THE STRUCTURE AND STEROCHEMISTRY OF ARTEMISIN*

ANTONIO G. GONZÁLEZ, JAIME BERMEJO, HORACIO MANSILLA, GUILLERMO M. MASSANET,
INMACULADA CABRERA, JUAN M. AMARO AND ANTONIO GALINDO

Department of Organic Chemistry and Biochemistry, University of La Laguna, Instituto de Productos Naturales,
Órganicos del CSIC, La Laguna, Tenerife, Canary Islands, Spain

(Revised received 14 March 1977)

Key Word Index—Artemisia maritima; Compositae; sesquiterpene lactone; artemisin.

Abstract—Artemisin was isolated from the aerial part of Artemisia maritima. Its structure and stereochemistry were
determined on the basis of chemical transformations and spectral evidence.

INTRODUCTION

As part of our researches into sesquiterpene lactones
from the Compositae, especially from the genus Artemisia,
we have begun a study of Artemisia maritima L ssp
Gallica Willd.

RESULTS AND DISCUSSION

Following the method described in the Experimental
we obtained a crystalline product with an intensely
bitter taste, mp 238–240°C, C16H22O4, [x]D 167° (1a).
The spectral data indicated a sesquiterpene lactone;
thus the IR spectrum showed absorption bands at
3570 (hydroxyl), 1770 (γ-lactone), 1650 and 920 cm⁻¹
(methylene double bond). The NMR spectrum showed
a broad singlet at δ 5.00 (2 protons, corresponding to
a methylene double bond), a group of signals centred
at δ 4.20 representative of a lactonic proton at C-6 and
a proton geminal to a hydroxyl group; a singlet at δ 0.86
corresponding to an angular methyl and a doublet at
δ 1.20 (J = 6 Hz) attributable to a secondary methyl.

We propose the relative configuration for this methyl
on the basis of the coupling constant [1, 2]. On treatment
of this product with acetic anhydride, a mono-acetate
was formed, mp 227–229°C, C17H24O5, [x]D 146° (1b). Its
IR spectrum showed that this substance had the same
absorptions as the original alcohol, plus the signal at
1720 cm⁻¹ characteristic of an acetate group. The signals
typical of secondary and tertiary methyls, as well as
those of lactonic proton (doublet at δ 4.28, J = 11 Hz)
and of the acetyl group (a singlet at δ 2.05), could be
observed in the NMR spectrum. The signal of the
proton geminal to the secondary hydroxyl showed a
paramagnetic shift (under acetylation) of 1.22 ppm,
appearing as a doublet of doublets at δ 5.42. At low field,
a doublet was seen at δ 5.05, attributable to an isolated
methylene. The presence of hydroxyl group absorptions
in the IR spectrum of the monoacetate (1b) suggested
the presence of a tertiary hydroxyl group.

The constants of artemisin, isolated by Rybalko et al.
[3] from Artemisia taurica, are identical to those of our
product. The Russian authors give a probable gross structure for artemisin (1a) without definitely establishing
the position of the secondary hydroxyl group, nor the
stereochemistry of the asymmetrical centres.

With the idea of determining these points, we carried
out a more intensive study of the structure and stereochemistry of artemisin. Using Grieco's procedure [4],
and subsequent phenylselenylation of the lactone, we obtained the phenylselenide (2). The oxidation
of this compound (2) with 50% H2O2 in THF/
acetic acid gave rise to a selenoxide (3), as intermediate product which suffered a syn-elimination to form product
4 which was identified as tansacetin [5] by comparing
its IR and NMR spectra with those of an authentic sample. This allowed us to determine the position and stereochemistry of the secondary and tertiary hydroxyls
(β-equatorial, 5α-axial, respectively) as well as the
disposition of the C-6 and C-7 hydrogens atoms (6β and
7α axial). NaBH4 reduction of 4 led to product 5, the
Rf values of which on TLC with various eluents were
identical to those displayed by artemisin. This confirmed
the z-orientation of the C-11 methyl group since this
type of reduction is highly stereospecific and always
yields the z-epimer [6]. From the foregoing data, we
deduced that the artemisin isolated in this laboratory from
Artemisia maritima is 1β,5α-dihydroxy-6β,7α,11H-selin-
4(15)-en-11z-methyl-6,12-olide (5).

