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SESQUITERPENE LACTONES OF *ARTEMISIA*. ARTECALIN FROM *A. CALIFORNICA* AND *A. TRIPARTITA* SSP. *RUPICOLA*

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Abstract—Artecalin (I), a sesquiterpene lactone of the Santanolide group, has been found in *Artemisia californica* Less. (section Abrotanum) and in *A. tripartita* Gray ssp. *rupicola* Beetle (section Seriphidium). By removal of the elements of water, artecalin is converted into tuberiferin, a constituent of a plant of the tribe Cichorieae.

INTRODUCTION

IN CONTINUATION of studies of the relationship between chemical constitution and systematics in the genus *Artemisia*, *A. californica* Less., a common perennial of Southern California and a member of the section Abrotanum, has been examined. The principal lactonic constituent is artecalin, a compound that had also been isolated as a minor component of the mixture of lactones present in *A. tripartita* Gray ssp. *rupicola* Beetle.[1]†

RESULTS AND DISCUSSION

Artecalin, $C_{15}H_{20}O_4$, is an α-methylene-γ-lactone (i.r. 1770 cm^{-1}) possessing a ketonic carbonyl group (i.r. 1700 cm^{-1}) and a hydroxyl group susceptible to acetylation with acetic anhydride-pyridine. The NMR spectra of artecalin and its acetate (II) indicated the presence of the structural elements shown in I, a conclusion that was substantiated by the transformations shown in the Fig. and described in the sequel.

The NMR spectrum of artecalin shows the pair of doublets of δ 5·45 and 5·93 (1 H each, $J=3$ Hz) typical of the exocyclic methylene group, and the expected signals for the methyl groups at C-4 and C-10. The structural analysis is more conveniently described in terms of NMR spectrum of the acetate (II), in which the proton at C-1 is clearly defined. Artecalin acetate shows signals for the methyl groups at C-10 (3 H singlet, δ 1·17) and C-4 (3 H doublet, δ 1·28, $J=6·5$ Hz) and for the acetyl methyl group (3 H singlet, δ 2·05). The lactonic proton at C-6 is seen as a well-defined triplet at δ 3·90 (1 H, $J=11$ Hz), its pattern being consistent with the *trans*-5,6/*trans*-6,7 disposition shown in I. The stereochemistry of the C-1 hydroxyl group is clearly revealed in the NMR spectrum of II by the appearance of the C-1 proton

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† The plants used in this study are recorded in vouchers placed in the UCLA Herbarium under the numbers AAB-81366-ATR, GHW-966-ATR and ROA-8767-ATR (*A. trip. rup.*); and ACAL-AM-50767, ACAL-AM-43167 and TAG-21067-ACAL (*A. calif.*). We are grateful to Professors A. A. Beetle, G. H. Ward and R. O. Asplund for collection and authentication of material.

[1] A. HOREAU and H. B. KAGAN, *Tetrahedron* **20**, 2431 (1964); A. HOREAU, *Tetrahedron Letters* 506 (1961).

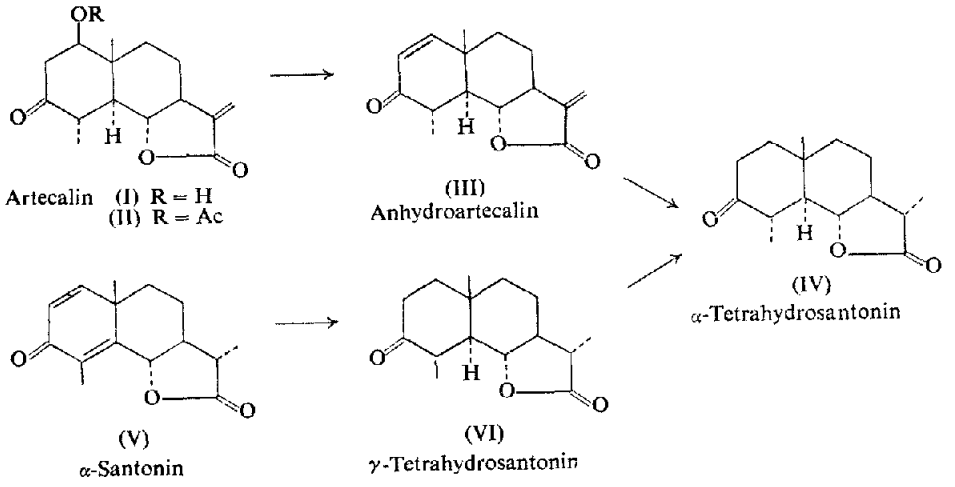
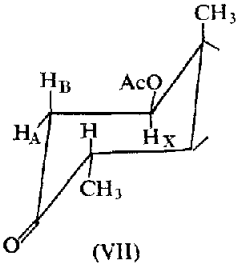


FIG. 1.

signal as a double doublet at δ 4·90 for the X component of an ABX pattern (VII). The coupling constants $J_{AX} = 6{\cdot}5$ Hz and $J_{BX} = 11$ Hz show the stereochemistry indicated in VII. Signals at δ 2·85 (H_A) and 2·43 (H_B) show geminal AB coupling of 16 Hz.



