271. *The Chemistry of Santonin. Part VI.* Some Reduction Products of* 6α(H),11β(H)-*Santonin.*

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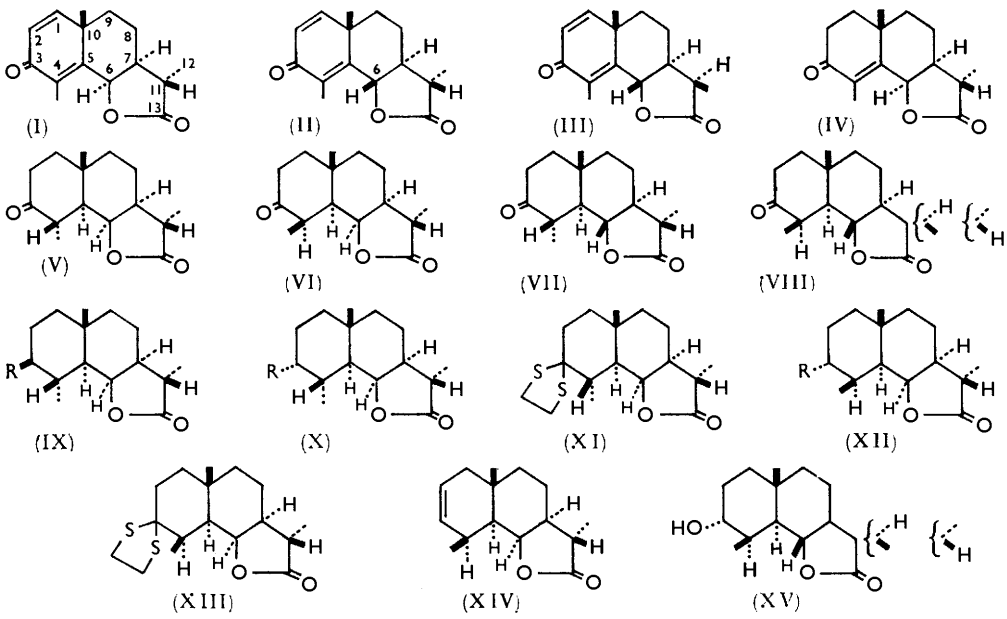
Reduction products of the 6α(H)-epimer (I) of 11β(H)-santonin (II) are described and their stereochemistry is discussed.

In previous papers[1,2] we discussed the stereochemistry of the reduction products of santonin (III) and its 11-epimer, 11β(H)-santonin (II). All those compounds are *trans*-fused lactones, and it seemed to be of interest to study the corresponding *cis*-lactones. This became possible when Ishikawa[3] showed that santonin (III) is epimerised at $C_{(6)}$ when treated with hydrogen chloride in dimethylformamide, without the molecule's undergoing to any large extent a concomitant dienone–phenol rearrangement. Barton[4] has similarly prepared 6α,11β(H)-santonin (I), the 6-epimer of 11β(H)-santonin, and it is with the reduction products of this ketone that the present paper is concerned.



From the stereochemistry of 6α,11β(H)-santonin (I) it would be expected that its hydrogenation products would be *trans*-decalins, corresponding to the adsorption of the α-face of the molecule on the catalyst and the addition of hydrogen from that side. We have confirmed this hypothesis.

Catalytic reduction of the potassium salt of the hydroxy-acid obtained from (I) gives, however, a *cis*-decalin and in this respect it behaves as do potassium santoninate and 11β(H)-santoninate.[1,2]

Hydrogenation of the epimer (I) in ethyl acetate over 10% palladised charcoal afforded

* Part V, *Tetrahedron*, 1958, **3**, 160. In the present paper we use the nomenclature of Cocker and Cahn, *Chem. and Ind.*, 1955, 384, and Cocker and McMurry, *J.*, 1955, 4430.

[1] Cocker and McMurry, *J.*, 1956, 4549, where previous references are cited.

[2] Cocker, Dodds, and McMurry, *Tetrahedron*, 1958, **3**, 160; cf. Banerji, Barton, and Cookson, *J.*, 1957, 5041.

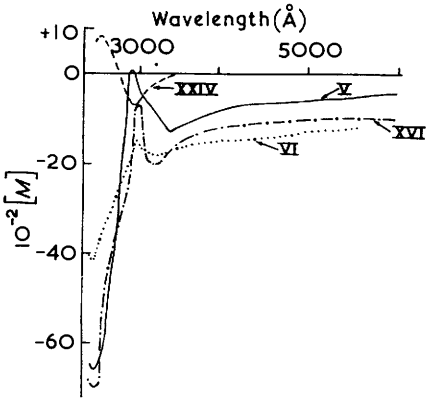
[3] Ishikawa, *J. Pharm. Soc. Japan*, 1956, **76**, 504; *Chem. Abs.*, 1957, **51**, 303.

[4] Barton, *Proc. Chem. Soc.*, 1958, 65.

a mixture of neutral and acidic products. We shall consider the chemistry of the neutral products first.

