358. *The Chemistry of ψ-Santonin. Part X.**

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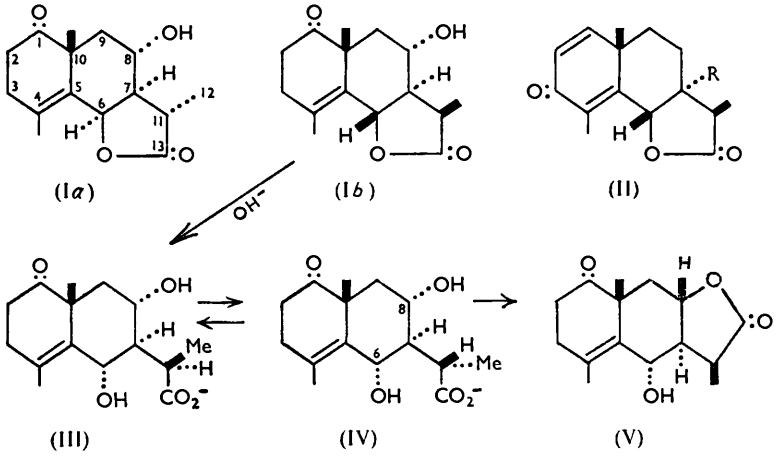
Revised structures are presented for ψ-santonic acid, (+)-β-desmotropo-ψ-santonin, and several related compounds. The stereochemistry of ψ-santonin and the reduction products of ψ-santonic acid are discussed.

(A) *Stereochemistry of ψ-Santonin.*—The structure of ψ-santonin has now been conclusively established [1,2] as (I), and recently we advanced the stereo-formula (I*a*) for it.[3] Independent evidence for the configurations shown in (I*a*) at $C_{(7)}$ and $C_{(8)}$ has been given by Dauben and Hance.[2] However, our evidence for the configuration at $C_{(6)}$ came from application of Klyne's rule [4] concerning the rotatory contribution of the potential hydroxyl group of the lactone ring and from the stability of the lactone in ψ-santonin. Klyne's rule, however, seems of doubtful validity when applied to lactones from allylic hydroxyl groups, as shown by its failure with santonin and 11β(H)-santonin.[5] Consequently, the *trans*-fused lactone of configuration (I*b*) becomes a possibility and evidence presented below shows that this structure explains the reactions of ψ-santonin better than (I*a*). Models of (I*b*) show that its stability should be at least equal to that of (I*a*).

ψ-Santonin is stable to potassium carbonate in boiling xylene, a reagent [6] which causes epimerisation of the 11-methyl group when in the unstable configuration. In the santonin (II; R = H) series the stable configurations have been shown by Cocker and McMurry [5]



to be: (*a*) with a *cis*-fused butanolide, that in which the 11-methyl group is *cis* to the 7-hydrogen atom, and (*b*) with a *trans*-fused butanolide, that in which the 11-methyl group is *trans* to the 7-hydrogen atom. Corollaries to these rules are that: (*c*) when two *cis*-fused butanolides are possible, that in which the 11-methyl group is *cis* to the 7-hydrogen atom will be favoured; and (*d*) when two *trans*-fused butanolides are possible, that in which the 11-methyl group is *trans* to the 7-hydrogen atom will be favoured. Thus the rules (*a*) and (*b*) indicate that ψ-santonin has the configuration shown in (I*a*) or (I*b*) at $C_{(11)}$, according to whether it possesses a *cis*- or a *trans*-fused butanolide structure.

When ψ-santonin is heated with potassium hydroxide to 150—160° and subsequently

* Part IX, *J.*, 1955, 588.

