236. *The Chemistry of Santonin. Part VII.* Some Reduction Products of* 6α(H)-*Santonin.*

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

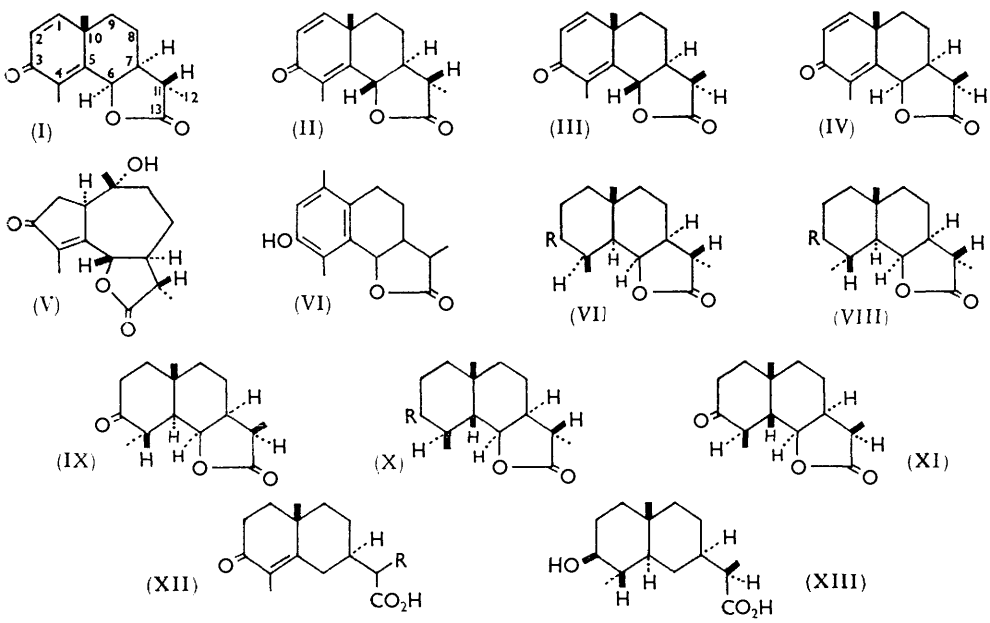
In earlier papers of this series [1-3] we described the reduction products of santonin (II),† of its 11-epimer (β-santonin) (III), and of the further stereoisomer (IV) which is derived from (III). We now describe the reduction products of the 6-epimer (I) of santonin. Recently, however, the stereochemistry of santonin has been amended. *X*-Ray crystallographic studies [4] of isophoto-α-santonic lactone (V), as well as detailed studies [5] of the chemistry of this lactone (V), have shown that santonin has the stereochemistry shown in

* Part VI, *J.*, 1962, 1432. We use the nomenclature of Cocker and Cahn, *Chem. and Ind.*, 1955, 384, and Cocker and McMurry, *J.*, 1955, 4430. α-Santonin is santonin, and β-santonin is 11α(H)-santonin.

† *Added, December 28th*, 1962.—Santonin has been shown by *X*-ray crystallography to be (II) (Asher and Sim, *Proc. Chem. Soc.*, 1962, 335).

[1] Cocker and McMurry, *J.*, 1956, 4549.
[2] Cocker, Dodds, and McMurry, *Tetrahedron*, 1958, **3**, 160.
[3] Cocker, Gobinsingh, McMurry, and Nisbet, *J.*, 1962, 1432.
[4] Asher and Sim, *Proc. Chem. Soc.*, 1962, 111.
[5] Barton, Miki, Pinhey, and Wells, *Proc. Chem. Soc.*, 1962, 112.

(II). Its configuration at C-11 is also supported by its degradation [6] to (+)-benzoylalanine. This configuration is the reverse of that widely accepted, which was derived [7] from a study of the stereochemistry of the desmotroposantonins (VI). The new configuration at C-11 will, therefore, have to be borne in mind by readers of earlier papers in this series.