One of the neutral products was the dihydro-compound, 3-oxo-6α(H),11β(H)-eudesm-4-en-6,13-olide (IV) which showed the expected ultraviolet absorption maximum at 2455 and 3150 Å (log ε 4·18 and 1·62, respectively) (cf. ref. 2). In the infrared region it showed maxima, in Nujol, at 1760 (lactone) and 1674 cm.$^{-1}$ (conjugated C=O). When freshly prepared catalyst was used with acetic acid as solvent, the reduction was rapid and 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (V) was obtained. This is the more stable of the 4-epimers; it showed maxima, in Nujol, at 1760 and 1712 cm.$^{-1}$ (C=O). The other tetrahydro-compound, 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (VI), which showed maximum absorption, in Nujol, at 1766 and 1705 cm.$^{-1}$, was obtained when the reduction was performed in ethyl acetate. The assignment of configuration to these tetrahydro-lactones (V) and (VI) is based on the facts that the latter is converted into the former on treatment with toluene-*p*-sulphonic acid or when its benzene solution is shaken with basic alumina, and the rotatory dispersion curves (see Figure) of (V) and (VI), kindly supplied by Professor W. Klyne, are similar to those of 3-oxo-5α(H),4,6,11β(H)- (VII), and 3-oxo-4,5α(H),6,11β(H)-eudesman-6,13-olide [VIII; 11β(H)], respectively.[2]

Optical rotatory dispersion curves



Reduction of 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (V) with potassium borohydride gave 3β-hydroxy-5,6α(H),4,11β(H)-eudesman-6,13-olide (IX; R = OH). The molecular rotation of the corresponding acetate (IX; R = OAc) is more negative than that of the alcohol itself (Table 1). On this evidence it would be concluded that the hydroxyl group had the α-configuration,[5] and hence must be axial. However, treatment of the alcohol (IX; R = OH) with phosphorus oxychloride and pyridine affords the chloro-compound (X; R = Cl) in good yield, a reaction typical of an equatorial hydroxyl group (cf. IX; R = β-OH). We confirmed this β-orientation by converting the ketone (V) into its thioketal (XI) and thence by reduction into the deoxy-lactone (IX; R = H).

TABLE 1.

Molecular rotations of 6α,11β(H)-santonin derivatives.

	R = OH	R = OAc	R = Cl	R = H	ΔAc	ΔOH	ΔOAc	ΔCl
(IX)	−93°	−141°	—	−188°	−48°	+95°	+47°	—
(X)	—	—	−294°	−188	—	—	—	−106°
(XII)	−237	−429	—	−132	−192	−105	−297	—

The molecular-rotation difference between the hydroxy-lactone (IX; R = OH) and deoxy-lactone (IX; R = H) is positive (Table 1), as required for a β-hydroxyl group. Further, the chloro-compound (X; R = Cl) is much more strongly lævorotatory than the hydroxy- (IX; R = OH) or deoxy-lactone (IX; R = H), implying that the chlorine is

[5] Klyne and Stokes, *J.*, 1954, 1979; Barton and Nickson, *J.*, 1954, 4665.

α-orientated. Since replacement of hydroxyl by chlorine generally leads to inversion of configuration (cf. ref. 1), the hydroxyl must be β-orientated.

The apparently anomalous molecular-rotation difference of the acetate (IX; R = OAc) and its alcohol (IX; R = OH) finds an explanation in their rotatory dispersion curves which cross close to the sodium-D line. From about 3800 Å downwards the acetate is the less negative in molecular rotation. A similar result was experienced by Zalkow, Markley, and Djerassi [6] in connexion with certain steroids, and it emphasises the importance of the optical rotatory dispersion curves.

Reduction of sodium 6β-hydroxy-3-oxo-5α(H),4,11β(H)-eudesman-13-oate (from V) with sodium in propan-2-ol gave 3β-hydroxy-5,6α(H),4,11β(H)-eudesman-6,13-olide (IX; R = OH), confirming the equatorial orientation of the hydroxyl group. The same alcohol was also obtained by hydrogenation of the keto-lactone (V) over a platinum catalyst in acetic acid and by aluminium amalgam in ether. The same alcohol was also obtained from the ketone (V) by hydrogenation over a platinum catalyst in acetic acid, and by reduction with aluminium amalgam in ether. The alcohol (IX; R = OH) was quantitatively oxidised to the ketone (V) with chromium trioxide in acetone.

Reduction of 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (VI) with borohydride or with platinum and hydrogen * gave an axial alcohol, 3α-hydroxy-4,5,6α(H),11β(H)-eudesman-6,13-olide (XII; R = OH). The stereochemistry of the hydroxyl group emerges from the following facts. (1) The alcohol gives an acetate (XII; R = OAc) with large negative shift in molecular rotation.[5] (2) Reduction of the ketone (VI) by way of the thioketal (XIII) gives the deoxy-lactone (XII; R = H), which is considerably less negative in molecular rotation than the alcohol (XII; R = OH). (3) Reaction of this alcohol with phosphorus oxychloride and pyridine induces dehydration to the octalin (XIV). This product shows no maximum in the ultraviolet spectrum, but at 2150 and 2200 Å ε is 1005 and 490, respectively. Part of this absorption is due to the lactone-carbonyl group. We have found that ε for the deoxy-lactone (XII; R = H) is 220 and 151, respectively, at these wavelengths, giving ε for the double bond as 785 and 339, respectively. These values are at about the boundary between those for di- and tri-substituted double-bond absorption.[7] However, ozonolysis of the octalin (XIV) afforded a product which gave a Schiff test but failed to give an iodoform reaction. In the infrared spectrum (KBr disc) there are bands at 1765 (lactone) and 1170 (C–O), and a strong band at 955 cm.$^{-1}$, which is not present in the lactone (XII; R = H). Below 900 cm.$^{-1}$ the unsaturated lactone (XIV) and the reduced lactone (XII; R = H) have identical absorption. The corresponding Δ^3-analogue of (XIV) would be expected to absorb in the 850 cm.$^{-1}$ region.[1,8] The band at 955 cm.$^{-1}$ is near the range normally associated [8] with *trans*-CHR=CHR, which system cannot be invoked here. We therefore tentatively suggest that this band comes from the *cis*-2-ene system of compound (XIV).