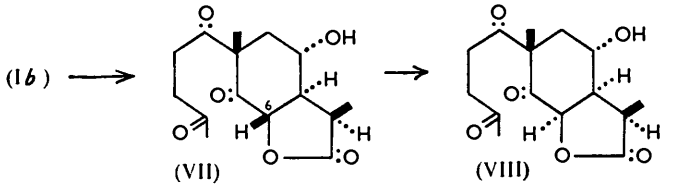
[1] Chopra, Cocker, Cross, Edward, Hayes, and Hutchinson, *J.*, 1955, 588.
[2] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[3] Chopra, Cocker, and Edward, *Chem. and Ind.*, 1954, 1535.
[4] Klyne, *ibid.*, p. 1198.
[5] Cocker and McMurry, *J.*, 1955, 4430.
[6] Cocker, Cross, and Lipman, *J.*, 1949, 959.

acidified an isomeric, lævorotatory compound, *iso*-ψ-santonin is obtained. This is shown by its light-absorption characteristics to have the same functional groups as ψ-santonin. It shows a single maximum at 2890 Å (log ε 1·56) characteristic of an isolated keto-group, but its absorption at 2200 Å (log ε 3·4) is characteristic of a tetrasubstituted double bond. In the infrared spectrum, peaks shown by *iso*-ψ-santonin at 1758 (butanolide), 1700 (ketone), 1655 (C=C), and 3500 cm.$^{-1}$ (hydroxyl) are almost identical with those shown by ψ-santonin.[1] On the basis that ψ-santonin has the structure (I*b*), the procedure by which *iso*-ψ-santonin is made can be expected to lead *via* the ion (III) of the hydroxy-acid, to epimerisation at $C_{(11)}$ to form the ion (IV).[7] This altered configuration will, according to rule (*d*) above, cause lactonisation of (IV) to involve the hydroxyl at $C_{(8)}$ rather than that at $C_{(6)}$, so that *iso*-ψ-santonin will be the linear compound (V). This formulation is supported by the fact that *iso*-ψ-santonin is stable to potassium carbonate in boiling xylene; if in *iso*-ψ-santonin the original lactone ring of ψ-santonin were present the 11-methyl group would be in the unstable configuration. Further, the hydroxyl group of *iso*-ψ-santonin is much more resistant to oxidation by chromic acid than that of ψ-santonin,[2] as would be expected from its hindered position in (V). Its resistance to oxidation with manganese dioxide [8] in an inert solvent may probably be traced to the same cause.

A similar explanation for these changes is impossible on the basis of the formulation (I*a*) for ψ-santonin, since the 11-methyl group is already in the configuration of greater stability, regardless of whether lactonisation takes place at the 6- or the 8-hydroxyl group. Consequently the derived *iso*-ψ-santonin would have the 11-methyl group in the unstable configuration.

A consequence of the formulation of ψ-santonin as (I*b*) is that the configurations at $C_{(6)}$, $C_{(7)}$, and $C_{(11)}$ become identical with those of santonin (II; R = H) and artemisin (II; R = OH).[9] This would be expected on biogenetic grounds. For the same reason the β-configuration of the angular 10-methyl group would be expected :[3] this configuration has been found in many sesquiterpenes of the eudesmane type,[10] and is supported by rotational evidence given below.

The stereo-formula (I*b*) leads to the formula (VII) for the primary product (A) of ozonisation.[1] The change of this product (A) into the isomer (B) under very mild alkaline treatment [1] is probably the result of epimerisation at $C_{(6)}$ to give the more stable *cis*-fused

