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Synthesis and crystal structure of a new methoxytrichloro derivative of achillin

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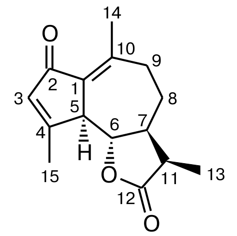
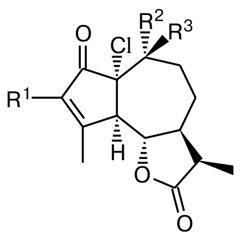
A new trichlorometoxy derivative of achillin was isolated from the mixture of chlorination products of achillin in MeOH. The structure of this product was established by X-ray diffraction analysis. This confirmed the previously proposed stereochemistry for the molecules of other two products of this reaction.

Key words: sesquiterpenoids; guaianolides; achillin; chlorination; X-ray diffraction analysis; 2D NMR spectroscopy.

Chlorination of the guaianolide achillin **1** in MeOH at ~20 °C results[1] in the predominant formation of methoxy dichlorides **2** and **3**, which are C(10)-epimers, with the intermediate formation of monochloride **4**. The structure of monochloride **4** has been proven by X-ray diffraction analysis. The probable configurations of the substituents at C(10) in the molecules of epimers **2** and **3** were proposed based on the results of quantum-chemical calculations.[2]



1



2—5

2: $R^1 = H$; $R^2 = CH_2OMe$; $R^3 = Cl$
3: $R^1 = H$; $R^2 = Cl$; $R^3 = CH_2OMe$
4: $R^1 = H$; $R^2 + R^3 = CH_2$
5: $R^1 = R^2 = Cl$; $R^3 = CH_2OMe$

We assumed that a decrease in the temperature of chlorination of lactone **1** would result in a higher solubility of chlorine and thus would increase the effective chlorine concentration in the reaction medium and change the composition of the reaction products. Indeed, when the reaction was carried out at –30 °C, the trichlorinated derivative of the starting lactone was isolated from the reaction mixture.[1] The structure of this product was established by X-ray diffraction analysis. This reaction gives in addition a mixture of nonidentified compounds.[1]

In this study, the structure of the major component of this mixture, compound **5**, was determined by X-ray diffraction analysis (Fig. 1).

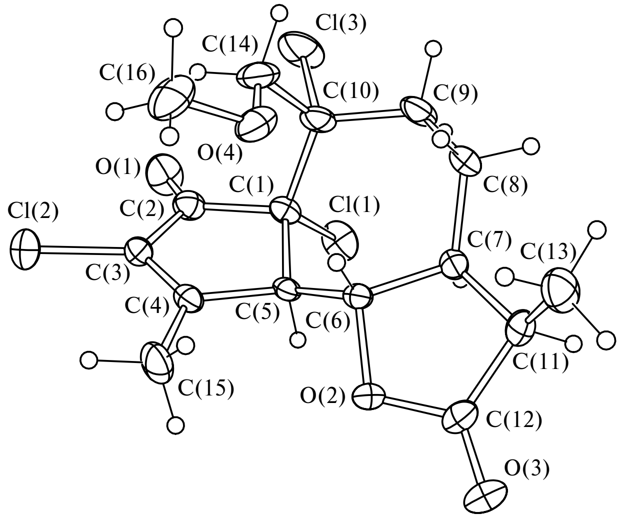


Fig. 1. Crystal structure of compound **5** according to X-ray diffraction data.

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The cyclopentene ring has an envelope conformation (the deviation of the C(1) atom from the plane is 0.336(4) Å). The conformation of the seven-membered ring is intermediate between the chair and twist-chair conformations. A similar conformation of these rings was found in the molecules of other chloro derivatives of achillin.[1,2] The conformation of the lactone ring of molecule **5** is close to the twist form. Note the presence of slightly shortened[3] intermolecular contacts in the packing of molecule **5**: C(7)—H...O(3) (H...O 2.40 Å, C—H...O 137°) and C(16)—H...Cl(3) (H...Cl 2.78 Å, C—H...Cl 138°).

The chemical shifts of the C(8) and C(9) signals in the ^{13}C NMR spectrum (Table 1) of product **5** are similar to those in the spectrum of epimer **3** but differ appreciably from those recorded for epimer **2**.[2] The fact that compound **5** is formally the 3-chloro derivative of epimer **3** also follows from the data of ^1H NMR spectroscopy (see Table 1). In particular, one of the doublets for the $C(14)H_2$ protons in the spectra of both lactones is additionally split to form doublets with J = 1 Hz ($^4J_{9A,14B}$). This is not observed in the spectrum of epimer **2**.