The reduction of the keto-lactone (VI) to the axial alcohol (XII; R = OH) with borohydride was at first not expected. However, we have found that the two keto-lactones [VIII; 11α,β(H)],[1,2] which also have an axial 4-methyl group, are reduced with borohydride to the axial, 3α-alcohols [XV; 11α,β(H)] whose identities are beyond doubt.[1,2] It appears, therefore, that hindrance around the keto-group of (VI) and (VIII) is sufficient to reverse the normal manner of approach of the borohydride.

The optical rotatory dispersion curve of the saturated keto-lactone (VI) is like that of the 3-oxo-4β-methyl-5α(H)-steroids in having a much reduced amplitude in its Cotton effect curve.[9] In such steroids there must be 1,3-diaxial interactions between the 4- and

* Or with aluminium amalgam in ether.

[6] Zalkow, Markley, and Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 6354; cf. Klyne, *J.*, 1953, 3072.
[7] Bladen, Henbest, and Wood, *Chem. and Ind.*, 1951, 866; Halsall, *ibid.*, p. 867.
[8] Jones and Sondorfy, "Technique of Organic Chemistry," Interscience Publ., Inc., New York, 1956, Vol. IX, p. 378.
[9] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362; Djerassi, Halpern, Halpern, and Riniker, *ibid.*, 1958, **80**, 4001.

the 10-methyl group which could be responsible for this reduction in amplitude. In compound (VI) there are further diaxial interactions possible as a result of the axial 6β-lactone group, but these are not notably reflected in the dispersion curve.

The hydroxy-acids corresponding to the *cis*-fused lactones described above cannot be isolated. Relactonisation on neutralisation of the sodium salts is very rapid. However, the molecular rotations of the sodium salts in aqueous-alcoholic solution of some of the hydroxy-acids are given in Table 2, and whilst too much reliance cannot be placed upon the value of the molecular rotations of sodium salts in solution [10] there is little doubt that

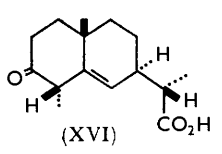
TABLE 2.

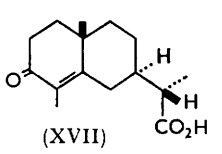
Lactone	$[M]_D$ Lactone	$[M]_D$ Salt	$\Delta[M]_D$	Lactone	$[M]_D$ Lactone	$[M]_D$ Salt	$\Delta[M]_D$
(V)	−225°	−68°	−157°	(IX; R = OH) ...	−93°	−27°	−66°
(VI)	−300	−68 *	—	(XII; R = OH) ...	−237	−85	−152

* Epimerisation at $C_{(4)}$ takes place on formation of sodium salt.

in our examples there is a large negative shift on lactonisation. This accords with the Hudson–Klyne lactone rule [11] and the stereochemistry at position 6.

Three acidic products were obtained on hydrogenation of 6α(H),11β(H)-santonin (I). One of these was 3-oxo-4,11β(H)-eudesm-5-en-13-oic acid (XVI) which showed maximum infrared absorption in Nujol at 3250—3400 (OH of CO_2H), 1705 (CO_2H and C=O), and 1640 cm.$^{-1}$ (C=C), and had a shoulder in the ultraviolet spectrum at 2950 Å (log ε 1·64). Assignment of configuration at position 4 is made on the basis of the similar amplitudes of the Cotton effect curves (see Figure) of the acid and 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (V). The lactone (VI) with the opposite (α-) configuration at $C_{(4)}$ has a much smaller amplitude in its Cotton effect curve; reference to this has been made above. Treatment of acid (XVI) with 4N-sodium hydroxide caused development of an absorption maximum


(XVI)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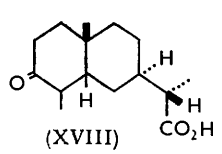
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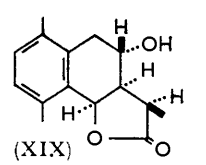
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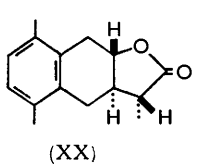
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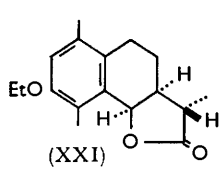
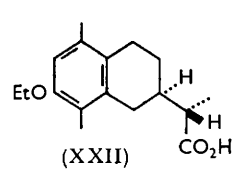

(XXI)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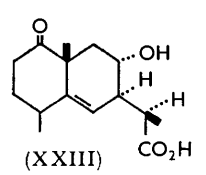
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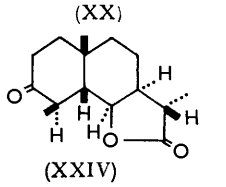
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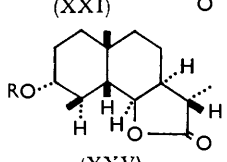
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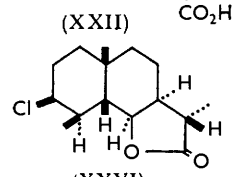
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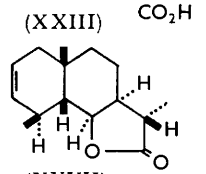
(XXVII)

at 2450 Å (log ε 3·9), no doubt due to the formation of the conjugated keto-acid (XVII) which, however, could not be isolated from solution. Nevertheless, treatment of acid (XVI) with toluene-*p*-sulphonic acid afforded this 4-enoic acid (XVII) which showed an ultraviolet maximum at 2520 Å (log ε 4·2), characteristic of its enone system. This acid also showed maxima at 1728, 1630, and 1595 cm.$^{-1}$ (in Nujol). It was also one of the products of hydrogenation of 6α(H),11β(H)-santonin (I) itself.