Reduction of compound (I) gives products analogous to those derived from its 11-epimer (IV). Reduction over palladised charcoal gives an acid fraction and 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (VII; R = O). The latter, on treatment with hot 5% sulphuric acid or toluene *p*-sulphonic acid, or when shaken with alumina in benzene, gives 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (VIII; R = O). The configuration of these lactones is established by a comparison of their rotatory dispersion curves with those of their 11α(H)-analogues.[3] Further, the lactone (VIII; R = O), on treatment with methanolic potassium hydroxide, gives a mixture of lactones, which, judged from its optical rotation, contains over 80% of the 11-epimer (IX).[3]

Reduction of 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (VII; R = O) with borohydride, aluminium amalgam, or hydrogen and Adams platinic oxide, gives in each case 3α-hydroxy-4,5,6α(H),11β(H)-eudesman-6,13-olide (VII; R = α-OH) whose acetate is more lævotatory than the alcohol (cf. ref. 3). The deoxy-compound (VII; R = H) (cf. ref. 3) is also more dextrorotatory than either the alcohol or its acetate, thus confirming the α-configuration of the hydroxyl group. Oxidation of the alcohol (VII; R = α-OH) affords the parent ketone (VII; R = O).

Reduction of the more stable lactone (VIII; R = O) takes place with the three reagents mentioned above, giving the alcohol (VIII; R = β-OH), whose acetate is more lævorotatory than the alcohol, thus behaving like its 11-epimer.[3] However, the alcohol gives a chloro-compound with phosphorus oxychloride and pyridine, showing that it is equatorial and, further, the deoxy-compound (VIII; R = H) is more lævorotatory than the alcohol. Hence the hydroxyl group is β-orientated.

Reduction of potassium 6α(H)-santoninate, derived from compound (I), over palladised

[6] Nakazaki and Arakawa, *Proc. Chem. Soc.*, 1962, 151.
[7] Cf. Cocker and McMurry, *Tetrahedron*, 1960, **8**, p. 196.

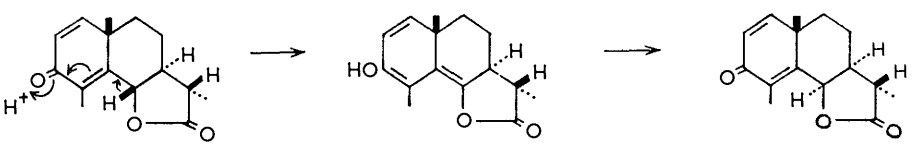
charcoal affords two keto-lactones, namely, a new compound 3-oxo-4,6α(H),5,11β(H)-eudesman-6,13-olide (X; R = O) and 3-oxo-4,6,11α(H),5β(H)-eudesman-6,13-olide (XI) previously described.[3] The former is stable to toluene-*p*-sulphonic acid and therefore has an equatorial 4-methyl group, and it is shown to be a *cis*-fused decalin (cf. ref. 3) by its conversion by methanolic potassium hydroxide into the 11-epimer (XI) of known structure.[3]

Reduction of the ketone (X; R = O) with borohydride or with Adams catalyst and hydrogen gives the α-alcohol (X; R = α-OH), by analogy with the formation of its 11-epimer.[3]

The acid fraction obtained by hydrogenation of 6α(H)-santonin over palladised charcoal is the deoxy-acid (XII; R = α-Me) which shows maxima at 2490 (log ε 4·2) and 3100 Å (log ε 1·9) in the ultraviolet region and at 2760 (CO_2H), 1739 (CO_2H), 1645, and 1613 cm.$^{-1}$ (C=C–C=O) in the infrared region. These agree well with the maxima obtained for this compound, previously prepared by the reduction of santonin with lithium in liquid ammonia,[8] and with those obtained for its 11α(H)-analogue.[3] We could not isolate the corresponding 5-enoic acid (cf. ref. 3).