On the basis of only spectral evidence, Tarasov et al.
[7] gave arsinbin the structure that we have established
for artemisin and they claimed that arsinbin and artemisin
are epimeric at C-11. They determined the C-11 con-
figuration of arsinbin by relating it to the downfield
shift (Δδ = +0.12 ppm) of the C-6 proton in β-santonin
as compared with z-santonin [8]. From the downfield
shift (Δδ = +0.23 ppm) of the C-6 protons in acetyl-
arsinbin and acetylartemisin, they conclude that the C-11
methyl group in arsinbin and β-santonin have the same
configuration. However, the formula they assign to
arsinbin (11z-methyl) contradicts this theory, while the
other configuration (11β-methyl) would favour their
**Monoacetylartemin.** Ca 55 mg of the alcohol was dissolved in Py and Ac₂O (2 ml) was added. The mixture was left for 12 hr and recovered in the normal way. The monoacetate thus obtained crystallized in EtOAc-petrol: mp 227–229°; MS m/e: 308 (M⁺); [α]D 146° (ca 0.23); IR νmax cm⁻¹: 3570, 1770, 1720, 1650 and 920; NMR: δ 1.00 (3H, s, C-10 Me), 1.25 (3H, d, J = 7 Hz, C-11 Me), 4.28 (1H, d, J = 11 Hz, C-6), 2.05 (3H, s, OAc), 5.05 (2H, d, J = 4.5 Hz, C-4=CH₂) and 5.42 (1H, dd, C-1) (Found: C, 65.97; H, 7.95. Calc for C₁₅H₂₄O₅: C, 66.21; H, 7.84%).

**Phenylethanol derivatives.** (i-Pr)₂NH (0.09 ml), BuLi (0.4 ml 2.1 in hexane) and dry THF (0.4 ml) were placed under dry Ar atmosphere and then cooled to -78°. The lactone (133 mg) was added slowly over 1 hr and then stirred for 20 min at -78°. Once the enolate had formed, diphenylselenide (188.5 mg) dissolved in dry THF (0.5 ml) containing HMPA (0.105 mg) was added rapidly in drops. After 40 min at -78°, the temp. was raised to -40° and the mixture stirred for 1.5 hr at that temp. The reaction was halted by the addition of 10% HCl. The resulting phenylethylselenide was recovered as normal, giving a yellow oil which could not be crystallized. MS m/e: 422 (M⁺) (C₁₉₅H₂₇O₄P(Se); NMR: δ 1.55 (3H, s, C-11 Me), 0.86 (3H, s, C-10 Me), 4.92 (2H, d, J = 12 Hz, C-4=CH₃) and 7.3-7.7 (5H, m, -C₅H₅).  

11-methylation. Phenylethylselenide (15 mg) in THF (1 ml) containing HOAc (0.01 ml) was cooled to 0° and 30% H₂O₂ soln (0.04 ml) was added. The mixture was stirred for 30 min at 0°, poured into a cold NaHCO₃ soln, then recovered by the standard process. Crystallization in EtOAc-petrol: mp 206-207°; IR νmax cm⁻¹: 3570, 1770, 1650 and 920; NMR: δ 6.12 and 5.45 (1H each, dd, J = 3.5 Hz, C-11=CH₂), 5.05 (2H, s, C-4=CH₂) 4.30 (1H, d, J = 11 Hz, C-6), 4.15 (1H, m, C-1) and 0.90 (3H, s, C-10 Me).

**Reduction with NaBH₄.** About 10 mg of the above product was dissolved in MeOH (8 ml), NaBH₄ (60 mg) added, and the mixture was stirred at 0° for 10 min. The MeOH was then eliminated and the residue acidified with 5% HCl; after the usual work-up, an oily substance was obtained. The Rf of artemin and this compound were identical in C₆H₆-EtOAc (7:3), EtOAc-petrol (1:1) and Me₂CO—(i-Pr)₂O (7:3).

**Acknowledgements—** We are indebted to Prof Herout of Prague for the IR and NMR spectra of tanaacetin.

**REFERENCES**