Another acidic product was a 3-oxo-11β(H)-eudesman-13-oic acid (XVIII) which showed a maximum at 1710 cm.$^{-1}$ (CO_2H and C=O).

[10] Sýkora and Románuk, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1909.
[11] Klyne, *Chem. and Ind.*, 1954, 1198.

Acids have not been isolated from the reduction products of santonin and of 11β(H)-santonin, in both of which the lactone is fused equatorially to the decalin system. There are many known cases, however, in addition to that mentioned above, where lactones axially fused to the decalin system undergo reductive cleavage. Dauben, Hayes, Schwarz, and McFarland [12] have shown that 6α(H)-santonin, the 6-epimer of (III), undergoes hydrogenation to give the 11-epimer of (XVIII) in addition to the reduced lactone. Miki [13] found that certain axially fused lactones are reductively cleaved with zinc and acetic acid. Thus isohypoartemisin (XIX) gives the lactone (XX) through an intermediate deoxy-acid. We have recently shown that the benzylic lactone (XXI), 6,7α(H),11β(H)-desmotroposantonin ethyl ether, affords solely the deoxy-acid (XXII) on hydrogenation over palladised charcoal. The formation of an acid (XVI) in the reduction of the lactone (I) also resembles the production of the unsaturated acid (XXIII) in the reduction of ψ-santonin.[14]

Catalytic hydrogenation of potassium 6α(H),11β(H)-santoninate, derived from (I), affords 3-oxo-4,6α(H),5,11β(H)-eudesman-6,13-olide (XXIV) (cf. refs. 1 and 2) which has a rotatory dispersion curve typical of a *cis*-A/B fused system (see Figure). This lactone was unaffected by toluene-*p*-sulphonic acid in acetic acid, showing that the 4-methyl group is equatorial and hence β-orientated. Reduction with potassium borohydride or with hydrogen over platinum in acetic acid afforded the equatorial alcohol (XXV; R = H), which was characterised as its acetate with strong negative shift in molecular rotation, indicating equatorial (α-) orientation of the hydroxyl group. Reaction of the alcohol (XXV; R = H) with phosphorus oxychloride gives the expected chloro-compound (XXVI) along with a molecular complex (cf. ref. 1) or mixture which we have so far not been able to resolve, of chloro-compound and an unsaturated compound, probably (XXVII). Like the unsaturated compound (XIV), the complex has an infrared band in the 950 cm.$^{-1}$ range.

The strong negative shift in molecular rotation on replacement of the hydroxyl group of (XXV; R = H) by chlorine suggests inversion at this centre in the formation of (XXVI):

XXV	(R = H)	+108°	XXV.....	(R = Ac)	−167°	$\Delta[M]_D$ −275°
XXVI		−74				

An attempt to form the diethyl ketal of 6α(H),11β(H)-santonin (I) by reaction with ethyl orthoformate and boron trifluoride in the cold led to recovery of starting materials. In the hot the product was 6,7α(H),11β(H)-desmotroposantonin ethyl ether (XXI), which was prepared for comparison from 6,7α(H),11β(H)-desmotroposantonin [15] (β-desmotroposantonin).

Experimental

Ultraviolet spectra were measured for ethanolic solutions, infrared spectra for Nujol suspensions, and $[\alpha]_D$ for chloroform solutions, unless otherwise stated.

6α(H),11β(H)-*Santonin* (I).—(*a*) 11β(H)-Santonin (15 g.) was heated at 95—99° for 5 hr. with a 5% solution of hydrogen chloride in dimethylformamide (170 c.c.). After cooling, the mixture was diluted to 500 c.c. and extracted several times with ether. The combined extracts were washed with 5% sodium hydrogen carbonate solution (20 c.c.), then with water (20 c.c.). After drying, the ethereal solution was concentrated, giving 6α(H),11β(H)-santonin (7·2 g.), which crystallised from aqueous ethanol as needles (7 g.), m. p. 191°, $[\alpha]_D^{18}$ −318° (*c* 0·85), $\lambda_{max.}$ 2460 (log ε 4·18), 3200 Å (log ε 1·6), $\nu_{max.}$ 1760, 1664, 1627 cm.$^{-1}$, in good agreement with Barton's values * (Found: C, 73·35; H, 7·3. Calc. for $C_{15}H_{18}O_3$: C, 73·1; H, 7·4%).

(*b*) The solution, after being heated for 5 hr., was neutralised whilst hot with 5% sodium hydrogen carbonate solution, and water was then added. The product was rapidly deposited.

* Personal information from Professor Barton.

