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SYNTHESIS OF 5β-CHLORO-4α-METHOXYSANTONIN OXIME

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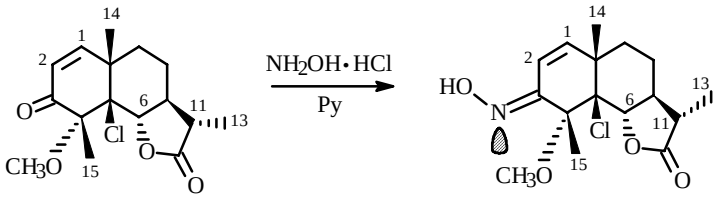
The new derivative 5β-chloro-4α-methoxysantonin oxime was prepared from 5β-chloro-4α-methoxysantonin by reaction with hydroxylamine hydrochloride in the presence of pyridine. The structure was established by IR, UV, and PMR spectroscopies.

Key words: sesquiterpene lactones, eudesmanolide, α-santonin, oxime formation.

The eudesmane sesquiterpene α-santonin is produced on an industrial scale from *Artemisia cina* Berg. This compound is used as starting material for further chemical modification in the total synthesis of natural compounds [1, 2].

Syntheses of chloro-derivatives of α-santonin have been published [3-5]. These derivatives may have high anti-tumor, antiviral, and other types of activities [6, 7].

Several chloro-derivatives of α-santonin were synthesized during a study of structure—activity relationships. The new compound 5β-chloro-4α-methoxysantonin **2** was prepared based on one of these.



1 **2**

Derivative **2** was prepared by reacting 5β-chloro-4α-methoxysantonin (**1**) with hydroxylamine hydrochloride in the presence of pyridine in 60% yield by the literature method [9].

The IR spectrum of **2** has characteristic absorption bands for C=O stretchings of the γ-lactone rings at 1790, C=N at 1650, =N–O– at 944, and C–Cl at 804 cm^{-1}. The UV spectrum exhibits an absorption maximum at 236 nm (log ε 3.75).

The PMR spectrum of **2** (Table 1) contains a 3H doublet for the methyl group of the lactone ring at 1.22 ppm with spin—spin coupling constant (SSCC) 7.0 Hz, a singlet for the angular methyl at 1.39 ppm, a singlet for the C-15 methyl at 1.71 ppm, a 3H singlet for the methoxy at 3.06 ppm, a doublet of quartets for the H-11 protons at 2.21 ppm with SSCC 12.0 and 7.0 Hz, a doublet for the lactone proton at 4.46 ppm with SSCC 11.5 Hz, and doublets for olefinic protons H-1 and H-2 with SSCC 10.5 Hz at weak field at 5.71 and 6.61 ppm, respectively.

The configuration of the N atom in **2** was determined as follows. It is known that oximes of α,β-unsaturated ketones react irreversibly at room or low temperature with sodium nitrite in the presence of acids [8]. Compound **2** remains inert under the conditions used to prepare heterocyclic derivatives of artemisia ketone [9], i.e., in the presence of $NaNO_2$ and AcOH and does not form nitrosation products of hydroxyimine. This indicates that the oxime group in **2** has the *E*-configuration, i.e., the unshared electron pair on the N atom is turned toward the methoxy and C-15 methyl, which create steric hindrance to attack by the nitrosonium cation.

Thus, reaction of **1** with hydroxylamine hydrochloride in pyridine produces a new derivative, the structure of which was established as 5β-chloro-4α-methoxy-3-hydroxyimino-7α,6,11β(H)-eudesm-1-en-6,12-olide (**2**) based on spectral data (IR, UV, and PMR).

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TABLE 1. PMR Data for 5β-Chloro-4α-methoxy-3-hydroximino-7α,6,11β(H)-eudesm-1-en-6,12-olide (**2**) (500 MHz, $CDCl_3$, δ, ppm, J/Hz)

Atom	δ, ppm, (J/Hz)
H-1	6.61 d (10.5)
H-2	5.71 d (10.5)
H-6	4.46 d (11.5)
H-11	2.21 dq (12.0, 7.0)
H-13	1.22 d (3H, 7.0)
H-14	1.39 s (3H)
H-15	1.71 s (3H)
OCH_3	3.06 s (3H)

EXPERIMENTAL

Melting points were determined on a Boetius apparatus. IR spectra were recorded on a Vector 22 instrument. PMR spectra were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^1H).

Column chromatography was performed on silica gel (KSK) using petroleum ether with increasing content of ethylacetate (from 0 to 30%) as eluent. TLC used Silufol plates and aqueous $KMnO_4$ (1%) as developer.

α-Santonin with mp 169-171°C was isolated from the aerial part of *Artemisia cina* Berg. ex Stechm [10] for chemical modifications.

Starting material 1 was prepared by chlorination of α-santonin with gaseous Cl_2 in CH_3OH by the literature method [5].

5β-Chloro-4α-methoxy-3-hydroxyimino-7α,6,11β(H)-eudesm-1-en-6,12-olide (2). Compound **1** (500 mg) was dissolved in Py (10 mL), treated with $NH_2OH \cdot HCl$ (1.0 g), boiled for 1 h, washed with HCl (15 mL, 5%) and water, dried over $MgSO_4$, and evaporated in vacuum. The solid was chromatographed to afford **2** (315 mg), mp 238-240°C (PE:EtOAc), 60% yield.

IR spectrum (KBr, ν, cm^{-1}): 3600 (OH), 2933, 1790 (C=O, γ-lactone), 1709, 1650 (C=N), 1456, 1377, 1244, 1176, 1043, 1031, 944 (=N–O–), 906, 863, 842, 804 (C–Cl), 784.

UV spectrum (EtOH, λ_{max}, nm): 236 (log ε 3.75).

Synthesis of 5β-Chloro-4α-methoxysantonin oxime. A solution of **2** (50 mg) in $CHCl_3$ (2 mL) was treated with finely ground $NaNO_2$ (40 mg). Glacial CH_3COOH (1 mL) was dropped in with constant stirring over 2 h. The reaction mixture was cooled to 2°C. According to TLC, the starting material was unreactive. The reaction mixture was treated with aqueous $NaHCO_3$ solution (5%) until the aqueous layer was neutral. The organic layer was dried over Na_2SO_4. The solvent was removed to afford **2** (45 mg) as an amorphous powder with mp 238-240°C (PE:ethylacetate).

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