399. *The Chemistry of ψ-Santonin. Part XI.* Its Absolute Configuration.*

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Previous configurational assignments to the centres at 7, 8, and 10 in ψ-santonin (I) have been confirmed by relating it to tetrahydroalantolactone (VII). The steric formula for tetrahydro-ψ-santonic acid (II) has been justified. The stereochemistry of these compounds at position 11 is discussed.

In a preliminary communication [1] we described the conversion of ψ-santonin [2-4] (I) through tetrahydro-ψ-santonic acid [4,5] (II) into the acid (V), which we now show to be 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid. The latter acid was previously obtained [6] from tetrahydroalantolactone whose absolute configuration at all centres except that at $C_{(11)}$ (but see below) has been shown to be as in (VII).[6,7] We now give details of the investigations previously outlined.[1]

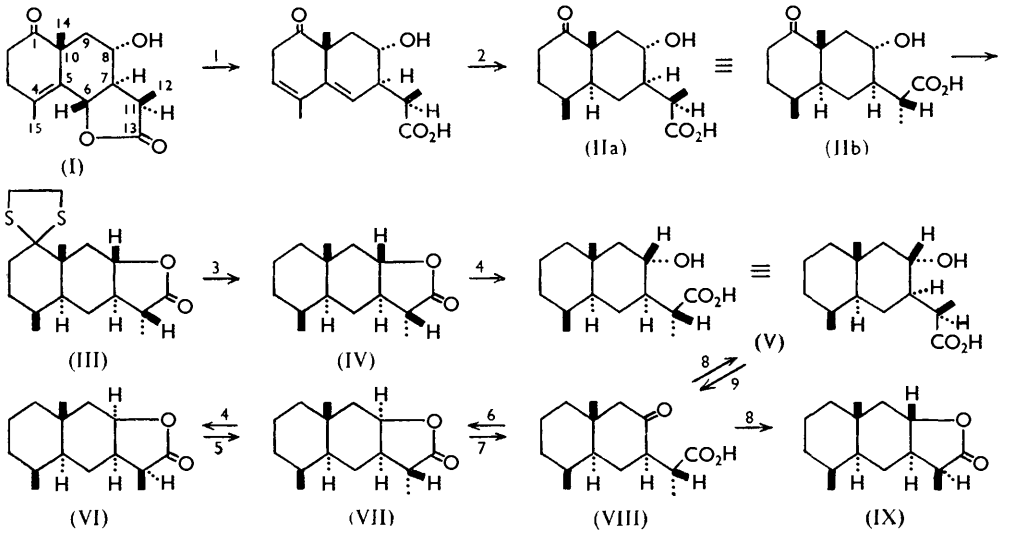
* Part X, *J.*, 1956, 1828. In the present paper we use Cocker and Cahn's nomenclature (*Chem. and Ind.*, 1955, 384). In the case of the acids (*e.g.*, II, III) the 11(H) is referred to as α- or β- by reference to the 11(H) of the angular lactones (*e.g.*, I).

[1] Cocker and McMurry, *Proc. Chem. Soc.*, 1958, 147.
[2] Chopra, Cocker, Cross, Edward, Hayes, and Hutchison, *J.*, 1955, 588.
[3] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[4] Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828.
[5] Cocker and Lipman, *J.*, 1949, 1170.
[6] Tsuda, Tanabe, Iwai, and Funakoshi, *J. Amer. Chem. Soc.*, 1957, **79**, 5721; cf. Tanabe, *Pharm. Bull. (Japan)*, 1958, **6**, 214, 218.
[7] Benešová, Sýkora, Herout, and Šorm, *Chem. and Ind.*, 1958, 363.

Tetrahydro-ψ-santonic acid [4,5] (II) was converted (Scheme A) into the ethylene dithioketal (III) by treatment with ethanedithiol and the boron trifluoride–ether complex,[8] lactonisation taking place in the process. When the dithioketal was treated with Raney nickel in boiling dioxan, the product (IV) was a gum, but on hydrolysis with 10% methanolic potassium hydroxide this gave pure 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid (V), identical with a sample prepared by the method of Tsuda *et al.*[6] from tetrahydroalantolactone (VII) by way of the keto-acid (VIII). We should, however, mention that our specimens melted at 183° and 185° respectively, some 10° higher than the quoted figure.[6]

The reactions involved in the conversion of ψ-santonin (I) into the hydroxy-acid (V) could not affect the configuration at positions 7, 8, and 10. Hence, since the absolute

Scheme A.