[12] Dauben, Hayes, Schwarz, and McFarland, *J. Amer. Chem. Soc.*, 1960, **82**, 2232.
[13] Miki, *J. Pharm. Soc. Japan*, 1955, **75**, 399.
[14] Chopra, Cocker, Cross, Edward, Hayes, and Hutchison, *J.*, 1955, 588; cf. ref. 12.
[15] Cf. Cocker and McMurry, *J.*, 1955, 4430.

Hydrogenation of 6α,11β(H)-*Santonin* (I).—(a) 3-*Oxo*-6α(H),11β(H)-*eudesm*-4-*en*-6,13-*olide* (IV). Compound (I) (4 g.) and 10% palladised charcoal (0·8 g.) in ethyl acetate (100 c.c.) were stirred in hydrogen for 24 hr., giving 3-*oxo*-6α(H),11β(H)-*eudesm*-4-*en*-6,13-*olide* which crystallised from aqueous ethanol as needles (0·75 g.), m. p. 145°, $[\alpha]_D^{18\cdot5}$ −109° (*c* 0·53) (Found: C, 72·0; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

(b) 3-*Oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (V). 6α(H),11β(H)-Santonin (2 g.) was hydrogenated for 24 hr. in acetic acid in presence of freshly prepared 10% palladised charcoal. The product was dissolved in ether and was washed with 5% sodium hydrogen carbonate solution (4 × 25 c.c.), then with water (2 × 20 c.c.). The ether was evaporated and the residue crystallised from aqueous ethanol, giving 3-*oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (1·2 g.) as needles m. p. 177—178°, $[\alpha]^{18}$ −91° (*c* 0·52 in $CHCl_3$), −89° (*c* 0·33 in MeOH) (Found: C, 71·7; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

(c) 3-*Oxo*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* (VI). 6α(H),11β(H)-Santonin (7 g.) was hydrogenated in ethyl acetate (250 c.c.) over 10% palladised charcoal (1 g.) for 3 hr. The methanol was removed and the product was washed with 5% sodium hydrogen carbonate solution. The residual solid (1·5 g.) was chromatographed on silica gel (18 g.) and eluted with benzene–light petroleum (1 : 1), giving 3-*oxo*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* which crystallised from aqueous ethanol as needles (1·8 g.), m. p. 165°, $[\alpha]_D^{19}$ −121° (*c* 0·25 in $CHCl_3$) (Found: C, 72·2; H, 8·95. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

Conversion of 3-*Oxo*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* (VI) *into* 3-*Oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (V).—(*a*) The tetrahydro-compound (VI) (1 g.) was set aside for 18 hr. with toluene-*p*-sulphonic acid (1 g.) in acetic acid (12 c.c.). Dilution with water and crystallisation of the deposited product from aqueous ethanol gave 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (V) (0·85 g.), m. p. and mixed m. p. 177°, $[\alpha]_D^{20}$ −93° (*c* 0·292). (*b*) The tetrahydro-compound (VI) (1 g.) in benzene (60 c.c.) was shaken with basic alumina (1 g.) for 5 hr. Filtration and evaporation of the solvent gave 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (0·8 g.), m. p. and mixed m. p. 175—176°, $[\alpha]_D^{19}$ −100° (*c* 0·225).

3β-*Hydroxy*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (IX; R = OH).—(*a*) 3-Oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (V) (0·8 g.) in methanol (18 c.c.) was mixed with potassium borohydride (80 mg.) in water (4 c.c.) and set aside for 18 hr. The solution was acidified and ammonium sulphate was added. The white precipitate recrystallised from aqueous ethanol, giving the required *alcohol* as needles (1 g.), m. p. 160—161°, $[\alpha]_D^{20}$ −37° (*c* 0·29), $\nu_{max.}$ 3550 (OH) and 1760 cm.$^{-1}$ (lactone) (Found: C, 71·6; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). Its *acetate* (IX; R = OAc) crystallised from aqueous ethanol as needles, m. p. 121°, $[\alpha]_D^{20}$ −48° (*c* 0·48), $\nu_{max.}$ 1771 (lactone), 1738 (acetate), 1238 cm.$^{-1}$ (acetate) (Found: C, 68·8; H, 9·0. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

(*b*) 3-Oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (0·55 g.) in glacial acetic acid (50 c.c.) was hydrogenated for 2 hr. over Adams platinic oxide (0·05 g.). The product, crystallised from ethyl acetate–light petroleum, gave 3β-hydroxy-5,6α(H),4,11β(H)-eudesman-6,13-olide (IX; R = OH) as needles (0·4 g.), m. p. and mixed m. p. 159°, $[\alpha]_D^{18}$ −38° (*c* 0·359).

(*c*) The keto-lactone (0·5 g.) was refluxed for 2 hr. with sodium hydroxide (0·3 g.) in methanol (5 c.c.) and water (1 c.c.). The solution was then refluxed with propan-2-ol (100 c.c.), sodium (5·5 g.) was added slowly, and refluxing was continued for 3 hr. The solution was cooled to 0°, neutralised with dilute acetic acid, concentrated under reduced pressure to 30 c.c., and extracted several times with ether. The ether extract was washed with 3% aqueous sodium hydrogen carbonate and with water. Evaporation of the dried ethereal solution gave 3β-hydroxy-5,6α(H),4,11β(H)-eudesman-6,13-olide (IX; R = OH) (0·2 g.), m. p. and mixed m. p. 160°, $[\alpha]_D^{19}$ −42° (*c* 0·316).