We mentioned earlier that the lactone (VIII; R = O) can be converted by methanolic potassium hydroxide into a mixture of lactones containing over 80% of its 11-epimer (IX). No reaction takes place when this product (IX) is treated with alkali, and hence the reaction is not an equilibration. Similarly the lactone (X; R = O) is converted into its 11-epimer (XI). Moreover, 6α(H)-santonin (I) is converted into 6,11α(H)-santonin (IV) by potassium t-butoxide [9] or, less effectively, by potassium carbonate in boiling xylene.[10] On the basis of our lactone rule,[1,11] the reverse transformations would have been expected since in lactones (I), (VIII; R = O) and (X; R = O) the 11-methyl group is *cis* with respect to the 7-hydrogen atom.

It might be asked, therefore, whether treatment of santonin (II) and 11α(H)-santonin (III) with hydrogen chloride in dimethylformamide does in fact give the isomers (I) and (IV), respectively. We have now shown that this is the case in the following way. Reduction of santonin (II) with lithium in liquid ammonia affords the deoxy-acid (XII; R = α-Me),[8] and the same acid is obtained when 6α(H)-santonin (I) is reduced with lithium in liquid ammonia or as mentioned above with palladised charcoal and hydrogen. A second deoxy-acid (XII; R = β-Me) is obtained when either 11α(H)-santonin (III) or 6,11α(H)-santonin (IV) is reduced. We have shown by the reduction of artemisin [12] that lithium in ammonia does not effect epimerisation at position 7, hence compounds (II) and (III) can only differ from (I) and (IV), respectively, in their configuration at position 6. The $C_{(6)}$-epimerisation of santonin can be portrayed as follows:



The *cis*-fused lactones (I) and (IV) are hydrogenolysed, whilst the *trans*-fused lactones (II) and (III) are unaffected [1-3] by treatment with hydrogen and a catalyst. This difference may be due partly to the quasi-axial character of the oxygen substituent at position 6, but a great driving force probably resides in the relatively planar lactone ring which can find a seat on the catalyst. It is of interest that the two pairs of *cis*-fused desmotroposantonins (VI) are readily hydrogenolysed [12] to two pairs of enantiomorphic deoxy-acids.

We can now comment on the conversion of lactones (VIII; R = O) and (X; R = O)

[8] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858.
[9] Barton, Levisalles, and Pinhey, *J.*, 1962, 3472.
[10] Cf. Cocker, Cross, and Lipman, *J.*, 1949, 959.
[11] Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828.
[12] Cocker and Nisbet, unpublished information.

into their 11-epimers (IX) and (XI), respectively by cold methanolic potassium hydroxide. This reagent will not effect inversion at position 11 in the *trans*-fused lactones.[1,2] The difference is due to the greater resistance to alkali of the *cis*- than of the *trans*-fused lactones. The tetrahydro-santonins and -11α(H)-santonins are hydrolysed about ten times faster than their 6-epimers.[12] Lactones can epimerise at the α-carbon atom with base more readily than their hydroxy-acids, since in the latter the carboxylate ion will oppose the formation of enolate ion which is necessary for epimerisation. Hydroxy-acids, therefore, usually require more vigorous conditions before inversion occurs at the α-carbon atom. Thus when ketones (VIII; R = O) and (X; R = O) are treated with methanolic potassium hydroxide there must be competition between inversion at position 11 and hydrolysis, giving products which contain some of the initial lactone. 6α(H)-Santonin (I) is only partly converted by this reagent into 6,11α(H)-santonin (IV). Both of these lactones are hydrolysed by it faster than their tetrahydro-compounds.[12] Potassium t-butoxide, a stronger base, however, effects the change (I) ⟶ (IV) in high yield,[9] presumably because enolisation is faster than hydrolysis.