Reagents: 1, H^+. 2, H_2–Pd. 3, Ni. 4, OH^-. 5, OMe^- for short time. 6, $NaBH_4$. 7, (*a*) OH^-, (*b*) CH_2N_2, (*c*) CrO_3, (*d*) OH^-. 8, Na–Pr^{i}OH. 9, (*a*) CH_2N_2, (*b*) CrO_3, (*c*) OH^-.

configuration of the lactone (VII) at all centres except $C_{(11)}$ is known,[6,7] ψ-santonin (I) must have the absolute configurations shown at these centres, and this assignment is in accord with our previous predictions.[2,4] Likewise, tetrahydro-ψ-santonic acid (II) has the previously predicted [4,5] configurations at centres 4, 5, 7, 8, and 10. The configuration at $C_{(10)}$ agrees with the assignment derived [9] from the rotatory dispersion curve of tetrahydro-ψ-santonic acid.

Recent work by Sumi, Dauben, and Hayes [10] confirmed our stereochemical assignments for ψ-santonin by relating it to artemisin. Artemisin has been shown [11] to be 8α-hydroxysantonin and hence has the absolute configuration shown in (X). Sumi *et al.*[10] used the reactions shown in Scheme B for the conversion of artemisin into the lactone (XI) which had previously [12] been obtained from anhydro-ψ-santonic acid [4] (XII), a rearrangement product of ψ-santonin (I); in this way they demonstrated that ψ-santonin has the same configuration as artemisin at positions 7, 8, and 11.

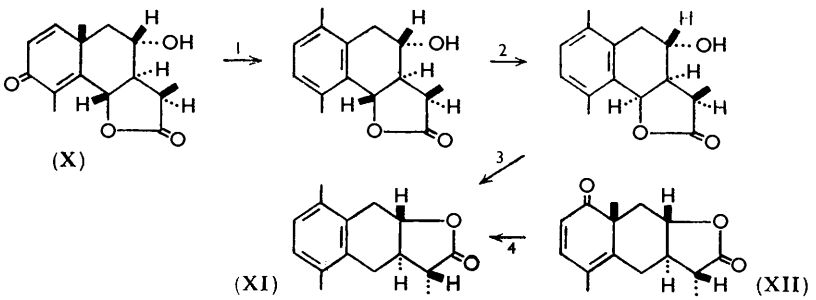
On combining our investigations with those of Sumi *et al.* it is clear that the steric

[8] Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.
[9] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362; Djerassi and Marshall, *ibid.*, 1958, **80**, 3987.
[10] Sumi, Dauben, and Hayes, *ibid.*, p. 5704.
[11] Sumi, *Proc. Japan Acad.*, 1956, **32**, 684; 1957, **33**, 153; *Pharm. Bull.* (*Japan*), 1957, **5**, 187; *J. Amer. Chem. Soc.*, 1958, **80**, 4869.
[12] Dauben, Hance, and Hayes, *ibid.*, 1955, **77**, 4609.

formula for ψ-santonin is (I),[2,4] except that the configuration at position 6 awaits direct establishment.

Mention can now be made of the configuration at position 11 of ψ-santonin (I) and its derivatives and of tetrahydroalantolactone (VII). Asselineau, Bory, and Lederer [13] have shown that when the last compound (VII) (m. p. 148°, $[\alpha]_D$ +16°) is heated at 210° with

Scheme B.

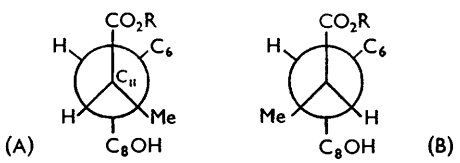


Reagents: 1, (*a*) NH_2·OH, (*b*) Zn–H_2SO_4. 2, (*a*) OH^-, (*b*) H^+. 3, Zn–AcOH. 4, (*a*) $NaBH_4$, (*b*) H^+.

potassium hydroxide and the product acidified, an isomeric lactone (m. p. 71°, $[\alpha]_D$ +26°) is obtained, and this must be the 11-epimer (VI) of tetrahydroalantolactone. Confirmation is given by the fact that when either epimer (VII) or (VI) is heated for a short time with sodium methoxide, a mixture rich in the former is obtained, but when the heating is protracted the only product is the latter.