(*d*) The keto-lactone (V) (0·5 g.) was refluxed for 4·5 hr. in ether (250 c.c.) with aluminium amalgam from aluminium strip (2·0 g.). The mixture was filtered and ether was removed giving a solid which on crystallisation from ethyl acetate–light petroleum gave the alcohol (IX; R = OH) (0·25 g.), m. p. and mixed m. p. 161—162°.

Oxidation of the alcohol. This compound (100 mg.) was set aside for 4 days with chromium trioxide (100 mg.) in acetone (40 c.c.). Filtration through charcoal and evaporation gave the ketone (V), m. p. and mixed m. p. 178° without further crystallisation.

3α-*Chloro*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (X; R = Cl).—A mixture of 3β-hydroxy-5,6α(H),4,11β(H)-eudesman-6,13-olide (IX; R = OH) (0·12 g.), pyridine (1 c.c.), and phosphorus oxychloride (20 mg.) was set aside overnight, then poured into water and extracted with ether.

The extract was washed with dilute sulphuric acid and then with water, dried, and evaporated. The solid residue crystallised from aqueous methanol, giving the *chloro-compound* (55 mg.) as needles, m. p. 155—156°, $[\alpha]_D^{19}$ −109° (*c* 0·169), $\nu_{max.}$ 1760 (lactone), 725 cm.$^{-1}$ (C–Cl) (Found: C, 66·6; H, 8·3. $C_{15}H_{23}ClO_2$ requires C, 66·5; H, 8·5%).

5,6α(H),4,11β(H)-*Eudesman*-6,13-*olide* (IX; R = H).—*Dithioketal* (XI) *of* 3-*oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide*. The keto-lactone (V) (0·1 g.) was mixed with ethane-1,2-dithiol, boron trifluoride–ether complex (0·1 c.c.) was added dropwise, and the mixture was set aside for 3 hr. Dilute sodium carbonate solution was added until the mixture was neutral, and the latter was then extracted with ether from which the required *dithioketal* was obtained. It crystallised from aqueous methanol as needles (60 mg.), m. p. 175°, $[\alpha]_D^{17}$ −63·4° (*c* 0·202), $\nu_{max.}$ 1765 cm.$^{-1}$ (lactone) (Found: C, 62·0; H, 8·3. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%).

Hydrogenolysis of the dithioketal. The dithioketal (40 mg.), Raney nickel (0·4 g.), and dioxan (15 c.c.) were refluxed for 16 hr., then filtered and evaporated under reduced pressure. The residue crystallised from aqueous methanol, giving 5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (20 mg.) as needles, m. p. 102°, $[\alpha]_D^{20}$ −80·0° (*c* 0·2), $\nu_{max.}$ 1760 cm.$^{-1}$ (lactone) (Found: C, 76·4; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

3α-*Hydroxy*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* (XII; R = OH).—(*a*) 3-Oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (VI) (1 g.) in methanol (20 c.c.) was mixed with potassium borohydride (80 mg.) in water (4 c.c.) and set aside overnight, then diluted with water and acidified. The solid product was collected and recrystallised from ethyl acetate–light petroleum, giving 3α-*hydroxy*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* as needles (1 g.), m. p. 173°, $[\alpha]_D^{19}$ −94° (*c* 0·13), $\nu_{max.}$ 3370—3360 (OH), 1768 cm.$^{-1}$ (lactone) (Found: C, 71·1; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). Its *acetate* crystallised from aqueous ethanol as needles, m. p. 183°, $[\alpha]_D^{20}$ −146° (*c* 0·28), $\nu_{max.}$ 1778 (lactone), 1738 (OAc), 1241 cm.$^{-1}$ (OAc) (Found: C, 69·05; H, 8·6. $C_{17}H_{26}O_4$ requires C, 69·3; H, 8·9%).

(*b*) 3-Oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (VI) (0·9 g.) in glacial acetic acid (50 c.c.) was hydrogenated over platinic oxide (0·05 g.) for 6 hr. After removal of catalyst and solvent the residue was dissolved in ether, and the solution was washed with 5% sodium hydrogen carbonate solution (10 c.c.) and dried. Removal of the solvent gave the required alcohol (0·72 g.), m. p. and mixed m. p. 173° (needles from ethyl acetate–light petroleum), $[\alpha]_D^{19}$ −94° (*c* 0·21).

(*c*) The keto-lactone (VI) (0·2 g.) was refluxed for 3 hr. in ether (50 c.c.) with aluminium amalgam from aluminium strip (0·5 g.). The mixture was filtered and ether was removed giving the alcohol (XII; R = OH) (0·2 g.), m. p. 157—163°. Crystallisation from ethyl acetate–ligroin gave needles, m. p. and mixed m. p. 176°.

Oxidation of the alcohol. This compound (0·27 g.) was set aside for 3 days with chromium trioxide (0·25 g.) in acetone (60 c.c.). The mixture was filtered through charcoal and the solvent was removed from the filtrate giving a product (0·25 g.), m. p. 132—135°. Crystallisation from ethyl acetate–ligroin gave the ketone (VI) (70 mg.) m. p. and mixed m. p. 162°. The infrared spectrum of the mother liquor showed that it contains a mixture of ketone and starting material.

