spectrometer (500.13 and 125.76 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$ with the use of standard programs (Bruker) for recording two-dimensional COSY and COLOC (7 Hz) NMR spectra. The high-resolution mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument. The optical rotation was measured (at 580 nm) on a Polamat A polarimeter in $CHCl_3$ (*c* 1.5).

Benzene was shaken with several portions of concentrated H_2SO_4 (10% by volume) for 20–30 min each until the acidic layer ceased to turn colored. Then benzene was washed with water, a 10% NaOH solution, and once again with water, dried over anhydrous $CaCl_2$, and distilled.

Pyridine was dried with granulated KOH for 3 days and then distilled over BaO.

Column flash chromatography was carried out on SiO_2 (Chemapol L 40/100 μm). TLC was performed on Silufol plates; spots were visualized by spraying with a 1% vanillin solution in H_2SO_4 and a 1% aqueous solution of $KMnO_4$.

The starting grossmisin (**1**) with m.p. 156–156.5 °C was isolated from the above-ground part of the plant *Achillea micrantha* Willd. according to a procedure reported previously.[4]

1α,10β-Dichloro-1,10-dihydrogrossmisin (2). Dry chlorine (which was dried by passing through vessels containing concentrated H_2SO_4, solid CaO, and solid P_4O_{10}) was bubbled through a solution of lactone **1** (200 mg) in PhH (10 mL) at 20 °C for 30 min until the starting compound **1** was completely consumed (TLC control). After removal of the solvent *in vacuo*, the resulting crystalline substance was chromatographed with the use of a 2 : 1 hexane–AcOEt mixture as the eluent to obtain a chromatographically homogeneous product (60 mg, R_f 0.68). Recrystallization from a 2 : 1 hexane–AcOEt mixture afforded dichlorolactone **2** in a yield of 45 mg (17.7%), m.p. 192–194 °C, $[\alpha]_{580}^{26}$ +269°. UV, λ_{max}/nm: 239 (ε 16080). IR, ν/cm^{-1}: 3610 (OH), 1777 (C=O γ-lactone), 1720 (C(2)=O), 1630 (C=C), 1349, 1262, 1179, 1063, 1022, 980, 843. MS, *m/z* (I_{rel} (%)): 282 [M(^{37}Cl) – Cl]$^+$ (33), 280 [M$^+$(^{35}Cl) – Cl] (100), 245 (23), 171 (52), 91 (34). Found, *m/z* 280.08623; calculated for $C_{15}H_{17}ClO_5$: 280.08661. ^1H NMR, δ: 1.39 (d, 3 H, $H_3C(13)$, $J_{11,13}$ = 7.5 Hz); 1.87 (br.s, 3 H, $H_3C(14)$); 2.24 (dd, H(9A), $J_{9A,9B}$ = 15.0 Hz, $J_{8,9A}$ = 5.0 Hz); 2.25 (br.s, 3 H, $H_3C(15)$); 2.74 (dd, H(9B), $J_{8,9B}$ = 10.5 Hz); 2.81 (ddd, 1 H, H(7), $J_{6,7}$ = $J_{7,8}$ = 10.5 Hz, $J_{7,11}$ = 7.5 Hz); 2.90 (quintet, 1 H, H(11), $J_{7,11}$ = $J_{11,13}$ = 7.5 Hz); 3.51 (br.d, 1 H, H(5), $J_{5,6}$ = 10.5 Hz); 4.10 (ddd, 1 H, H(8), $J_{8,9A}$ = 5.0 Hz, $J_{8,9B}$ = $J_{7,8}$ = 10.5 Hz); 4.88 (t, 1 H, H(6), $J_{6,7}$ = $J_{5,6}$ = 10.5 Hz); 6.14 (br.s, 1 H, H(3)). The data of ^{13}C NMR spectroscopy are given in Table 1. The crystals were used for X-ray diffraction study.

Table 1. Data of ^{13}C NMR spectroscopy for compounds **2** and **5** (δ)[a]

Atom	2	5	Atom	2	5
C(1)	74.56 s	131.21 s	C(9)	48.73 t	46.07 t
C(2)	197.72 s	195.20 s	C(10)	69.83 s	147.33 s
C(3)	130.03 d	135.72 d	C(11)	38.19 d	39.36 d
C(4)	175.79 s	169.49 s	C(12)	177.98 s	177.07 s
C(5)	64.04 d	53.85 d	C(13)	10.43 q	12.29 q
C(6)	76.31 d	78.17 d	C(14)	30.41 q	23.37 q
C(7)	49.22 d	54.72 d	C(15)	19.16 q	19.67 q
C(8)	66.15 d	53.99 d			

[a] The assignment of the signals was made based on the data of the two-dimensional ^{13}C–^1H (COSY and COLOC) and ^1H–^1H (COSY) NMR spectroscopy.