(VII)

The β-disposition of the C-1 hydroxyl group was further confirmed by application of the Horeau method for the determination of the stereochemistry of secondary hydroxyl groups.[1]

Treatment of artecalin acetate (II) with sodium acetate in ethanol resulted in the smooth elimination of acetic acid and the formation of the α,β-unsaturated ketone, anhydroartecalin (III). The NMR spectrum of III shows the characteristic pattern of the protons at C-1/2 as a pair of one-proton doublets at δ 6·75 (C-1) and 5·90 (C-2) with $J = 10$ Hz. The other details of the spectrum are in accord with structure III.

Final proof of these structures and for the stereochemistry was achieved by the conversion of anhydroartecalin, by catalytic hydrogenation, into the known compound α-tetrahydrosantonin (IV). The latter was prepared from α-santonin (V), by way of γ-tetrahydrosantonin (VI), by methods that have been described.[2] The specimens of IV prepared from III and from V were identical in all respects.

Anhydroartecalin (III) has the structure and stereochemistry reported for tuberiferine, isolated from a species of *Sonchus* (tribe Cichorieae); and the comparison of the properties

[2] W. COCKER and T. B. H. MCMURRAY, *J. Chem. Soc.* 4549 (1956); J. B. HENDRICKSON and T. L. BOGARD, *J. Chem. Soc.* 1678 (1962).

found for III and reported for tuberiferine[3] indicate their identity. Although the m.p. of our material (175°) does not agree closely with that reported for tuberiferine (160–162°), the optical rotations ($[\alpha]_D^{20}+9{\cdot}2$ and $[\alpha]_D^{27}+8{\cdot}6$ for III) are in substantial agreement. However, in view of our observations that artecalin and its derivatives do not show sharp m.ps but appear to polymerize during the heating process to form gels rather than clear liquid melts the lack of agreement in the m.ps of III and tuberiferine does not appear to us to be significant.

The occurrence of artecalin in species belonging to different sections[4] of the genus *Artemisia* may be compared with the occurrence of vulgarin (tauremisin-A) in species of sections *Abrotanum* and of *Seriphidium*,[5,6] and in the occurrence of other 1-oxygenated sesquiterpene lactones in *A. douglasiana* Bess. (Abrotanum)[7,8] and in a santonin-containing member of the section *Seriphidium*.[9] These observations provide chemical characters that could be used to support the view of Hall and Clements[4] that there is a close phylogenetic relationship between *Seriphidium* and certain members of *Abrotanum*. They do not, however, provide support for the suggestion[4] that *Artemisia californica* and the members of *Seriphidium* are so phylogenetically isolated that they are to be represented by divergent lines from the base on a phylogenetic chart. Further conclusions as to the phylogenetic relationships in the *Artemisia* must, however, wait upon further investigations of the chemical characters of members of these groups.

EXPERIMENTAL

Isolation of Artecalin (I)

(A) Three collections of *Artemisa tripartita* ssp. *rupicola*, collected near Laramie, Wyoming (see footnote † on p. 1297), were extracted with $CHCl_3$, and the extracts worked up in the usual manner. Hot water extracts of the total extractives were extracted with $CHCl_3$ and the residue from this solution chromatographed on a silica gel column. This plant is rich in a number of constituents,[10] and artecalin was isolated in but 0·001 per cent yield after extensive rechromatography followed by TLC examination of eluate fractions. (B) Extraction of several collections of *A. californica*[11] obtained near Malibu, California in the manner described in (A) yielded artecalin in 0·004 per cent yield. No other characterizable sesquiterpene lactones were obtained in a pure state. Herniarin (7-methoxycoumarin), a constituent of other *Artemisia* species[12] was also isolated.