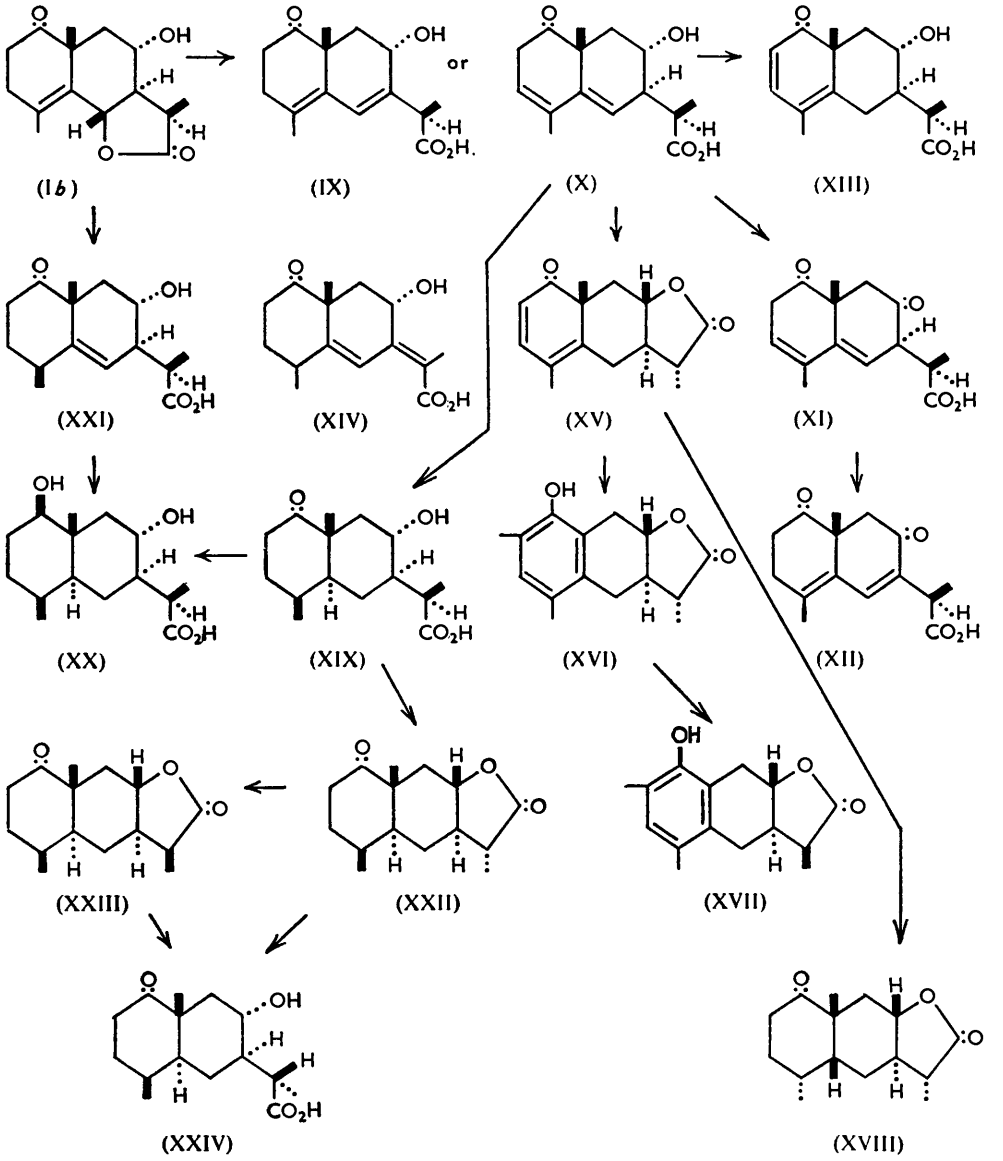


lactone (VIII). This formulation of (B) is supported by its fission by barium hydroxide to lævulic acid. A dibutanolide formulation was advanced previously for (B) because of the apparent absence in the infrared spectrum of the hydroxyl frequency present in (A); however, a re-examination of the spectrum has shown a weak band at 3540 cm.$^{-1}$ and stronger bands at 1152 and 1360 cm.$^{-1}$, probably to be attributed to hydroxyl.

(B) *ψ-Santonic Acid.*—The reformulation of ψ-santonin as (I) necessitates a revision of the structures hitherto assigned to ψ-santonic acid [11,12] and compounds related to it. Cocker [13] and Dauben, Hance, and Hayes [14] have shown that the spectroscopic properties of this acid indicate a conjugated diene system, which from its mode of formation could be