4,5,6α(H),11β(H)-*Eudesman*-6,13-*olide* (XII; R = H).—*Dithioketal* (XIII) *of* 3-*oxo*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide*. A mixture of the keto-lactone (VI) (0·7 g.), ethane-1,2-dithiol (1 c.c.), and boron trifluoride–ether complex (1 c.c.) (added slowly) was set aside overnight and worked up as described for compound (XI) above. The *dithioketal* (XIII) crystallised from aqueous methanol as needles (0·5 g.), m. p. 164°, $[\alpha]_D^{19}$ −83·4° (*c* 0·32), $\nu_{max.}$ 1760 cm.$^{-1}$ (lactone) (Found: C, 62·4; H, 8·0. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%).

Hydrogenolysis of the dithioketal. A mixture of the dithioketal (0·26 g.), Raney nickel (1 g.) and dioxan (10 c.c.) was refluxed overnight, giving 4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* (XII; R = H) (0·15 g.) as needles (from aqueous methanol), m. p. 108—109°, $[\alpha]_D^{18}$ −56·1° (*c* 0·344), $\nu_{max.}$ 1765 cm.$^{-1}$ (lactone) (Found: C, 76·2; H, 9·8. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

4,5,6α(H),11β(H)-*Eudesm*-2-*en*-6,13-*olide* (XIV).—The hydroxy-lactone (XII; R = OH) (0·2 g.) was mixed with pyridine (1 c.c.) and phosphorus oxychloride (30 mg.) and set aside overnight. The mixture was worked up in the usual way, giving 4,5,6α(H),11β(H)-*eudesm*-2-*en*-6,13-*olide* (0·1 g.) as needles (from aqueous methanol), m. p. 115°, $[\alpha]_D^{19}$ −41·7° (*c* 0·165) (Found: C, 77·3; H, 9·05. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

3-*Oxo*-4,11β(H)-*eudesm*-5-*en*-13-*oic Acid* (XVI).—Acidification of the sodium hydrogen

carbonate extracts obtained in the preparation of compound (V) gave 3-*oxo*-4,11β(H)-*eudesm*-5-*en*-13-*oic acid* (XVI) (2 g.) which recrystallised from aqueous ethanol as needles, m. p. 145°, $[\alpha]_D^{21}$ +1·9° (*c* 0·203) (Found: C, 69·4; H, 9·4. $C_{15}H_{22}O_3,\frac{1}{2}H_2O$ requires C, 69·5; H, 8·9%).

3-*Oxo*-11β(H)-*eudesm*-4-*en*-13-*oic Acid* (XVII).—(*a*) A solution of the acid (XVI) (1 g.) and toluene-*p*-sulphonic acid (0·8 g.) in acetic acid (20 c.c.) was set aside overnight, diluted with water, and extracted with ether. The extract was washed with water (to remove acetic acid) and dried, and the solvent was removed. The residue crystallised from aqueous ethanol, giving 3-*oxo*-11β(H)-*eudesm*-4-*en*-13-*oic acid* (0·64 g.) as needles, m. p. 117°, $[\alpha]_D^{18}$ +119° (*c* 0·35). (*b*) This acid was also isolated (2·1 g.), by extraction with sodium hydrogen carbonate solution, from the products of hydrogenation of 6α(H),11β(H)-santonin (4 g.) in ethyl acetate containing freshly prepared palladised charcoal. It had m. p. and mixed m. p. 117° and $[\alpha]_D^{21}$ +121° (*c* 0·378) (Found: C, 71·7; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

3-*Oxo*-4ξ(H),5ξ(H),11β(H)-*eudesman*-13-*oic Acid* (XVIII).—This *acid* was isolated (1·4 g.) from sodium hydrogen carbonate washings of the product obtained in the preparation of (VI). After two recrystallisations from aqueous ethanol it formed rhombs, m. p. 193°, $[\alpha]_D^{20}$ +2° (*c* 0·48) (Found: C, 71·1; H, 9·4. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

Reduction of Potassium 6β-*Hydroxy*-3-*oxo*-11β(H)-*eudesm*-1,3-*dien*-13-*oate* [6α(H),11β(H)-*Santoninate*].—6α(H),11β(H)-Santonin (I) (1·2 g.) was refluxed for 15 min. in methanol (90 c.c.) with potassium hydroxide (0·8 g.). The mixture was cooled and then shaken in hydrogen with 10% palladised charcoal (0·2 g.). After filtration, the solution was acidified, then refluxed for 0·5 hr., and the methanol was removed by distillation. Water (20 c.c.) was added, giving 3-*oxo*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide* (XXIV) (0·92 g.) which crystallised from aqueous ethanol in needles, m. p. 203—204°, $[\alpha]_D^{28}$ −27° (*c* 0·318) (Found: C, 71·9; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). It (0·2 g.) was recovered unchanged after being kept overnight with toluene-*p*-sulphonic acid (0·4 g.) in acetic acid (15 c.c.).

3α-*Hydroxy*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide* (XXV; R = H).—(*a*) The compound (XXIV) (0·3 g.) in acetic acid (100 c.c.) was stirred in hydrogen with Adams catalyst (0·15 g.). After filtration, the solvent was evaporated, and the residue was washed in ether with 5% sodium hydrogen carbonate and with water and dried. Evaporation and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 40—60°) gave 3α-*hydroxy*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide* (XXV; R = H) (0·2 g.) as needles, m. p. 160—161°, $[\alpha]_D^{27}$ +43° (*c* 0·27), $\nu_{max.}$ 3450 (OH), 1755 cm.$^{-1}$ (lactone) (Found: C, 71·1; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

