tartrate crystallized over 3 days. The precipitates were washed, dried and weighed for estimation of tartrate present.

Uronic acid present was determined in 15-ml. aliquot portions by measurement of the carbon dioxide evolved when the solutions were made 12% in hydrochloric acid and heated.[13,14] Yields of glyoxylic and tartaric acids are shown in Table II and the yields of uronic acids are shown in Table III.

Carbon Dioxide Evolved.—Four grams of sodium alginate was dissolved in each of four 300-ml. portions of water and the solutions adjusted one each to *p*H 3, 5, 7 and 9. Adjustment to *p*H 3 was obtained by addition of hydrochloric acid to lower the *p*H value, which then was buffered at 3 by addition of monopotassium phosphate. Adjustment to *p*H 5 and 7 was obtained by addition of small quantities of mono- and dipotassium phosphate in appropriate ratios. Adjustment to *p*H 9 was obtained with dipotassium phosphate. To each solution in a closed vessel hypochlorite solution was added to the level of 3 moles per mole of sugar unit and the volumes adjusted to 450 ml. each. Evolution of carbon dioxide was measured as described in an earlier report.[2c] Results are shown in Table I.

LAFAYETTE, IND.

(13) K. U. Lefèvre and B. Tollens, *Ber.*, **40**, 4513 (1907).

(14) R. L. Whistler, A. R. Martin and M. Harris, *J. Research Natl. Bur. Standards*, **24**, 13 (1940).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TAKEDA PHARMACEUTICAL INDUSTRIES, LTD., AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Stereochemical Correlation of (−)-α-Santonin, Artemisin and ψ-Santonin

BY M. SUMI, WILLIAM G. DAUBEN AND WILLIAM K. HAYES

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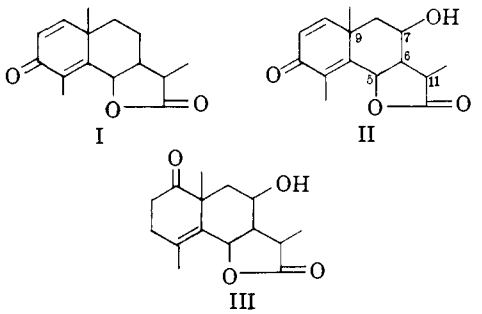
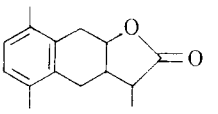
Artemisin, the 7-hydroxy derivative of (−)-α-santonin, has been degraded to α-(1,4-dimethyl-7-hydroxy-5,6,7,8-tetrahydro-6-naphthyl)-propionic acid lactone (IV), a compound also derivable from ψ-santonin. This result establishes a common stereochemistry for C_6, C_7 and C_{11} in these two series of sesquiterpenic acid lactones. Other workers previously have established a similar relationship for the C_9-angular methyl group.

From a variety of species of Artemisia, the sesquiterpenic acid lactones (−)-α-santonin (I), artemisin (II) and ψ-santonin (III) have been obtained.[1] These compounds all possess a common



