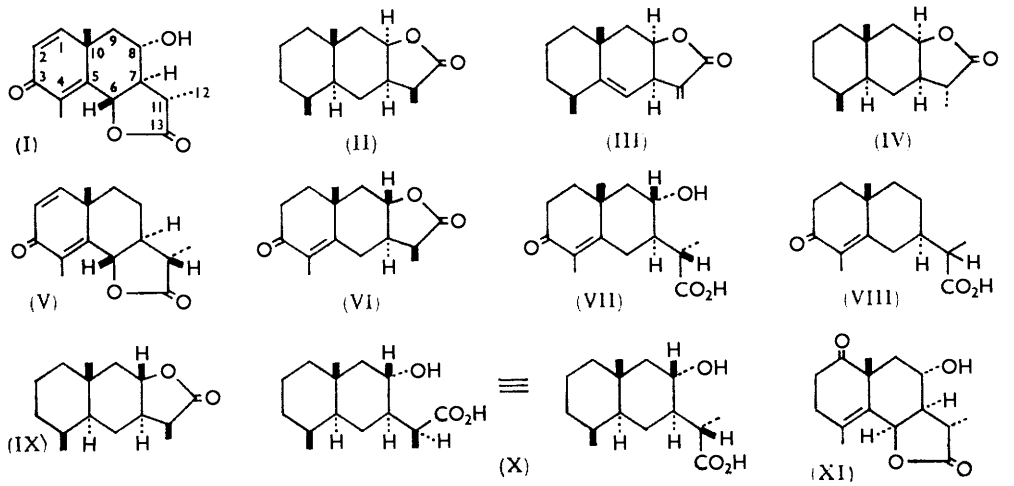
83. *The Stereochemistry of Tetrahydroalantolactones.*

By Wesley Cocker and M. A. Nisbet.

Artemisin (I), of known stereochemistry, has been related to tetrahydroalantolactone (II).

When alantolactone (III) is reduced over a catalyst it gives a tetrahydro-compound whose stereochemistry has been given as (IV).[1-4] The configuration at C-11 was based [4] on the probable 1,4-addition of hydrogen, from the α-face of the molecule, to the unsaturated lactone system of (III), followed by isomerisation to (IV). Application of our lactone rule [5] would make this the more stable of the two C(11)-epimers as is required by the chemistry of this tetrahydro-compound. However, the recent discovery [6] that santonin (V) has the 11β(H)- rather than the 11α(H)-configuration widely believed, has cast doubt on the validity of this lactone rule. We have now shown that in fact this tetrahydroalantolactone is (II) by relating it to artemisin. Artemisin has been related [7] to santonin and therefore has structure (I), and hence the tetrahydroalantolactone can be related to santonin.



Reduction of artemisin with lithium in liquid ammonia affords the deoxy-lactone (VI), presumably by way of the acid (VII). This reaction has been applied to santonin,[8,9] to its 11-epimer,[9] and to their 6-epimers,[9] where it affords acids of general formula (VIII). The conversion of (VI) into its dithioketal takes place with ease, and the latter is hydrogenolysed with Raney nickel in dioxan giving a gum whose spectrum suggests partial reduction of the 4,5-double bond (ε = 666 at 2200 Å; contribution of lactone about 150). Completion of the reduction over palladised charcoal gives (IX) as a glass,[2,3] but this on mild hydrolysis with alkali affords the known hydroxy-acid (X).[2,3] Since, by oxidation

[1] Benešova, Sýkora, Herout, and Sörm, *Chem. and Ind.*, 1958, 363.
[2] Tsuda, Tanabe, Iwai, and Funakoshi, *J. Amer. Chem. Soc.*, 1957, **79**, 5721.
[3] Cocker, McMurry, and Hopkins, *J.*, 1959, 1998.
[4] Cocker, Hopkins, McMurry, and Nisbet, *J.*, 1961, 4721; cf. Cocker and McMurry, *Tetrahedron*, 1960, **8**, 181.
[5] Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828.
[6] Asher and Sim, *Proc. Chem. Soc.*, 1962, 111, 355; Barton, Miki, Pinhey, and Wells, *ibid.*, p. 112.
[7] Sumi, *Pharm. Bull. Japan*, 1957, **5**, 187; *Proc. Japan Acad.*, 1957, **33**, 153; *J. Amer. Chem. Soc.*, 1958, **80**, 4869.
[8] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858.
[9] Cocker and Nisbet, unpublished results, communicated at 2nd International Symposium on the Chemistry of Natural Products, Prague, 1962.