The behaviour described in the preceding paragraph is reminiscent of the chemistry of the desmotroposantonins.[14] Short treatment of the lactones with sodium methoxide will leave the lactone rings largely intact. Under these conditions, the lactone (VI) is epimerised at position 11 whilst the compound (VII) is unchanged. Lactone (VII), therefore, is more stable than (VI). Hence, according to the rules propounded by Chopra *et al.*,[4] the former (VII), which is a *cis*-fused lactone,[6] must have its 11-methyl group *cis* with respect to the 7-hydrogen atom, *i.e.*, there is a α-methyl group at position 11. We have confirmed this assignment by showing that tetrahydroalantolactone (VII) is stable to protracted heating with anhydrous potassium carbonate in boiling xylene. These are conditions which do not hydrolyse the lactone ring but invert position 11 when this is in the less stable configuration.[4,5,14]

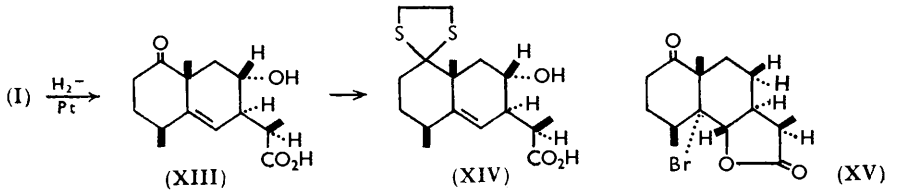
The acid or ester which is produced when the lactone (VII) is heated with potassium hydroxide or for long periods with methoxide will, however, have the less stable configuration at position 11, as shown in conformation (A), and will undergo inversion there [14] to afford the acid or ester which can adopt conformation (B). Relactonisation will then give the 11-epimer of tetrahydroalantolactone, namely, (VI).[13]



In the formation of 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid (V) from tetrahydroalantolactone (VII) (Scheme A), the intermediate ketone (VIII) is reduced when heated for several hours with sodium in propan-2-ol. These are conditions [13,14] which

[13] Asselineau, Bory, and Lederer, *Bull. Soc. chim. France*, 1955, 1524.
[14] Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Chopra, Cocker, and Edward, *ibid.*, 1955, 41.

could lead to epimerisation at position 11 (cf. our preliminary communication [1]). We have now shown that no such epimerisation takes place in the sequence (VII) ⟶ (VIII) ⟶ (V), since it can be reversed. Thus when the methyl ester of acid (V) is oxidised, and the product reduced by sodium borohydride, tetrahydroalantolactone (VII) is obtained. In consequence, the acid (V) must have the configuration shown and its lactone,[6] m. p. 74—75°, $[\alpha]_D$ −29·3°, must have structure (IV) with an 11α-methyl group. This is the more unstable [4] of the two *trans*-fused lactones epimeric at position 11.[6] That this is the case is shown as follows. Reducing the keto-acid (VIII) with sodium and propan-2-ol gives the hydroxy-acid (V) and a lactone, m. p. 112—113° (lit.,[6] m. p. 108—109°, $[\alpha]_D$ −19·5°). This lactone can only have structure (IX), that of the 11-epimer of (IV), since the structures of three of the four possible lactones, namely, (IV), (VI), and (VII), have already been assigned. We need not consider the possible epimerisation at position 7 since the large group there must be equatorial. The fact that the new lactone is formed merely by acidification of the alkaline mixture after reduction of acid (VIII) shows that the new lactone is more stable than (IV), whose corresponding hydroxy-acid (V) is not lactonised under similar conditions [cf. the greater resistance to lactonisation of 11β(H)-santoninic acid than of santoninic acid; [15] at the same time one should distinguish the absolute stability of the hydroxy-acid at position 11 from its resistance to lactonisation].



(XIII) (XIV) (XV)

(XVI) (XVII) (XVIII)

The configuration at position 11 in ψ-santonin can now be assessed. The dithioketal (III) must, like its successor (IV) in Scheme A, have the more unstable 11α-methyl configuration. Obviously tetrahydro-ψ-santonic acid must have the configuration at position 11 shown in (IIb ≡ IIa) (we use this symbol to draw attention to the rotation about $C_{(7)}$–$C_{(11)}$, which is necessary to convert a linear into an angular lactone and *vice versa*). Hence ψ-santonin must have an 11β-methyl group.

