932. *Some Reduction Products of Helenin.*

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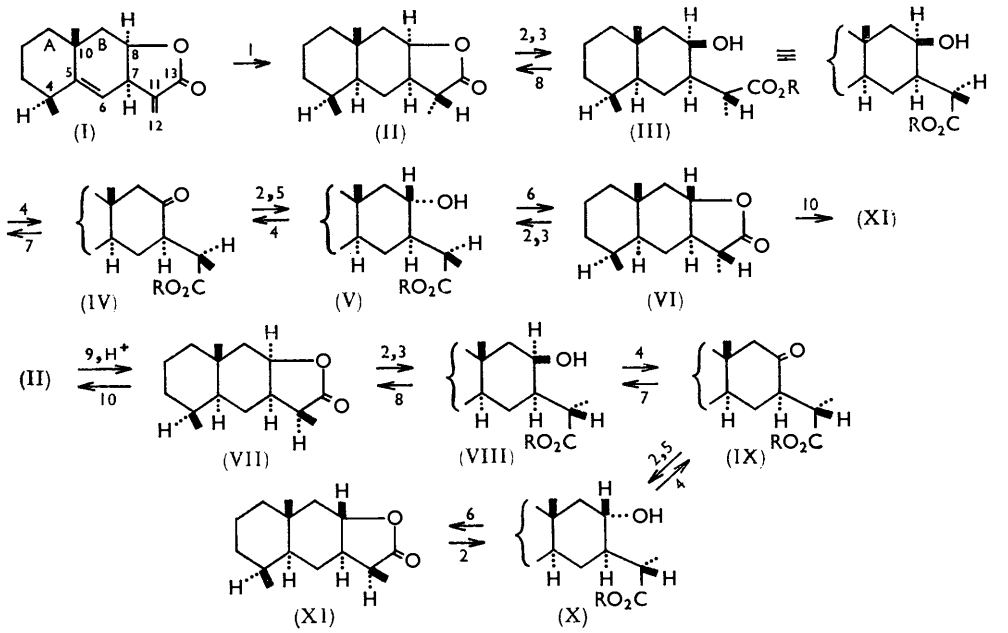
Several tetrahydroalantolactones have been inter-related, and their stereochemistry is here discussed.

HELENIN consists of a mixture of alantolactone (I), isoalantolactone, and dihydroisoalantolactone, in which alantolactone is predominant. Hydrogenation of helenin over a metal catalyst affords a tetrahydroalantolactone,[1] whose stereo-formula is known to be



Reagents: 1, H_2–Pt. 2, OH^-. 3, CH_2N_2. 4, $Na_2Cr_2O_7$–AcOH. 5, Na–Pr^{i}OH. 6, *p*-$C_6H_4Me{\cdot}SO_3H$. 7, KBH_4. 8, Heat. 9, OH^- at 210°. 10, K_2CO_3 in tetralin.

(II).[2,3,4] The course of this hydrogenation is interesting in that hydrogen is added to the 5,6-double bond from the less hindered α-side of the molecule, whilst the other double bond is apparently attacked from the β-side. It is probable, however, that 1,4-addition of hydrogen to the unsaturated lactone system takes place and is followed by isomerisation of the resulting enol to the more stable lactone (II).[5] This lactone has been converted[3,4] into the corresponding *trans*-fused lactone (VI) through the stages (III; R = H) ⟶ (III; R = Me) ⟶ (IV; R = Me) ⟶ (IV; R = H) ⟶ (V; R = H) ⟶ (VI), by employing the reagents shown in the Chart. The lactone (VI) may be reconverted into tetrahydroalantolactone (II) in good yield,[4] by methods also given in the Chart, showing that the series of reactions (II) ⇄ (VI) involves only the configuration at $C_{(8)}$. We have already referred to our successful repetition of the reaction sequence (II)

[1] Ruzicka and van Melsen, *Helv. Chim. Acta*, 1931, **14**, 397; Hansen, *Ber.*, 1931, **64**, 943.
[2] Kovács, Herout, Horák, and Šorm, *Coll. Czech. Chem. Comm.*, 1956, **21**, 225; Benešova, Sýkora, Herout, and Šorm, *Chem. and Ind.*, 1958, 363.
[3] Tsuda, Tanabe, Iwai, and Funakoski, *J. Amer. Chem. Soc.*, 1957, **79**, 5721; cf. Cocker and McMurry, *Tetrahedron*, 1960, **8**, 181.
[4] Cocker, McMurry, and Hopkins, *J.*, 1959, 1998.
[5] Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828.

to (V; R = H) in an earlier paper;[4] we reported the melting point of the hydroxy-acid (V; R = H) to be 185°, some 10° higher than the previous figure.[3] We have now found, however, that lactonisation of the acid (V; R = H) with toluene-*p*-sulphonic acid in benzene gives a low-melting lactone (VI) (m. p. 38°, $[\alpha]_D$ −70·9°); the compound described by earlier workers[3] had m. p. 75°, $[\alpha]_D$ −29·3°). We have also obtained the low-melting lactone (VI) by treating the hydroxy-acid (V; R = H) with (*a*) boron trifluoride–ether complex and (*b*) toluene-*p*-sulphonic acid in acetic acid, and by treating the methyl ester (V; R = Me) with toluene-*p*-sulphonic acid in benzene. From the hydroxy-acid (V; R = H) in methanolic hydrochloric acid, conditions under which Tsuda *et al.*[3] claim to have obtained the lactone, m. p. 75°, we obtained the methyl ester (V; R = Me) (m. p. 73°; $[\alpha]_D$ +42·3°) which has a similar melting point to this lactone but is quite dissimilar in specific rotation.