[7] Chopra, Cocker, and Edward, *Chem. and Ind.*, 1955, 41.
[8] Ball, Goodwin, and Morton, *Biochem. J.*, 1948, **42**, 516; Sondheimer, Amendolla, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5930, 5932, with references therein to earlier work.
[9] Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Corey, *J. Amer. Chem. Soc.*, 1955, **77**, 1044.
[10] Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313; Barton and Tarlton, *J.*, 1954, 3492; Ayer and Taylor, *ibid.*, p. 3027; Howe and McQuillin, *J.*, 1955, 2423.
[11] Clemo and Cocker, *J.*, 1946, 30.
[12] Cocker and Lipman, *J.*, 1949, 1170.
[13] Cocker, *Chem. and Ind.*, 1955, 1484.
[14] Dauben, Hance, and Hayes, *J. Amer. Chem. Soc.*, 1955, **77**, 4609

(IX) or (X). Dauben and his co-workers chose the latter structure, partly because they did not succeed in oxidising ψ-santonic acid with manganese dioxide. However, one of us has carried out this reaction. The product is undoubtedly the conjugated dienone (XII), having maximal absorption in ethanol at 3100 Å (log ε 3·77) in good agreement with the calculated value [15] (3140 Å). The functional groups are also indicated by infrared bands



(potassium bromide disc) at 1756 cm.$^{-1}$ (ketone) and at 1663, 1643, and 1616 cm.$^{-1}$ (conjugated dienone). Dauben and Hance [2] obtained an impure specimen of the methyl ester ($\varepsilon_{max.}$ 3070 Å in EtOH) of this acid (XII) by a different route. An impure disemicarbazone of (XII) showed maximal absorption at 2176 (log ε 4·21) and 3250 Å (log ε 3·70), characteristic of the semicarbazone of isolated ketone and of conjugated dienone systems respectively.

[15] Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72.

While this reaction has been considered as evidence for the allyl alcohol [8,13] structure (IX) of ψ-santonic acid, it is not conclusive because βγ-unsaturated alcohols are sometimes oxidised by manganese dioxide.[16] The primary oxidation product of the alcohol (X) would be the unconjugated dienone (XI), which could rearrange to (XII) during working up of the very slightly acidic reaction mixture. We now therefore consider that on balance the evidence favours formulation (X) rather than (IX) for ψ-santonic acid. In particular it explains [14] the slow base-catalysed isomerisation of ψ-santonic acid.[12] Unfortunately, the product is obtained pure only in very low yield, so that detailed examination of it has not been possible. However, its absorption ($\lambda_{max.}$ 3325 Å; log ε 3·56, in EtOH; infrared bands at 1653, 1627, and 1567 cm.$^{-1}$) is characteristic of a homoannular dienone system,[14] and suggests the structure (XIII), rather than its isomer, the unsaturated acid (XIV). Compound (XIII) would be formed by the base-catalysed isomerisation of (X) but not of (IX). Accordingly ψ-santonic acid (X) is 8α-hydroxy-1-oxoeudesma-3 : 5-dien-13-oic acid.[5]

If formula (X) is accepted, it becomes possible to deduce the stereochemistry of the various compounds derived from ψ-santonic acid.[12] Anhydro-ψ-santonic acid (XV) [13,14] must have a *trans*-fused lactone ring. Since this compound is converted into (+)-β-desmotropo-ψ-santonin * under conditions unlikely to cause any rearrangement,[17] it follows that the structure and stereochemistry of the latter is represented by (XVI). Its epimerisation to (+)-α-desmotropo-ψ-santonin [6] (XVII) would then be expected from rule (*b*) above. The stability of the *trans*-fused lactone of (+)-β-desmotropo-ψ-santonin is surprising; however, Corey and Sneem's [18] calculations seem to indicate that at this position a *trans*- is less strained than a *cis*-fused lactone.