We have made several attempts to determine the configuration at position 6 in ψ-santonin. These involved at one stage the removal of the keto-group *via* an ethylene dithioketal. Starting from 8α-hydroxy-1-oxo-4 : 11α(H)-eudesm-5-en-13-oic acid (XIII) (formerly called dihydro-ψ-santonin [4,16]) we prepared the dithioketal (XIV) which was not desulphurised by Raney nickel. The same dithioketal (XIV) was formed when the bromolactone (XV) [17] was treated with ethanedithiol and boron trifluoride, the thiol acting as a reducing agent.

ψ-Santonin itself afforded a dithioketal on treatment with ethanedithiol and toluene-*p*-sulphonic acid. By analogy with ψ-santonic acid [4] this product must have structure (XVI). Neither this nor the corresponding hydroxy-acid (XVII) could be desulphurised.

It is interesting that in one reduction of " helenin " over Raney nickel in methanol

[15] Miki, *J. Pharm. Soc. Japan*, 1955, **75**, 416.
[16] Clemo and Cocker, *J.*, 1946, 30.
[17] Cocker and Hornsley, *J.*, 1947, 1157.

dihydro*iso*alantolactone (XVIII) was obtained.[18] It showed maxima (KBr disc) at 1761 (butanolide), 1650 (isolated C=C), and 890 cm.$^{-1}$ (C=CH_2). The dihydro-compound is unchanged when refluxed for 24 hours with potassium carbonate in xylene, as would be expected since it is reduced to tetrahydroalantolactone (VII).

Experimental

Infrared spectra were measured with a Hilger 800 double-beam instrument. $[\alpha]_D$ refer to $CHCl_3$ solutions unless otherwise stated.

8α-*Hydroxy*-4 : 5 : 11α(H)-*eudesman*-13-*oic Acid* (V).—This acid, prepared from alantolactone by the method of Tsuda, Tanabe, Iwai, and Funakoshi,[6] had m. p. 185°, $[\alpha]_D^{17}$ +61·5° (*c* 0·67 in MeOH) {lit.,[6] m. p. 174°, $[\alpha]_D^{25}$ +66·6° (*c* 1·5 in EtOH)} (Found: C, 71·2; H, 9·9. Calc. for $C_{15}H_{26}O_3$: C, 70·8; H, 10·3%).

4 : 5α(H),11β(H)-*Eudesman*-8α : 13-*olide* 1-(*Ethylene Dithioketal*) (III).—A mixture of tetrahydro-ψ-santonic acid (0·5 g.) [4,5] and ethanedithiol (0·6 c.c.) was slowly treated with freshly distilled boron trifluoride–ether complex [8] (0·6 c.c.). After 3 hr. water was slowly added, then sodium carbonate to alkalinity, and the mixture was extracted with ether, from which a pale yellow gum was obtained. Trituration with methanol gave a solid which on crystallisation from ethanol afforded the *dithioketal* as prisms (50 mg.), m. p. 175—176°, $\nu_{max.}$ 1767 cm.$^{-1}$ (lactone) (Found: C, 62·9; H, 7·5. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%).

8α-*Hydroxy*-4 : 5 : 11α(H)-*eudesman*-13-*oic Acid* (V).—A mixture of the above dithioketal (90 mg.), Raney nickel (1 g.), and dioxan (30 c.c.) was refluxed for 8 hr., then filtered and evaporated at 90° under reduced pressure. The residual glass was refluxed for 2 hr. with 10% aqueous potassium hydroxide (2 c.c.) in methanol (10 c.c.). Evaporation of the solvent and acidification of the residue gave a solid (30 mg.), m. p. 155—160°, which on crystallisation from ethanol afforded 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid (V), $[\alpha]_D^{17}$ +59·9° (*c* 0·11 in MeOH), m. p. 183°, alone or on admixture with a specimen prepared from alantolactone.

Attempted Conversion of Tetrahydroalantolactone (VII) *into its* 11-*Epimer* (VI).—The lactone (VII) (0·5 g.) in *m*-xylene (10 c.c.) was gently refluxed with freshly ignited potassium carbonate (0·5 g.) for 21 hr. The mixture was filtered whilst hot and the xylene was removed under reduced pressure, giving unchanged material, m. p. and mixed m. p. 148° (0·45 g. of material of m. p. 145—146°).