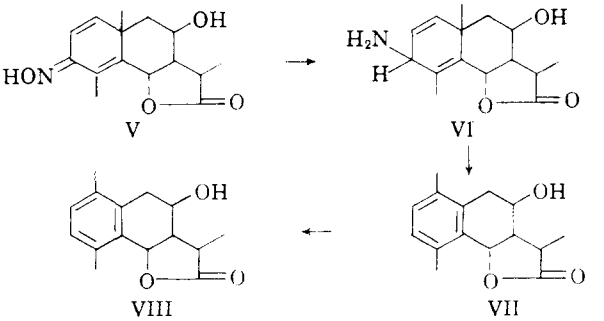
I II III

carbon skeleton but differ as to the number and placement of certain functional groupings. In view of the several common structural characteristics as well as common biological origins of these compounds, it was of interest to relate the absolute configurations of the various asymmetric centers present in them. It has been shown[2] recently that artemisin (II) is a 7-hydroxy derivative of (−)-α-santonin. Since II possesses characteristics of santonin in ring A and characteristics of ψ-santonin in ring B, it can serve as a relay in the correlation of the configurations of these two series of sesquiterpenic acid lactones. Of the five asymmetric centers in ψ-santonin (III), it already has been established, on the basis of optical rotatory dispersion measurements,[3] that the C_9-angular methyl group has the same absolute configuration as in (−)-α-santonin. The remaining centers are in ring B and by conversion of artemisin (II) to α-(1,4-dimethyl-7-hydroxy-5,6,7,8-tetrahydro-6-naphthyl)-propionic acid lactone (IV), which has been prepared from ψ-santonin,[4] the stereochemistry of C_6, C_7 and C_{11} of the two series could be related.



IV

Artemisin (II) was converted to its oxime V which upon reaction with zinc and sulfuric acid in the presence of copper sulfate was transformed into artemisinamine sulfate (VI). Due to the instability of the amine, it was not isolated but was heated directly with aqueous acid in order to transform it into hypoartemisin (VII). When the latter compound was heated in acetic acid with zinc, the conditions required to convert hyposantonin to hyposantonous acid,[1] only acetylation of the hydroxyl group occurred. Since, in general, a *cis*-lactone undergoes reductive fission more readily



V VI VIII VII

than the *trans* isomer, hypoartemisin with the *trans*-lactone was converted into its *cis* isomer, iso-

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(2) M. Sumi, *Proc. Japan Acad.*, **32**, 684 (1956); **33**, 153 (1957); *Pharm. Bull.*, **5**, 187 (1957).

(3) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956); see also, H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1956).

(4) W. G. Dauben, P. D. Hance and W. K. Hayes, THIS JOURNAL, **77**, 4609 (1955).

hypoartemisin (VIII), by saponification of the lactone followed by acidification. Since such a transformation sequence when applied to the conversion of hyposantonin to isohyposantonin has been shown to involve only the lactone fusion stereochemistry,[1] a similar change can be assumed in the isohypoartemisin preparation. When the *cis*-lactone VIII was heated in glacial acetic acid in the presence of zinc, it was transformed directly to the tetralin lactone derivative IV.

In the degradation of ψ-santonin (III) and artemisin (II) to the lactone IV, three asymmetric centers, C_6, C_7 and C_{11}, of the original molecule were retained. The chemistry involved in these transformations should not have affected these three centers. Thus, the present work when coupled with the previous results[3] shows that (−)-α-santonin, artemisin and ψ-santonin possesses the same configuration at C_6, C_9 and C_{11} and that the C_7-hydroxyl group in ψ-santonin and artemisin also are of the same configuration. The stereochemical relationship of C_5 still awaits direct establishment.[5]

Experimental[6]

Hypoartemisin (VII).—To a solution of 790 mg. of artemisin oxime in 32 ml. of 90% ethanol there was added, in turn, 1.5 ml. of concd. sulfuric acid, several drops of aqueous cupric sulfate solution and 5 g. of zinc powder. The mixture was stirred at 33° for 30 hours, the zinc filtered and washed with ethanol. The combined filtrates were concentrated under reduced pressure until almost all of the solvent had been removed. The concentrated solution was cooled but no solid separated. Upon dilution with 15 ml. of water, a small amount of solid separated which was filtered and not further investigated.

The aqueous alcoholic filtrate was refluxed for 45 minutes during which time it became turbid and a crystalline solid separated. After cooling, the solid was filtered (350 mg.) and recrystallized from ethanol, m.p. 198°, $[\alpha]^{20}D$ +73° (*c* 0.5), λ_{max}^{EtOH} 270 mμ (log ϵ 2.77).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.94; H, 7.33.