Thus, the unambiguous determination of the structure of methoxy trichloride **5** validates the assumption concerning the stereochemistry of the C(10) asymmetric center in dichloride **2** and its C(10)-epimer **3**, which has been made previously relying only on the data from molecular mechanics calculations.[2]

Table 1. Data from ^{13}C and ^1H NMR spectra for compounds **5** ($CDCl_3$)

Atom	δ (J/Hz)	
	^{13}C	^1H
1	75.22 s	—
2	189.11 s	—
3	129.91 s	—
4	164.26 s	—
5	61.39 d	3.67 (dq, $J_{5,6}$ = 9.0, $J_{5,15}$ = 1.5)
6	81.55 d	4.54 (dd, $J_{6,7}$ = 10.6)
7	40.36 d	2.92 (m)
8	23.74 t	1.80 (m, 8 A); 1.64 (m, 8 B)
9	39.41 t	2.82 (dddd, 9 A, J_{gem} = 15, ^3J = 13, ^3J = 5, $^4J_{9A,14B}$ = 1); 2.27 (dt, 9 B, J_{gem} = 15, ^3J = 4)
10	75.99 s	—
11	38.74 d	2.74 (quint, $J_{7,11}$ = $J_{11,13}$ = 7.5)
12	178.61 s	—
13	10.62 q	1.18 (d, 3 H, $J_{11,13}$ = 7.5)
14	76.53 t	3.49 (d, H(14A), J_{gem} = 11.0); 3.40 (dd, H(14B), J_{gem} = 11.0, $J_{9A,14B}$ = 1)
15	15.15 q	2.26 (d, 3 H, $J_{5,15}$ = 1.5)
OMe	59.11 q	3.23 (s, 3 H)

Experimental

Melting points were determined on a Boetius hot stage. IR spectra were recorded on a Vector 22 instrument. NMR spectra were run on a Bruker DRX-500 spectrometer (operating at 500.13 MHz for ^1H and at 125.76 MHz for ^{13}C) using standard Bruker software for recording the 2D COSY and COLOC spectra (7 Hz).

High-resolution mass spectra (EI, 70 eV) were measured on a Finnigan MAT 8200 mass spectrometer. Optical rotation was measured at 580 nm on a Polamat A polarimeter. Column flash chromatography was carried out on Chemapol 40/100 SiO_2 using light petroleum—ethyl acetate mixtures with increasing (0 to 60%) content of the latter component as the eluent. TLC was carried out on Silufol plates, which were visualized by spraying with a 1% solution of vanillin in H_2SO_4.

The starting achillin (**1**) with m.p. 145.5—146.5 °C was isolated by a previously described procedure[4] from the above-ground part of the plant *Achillea micrantha* Willd.

Chlorination of lactone **1** at −30 °C and separation of the reaction products was described in our previous publication.[1] Repeated chromatography of the fraction not separated previously[1] in the product mixture resulted on the isolation of compound **5** in 20% yield.

1α,3,10α-Trichloro-1,10-dihydro-14-methoxyachillin (5). The crystals with m.p. 176—178 °C (light petroleum—ethyl acetate), $[\alpha]^{22}_{580}$ +198 (c 1.18; acetone). UV (EtOH), λ_{max} 250 nm (ε = 6055). IR (KBr), ν/cm^{-1}: 1782 (γ-lactone), 1731 (C=O), 1622 (C=C), 1160, 1098, 1037, 997, 965, 907, 735, 718 (C—Cl); 688, 660. MS, m/z (I_{rel} (%)): 345 $[M(^{35}Cl) - Cl]^+$ (7), 309 $[M(^{35}Cl) - 2\ Cl - H]^+$ (100), 277 (12), 221 (7), 112 (10), 111(10), 55 (14), 45 (71). Found, m/z 345.06684. Calculated for $C_{16}H_{19}Cl_2O_4$: 345.06603. Found, m/z 309.08992; calculated for $C_{16}H_{18}ClO_4$: 309.08935.

X-ray diffraction experiment was carried out on a Bruker P4 diffractometer (Mo-Kα radiation with a graphite monochromator, 2θ/θ-scan mode in the region 2θ < 50°). A crystal of compound **5** with dimensions 1.00×0.4×0.4 mm^3 was selected for the experiment. The crystals are orthorhombic, a = 7.6479(5), b = 13.5443(8), c = 16.394(1) Å, V = 1698.1(2) Å^3, space group $P2_12_12_1$, Z = 4, $C_{16}H_{19}Cl_3O_4$, d_{calc} = 1.493 g cm^{-3}, μ = 0.556 mm^{-1}. The intensities of 1732 independent reflections were measured. An absorption correction was applied for the crystal habitus (transmission 0.73—0.87). The structure was solved by the direct method using the SHELXS-97 program package, while the positions of H atoms were calculated geometrically. The structure parameters were refined by the least-squares method in the full-matrix anisotropic approximation by the SHELXS-97 program package. The parameters of the H atoms in each cycle of refinement were calculated from the coordinates of the corresponding C atoms. The final structure refinement was carried out for all F^2 to wR_2 = 0.1218, S = 1.077; 209 parameters were refined (R = 0.0421 for 1658 $F > 4\sigma$). The Flack parameter is −0.05(13), which corresponds to the absolute configuration of the molecule under study indicated in formula **5**. The coordinates and the thermal factors of atoms are deposited with the Cambridge Structural Database.

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