Although we have used a variety of conditions we have no evidence that any of the lactones mentioned above undergoes inversion at position 11 under the influence of acid.

We referred above to the hydrogenolysis of 6,11α(H)-santonin [3] giving the acid (XII; R = β-Me). We have now shown that this acid is produced when 6,11α(H)-santonin is refluxed with zinc in ethanolic acetic acid. Further reduction of the acid (XII; R = β-Me) over Adams catalyst gives 3β-hydroxy-4β(H),5,11α(H)-eudesman-13-oic acid (XIII) (cf. ref. 3). We use this stereoformula since the acid can also be obtained by the reduction of 3-oxo-4β(H),11α(H)-eudesm-5-en-13-oic acid.[3] The same acid is also obtained by reduction with borohydride of an acid referred to as 3-oxo-4ξ(H),5ξH,11β(H)-eudesman-13-oic acid by us in Part VI.[3] The latter is thus 3-oxo-4β(H),5,11α(H)-eudesman-13-oic acid.

Experimental

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

Hydrogenation of 6α(H)-*Santonin.*—3-*Oxo*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* (VII; R = O). A solution of 6α(H)-santonin [13] (3·6 g.) in ethyl acetate (120 c.c.) containing 10% palladised charcoal (0·9 g.) was stirred in hydrogen for 2 hr., filtered, and concentrated to 30 c.c. On storage the required *lactone* was obtained; it crystallised from ethyl acetate–light petroleum as rhombs, m. p. 196—197°, $[\alpha]_D$ −136·6° (*c* 0·6), $\nu_{max.}$ 1764 (lactone), 1706 cm.$^{-1}$ (cyclohexanone) (Found: C, 71·8; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). Complete removal of solvent from the hydrogenation mixture gave an oil which was washed with 5% sodium hydrogen carbonate, yielding more lactone, m. p. 194—195°. The total yield of lactone was 2·8 g.

In a similar experiment carried out for 8 hr. two lactones were obtained. The above lactone (2·5 g.) was separated from its 4-epimer (VIII; R = O) (90 mg.) (see below) by fractional crystallisation from ethyl acetate–light petroleum.

3-*Oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (VIII; R = O).—A solution of 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (0·5 g.) in acetic acid (15 c.c.) containing toluene-*p*-sulphonic acid (0·45 g.) was set aside overnight. The mixture, diluted with water, then gave the required isomeric *lactone* which crystallised from ethyl acetate–light petroleum as needles (0·21 g.), m. p. 166—167°, $[\alpha]_D^{28}$ −113·8 (*c* 0·6), $\nu_{max.}$ 1776 (lactone) and 1706 cm.$^{-1}$ (cyclohexanone) (Found: C, 72·2; H, 9·2. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). The same lactone was obtained (0·45 g.; m. p. 166—167°) when 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (0·5 g.) was shaken for 15 min. at 40° in benzene (100 c.c.) with Woelm's basic alumina (5 g.).

3α-*Hydroxy*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* (VII; R = α-OH).—(*a*) A mixture of 3-oxo-4,5,6α(H),11β(H)-eudesman-6,13-olide (0·6 g.), sodium borohydride (0·1 g.), methanol (30 c.c.), and water (5 c.c.) was set aside overnight, then acidified and concentrated to 10 c.c. Extraction with ether gave the required *lactone* which crystallised from ethyl acetate–light

[13] Ishikawa, *J. Pharm. Soc. Japan*, 1956, **76**, 504.