Hypoartemisin Acetate.—Hypoartemisin (150 mg.) was heated for 10 hours in acetic acid with 1 g. of zinc powder. After the zinc was filtered, the filtrate was concentrated under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water, aqueous sodium carbonate and water, dried and solvent evaporated to yield 90 mg. of a crystalline solid, m.p. 160–170°. The material was recrystallized from ethanol, m.p. 173°, $[\alpha]^{20}D$ +60° (*c* 1.0); λ_{max}^{EtOH} 269.5 mμ (log ϵ 2.77), 278.5 mμ (log, ϵ 2.77); $\nu_{max}^{CHCl_3}$ 1770 cm.$^{-1}$ (lactone), 1731 cm.$^{-1}$ (acetate) no hydroxyl band.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.47; H, 6.94.

Isohypoartemisin (VIII).—Hypoartemisin (300 mg.) was dissolved in 90 ml. of 90% ethanol containing 280 mg. of potassium hydroxide and the solution was refluxed for 2 hours. After cooling, the reaction mixture was acidified with 5% hydrochloric acid, the ethanol removed under reduced pressure and the residual mixture extracted with ether. The extract was washed with water, dried and the ether evaporated. The crude product (150 mg., m.p. 121–130°) was recrystallized from ethyl acetate–petroleum ether (b.p. 30–70°), m.p. 131–133°, $[\alpha]^{23}D$ −80° (*c* 1.0), λ_{max}^{EtOH} 271 mμ (log ϵ 2.93), 280 mμ (log ϵ 2.96).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.16; H, 7.23.

α-(1,4-Dimethyl-7-hydroxy-5,6,7,8-tetrahydro-6-naphthyl)-propionic Acid Lactone (IV).—A solution of 100 mg. of isohypoartemisin in 25 ml. of glacial acetic acid was refluxed with 2 g. of zinc powder for 10 hours. The solution was filtered, concentrated under reduced pressure and extracted with ethyl acetate. The extract was washed with water, aqueous sodium carbonate and water and the solvent evaporated to yield 20 mg. of crystalline solid. The material was recrystallized from ligroin (b.p. 70–85°), m.p. 142–144°, $[\alpha]^{25}D$ +39° (*c* 0.90, EtOH), $[\alpha]^{25}D$ +51° (*c* 1.04, chf.), λ_{max}^{EtOH} 267 mμ (log ϵ 2.61), 276 mμ (log ϵ 2.55). The melting point was not depressed upon mixing with an authentic sample prepared from ψ-santonin.[4] The infrared spectra of both samples were identical.

Acknowledgment.—The authors are indebted to Professor H. H. Inhoffen for kindly supplying the artemisin.

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(5) ADDED IN PROOF.—Since submission of this manuscript, W. Cocker and T. B. H. McMurry (*Proc. Chem. Soc.*, 147 (1958)) have correlated the stereochemistry of positions 6, 7 and 9 of ψ-santonin with tetrahydroalantolactone, the absolute configuration of which has been established previously.

(6) All melting points are uncorrected. Rotations were measured in ethanol.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF ETHICON, INC.]

Keto Fatty Acids Derived from Castor Oil. I. Unsaturated Acids[1]

BY JOSEPH NICHOLS AND EDGAR SCHIPPER

RECEIVED APRIL 21, 1958

The chromic acid and Oppenauer oxidation of ricinoleic and ricinelaidic acid to unsaturated keto acids has been investigated. The structure of the chromic acid oxidation product of 12-oxo-*cis*-9 or 12-oxo-*trans*-9-octadecenoic acid has been elucidated and the compound shown to be 9,12-dioxo-*trans*-10-octadecenoic acid.

In recent years there has been increasing interest in the role of unsaturated fatty acids as nutritional factors, especially as related to the problem of atherosclerosis.[2] The inhibition of bacterial and fungal organisms by fatty acids and their derivatives also has received considerable attention.[3] While the exact mode of action of these fatty acids in bacterial and mammalian metabolism has not been established, sufficient evidence has accumulated which points to their involvement in important enzyme systems.[4] It seemed

(1) Presented in part at the 126th Meeting of the American Chemical Society in New York, N. Y., September, 1954.

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