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SYNTHESIS OF A NEW CHLORODERIVATIVE OF GROSSHEMIN GUAIANOLIDE

**S. A. Ivasenko, A. T. Kulyyasov,
and S. M. Adekenov**

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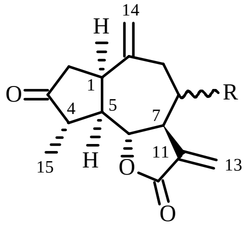
Natural chloroderivatives of sesquiterpene lactones are widely distributed in plants [1] and possess distinct biological activity.

In continuation of studies on the chemical modification of sesquiterpene lactones to produce new chloroderivatives with antitumor activity [1-5], we synthesized a new chloroderivative **2** based on the known and available grosshemin guaianolide **1**, a component of the aerial part of *Chartolepis intermedia* Boiss. grown in central Kazakhstan [6].



1: R = α-OH;
2: R = β-Cl

Treatment of **1** (200 mg) with PCl_5 (150 mg) in $CHCl_3$ (10 mL) in the presence of pyridine (5 mL) at room temperature forms **2** with mp 170-172°C (ethylacetate) in 67% yield. This is the product of substituting the OH by Cl. Compound **2** was purified by column chromatography over KSK silica gel with elution by a mixture of petroleum ether and ethylacetate (from 0 to 30%).

The IR spectrum of **2** exhibits the following absorption bands: 3081, 2934, 1780 (C=O of γ-lactone), 1765 (C=O), 1687, 1641, 1619, 1400, 1311, 1243, 1155, 1007, 962, 913, 812 (C–Cl), 650, 497.

The PMR spectrum (Table 1) of **2** contains a 3H doublet for the methyl group with H-15 at 1.17 ppm with SSCC 7.0 Hz, doublets of doublets for methylene protons H-2a and H-2b at 2.97 ppm (14.0 and 4.0 Hz) and 2.82 ppm with SSCC 14.0 and 3.0 Hz, a doublet of quartets for methine proton H-4 at 2.90 ppm with SSCC 7.0 and 7.0 Hz, a multiplet for methine proton H-7 at 3.78 ppm, a doublet of doublets for lactone proton H-6 at 4.51 ppm with SSCC 9.5 and 8.5 Hz, a multiplet for hemichloride proton H-8 at 5.07 ppm, doublets for protons of the lactone exomethylene group H-13a and H-13b at 6.30 ppm with SSCC 3.5 Hz and 5.83 ppm with SSCC 3.0 Hz, respectively, and broad singlets for protons of the exocyclic double bond H-14a and H-14b at 5.09 and 4.87 ppm, respectively.

The configuration of the asymmetric center on C-8, as expected [7], is inverted with respect to the starting one, as indicated by the small vicinal SSCC $J_{8,7} \sim 1.0$ Hz, which is consistent with the *cis*-orientation of protons H-7 and H-8 (Table 1).

Thus, reaction of grosshemin guaianolide with PCl_5 in $CHCl_3$ in the presence of pyridine produced a new chloroderivative, the structure of which was determined as 8β-chloro-3-oxo-1,5,7,8α,4,6β(H)-guai-11(13),10(14)-dien-6,12-olide.

Institute of Phytochemistry, Ministry of Education and Science of the Republic of Kazakhstan, 470032, Karaganda, ul. Gazalieva 4, fax (3212) 43 37 73, e-mail: arglabin@phyto.kz. Translated from Khimiya Prirodnykh Soedinenii, No. 6, p. 497, November-December, 2003. Original article submitted July 29, 2003.

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TABLE 1. PMR of 8β-Chloro-3-oxo-1,5,7.8α,4,6β(H)-guai-11(13),10(14)-dien-6,12-olide (**2**) (500 MHz, acetone-d_6)

H atom	δ, ppm, (J/Hz)
H-2a	2.97 dd (14.0, 4.0)
H-2b	2.82 dd (14.0, 3.0)
H-4	2.90 d qv (7.0, 7.0)
H-6	4.51 dd (9.5, 8.5)
H-7	3.78 m
H-8	5.07 ddd (5.0, 3.0, $^3J_{8,7}$ ~ 1.0)
H-9a	2.67 (15.0, 5.0)
H-9b	2.40 (15.0, 3.0)
H-13a	6.30 d (3.5)
H-13b	5.83 d (3.0)
H-14a	5.09 br.s
H-14b	4.87 br.s
H-15	1.17 d (3H, 7.0)

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