Conversion of 8α-*Hydroxy*-4 : 5 : 11α(H)-*eudesman*-13-*oic Acid* (V) *into Tetrahydroalantolactone* (VII).—The acid, m. p. 184° (10 mg.), was treated with excess of diazomethane in ether, and after 1 hr. the solvent was removed. The product, dissolved in acetic acid (2 c.c.), was set aside for 1·5 hr. with sodium dichromate (100 mg.) in acetic acid (4 c.c.). The excess of dichromate was decomposed with ethanol, and the solvents were removed under reduced pressure. The residue was extracted with ether, washed with water and sodium hydrogen carbonate solution, and dried. Removal of solvent gave a product which was dissolved in methanol (15 c.c.), mixed with potassium borohydride (50 mg.) in water (5 c.c.), and set aside for 14 hr. The solution was poured into water (40 c.c.), acidified with dilute acetic acid, saturated with ammonium sulphate, and extracted with ether. Removal of ether gave a residue which was heated at 100° for 3 min. and then crystallised from ethanol from which tetrahydroalantolactone (6 mg.), m. p. and mixed m. p. 140°, was obtained.

8α-*Hydroxy*-4 : 11α(H)-*eudesm*-5-*en*-13-*oic acid* 1-(*Ethylene Dithioketal*) (XIV).—Anhydrous hydrogen chloride was passed during 2 hr. into a mixture of 8α-hydroxy-1-oxo-4 : 11α(H)-eudesm-5-en-13-oic acid [15] (XIII) (0·6 g.) and ethanedithiol (1 c.c.). The product was diluted with ether, washed with water, and dried. Removal of the solvent gave the *dithioketal* (0·55 g.) as plates (from ethyl acetate–light petroleum), m. p. 180—181°, $[\alpha]_D^{19}$ +83·4° (*c* 0·82) (Found: C, 60·0; H, 7·3. $C_{17}H_{26}O_3S_2$ requires C, 59·6; H, 7·6%). The same product was obtained when boron trifluoride–ether was used as catalyst.

When the bromo-lactone [17] (XV) (0·55 g.) obtained from 8α-hydroxy-1-oxo-4 : 11α(H)-eudesm-5-en-13-oic acid was set aside for 24 hr. with ethanedithiol (1 c.c.) and boron trifluoride–ether (1 c.c.), the product was the same dithioketal (0·4 g.), m. p. and mixed m. p. 181°. No reaction took place between the bromo-lactone, ethanedithiol, and anhydrous hydrogen chloride.

11β(H)-*Eudesma*-3 : 5-*dien*-8α : 13-*olide* 1-(*Ethylene Dithioketal*) (XVI).—ψ-Santonin (1 g.),

[18] Cf. Ruzicka and van Melsen, *Helv. Chim. Acta*, 1931, **14**, 379; Ukita, Matsuda, and Nakazawa, *J. Pharm. Soc. Japan*, 1952, **72**, 796; cf. ref. 13.

ethanedithiol (1 c.c.), toluene-*p*-sulphonic acid (40 mg.), and benzene (50 c.c.) were refluxed with continuous removal of water in a Dean and Stark apparatus for 3 hr. The solution was shaken with water, the benzene layer dried, and the solvent was removed. The residue was crystallised from ethyl acetate, giving the *dithioketal* (0·28 g.) as rhombs, m. p. 185—186°, $[\alpha]_D^{19}$ +85·3° (*c* 1·3), $\nu_{max.}$ 1773 (γ-lactone), 1003 (*trans*-γ-lactone), and 860 cm.$^{-1}$ (trisubstituted double bond) (Found: C, 63·5; H, 7·2. $C_{17}H_{22}O_2S_2$ requires C, 63·3; H, 6·8%).

8α-*Hydroxy*-11α(H)-*eudesma*-3 : 5-*dien*-13-*oic Acid* 1-(*Ethylene Dithioketal*) (XVII).—The previous compound (0·15 g.) was refluxed for 1 hr. with potassium hydroxide (0·5 g.) and methanol (10 c.c.). Removal of solvent and acidification of the residue afforded the *hydroxy-acid* (0·1 g.), needles (from aqueous methanol), m. p. 186—187°, $[\alpha]_D^{20}$ +173·4° (*c* 0·47 in MeOH) (Found: C, 60·7; H, 7·35. $C_{17}H_{24}O_3S_2$ requires C, 60·0; H, 7·1%).

Hydrogenation of "Helenin."—"Helenin" (10 g.) in methanol (100 c.c.) was stirred in hydrogen for 14 hr. with Raney nickel (3 g.). Filtration and removal of solvent gave a residue which after two crystallisations from ethanol gave dihydro*iso*alantolactone (XVIII) (4 g.) as needles, m. p. 174° (Found: C, 76·75; H, 9·5. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·5%).

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