petroleum as needles (0·22 g.), m. p. 153—154°, $[\alpha]_D^{17}$ −130·4° (*c* 0·22), $\nu_{max.}$ 3546 (OH) and 1764 cm.$^{-1}$ (lactone) (Found: C, 71·6; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). (*b*) A mixture of the ketone (VII; R = O) (0·2 g.)with aluminium amalgam (Al, 1 g.) in moist ether (200 c.c.) was refluxed for 4 hr., giving the lactone (0·12 g.), m. p. 154—155°, $[\alpha]_D^{17}$ −130° (*c* 0·2). (*c*) The lactone (VII; R = O) (0·5 g.) was hydrogenated for 4 hr. over Adams platinic oxide (0·2 g.) in ethyl acetate (100 c.c.), giving the hydroxy-lactone (0·45 g.), m. p. 154—155°, $[\alpha]_D^{17}$ −124·7° (*c* 0·36). Its *acetate* (VII; R = α-OAc) crystallised from aqueous ethanol as needles, m. p. 181—182°, $[\alpha]_D^{28.5}$ −192° (*c* 0·36), $\nu_{max.}$ 1765 (lactone), 1744 (ester), and 1245 cm.$^{-1}$ (acetate) (Found: C, 69·3; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

Oxidation of the Hydroxy-lactone (VII; R = α-OH).—This compound (0·1 g.) was set aside overnight with chromium trioxide (30 mg.) in acetone (5 c.c.). The product, without purification, was substantially the keto-lactone (VII; R = O) (70 mg.), m. p. and mixed m. p. 190—191°.

4,5,6α(H),11β(H)-*Eudesman*-6,13-*olide* (VII; R = H).—*Dithioketal* [VII; R = (·CH_2·S·)$_2$] *of* 3-*oxo*-4,5,6α(H),11β(H)-*eudesman*-6,13-*olide*. The keto-lactone (87 mg.) was mixed with ethane-1,2-dithiol (1 c.c.) and boron trifluoride–ether complex (1 c.c.) and set aside overnight. The required *dithioketal* (36 mg.) crystallised from aqueous methanol as needles, m. p. 152°, $\nu_{max.}$ 1769 cm.$^{-1}$ (lactone) (Found: C, 62·1; H, 7·8. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%).

Hydrogenolysis of the dithioketal. This compound (0·3 g.) was refluxed for 16 hr. in dioxan (15 c.c.) with Raney nickel (0·8 g.). The mixture was filtered and evaporated (reduced pressure) and the residue was crystallised thrice from aqueous methanol, giving 4,5,6α(H),11β(H)-*eudesman*-6,13-*olide* as needles (0·1 g.), m. p. 89—90°, $[\alpha]_D$ −71·2° (*c* 0·19), $\nu_{max.}$ 1774 cm.$^{-1}$ (lactone) (Found: C, 76·4; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

3β-*Hydroxy*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (VIII; R = β-OH).—(*a*) A mixture of 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (0·4 g.), sodium borohydride (50 mg.), ethanol (20 c.c.), and water (3 c.c.) was set aside overnight, and then worked up in the usual way. The required hydroxy-lactone was difficult to crystallise, but a microcrystalline *product* (0·22 g.) (from ethyl acetate–light petroleum) was obtained, with m. p. 105°, $[\alpha]_D$ −94·6° (*c* 0·3), $\nu_{max.}$ 3278 (OH) and 1769 cm.$^{-1}$ (lactone) (Found: C, 71·25; H, 9·5. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). (*b*) Reduction of the lactone (VIII; R = O) (0·5 g.) in acetic acid (20 c.c.) over Adams platinic oxide (0·1 g.) for 20 hr. gave a product, m. p. 107—108° (from ethyl acetate–light petroleum), $[\alpha]_D$ −107·5° (*c* 0·26). (*c*) A mixture of the lactone (VIII; R = O) (0·2 g.), moist ether (170 c.c.), and aluminium amalgam (Al, 0·1 g.) was refluxed for 4 hr. giving 3β-*hydroxy*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* as needles (0·15 g.), m. p. 112—113°, $[\alpha]_D$ −101·6°. The products from experiments (*a*), (*b*), and (*c*) had identical infrared spectra. The *acetate* (needles from ethyl acetate–light petroleum) had m. p. 172—173°, $[\alpha]_D^{28.5}$ −115° (Found: C, 69·5; H, 9·1. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

Oxidation of the hydroxy-lactone. A mixture of this compound (0·1 g.), sodium dichromate (0·5 g.), and acetic acid (10 c.c.) was set aside overnight, giving 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (80 mg.), m. p. and mixed m. p. 160°.