(*b*) The keto-lactone (XXIV) (0·4 g.) in ethanol (50 c.c.) was kept overnight with sodium borohydride (50 mg.) in water (5 c.c.). The mixture was worked up in the usual way, giving the hydroxy-lactone (XXV; R = H) (0·18 g.), m. p. and mixed m. p. 161°. Its *acetate* crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 183°, $[\alpha]_D^{27}$ −57° (*c* 0·24), $\nu_{max.}$ 1766 (lactone), 1742 (OAc), and 1245 cm.$^{-1}$ (OAc) (Found: C, 69·4; H, 9·0. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

Reaction of Phosphorus Oxychloride with the Alcohol (XXV; R = H).—The alcohol (0·3 g.) was set aside overnight with phosphorus oxychloride (0·2 g.) and pyridine (1·5 c.c.) and then poured into water. The mixture was extracted with ether, and the extract was washed with dilute acid and with water. The solvent was removed, giving a solid, m. p. 90—100°, which was chromatographed on acid alumina with benzene–light petroleum. The early fractions contained a complex of the chloro-compound (XXVI) and 4,6α(H),5,11β(H)-eudesm-2-en-6,13-olide (XXVII), which crystallised from aqueous methanol as needles (0·19 g.), m. p. 125—126°, $[\alpha]_D^{20}$ +14·4° (*c* 0·17), $\nu_{max.}$ (KBr disc) 1764 (lactone), 1176 (C–O), 947, 753 cm.$^{-1}$ (C–Cl) (Found: C, 70·9; H, 8·6. Calc. for $C_{15}H_{22}O_2$,$C_{15}H_{23}ClO_2$: C, 71·7; H, 9·0%). Later fractions contained the *chloro-compound* (XXVI) (0·07 g.), m. p. 159—160°, $[\alpha]_D^{20}$ −27·2° (*c* 0·66), $\nu_{max.}$ 1764 (lactone), 1169 (C–O) and 753 cm.$^{-1}$ (C–Cl) (Found: C, 66·5; H, 8·7. $C_{15}H_{23}ClO_2$ requires C, 66·5; H, 8·5%).

Reaction of 6α(H),11β(H)-*Santonin* (I) *with Ethyl Orthoformate.*—Boron trifluoride–ether complex (0·1 c.c.) was added to a solution of the santonin isomer (I) (0·4 g.) in ethanol (15 c.c.) containing ethyl orthoformate (0·2 g.), and the mixture was refluxed for 4 hr. After cooling, the mixture was poured into excess of 1% aqueous sodium hydrogen carbonate and extracted with ether, yielding the *ethyl ether* (XXI) of 6,7α(H),11β(H)-desmotroposantonin (0·31 g.) as needles (from aqueous methanol), m. p. 167—168° (undepressed by a specimen prepared from the desmotroposantonin and ethyl sulphate), $[\alpha]_D^{20}$ −96·3° (*c* 0·31), $\lambda_{max.}$ 2860 Å (log ε 3·5), $\nu_{max.}$

1750 (lactone), 1595 cm.$^{-1}$ (aromatic) (Found: C, 74·0; H, 8·1. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%).

Catalytic Reduction of the Ether (XXI).—The ether (0·3 g.) in ethyl acetate (30 c.c.) was shaken with 10% palladised charcoal (0·5 g.) in hydrogen for 18 hr. The filtered solution was extracted with 3% sodium hydrogen carbonate solution, and the extract was acidified, giving the 11β(H)-*santonous acid ethyl ether* (XXII) (0·2 g.), m. p. 121—122°, $[\alpha]_D^{20}$ +48·9° (*c* 0·335), $\lambda_{max.}$ 2870 Å (log ε 3·2), $\nu_{max.}$ 1710 (CO_2H), 1585, and 1595 cm.$^{-1}$ (aromatic) (Found: C, 73·5; H, 8·6. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·75%).

Borohydride Reduction of 3-*Oxo*-4,5,11α(H),6β(H)- *and* 3-*Oxo*-4,5α(H),6,11β(H)-*eudesman*-6,13-*olide* (VIII) (with B. J. Donnelly). 3-Oxo-4,5,11α(H),6β(H)-eudesman-6,13-olide (140 mg.) in methanol (4 c.c.) and water (1 c.c.) was slowly treated with potassium borohydride (14 mg.) in water (1 c.c.). After 2·5 hr. the mixture was acidified and methanol was removed under reduced pressure. The oily product became solid when scratched and crystallised from ethanol, giving 3α-hydroxy-4,5,11α(H),6β(H)-eudesman-6,13-olide [XV; 11α(H)] (80 mg.) as needles, m. p. and mixed m. p. with an authentic specimen,[1] 110°, $[\alpha]_D^{18}$ +40·7° (lit.,[1] +36°). Its acetate had m. p. 200° (lit.,[1] 199—200°), $[\alpha]_D^{18}$ +18·1° (lit.,[1] +15·4°).

3-Oxo-4,5α(H),6,11β(H)-eudesman-6,13-olide (700 mg.) was similarly reduced in methanol (70 c.c.) with borohydride (100 mg.) in water (4 c.c.). The product, extracted with ethyl acetate, was 3α-hydroxy-4,5α(H),6,11β(H)-eudesman-6,13-olide (500 mg.), m. p. and mixed m. p. with an authentic specimen,[2] 147—148°, $[\alpha]_D^{18}$ +100° (lit.,[2] +94°). Its acetate had m. p. 172—173° (lit.,[2] 170—172°), $[\alpha]_D^{18}$ +53° (lit.,[2] +55·7°).

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