When heated with potassium hydroxide, the lactone (II) [effectively the hydroxy-acid (III; R = H)] gives the hydroxy-acid (VIII; R = H) as its potassium salt, though the hydroxy-acid itself has not been isolated. Acidification of this salt affords the 8α,11β(Me)-lactone (VII).[6] We have now shown that this lactone (VII) is converted into its isomer (II) by potassium carbonate in hot tetralin.[7] These experiments confirm our earlier hypotheses[5] concerning the relative stabilities of the 11-epimeric *cis*-fused lactones and the corresponding hydroxy-acids. The lactone (II) should be more stable at $C_{(11)}$ than the lactone (VII) since the former is a *cis*-fused lactone in which the 11-methyl group is *cis* with respect to the 7-hydrogen atom. Conversely the corresponding hydroxy-acid (III; R = H) should be less stable at $C_{(11)}$ than the hydroxy-acid (VIII; R = H).

Hydrolysis of the lactone (VII) with 4% aqueous potassium hydroxide, and esterification of the resulting acid with diazomethane, afford the hydroxy-ester (VIII; R = Me) as an unstable oil which readily reverts to the lactone (VII). Oxidation of the hydroxy-ester with chromium trioxide gives the keto-ester (IX; R = Me), again as an oil, which on alkaline hydrolysis affords the corresponding keto-acid (IX; R = H) (but see below). This acid has the same configuration at position 11 (β-Me) as lactone (VII), since it can be reconverted into the latter in good yield by treatment with borohydride followed by acidification. On the other hand, the keto-acid (IX; R = H) is reduced with sodium in propan-2-ol to the hydroxy-acid (X; R = H) which affords the *trans*-lactone (XI) on treatment with toluene-*p*-sulphonic acid. No configurational change other than that at $C_{(8)}$ takes place in the sequence (IX; R = H) ⟶ (XI) since the reactions can be reversed. In accordance with our previous experience,[5] the lactone (XI) should have greater stability at $C_{(11)}$ than its epimer (VI), since these are *trans*-lactones in which the former has the 11-methyl group *trans* to the 7-hydrogen atom. We have confirmed our deductions by the conversion of the lactone (VI) into its isomer (XI) by potassium carbonate in hot tetralin.[7] We have thus related the four lactones (II), (VI), (VII), and (XI) stereochemically.

Klyne's lactone rule[8] confirms the stereochemistry at position 8 in the lactones (VI) and (XI) as shown in the Table. The hydroxy-acids (III and VIII; R = H) are too

Hydroxy-acid	$[M]_D$	Lactone	$[M]_D$	$\Delta[M_D]$
(V; R = H)	+116·8°	(VI)	−167·3°	−284·1°
(X; R = H)	+63·5	(XI)	−41·1	−104·6
(III; R = H) *	+33·1	(II)	+36·5	+3·4
(VIII; R = H) *	+56·3	(VII)	+68·4	+12·1

* $[M]_D$ measured as sodium salts in aqueous-methanolic solution.

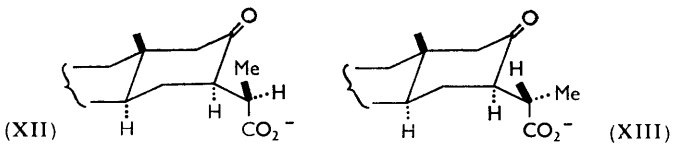
unstable to allow measurement of their molecular rotations. The small shifts in molecular rotations in passing from their sodium salts to the corresponding lactones are in the correct

[6] Asselineau, Bory, and Lederer, *Bull. Soc. chim. France*, 1955, 1524.
[7] Cocker, Cross, and Lipman, *J.*, 1949, 959.
[8] Klyne, *Chem. and Ind.*, 1954, 1198.

direction for our stereo-formulæ (II) and (VII). However, molecular rotations of sodium salts in solution are sometimes anomalous,[9] and too much reliance cannot be placed upon conclusions drawn in this way.

Whilst the *cis*-lactone (II) is readily converted [6] into the *cis*-lactone (VII) by heating it with potassium hydroxide at 210° or with sodium methoxide (reactions which involve respectively the anions of the corresponding acids, and the esters), neither of the *trans*-hydroxy-acids or esters (V; R = H, Me) and (X; R = H, Me) is similarly affected (cf. refs. 4, 5). These conversions need further investigation.