The hydrogenation of anhydro-ψ-santonic acid (XV), like that of cholesta-2 : 4-diene,[19] would be expected to take place from the more accessible top side of the molecule, so that the tetrahydro-compound (XVIII) would have a *cis*-A/B ring fusion. On the other hand, the hydrogenation of ψ-santonic acid to tetrahydro-ψ-santonic acid (XIX) would be expected [20] to result in a *trans*-A/B ring fusion. Some support for the *trans*-configuration is given by negative shift in molecular rotation ($\Delta[M]_D$ −97°) in going from tetra- to hexahydro-ψ-santonic acid (XX); a similar shift is found in going from cholestan-1-one to cholestan-1α-ol ($\Delta[M]_D$ −304°) or -1β-ol ($\Delta[M]_D$ −356°).[21] Since the 1β(equatorial)-hydroxy-compound is produced from cholestan-1-one either by reduction with sodium in propanol or by catalytic hydrogenation in acetic acid,[21] it seems likely that hexahydro-ψ-santonic acid (XX) has also a 1β-hydroxy-configuration; this is supported by the identity of hexahydro-ψ-santonic acid with hexahydro-ψ-santonin. Under the latter name the compound was prepared from dihydro-ψ-santonin (XXI) by a two-stage process involving reduction of the ketone group with sodium amalgam, as well as directly from ψ-santonin by catalytic hydrogenation.[11] Evidently the usual rules distinguishing the stereochemistry of reduction by sodium and by catalytic hydrogen do not apply at the highly hindered 1-position.

The catalytic reduction of dihydro- (XXI) to hexahydro-ψ-santonin (XX) can be considered, from analogy with the hydrogenation of Δ^5-steroids, to be further evidence for the *trans*-A/B fusion in (XX).

Tetrahydro-ψ-santonic acid (XIX) is dehydrated by acetic anhydride to the lactone, α-anhydrotetrahydro-ψ-santonic acid, now formulated as (XXII). This accounts for the easy isomerisation to β-anhydrotetrahydro-ψ-santonic acid (XXIII) [rule (*b*)], and the

* The prefixes α- and β- were previously [6] used to denote compounds of lower and higher melting point respectively. They have no stereochemical significance. It is now proposed [5] to name the parent skeleton of the desmotropo-compounds simply desmotropo-ψ-santonin. (+)-β-Desmotropo-ψ-santonin (XVI) is thus 7α(H) : 8β(H) : 11β(H)-desmotropo-ψ-santonin; (+)α-desmotropo-ψ-santonin (XVII) differs from this only in configuration at $C_{(11)}$.

[16] Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62.
[17] Barton, *J. Org. Chem.*, 1950, **15**, 466.
[18] Corey and Sneem, *J. Amer. Chem. Soc.*, 1955, **77**, 2505.
[19] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 1949, p. 252.
[20] Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567.
[21] Striebel and Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.

alkaline hydrolysis of both the α- and the β-compounds to a third, isomeric tetrahydro-ψ-santonic acid (XXIV), epimerisation of (XXII) at $C_{(11)}$ evidently taking place before hydrolysis.

The rotations of several compounds reported previously have been redetermined, and the values of the molecular rotations are shown below. In all cases lactonisation involving the 8-hydroxyl group leads to a negative shift in molecular rotation, in agreement with Klyne's rule.[4] The molecular rotation of the acetate of anhydrohexahydro-ψ-santonic acid is known, but not that of the parent 1-hydroxy-compound, which probably differs by about −50°, so that the $\Delta[M]_D$ of −295° is probably too small.

	Lactone	Hydroxy-acid	$\Delta[M_D]$
iso-ψ-Santonin (V)	−308°	+24°*	−332°
Tetrahydroanhydro-ψ-santonic acid (XVIII)	+50	+313 *	−263
(+)-β-Desmotropo-ψ-santonin (XVI)	−132	+261	−393
α-Anhydrotetrahydro-ψ-santonic acid (XXII)	−332	+238	−570
β-Anhydrotetrahydro-ψ-santonic acid (XXIII)	−94	+295	−389
Anhydrohexahydro-ψ-santonic acid [lactone of (XX)]	−133 (acetate)	+162	(−295)

* K salt in dilute EtOH.

Investigation of the carbonyl stretching frequencies of the *trans*-fused lactones mentioned above shows that they vary from 1754 to 1777 cm.$^{-1}$.

Further work in the chemistry of ψ-santonin is halted because of the inaccessibility of this compound.

Experimental

ψ-Santonic Acid.—Concentrated hydrochloric acid (6 c.c.) was added with stirring to finely powdered ψ-santonin (2 g.), and more hydrochloric acid (up to 2 c.c.) was added to give a clear solution. When stirring was continued for a few minutes the required acid began to separate. It was collected (1·5 g.; m. p. 168—170°) and crystallised from alcohol as needles, m. p. 176°.[11] The acid before crystallisation is sufficiently pure for most purposes.