X-ray diffraction study of compound 2 was performed on a Bruker P4 diffractometer (Mo-Kα radiation; graphite monochromator; $2\theta/\theta$ scanning technique; $2\theta < 50°$) from a crystal of dimensions of 0.21 × 0.14 × 0.08 mm. The crystals are orthorhombic: a = 8.042(2), b = 12.815(2), c = 14.387(3) Å, V = 1482.7(5) Å^3, space group $P2_12_12_1$, Z = 4, $C_{15}H_{18}Cl_2O_4$, d_{calc} = 1.493 g cm^{-3}, μ = 0.450 mm^{-1}. The intensities of 1517 independent reflections were measured. The structure was solved by the direct method using the SHELXS-97 program package. The positions of the hydrogen atoms were calculated geometrically. The final refinement of the structural parameters was performed by the full-matrix least-squares method in the anisotropic-isotropic (for H atoms) approximation using the SHELXL-97 program package based on all F^2 to wR_2 = 0.1277, S = 1.070; 263 parameters were refined (R = 0.0449 using 1386 reflections with $F > 4\sigma$). The absolute configuration of molecule **2** was determined based on Flack's parameter (−0.07(14)). The coordinates and the equivalent thermal parameters of the nonhydrogen atoms were deposited with the Cambridge Structural Database.

8β-Chloroachillin (5). Pyridine (2 mL) was added to a solution of lactone **1** (100 mg) in $CHCl_3$ (15 mL) at 20 °C and then finely dispersed PCl_5 (70 mg) was added portionwise with continuous stirring. After 30 min, the reaction mixture was washed with 5% HCl (15 mL) and then with water. The resulting solution was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Chromatography of the residue (a 3 : 1 light petroleum–Et_2O mixture as the eluent) afforded colorless crystals of chlorolactone **5**, m.p. 114–115 °C, $[\alpha]_{580}^{22}$ +73.3°. The yield was 90 mg (84%). UV, λ_{max}/nm: 254 (ε 17100). IR, ν/cm^{-1}: 1780 (γ-lactone), 1687 (C(2)=O), 1640 and 1620 (two conjugated C=C), 1261, 1224, 1196, 1179, 1009, 867. MS, *m/z* (I_{rel} (%)): 282 [M^+(^{37}Cl)] (33), 280 [M^+(^{35}Cl)] (100), 265 (5), 245 (26), 244 (29), 217 (13), 201 (27), 199 (21), 187 (21), 173 (33), 171 (71), 159 (27), 145 (23), 91 (39), 77 (20), 44 (22). Found, *m/z*: 280.08816, calculated for $C_{15}H_{17}ClO_3$: 280.08661. ^{1}H NMR, δ: 1.35 (d, 3 H, $H_3C(13)$, $J_{11,13}$ = 7.6 Hz); 2.25 (br.s, 3 H, $H_3C(15)$); 2.40 (br.s, 3 H, $H_3C(14)$); 2.70 (dd, 1 H, H(9A), $J_{8,9A}$ = 6.0 Hz; $J_{9A,9B}$ = 15.0 Hz); 2.74 (br.dd, 1 H, H(7), $J_{7,11}$ = 7.6 Hz, $J_{6,7}$ = 10.5 Hz); 2.81 (quintet, 1 H, H(11), $J_{7,11}$ = $J_{11,13}$ = 7.6 Hz); 2.87 (br.d, 1 H, H(9B), $J_{9A,9B}$ = 15.0 Hz); 3.32 (d, 1 H, H(5), $J_{5,6}$ = 10.5 Hz); 4.30 (t, 1 H, H(6), $J_{5,6}$ = $J_{6,7}$ = 10.5 Hz); 4.53 (br.d, 1 H, H(8), $J_{8,9A}$ = 6.0 Hz, $J_{8,9B}$ ~ 1 Hz); 6.13 (br.s, 1 H, H(3)). The data of ^{13}C NMR spectroscopy are given in Table 1.

This work was financially supported by the Ministry of Sciences and High Education of the Kazakhstan Republic (Program of Basic Research, Project F0092) and by the Russian Foundation for Basic Research (Project No. 96-07-89187).

References

1. K. C. Engvild, *Phytochemistry*, 1986, **25**, 781.
2. A. G. Berdin, C. M. Adekenov, V. A. Raldugin, M. M. Shakirov, A. G. Druganov, A. T. Kulyyasov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 2010 [*Russ. Chem. Bull.*, 1999, **48**, 1987 (Engl. Transl.)].
3. O. V. Alebastrov, V. A. Raldugin, M. M. Shakirov, I. Yu. Bagryanskaya, Yu. V. Gatilov, A. T. Kulyyasov, C. M. Adekenov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1635 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1624 (Engl. Transl.)].
4. S. M. Adekenov, N. M. Gafurov, A. Zh. Turmukhambetov, and V. I. Ivlev, *Khim. Prirod. Soedin.*, 1987, 305 [*Chem. Nat. Comp.*, 1987 (Engl. Transl.)]
5. A. D. Kagarlitskii, S. M. Adekenov, and A. N. Kupriyanov, *Seskviterpenovye laktony rastenii Tsentral'nogo Kazakhstana* [*Sesquiterpene Lactones from Plants of Central Kazakhstan*], Izd-vo Nauka Kaz. SSR, Alma-Ata, 1987, 240 pp. (in Russian).
6. H. Takyanagi, H. Ogura, and T. B. H. McMurry, *Chem. Pharm. Bull.*, 1990, **38**, 581.
7. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans 2*, 1987, S1.
8. Yu. V. Zefirov and P. M. Zorkii, *Zh. Strukt. Khim.*, 1976, **17**, 994 [*J. Struct. Chem., (USSR)*, 1976, **17** (Engl. Transl.)].
9. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, Ithaca, 1969.

Received November 4, 1999;
in revised form July 6, 2000