Hydrolysis of the keto-ester (IX; R = Me) with alkali never gave a good yield of its crystalline acid (IX; R = H). We thought that this might be due to equilibration at position 11 with formation of some of the oily keto-acid (IV; R = H). Since the potassium salts of the keto-acids are stable to alkali under the conditions of hydrolysis of the esters, equilibration would have to take place before the ester hydrolysis. Some support for this suggestion was obtained when the esters (IV; R = Me) and (IX; R = Me) were treated with 3% sodium methoxide in methanol. The oily products from the two esters had the same specific rotation and roughly corresponded to a 2 : 1 mixture of the isomers (IV; R = Me) and (IX; R = Me) respectively, though the change in rotation was small. Reduction of each product with borohydride gave a mixture from which lactone (II) was isolated. The other lactone (VII) could not, however, be isolated. The behaviour of the keto-esters may be explained on the basis of interaction between keto- and ester groups, as suggested by Mazur and Sondheimer.[10] This interaction would bring the two carbonyl groups into close proximity, and the 11-epimers (IV and IX; R = Me) would have the relative order of stability of the *cis*-fused lactones (II) and (VII).



If either of the keto-acids (IV; R = H) and (IX; R = H) is heated with alkali at 220°, acidification then gives a mixture from which only one acid (IX; R = H) is obtained. The carboxylate anions of acids (IV and IX; R = H) must exist as (XII) and (XIII) and the latter is the more stable. In these structures we take no account of the enolates which may be produced. Enolisation of the 8-keto-group would enhance the repulsion of the carboxylate ion.

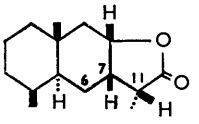
Ukita and Nakasawa [11] recently reported the preparation of a keto-acid, m. p. 153—154°, $[\alpha]_D$ +0·8°, from the lactone (II) under the conditions described for the sequence (II) ⟶ (III) ⟶ (IV; R = H). As mentioned above, we have always obtained the keto-acid as an oil, and Tsuda *et al.*[3] also obtained it as an oil, which we believe is correctly represented by the stereo-formula (IV; R = H). It appears to us that the acid described by Ukita and Nakasawa [11] is the isomer (IX; R = H) which we obtained crystalline, with m. p. 150°, $[\alpha]_D$ −11·7°, and that equilibration of the esters (IV and IX; R = Me) took place under the conditions of ester-hydrolysis employed by Ukita and Nakasawa. It is clear, therefore, that care must be taken in interpreting the results of such reactions which involve alkaline conditions, unless the reactions can be reversed to give starting materials in good yields.

We must now comment on the lactone, m. p. 110—112°, $[\alpha]_D$ −29·2°, which is obtained [3,4] in low yield along with the hydroxy-acid (V; R = H) when the keto-acid (IV; R = H) is reduced with sodium in propan-2-ol. In our earlier paper [4] we assigned to this lactone the configuration shown as (XI) on the ground that three of the four possible

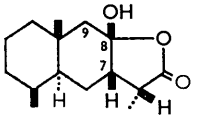
[9] Sýkora and Románuk, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1909.
[10] Mazur and Sondheimer, *Experientia*, 1960, **16**, 181.
[11] Ukita and Nakasawa, *J. Amer. Chem. Soc.*, 1960, **82**, 2224.

lactones (II, VI, VII) differing in configuration only at positions 8 and 11 were already known. Since we have now prepared and stereochemically related all four lactones, our earlier conclusion was invalid. We have now shown that the lactone has structure (XIV) with the " unnatural " configuration at position 7.

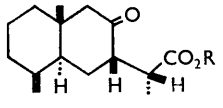
We arrive at our assignment of structure on the following grounds. The lactone, m. p. 112°, can be obtained by borohydride reduction of the acidic hydroxy-lactone, now shown to be (XV), which was obtained [3] in low yield, together with the oily keto-acid (IV; R = H), by alkaline hydrolysis of the keto-ester (IV; R = Me). The mild conditions of the reduction imply a close relationship between (XIV) and (XV). The 7β(H)-hydroxy-lactone (XV) shows maxima at 3350 (OH) and 1740 cm.$^{-1}$ (lactone), and on hydrolysis with sodium hydroxide in methanol affords the 7α(H)-keto-acid (IV), characterised by reduction with borohydride to tetrahydroalantolactone (II) and with sodium in propan-2-ol to the hydroxy-acid (V). The hydrolysis of hydroxy-lactone (XV) to acid (IV) shows that the former is either the 7α(H)-hydroxy-lactone corresponding to (IV) or the 7β(H)-isomer (XV) which is converted into (IV) *via* the 7β(H)-keto-acid (XVI; R = H) which has an axial three-carbon side chain. Borohydride reduction of the hydroxy-lactone (XV) gives a lactone differing from (II) and (VI), which indicates the structure (XV) assigned to the hydroxy-lactone. The hydroxy-lactone (XV) is probably derived from the corresponding keto-acid (XVI; R = H) which we can assume to be present in small quantities in equilibrium with the much more stable 7α(H)-keto-acid (IV; R = H) during alkaline hydrolysis of the ester of the latter.