of its methyl ester followed by reduction of the ketone with borohydride and subsequent lactonisation, (X) affords (II),[2,3] a reaction which can be reversed when sodium in propan-2-ol is used as reducing agent, lactone (II) must have the configuration shown at C-11.

ψ-Santonin (XI) has been related[3] to tetrahydroalantolactone (II). The work now described provides a link between ψ-santonin, artemisin, and santonin. All three compounds have the 11β(H)-configuration.

Experimental

Reduction of Artemisin.—3-Oxo-8β(H),11α(H)-*eudesm*-4-*en*-8,13-*olide* (VI). Artemisin (4 g.) in tetrahydrofuran (50 c.c.) was slowly added with stirring to a solution of lithium (1·2 g.) in liquid ammonia (300 c.c.), stirring was continued for 3 hr. and the mixture was set aside overnight. Ammonia was allowed to evaporate, and the residue dissolved in ice–water, acidified with N-sulphuric acid, and extracted with ether. The ethereal solution was extracted with 5% sodium carbonate, and the extract was acidified and extracted with ether yielding an oil. This was dissolved in benzene (50 c.c.) and refluxed for 2 hr. with toluene-*p*-sulphonic acid (0·3 g.). The solution was cooled, washed with 5% sodium hydrogen carbonate and dried, thus giving 3-*oxo*-8β(H),11α(H)-*eudesm*-4-*en*-8,13-*olide* as plates (1·9 g.), m. p. 142° (from ethyl acetate–light petroleum, $[\alpha]_D^{18}$ +19·4° (*c* 0·24), $\lambda_{max.}$ 2480 (log ε 4·0), 3100 Å (log ε 1·9), $\nu_{max.}$ 1775 (lactone), 1661, 1613 cm.$^{-1}$ (C=C–C=O) (Found: C, 72·5; H, 8·5. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

Dithioketal of 3-*Oxo*-8β(H),11α(H)-*eudesm*-4-*en*-8,13-*olide*.—The keto-lactone (VI) (0·15 g.) was mixed with ethane-1,2-dithiol (0·15 c.c.), boron trifluoride–ether complex (0·2 c.c.) was slowly added, and the mixture was set aside overnight. The required *dithioketal* consisted of needles (0·11 g.), m. p. 158° (from aqueous ethanol), $[\alpha]_D^{19}$ + 43·6° (*c* 0·23), $\nu_{max.}$ 1761 cm.$^{-1}$ (lactone) (Found: S, 20·0. $C_{17}H_{24}O_2S_2$ requires S, 19·8%).

8α-*Hydroxy*-4,5,α(H),11β(H)-*eudesman*-13-*oic Acid* (X).*—The dithioketal (0·1 g.) was refluxed for 18 hr. with Raney nickel (0·4 g.) in dioxan (12 c.c.), giving an oil (70 mg.), $\nu_{max.}$ 1775 cm.$^{-1}$, which was hydrogenated in ethyl acetate (30 c.c.) over 10% palladised charcoal (0·1 g.). The product, a gum, was refluxed for 1·5 hr. with potassium hydroxide (0·1 g.) in methanol (2·5 c.c.). Water (2 c.c.) was then added, the solution was acidified, and the product was extracted with ether, giving the required acid (40 mg.) (plates from aqueous methanol), m. p. and mixed m. p. 179—180°,[2,3] $[\alpha]_D^{18}$ +69·0° (*c* 0·034), $\nu_{max.}$ 3450, 1706 cm.$^{-1}$.

University Chemical Laboratory,
Trinity College, Dublin.

[*Received, July 23rd*, 1962.]

* We use the nomenclature, for this acid, adopted previously.[3]