5,6α(H),4,11β(H)-*Eudesman*-6,13-*olide* (VIII; R = H).—*Dithioketal* [VIII; R = (·CH_2·S·)$_2$] *of* 3-*oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide*. The keto-lactone (0·75 g.), treated with ethane-1,2-dithiol (1 c.c.) and boron trifluoride–ether complex (1 c.c.), gave the required *dithioketal* (0·6 g.), which crystallised from aqueous methanol in prisms, m. p. 214—216°, $[\alpha]_D^{17}$ −84·7° (*c* 0·55), $\nu_{max.}$ 1786 cm.$^{-1}$ (lactone) (Found: C, 62·2; H, 7·8. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%).

Hydrogenolysis of the dithioketal. This compound (0·12 g.), when refluxed with Raney nickel (0·2 g.) in dioxan (30 c.c.) for 16 hr., gave 5,6α(H),4,11β(H)-*eudesman*-6,13-*olide*, which crystallised from aqueous methanol as colourless needles (71 mg.), m. p. 99—100°, $[\alpha]_D$ −139·5° (*c* 0·5), $\nu_{max.}$ 1786 cm.$^{-1}$ (lactone) (Found: C, 76·4; H, 10·6. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

3-*Chloro*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide* (VIII; R = Cl).—A mixture of 3β-hydroxy-5,6α(H),4,11β(H)-eudesman-6,13-olide (0·14 g.), phosphorus oxychloride (30 mg.), and pyridine (1 c.c.) was set aside for 15 hr. The *chloro-compound* crystallised from ethyl acetate–light petroleum as prisms (72 mg.), m. p. 120—122° (Found: C, 66·7; H, 8·5. $C_{15}H_{23}ClO_2$ requires C, 66·5; H, 8·5%).

3-*Oxo*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide* (X; R = O).—6α(H)-Santonin (1·9 g.) was refluxed for 20 min. with potassium hydroxide (0·95 g.) in methanol (100 c.c.). The cooled

solution was shaken for 4 hr. in an atmosphere of hydrogen with 10% palladised charcoal (0·8 g.), then filtered, concentrated to 50 c.c., and acidified. Potassium chloride was deposited; sufficient water was added to dissolve this, and the solution was set aside. A solid (0·53 g.) separated, which crystallised from ethyl acetate–light petroleum, giving 3-oxo-4,6,11α(H),5β(H)-eudesman-6,13-olide (XI), m. p. and mixed m. p. 200—201°.[3] The aqueous mother liquors therefrom were extracted with ether which removed an oil. Ligroin (b. p. 60—80°) was added to this oil, giving a solid, m. p. 123—127°, which was crystallised from ethyl acetate–light petroleum; this was 3-*oxo*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide*, rhombs (0·37 g.), m. p. 134—135°, $[\alpha]_D$ −41·3° (*c* 0·34), $\nu_{max.}$ 1764 (lactone), 1714 cm.$^{-1}$ (cyclohexanone) (Found: C, 72·2; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). It was stable to toluene-*p*-sulphonic acid, and to being shaken with alumina in benzene.