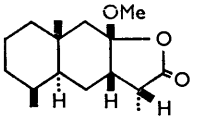
(XIV)



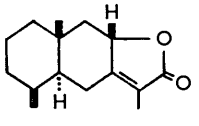
(XV)



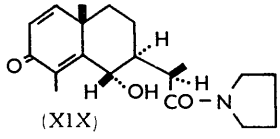
(XVI)



(XVII)



(XVIII)



(XIX)

Reaction of diazomethane with the lactone (XV) affords a product which crystallises well but shows three infrared maxima, at 1755 (lactone), 1740 (CO_2Me), and 1710 cm.$^{-1}$ (ketone), and an ultraviolet peak at 2900 Å (log ε 1·49) compared with 2810 Å (log ε 1·94) for the ester (IX; R = Me). The peak at 1755 cm.$^{-1}$ could be attributed to the methoxy-lactone (XVII) though there is no other evidence of its presence.

We have confirmed the finding that the hydroxy-lactone (XV) with either phosphorus oxychloride in pyridine or toluene-*p*-sulphonic acid in benzene affords [3] the unsaturated lactone (XVIII). This product shows maximum absorption at 2200 Å (log ε 4·05). Matsumura, Iwai, and Ohki [12] record $\lambda_{max.}$ 2250 Å (log ε 3·93). The dehydration might be expected to afford an 8,9-double bond, but models of this unsaturated compound show it to be highly strained, and dehydration must proceed in the other direction to give the 7,8-double bond (a *cis*-elimination), which rearranges in the acid conditions to the 7,11-position.

The structure (XV) for the hydroxy-lactone leads to the structure (XIV) for the lactone, m. p. 112°. We assign to it the 8β(H)-configuration for two reasons. (*a*) The alcoholic hydroxyl group participating in the lactone formation is formed by reduction of the 8-keto-group with sodium in propan-2-ol, and hence must be equatorial. (*b*) The lactone must

[12] Matsumura, Iwai, and Ohki, *J. Pharm. Soc. Japan*, 1954, **74**, 1029.

be *cis*-fused since the corresponding *trans*-fused lactone requires that ring B should exist in a boat form, which would be difficult to prepare from the hydroxy-acid [13] and would be readily hydrolysed to the latter. In fact, the lactone (XIV) is difficult to hydrolyse, and hydrolysis and careful acidification of the lactone affords only starting material.

The 11β(H)-configuration assigned to lactone (XIV) is the less stable of the two possibilities since there is considerable interference between the 6-methylene and the 11α-methyl group. We were unable, however, to epimerise this centre by the use of potassium carbonate in boiling tetralin, and potassium hydroxide at 210° does not affect it. Epimerisation with potassium carbonate in tetralin is almost certainly a surface reaction and the less planar molecule of (XIV) produced by the large axial 7-substituent may prevent the reaction from occurring. A lactone with the $C_{(11)}$-configuration of lactone (XIV) would not be expected to epimerise with potassium hydroxide.[4,5] Our assignment of configuration at position 11 is therefore based on the production of keto-acid (IV) when the lactone (XV) is hydrolysed. This keto-acid is the less stable (see above) of the two 11-epimers and therefore cannot have undergone epimerisation at position 11.

The lactone (XIV) gives a sparingly soluble sodium salt, attempted oxidation of which with *N*-bromosuccinimide in phosphate buffer,[14] or with chromium trioxide in pyridine, yielded only the starting material. The lactone was unaffected by pyrrolidine in benzene, under which conditions santonin yielded the hydroxy-amide (XIX).

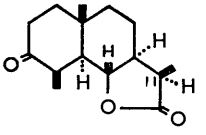
Experimental

Infrared spectra were measured with a Perkin-Elmer Infracord spectrophotometer for Nujol suspensions unless otherwise stated. $[\alpha]_D$ refers to $CHCl_3$ solutions unless otherwise stated.

Methyl 8α-*Hydroxy*-4,5,11α(H)-*eudesman*-13-*oate* * (V; R = Me).—(*a*) The hydroxy-acid [3,4] (V; R = H) (100 mg.) in methanol (5 c.c.) was set aside with an excess of ethereal diazomethane. The product was the *hydroxy-ester* (V; R = Me) (80 mg.) which crystallised from aqueous methanol as plates, m. p. 73—74°, $[\alpha]_D^{16}$ +42·5° (*c* 0·20), $\nu_{max.}$ 3450 (OH), 1725 cm.$^{-1}$ (ester) (Found: C, 71·2; H, 10·4. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%). (*b*) The hydroxy-acid (270 mg.) was refluxed with methanol (10 c.c.) and 10% hydrochloric acid (5 c.c.) for 5 min. The product, crystallised from aqueous methanol, was the hydroxy-ester (200 mg.), m. p. and mixed m. p. 73°.