Artecalin (I), colorless granules from ethyl acetate, m.p. 225–227° (to a gel), $[\alpha]_D^{23}+45°$ (c=0·01, $CHCl_3$); λ_{max} 210 nm (log ϵ 4·0); i.r. 3500, 1770, 1700 cm^{-1}. *Anal.* Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63. Found: C, 68·24; H, 7·64 per cent. Mol. wt. (mass spectrum), 264. Artecalin, acetylated with acetic anhydride-pyridine in the usual way, formed the acetate (II); crystallized from ethyl acetate, it was obtained as colorless prisms which did not melt sharply but appeared to polymerize and to decompose as the temperature exceeded 250°. *Anal.* Calc. for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24. Found: C, 66·78, H, 7·15 per cent. Mol. wt. (mass spectrum), 306.

Anhydroartecalin (III)

A. From artecalin. A solution of 81 mg of artecalin in 2 ml of formic acid was left overnight and then evaporated to dryness under vacuum. The crude product was purified by passage through a column of silica

[3] J. B. BARRERA, J. L. BRETON, M. FAJARDO and A. G. GONZALES, *Tetrahedron Letters* 3475 (1967).
[4] Section classification is not fully agreed upon by all authorities. We use the designations of H. M. Hall and F. E. Clements, Carnegie Inst. of Washington, Publ. No. 326, 1923. P. POLJAKOV, *Flora U.S.S.R.* **26**, 425 (1961), adopts a different arrangement; but in neither classification are *A. californica* and members of the group to which *A. tripartita* belongs regarded as closely allied.
[5] T. A. GEISSMAN and G. A. ELLESTAD, *J. Org. Chem.* **27**, 1855 (1962).
[6] K. S. RYBALKO and L. DOLEJS, *Coll. Czech. Chem. Commun.* **26**, 2909 (1961).
[7] S. MATSUEDA and T. A. GEISSMAN, *Tetrahedron Letters* 2013 (1967).
[8] S. MATSUEDA and T. A. GEISSMAN, *Tetrahedron Letters* 2159 (1967).
[9] W. G. DAUBEN, J. S. P. SCHWARZ, W. K. HAYES and P. D. HANCE, *J. Am. Chem. Soc.* **82**, 2239 (1960).
[10] T. A. GEISSMAN, M. A. IRWIN and T. G. WADDELL, unpublished observations.
[11] Although different populations of a given species often show marked differences in chemical constituents, all of the *A. californica* samples were subjected to preliminary assay by TLC and found to be substantially identical.
[12] For example, T. A. GEISSMAN, *J. Org. Chem.* **31**, 2523 (1966).

gel (benzene-$CHCl_3$) and, after recrystallization from ethyl acetate–ether, formed colorless prisms, m.p. 175–177° to a glass.

B. From artecalin acetate. A solution of 130 mg of II and 420 mg of anhydrous NaOAc in 25 ml of ethanol was refluxed for 1 hr, cooled, diluted with water and extracted with $CHCl_3$. The residue from the $CHCl_3$ solution was recrystallized from ethyl acetate to give 82 mg of anhydroartecalin. The compound melted at 171–175° to a glass; it had $[\alpha]_D^{27}$ +8·6° (c=0·027, $CHCl_3$). It was also noted that upon exposure to hot solvents the compound was partially transformed into insoluble, polymeric material. *Anal.* Calc. for $C_{15}H_{18}O_3$: C, 73·14; H, 7·37. Found: C, 73·48; H, 7·39 per cent. Mol. wt. (mass spectrum), 246.

α-Tetrahydrosantonin (IV)[3]

A. From santonin (V). α-Santonin was hydrogenated (Pd–C ethyl acetate) to yield γ-tetrahydrosantonin, m.p. 146–148°. This was converted into α-tetrahydrosantonin by the action of $HClO_4$ in ethanol. The product had m.p. 156–158°.[3] *Anal.* Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86. Found: C, 72·12; H, 8·89%.

B. From anhydroartecalin. Hydrogenation of anhydroartecalin with Pd–C in methanol resulted in the absorption of two moles of H_2. The product was recrystallized from ethyl acetate to yield α-tetrahydrosantonin as colorless prisms, m.p. 156–158°. The m.p. was unaltered by admixture with the compound prepared from santonin.

Configuration at C-1 of Artecalin[2]

A solution of 115 mg of artecalin and 285 mg of (±)-α-phenylbutyric anhydride in 2·5 ml of pyridine was allowed to stand for 48 hr, at which time TLC examination showed that the reaction was complete. The mixture was taken up in $CHCl_3$ and the α-phenylbutyric acid recovered by extraction with aqueous $NaHCO_3$. The recovered acid (180 mg) was dissolved in 1 ml of $CHCl_3$ and showed $[\alpha]_D^{28}$ +11·2°.

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