3α-*Hydroxy*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide* (X; R = α-OH).—(*a*) The preceding compound (0·5 g.), ethanol (20 c.c.), water (2 c.c.), and sodium borohydride (90 mg.) were set aside overnight, and the mixture was then acidified. The deposited solid crystallised from ethyl acetate–light petroleum, giving 3α-*hydroxy*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide* as rhombs (0·24 g.), m. p. 176—178°, $[\alpha]_D^{28}$ −73° (*c* 0·37), $\nu_{max.}$ 3470 (OH), 1767 cm.$^{-1}$ (lactone) (Found: C, 71·3; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). (*b*) The keto-lactone (0·5 g.) was reduced in acetic acid (50 c.c.) over Adams platinic oxide (0·1 g.), giving the hydroxy-lactone (0·35 g.), m. p. and mixed m. p. 176—178°, $[\alpha]_D$ −75·8° (*c* 0·13).

3-*Oxo*-11β(H)-*eudesm*-4-*en*-13-*oic Acid* (XII; R = α-Me).—The acidic fraction obtained from the hydrogenation of 6α(H)-santonin (1·5 g.) in ethyl acetate (35 c.c.) over 10% palladised charcoal (1 g.) was a gum which became solid on storage. This was an unsaturated acid (XII; R = α-Me) (0·9 g.) that crystallised from ethyl acetate–light petroleum in rhombs, m. p. 125—126°, $[\alpha]_D^{28.5}$ +113·6° (*c* 0·4) (lit.,[8] gives $[\alpha]_D$ +11·4°, but Professor Jeger has informed us that this figure should be 114°), $\lambda_{max.}$ 2490 (log ε 4·2) and 3100 Å (log ε 1·9), $\nu_{max.}$ 2760 (CO_2H) 1739 (CO_2H), 1645 (C=C–C=O), and 1613 cm.$^{-1}$ (C=C) (Found: C, 71·9; H, 8·8. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9%).

Reaction of 3-*Oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide with Methanolic Potassium Hydroxide*.—The keto-lactone (0·1 g.) (m. p. 166—167°) was set aside overnight with potassium hydroxide (0·4 g.) and methanol (10 c.c.). Methanol was then removed by rapid distillation, and the residue was dissolved in water and acidified. The product, a white solid (85 mg.), had m. p. 145—148°, $[\alpha]_D^{16}$ −95·2°, $\nu_{max.}$ 1770 (lactone) and 1705 cm.$^{-1}$ (cyclohexanone). The rotation corresponds to that of a mixture of the two 11-epimers containing 82% of 5,6,11α(H),4β(H)-eudesman-6,13-olide (IX), $[\alpha]_D$ −91°.[3]

Reaction of 3-*Oxo*-4,6α(H),5,11β(H)-*eudesman*-6,13-*olide with Methanolic Potassium Hydroxide*.—This keto-lactone (0·2 g.) was set aside overnight at 29° with 4·8% methanolic potassium hydroxide (50 c.c.). The product was acidified, diluted to 200 c.c., and extracted with ether. The extract was washed with 5% sodium hydrogen carbonate, giving an oil which became solid when scratched. It crystallised from ethyl acetate–light petroleum, giving starting material (0·09 g.), m. p. 124°. Concentration of the mother-liquors gave a solid (0·06 g.), m. p. 178—185°, raised to 200° on further crystallisation from ethyl acetate–light petroleum. The m. p. was not depressed on admixture with 3-oxo-4,6,11α(H),5β(H)-eudesman-6,13-olide.[3]

Action of 5% *Sulphuric Acid* on 3-*Oxo*-5,6α(H),4,11β(H)-*eudesman*-6,13-*olide*.—The finely powdered keto-lactone (0·5 g.) was heated for 4 hr. at 95° with concentrated sulphuric acid (1·5 c.c.) in water (50 c.c.). After about 15 min. the lactone became crystalline. The mixture was cooled and the product (0·47 g.) was collected. It had m. p. and mixed m. p. with starting material 166—168°, $[\alpha]_D$ −118·5° (*c* 0·5), without crystallisation.