4,5α(H),8,11β(H)-*Eudesman*-8,13-*olide* (VI).—(*a*) The hydroxy-acid (V; R = H) (40 mg.) was refluxed in benzene (5 c.c.) with toluene-*p*-sulphonic acid (9 mg.) for 30 min. The product was chromatographed on " Woelm " brand acid alumina, and eluted with mixtures of light petroleum (b. p. 40—60°) and benzene. The *lactone* (VI) (31 mg.) obtained was crystallised from 95% methanol, forming plates, m. p. 38°, $[\alpha]_D^{14·5}$ −70·9° (*c* 0·43), $\nu_{max.}$ 1795 (lactone) 1285 cm.$^{-1}$ (C–O) (Found: C, 75·6; H, 10·4. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%). (*b*) Similar treatment of the hydroxy-ester (V; R = Me) (12 mg.) afforded the lactone (VI) (9 mg.), m. p. and mixed m. p. 34°. (*c*) The hydroxy-acid (V; R = H) (500 mg.) was set aside for 1 hr. with boron trifluoride–ether complex (7 c.c.). The product, chromatographed as described above, gave the lactone (200 mg.), m. p. and mixed m. p. 34°. (*d*) The hydroxy-acid (V; R = H) (150 mg.) was refluxed in acetic acid (10 c.c.) with toluene-*p*-sulphonic acid

* In the present paper we preserve the nomenclature of our previous paper.[4] This means that the configuration of the 11-hydrogen atom in the acids and esters is related to the 11(H) of the angular lactones, *e.g.*:



[13] Johnson, Bauer, Margrave, Frisch, Dredger, and Hubbard, *J. Amer. Chem. Soc.*, 1961, **83**, 606.
[14] Tahara, *J. Org. Chem.*, 1956, **21**, 442.

(100 mg.) for 30 min., then cooled and poured into water (100 c.c.). The product isolated from ethereal solution was the lactone (VI) (100 mg.), m. p. and mixed m. p. 36°.

Hydrolysis of 4,5α(H),8,11β(H)-*Eudesman*-8,13-*olide* (VI).—The lactone (50 mg.) in methanol (5 c.c.) was refluxed for 2 hr. with 1% methanolic sodium hydroxide (10 c.c.). The mixture was then cooled, poured into water, and neutralised with dilute hydrochloric acid. Methanol was removed under reduced pressure, and the residue was extracted with ether (2 × 10 c.c.). Removal of solvent from the dried extract gave the hydroxy-acid (V; R = H) (40 mg.) which crystallised as plates, m. p. and mixed m. p. 183°.

Epimerisation of 4,5,8,11α(H)-*Eudesman*-8,13-*olide* [6] (VII) *to* 4,5,8α(H),11β(H)-*Eudesman*-8,13-*olide* (II).—The lactone (200 mg.) (Found: C, 76·2; H, 10·45. Calc. for $C_{15}H_{24}O_2$: C, 76·2; H, 10·2%) was refluxed with freshly ignited potassium carbonate (200 mg.) in anhydrous tetralin (10 c.c.) for 4 hr. After filtration, the solvent was removed under reduced pressure, leaving an oil which was chromatographed on "Woelm" brand acid alumina with benzene–light petroleum, giving a solid product. Crystallisation from methanol gave tetrahydroalantolactone (II) (100 mg.), m. p. and mixed m. p. 144—145°.

8-*Oxo*-4,5α(H),11β(H)-*eudesman*-13-*oic Acid* (IX; R = H).—4,5,8,11α(H)-Eudesman-8,13-olide [6] (VII) (2·4 g.) was refluxed with potassium hydroxide (2·2 g.) in water (55 c.c.) until the mixture was homogeneous. The solution was cooled to −5°, ether (100 c.c.) was added, and the mixture was stirred vigorously and carefully neutralised with dilute acetic acid. The ether layer was separated, an excess of ethereal diazomethane was immediately added, and the solution was set aside at −5° for 1 hr. and at 20° for 1 hr. Removal of the solvent afforded the hydroxy-ester (VIII; R = Me) (2·2 g.) as an oil, $[\alpha]_D^{18}$ −4·7° (*c* 0·81), $\nu_{max.}$ 3450 (OH), 1740 cm.$^{-1}$ (CO_2Me). The hydroxy-ester (2·0 g.) in acetic acid (35 c.c.) was added to sodium dichromate (1·0 g.) in acetic acid (35 c.c.), and the mixture was set aside for 1 hr. The excess of dichromate was then reduced with ethanol, and the solution was concentrated under reduced pressure to 30 c.c., poured into water, and extracted with ether (3 × 25 c.c.). The extract was washed with 5% sodium hydrogen carbonate solution and with water. Removal of the solvent afforded the keto-ester (IX; R = Me) as an oil (1·8 g.), $\nu_{max.}$ 1748 (CO_2Me), shoulders at 1786 (lactone?) and 1721 cm.$^{-1}$ (ketone). This product was refluxed for 1·5 hr. with potassium hydroxide (1·0 g.), methanol (15 c.c.) and water (5 c.c.), then the whole was poured into water and extracted with ether (2 × 20 c.c.). The alkaline solution was acidified and extracted with ether (2 × 20 c.c.). The combined ethereal extracts were washed with 10% sodium hydrogen carbonate which was acidified and extracted with ether (3 × 25 c.c.). These combined extracts were washed with water, dried, and evaporated, giving 8-*oxo*-4,5(H),11β(H)-*eudesman*-13-*oic acid* (IX; R = H) (1·2 g.) which crystallised from aqueous ethanol as needles, m. p. 152°, $[\alpha]_D^{19}$ −11·7° (*c* 0·33 in MeOH), $\nu_{max.}$ 1720 cm.$^{-1}$ (C=O and CO_2H) (Found: C, 71·3; H, 9·5. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