Oxidation of ψ-Santonic Acid.—**1 : 8-*Dioxoeudesma*-4 : 6-*dien*-13-*oic acid*** (XII). ψ-Santonic acid (0·7 g.), in chloroform (200 c.c.), was shaken for 3 days with manganese dioxide [8] (2 g.) at room temperature. After filtration and removal of solvent in a vacuum at 40—50° an oil was obtained, which solidified (0·5 g.; m. p. 150—155°) when rubbed with light petroleum. Crystallisation from ethyl acetate–light petroleum gave the *diketo-acid* as pale yellow needles, m. p. 171—172° (depressed to 150° with ψ-santonic acid), $[\alpha]_D^{20}$ +305° (*c*, 0·608 in $CHCl_3$), $\lambda_{max.}$ 3100 (infl. 3600) Å [log ε 3·75 (2·76) in EtOH] (Found : C, 68·7, 68·5; H, 7·1, 7·0. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). It gives a crude semicarbazone, m. p. *ca.* 220°. Its *tetrahydro*-compound, prepared by reduction in ethyl acetate over palladised charcoal, crystallised from ethyl acetate as colourless rhombs, m. p. 181°, $\lambda_{max.}$ 2910 Å (ε 41·8 in EtOH) (Found : C, 67·7; H, 8·6. $C_{15}H_{22}O_4$ requires C, 67·7; H, 8·3%).

The hydrate of tetrahydro-ψ-santonic acid,[12] m. p. 191—192°, had $[\alpha]_D^{25}$ +83·5° (in $CHCl_3$), $\lambda_{max.}$ 2920 Å (ε 54 in EtOH). It showed bands at 1709 (C=O and CO_2H) and 3618 cm.$^{-1}$ (hydroxyl).

Hexahydro-ψ-santonic acid (hexahydro-ψ-santonin),[11,12] m. p. 188—189°, had $[\alpha]_D^{18·5}$ +56·1° (in $CHCl_3$). Its acetate (lactone), m. p. 126—126·5°, had $[\alpha]_D^{20}$ −45·2°. It showed bands at 1721 (acetate) and 1776 cm.$^{-1}$ (butanolide) in $CHCl_3$.

Isomerisation of ψ-Santonin.—A mixture of ψ-santonin (3 g.), potassium hydroxide (6 g.), and water (6 c.c.) was heated at 165—170° for 4 hr. The dark brown mixture was dissolved in water (50 c.c.) and extracted continuously for 48 hr. with benzene. The extract was decolorised with charcoal and concentrated, giving a solid (2 g.; m. p. 150—160°). Repeated crystallisation from benzene gave *iso-ψ-santonin* (0·2 g.) as needles, m. p. 205°, $[\alpha]_D^{16}$ −116·5° (*c* 0·25 in 1 : 1 water–ethanol) (Found : C, 68·2; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%). Its solubility in water is greater than that of ψ-santonin.

Conversion of Anhydro-ψ-santonic Acid into (+)-β-Desmotropo-ψ-santonin.—The anhydro-compound (0·5 g.) was warmed at 48—55° for 4 hr. with a solution of concentrated sulphuric acid (2·5 c.c.) in water (3·7 c.c.). The product (0·5 g.; m. p. 145—150°) was collected. One crystallisation from dilute alcohol gave (+)-β-desmotropo-ψ-santonin (0·3 g.), m. p. 186° undepressed on admixture with an authentic specimen.[6]

Isolation of an Unidentified Degradation Product of ψ-Santonin.—Hydrolysis of the ozonisation product (A) (7·5 g.) with barium hydroxide as previously described [1] and distillation of the barium-free solution gave lævulic acid and a syrup which on long storage deposited colourless plates (0·1 g.), m. p. 199—202°. Crystallisation from water gave a *substance* (D), m. p. 209° (Found : C, 67·5; H, 6·4. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%).

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