Reactions of 6α(H)- *and* 6,11α(H)-*Santonin*.—(*a*) *Conversion into desmotroposantonins*. 6α(H)-Santonin (0·1 g.) was added to a mixture of acetic anhydride (2 c.c.) and concentrated sulphuric acid (0·1 c.c.) and set aside for 1 hr., giving 6,7α(H),11β(H)-desmotroposantonin acetate (90 mg.), that had m. p. and mixed m. p. 158—159° and $[\alpha]_D^{16}$ −140° (*c* 0·2) without purification. 6,11α(H)-Santonin (0·2 g.), similarly treated, gave a product (190 mg.), m. p. 150° raised to 156—157° on crystallisation from ethyl acetate–ligroin, $[\alpha]_D$ −92°, undepressed on admixture with an authentic specimen 6,7,11α(H)-desmotroposantonin acetate. (*b*) *Reaction with base*. 6α(H)-Santonin (0·2 g.) was refluxed in tetralin (60 c.c.) with anhydrous potassium carbonate (0·6 g.) for 24 hr. The mixture was filtered and evaporated to dryness in a vacuum, giving a gum which hardened when scratched under light petroleum (b. p. 40—60°). The gum was transferred in ethyl acetate to an alumina column (Woelm brand, neutral, 20 g.). Elution

with 1 : 1 benzene–ether gave a light yellow solid, m. p. 160—168°, which after two crystallisations from ethyl acetate–light petroleum gave 6,11α(H)-santonin (0·054 g.), m. p. and mixed m. p. 186—188°.

6,11α(H)-Santonin (0·5 g.) was treated as described for 6α(H)-santonin. The product crystallised as needles (0·38 g.), m. p. and mixed m. p. with starting material 189—190°.

Reduction of 6,11α(H)-*Santonin* (IV).—(*a*) *With lithium in liquid ammonia.* When this lactone (3 g.) was reduced in the conditions previously described [8] the product was 3-oxo-11α(H)-eudesm-4-en-13-oic acid (XII; R = β-Me) (1·7 g.), m. p. and mixed m. p. 116, $[\alpha]_D$ +121°.[3] (*b*) *With zinc dust.* The lactone (3 g.) was stirred and refluxed for 30 hr. in ethanol (120 c.c.), acetic acid (80 c.c.), and water (40 c.c.) with zinc dust (7 g.). The organic solvents were removed under reduced pressure and water was added, giving the acid which was cystallised from aqueous ethanol as needles, m. p. and mixed m. p. 115° (Found: C, 71·7, 71·8; H, 9·2, 9·3. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9%).

3β-*Hydroxy*-4β(H),5,11α(H)-*eudesman*-13-*oic Acid* (XIII).—(*a*) The preceding compound (0·1 g.) in ethanol (30 c.c.) was stirred in hydrogen with Adams catalyst (0·1 g.). The required *acid*, needles from aqueous ethanol, had m. p. 186—187°, $[\alpha]_D$ +1·8° (*c* 0·18), $\nu_{max.}$ 3550 (OH), 1690 cm.$^{-1}$ (CO_2H) (Found: C, 70·6; H, 10·25. $C_{15}H_{26}O_3$ requires C, 70·8; H, 10·3%). (*b*) 3-Oxo-4β(H),11α(H)-eudesman-13-oic acid [3] (0·21 g.) was set aside for 3 hr. with potassium borohydride (0·21 g.) in ethanol (5 c.c.) and water (3 c.c.). The product (XIII) had m. p. and mixed m. p. 186—187°. (*c*) 3-Oxo-4β(H),5,11α(H)-eudesman-13-oic acid [3] (0·2 g.) in methanol (10 c.c.) was added to potassium borohydride (90 mg.) in water (1 c.c.), and the mixture was set aside overnight. The product was as above, having m. p. and mixed m. p. 185—186°.

The authors thank Edinburgh Pharmaceutical Industries Ltd. for gifts of santonins, Professor W. Klyne for optical rotation data, and Professor L. J. Haynes for permitting some of this work to be performed in his laboratory.

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[*Received, July 25th,* 1962.]