Reduction of 8-*Oxo*-4,5α(H),11β(H)-*eudesman*-13-*oic Acid* (IX; R = H) *with Potassium Borohydride*.—The keto-acid (39 mg.) in methanol (3 c.c.) containing sodium hydrogen carbonate (39 mg.) was treated with a solution of potassium borohydride (50 mg.) in water (1 c.c.), and the mixture was set aside overnight. It was then acidified and diluted with water (10 c.c.), and the deposited solid was crystallised from aqueous ethanol, giving 4,5,8,11α(H)-eudesman-8,13-olide (VII) (29 mg.) as needles, m. p. and mixed m. p. 69—70°.

8α-*Hydroxy*-4,5α(H),11β(H)-*eudesman*-13-*oic Acid* (X; R = H).—Sodium (10 g.) was added slowly to a boiling solution of 8-oxo-4,5α(H),11β-eudesman-13-oic acid (IX; R = H) (800 mg.) in propan-2-ol (100 c.c.), and the mixture was refluxed for a further 3 hr. Further propan-2-ol (30 c.c.) was added to dissolve the remaining sodium, and the mixture was refluxed for 0·5 hr., cooled to 0°, and neutralised with acetic acid. The volume of the mixture was reduced to 30 c.c. under reduced pressure, and the residue was diluted with water (150 c.c.), and extracted with ether (3 × 20 c.c.). The combined extracts were washed with 5% sodium hydrogen carbonate solution, and the washings were acidified. The deposited solid crystallised from aqueous methanol, giving 8α-*hydroxy*-4,5α(H),11β(H)-*eudesman*-13-*oic acid* (X; R = H) as needles (300 mg.), m. p. 162—163°, $[\alpha]_D^{16}$ +25° (*c* 0·27 in MeOH), $\nu_{max.}$ 3550 (OH), 1685 cm.$^{-1}$ (CO_2H) (Found: C, 70·9; H, 10·15. $C_{15}H_{26}O_3$ requires C, 70·8; H, 10·3%). The neutral fraction remaining in the ether solution after it had been washed with sodium hydrogen carbonate afforded a solid which on purification on "Woelm" brand acid alumina (benzene solution; benzene–light petroleum as eluants) gave the lactone (XIV) (70 mg.), m. p. 110°, $[\alpha]_D^{14}$ −29·4° (*c* 0·47), $\nu_{max.}$ 1795 (lactone), 1280 (C–O), and 995 cm.$^{-1}$ (Found: C, 76·2; H,

10·2. Calc. for $C_{15}H_{24}O_2$: C, 76·2; H, 10·2%). This lactone gave no depression of m. p. with the lactone [3,4] obtained along with the hydroxy-acid (V; R = H) when the keto-acid (IV; R = H) was reduced with sodium in propan-2-ol.

4,5,11α(H),8β(H)-*Eudesman*-8,13-*olide* (XI).—The hydroxy-acid (X; R = H) (500 mg.) was refluxed for 30 min. with toluene-*p*-sulphonic acid (100 mg.) and acetic acid (7 c.c.), and the mixture was cooled and poured into water. It was extracted with ether (2 × 10 c.c.), and the combined extracts were washed with 5% sodium hydrogen carbonate solution and with water. The solvent was removed, giving the *lactone* (XI) (400 mg.) which crystallised from methanol as needles, m. p. 92·5° (depressed to 82° by admixture with previous lactone), $[\alpha]_D^{19}$ −17·4° (*c* 0·6), $\nu_{max.}$ 1798 (lactone), 1280 cm.$^{-1}$ (C–O) (Found: C, 76·8; H, 10·25. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%).

Hydrolysis of 4,5,11α(H),8β(H)-*Eudesman*-8,13-*olide* (XI).—The lactone (XI) (20 mg.) in methanol (5 c.c.) was refluxed for 2 hr. with 1% methanolic sodium hydroxide (10 c.c.) and then poured into water. The mixture was acidified and then extracted with ether (2 × 10 c.c.) from which 8α-hydroxy-4,5α(H),11β(H)-eudesman-13-oic acid (X; R = H) (15 mg.) was obtained as plates (from aqueous methanol), m. p. and mixed m. p. 161—162°.

Methyl 8α-*Hydroxy*-4,5α(H),11β(H)-*eudesman*-13-*oate* (X; R = Me).—A solution of the hydroxy-acid (X; R = H) (100 mg.) in methanol (5 c.c.) was treated with an excess of diazomethane in ether, and the mixture was set aside for 1 hr. The product was the required *ester* (X: R = Me) (80 mg.) which crystallised from aqueous methanol as needles, m. p. 110°, $[\alpha]_D^{18}$ +50° (*c* 0·05), $\nu_{max.}$ 3250 (OH), 1740 cm.$^{-1}$ (ester) (Found: C, 71·6; H, 10·5. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%).

Reconversion of Methyl 8α-*Hydroxy*-4,5α(H),11β(H)-*eudesman*-13-*oate* (X; R = Me) *into* 4,5,8,11α(H)-*Eudesman*-8,13-*olide* (VII).—The hydroxy-ester (X; R = Me) (100 mg.) was added to sodium dichromate (80 mg.) in acetic acid (8 c.c.) and set aside for 1 hr. The excess of dichromate was decomposed with ethanol, and the solution was concentrated under reduced pressure to 1 c.c. Water was added, the mixture was extracted with ether, and the ethereal extract was washed with 5% sodium hydrogen carbonate and then with water. The solvent was removed, giving the oily keto-ester (IX; R = Me). This was set aside overnight with potassium borohydride (80 mg.) in water (0·5 c.c.) and methanol (5 c.c.). The resulting solution was then filtered and acidified, giving the lactone (VII) (50 mg.) which, when crystallised from aqueous methanol, had m. p. and mixed m. p. 71°.

Epimerisation of 4,5α(H),8,11β(H)-*Eudesman*-8,13-*olide* (VI) *to* 4,5,11α(H),8β(H)-*Eudesman*-8,13-*olide* (XI).—The lactone (VI) (100 mg.) was refluxed for 5 hr. in anhydrous tetralin (10 c.c.) with freshly ignited potassium carbonate (100 mg.). The mixture was filtered, and the tetralin was removed under reduced pressure, giving an oily residue which was chromatographed on "Woelm" brand acid alumina with light petroleum (b. p. 60—80°) and benzene. The solid obtained was crystallised from aqueous methanol, giving 4,5,11α(H),8β(H)-eudesman-8,13-olide (XI) (50 mg.) as needles, m. p. and mixed m. p. 89—91°, $[\alpha]_D^{18}$ −21·5° (*c* 0·20) (Found: C, 75·8; H, 10·1%).

Equilibration of the Keto-esters (IV; R = Me) *and* (IX; R = Me).—(*a*) Methyl 8-oxo-4,5,11α(H)-eudesman-13-oate (IV; R = Me) (60 mg.), $[\alpha]_D^{19}$ −19·6° (*c* 0·20), and 3% methanolic sodium methoxide (3 c.c.) were refluxed for 2 hr. The solution was neutralised with acetic acid, poured into water, and extracted with ether. The extract was washed with water, dried, and treated with diazomethane. Removal of the solvent afforded an oil (54 mg.), $[\alpha]_D^{19}$ −23·2° (*c* 0·537). Reduction of the oil (50 mg.) in methanol (3 c.c.) with potassium borohydride (10 mg.) in water (0·5 c.c.) afforded, after acidification, the lactone (II) (29 mg.) as needles, m. p. 130—134°.

(*b*) Similar treatment of the oily methyl 8-oxo-4,5α(H),11β(H)-eudesman-13-oate (IX; R = Me) (900 mg.), $[\alpha]_D^{19}$ −24·7° (*c* 0·41), with 3% sodium methoxide (6 c.c.) afforded an oil (840 mg.), $[\alpha]_D^{18}$ −22·8° (*c* 0·44). Reduction with potassium borohydride and acidification afforded the lactone (II) (400 mg.), m. p. 135—138°.

Equilibration of the Keto-acids (IV; R = H) *and* (IX; R = H).—(*a*) A mixture of 8-oxo-4,5,11α(H)-eudesman-13-oic acid (IV; R = H) (290 mg.), $[\alpha]_D^{16}$ +12·4° (*c* 0·25 in MeOH), potassium hydroxide (400 mg.), and water (0·5 c.c.) was heated to 220° during 25 min. The mixture of acids (220 mg.) isolated on acidification had a similar spectrum to that of (IV; R = H) and (IX; R = H) and had $[\alpha]_D^{19}$ −7·2° (*c* 0·37 in MeOH). Crystallisation from light petroleum (b. p. 60—80°) gave the keto-acid (IX; R = H) (80 mg.), m. p. and mixed m. p.

150°. (*b*) Similar treatment of 8-oxo-4,5α(H),11β(H)-eudesman-13-oic acid (IX; R = H) (50 mg.), $[\alpha]_D^{19}$ −11·7° (*c* 0·33 in MeOH), afforded a mixture of acids (40 mg.), $[\alpha]_D^{19}$ −8·0° (*c* 0·19 in MeOH). Crystallisation from light petroleum (b. p. 60—80°) afforded the keto-acid (IX; R = H) (22 mg.), m. p. and mixed m. p. 150°.

8β-*Hydroxy*-4,5α(H),7,11β(H)-*eudesman*-8,13-*olide* (XV).—The product (7 g.) from the hydrolysis of the keto-ester (IV; R = Me) was dissolved in ligroin (200 c.c.) and set aside overnight at 0°. The *lactone* (XV) (350 mg.) separated as cubes, m. p. 147—148°, $[\alpha]_D^{18}$ +9·3° (*c* 0·29) (Tsuda *et al.*[3] record m. p. 141—143°, $[\alpha]_D$ +10·5°) (Found: C, 71·5; H, 9·4. Calc. for $C_{15}H_{24}O_3$: C, 71·4; H, 9·6%).

Treatment of the Hydroxy-lactone (XV) *with Alkali.*—The lactone (360 mg.) was refluxed for 2 hr. with sodium hydroxide (100 mg.) in methanol (4·5 c.c.) and water (0·5 c.c.). The acidic product was an oil (0·02 g.), $\nu_{max.}$ 1685 cm.$^{-1}$, which was set aside overnight with potassium borohydride (20 mg.) in methanol (2 c.c.) and water (0·2 c.c.). The mixture was then acidified, water was added, and the solid product (113 mg.) was collected. Crystallisation from ethanol gave 4,5,8α(H),11β(H)-eudesman-8,13-olide (II), m. p. and mixed m. p. 142°, $[\alpha]_D^{19}$ +8·8° (*c* 0·1).

Reduction of the Hydroxy-lactone (XV) *with Sodium in Propan-2-ol.*—A boiling solution of the lactone (50 mg.) in propan-2-ol (20 c.c.) was slowly treated with sodium (2·5 g.), and the solution was refluxed for a further 3 hr. It was cooled to 0°, neutralised with acetic acid, then concentrated under reduced pressure to 15 c.c., poured into water, and extracted with ether. The ethereal solution was extracted with 3% sodium hydrogen carbonate solution, and the extract was acidified. The solid product was collected and crystallised from aqueous methanol as plates (23 mg.), m. p. 181° alone or mixed with 8α-hydroxy-4,5,11α(H)-eudesman-13-oic acid (V).

Reduction of the Hydroxy-lactone (XV) *with Potassium Borohydride.*—The lactone (30 mg.) in methanol (5 c.c.) was set aside for 26 hr. with potassium borohydride (100 mg.) in water (0·5 c.c.). The mixture was acidified and diluted with water, giving a solid which crystallised from aqueous ethanol as needles (20 mg.), m. p. and mixed m. p. with lactone (XIV) [3,4] 110°, $[\alpha]_D^{17}$ −30·5° (*c* 0·17), $\nu_{max.}$ 1780 cm.$^{-1}$.

Reaction of the Hydroxy-lactone (XV) *with Diazomethane.*—The lactone (80 mg.) in ether (10 c.c.) was treated at 0° with an excess of ethereal diazomethane. After 12 hr. the solvent was removed, giving *methyl* 8-*oxo*-4,5α(H),7,11β(H)-*eudesman*-13-*oate* (XVI; R = Me) which crystallised from aqueous ethanol as needles, m. p. 80—81°, $[\alpha]_D^{18}$ −74·2° (*c* 0·33) (Found: C, 71·7; H, 9·7. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%).

Attempted Epimerisation of the Lactone (XIV).—(*a*) The lactone (100 mg.) was refluxed for 5·5 hr. with freshly ignited potassium carbonate (500 mg.) in tetralin (2 c.c.). The mixture was filtered and the solvent removed under reduced pressure, giving starting material (90 mg.), m. p. and mixed m. p. 112°. (*b*) The lactone (100 mg.) was fused with potassium hydroxide (200 mg.) at 210° for 20 min. The melt was dissolved in water and acidified, giving starting material (80 mg.), m. p. and mixed m. p. 112°.

1-[6α-*Hydroxy*-3-*oxo*-11α(H)-*eudesma*-1,4-*dien*-13-*oyl*]*pyrrolidine* (*Santoninpyrrolidinamide*) (XIX).—Santonin (1 g.) was refluxed in benzene (20 c.c.) with pyrrolidine (1 c.c.) for 4 hr. The solution was washed with dilute hydrochloric acid, then with water, and dried. The benzene was removed, giving the *amide* (800 mg.) as plates (from ethyl acetate–light petroleum), m. p. 159—160°, $[\alpha]_D^{16}$ −45·6° (*c* 1·47), $\nu_{max.}$ (in $CHCl_3$) 3490b,s (OH), 1667 (ketone), 1630 cm.$^{-1}$ (amide and conjugated C=C) (Found: C, 72·3; H, 8·5. $C_{19}H_{27}NO_3$ requires C, 71·9; H, 8·6%).

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