1008. *Sesquiterpenoids. Part IX.* Stereospecificity in the Conversion of the Grouping* ·CO·ĊH·ĊH·CO· *into* ·CO·Ċ:Ċ·CO· *by Selenium Dioxide.*

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Five stereoisomeric methyl 3 : 6-dioxoeudesmanoates have been prepared and their configurations determined. The relative rates of oxidation of these diketones by selenium dioxide to methyl 3 : 6-dioxoeudesm-4-enoate have been measured. The compounds with the 4 : 5-hydrogen atoms *cis* are oxidised faster than those with the *trans*-relationship. Oxidation rates for other diketones have been determined in support of this generalisation. The mechanism of these oxidations has been discussed further. Some of the results reported here have been the subject of a preliminary communication.[1]

This investigation is concerned with the preparation and reactivity of a series of compounds containing the saturated 1 : 4-dione grouping (I). The main objective of our work was to examine further the postulate [2] that the ease of their dehydrogenation to the unsaturated 1 : 4-dione system (II) by selenium dioxide was a function of the stereochemical relationship of the hydrogen atoms at positions 2 and 3. We describe first the preparation of some of these diketones derived from santonin.

(I) —CO—ĊH—ĊH—CO— ⟶ —CO—Ċ=Ċ—CO— (II)

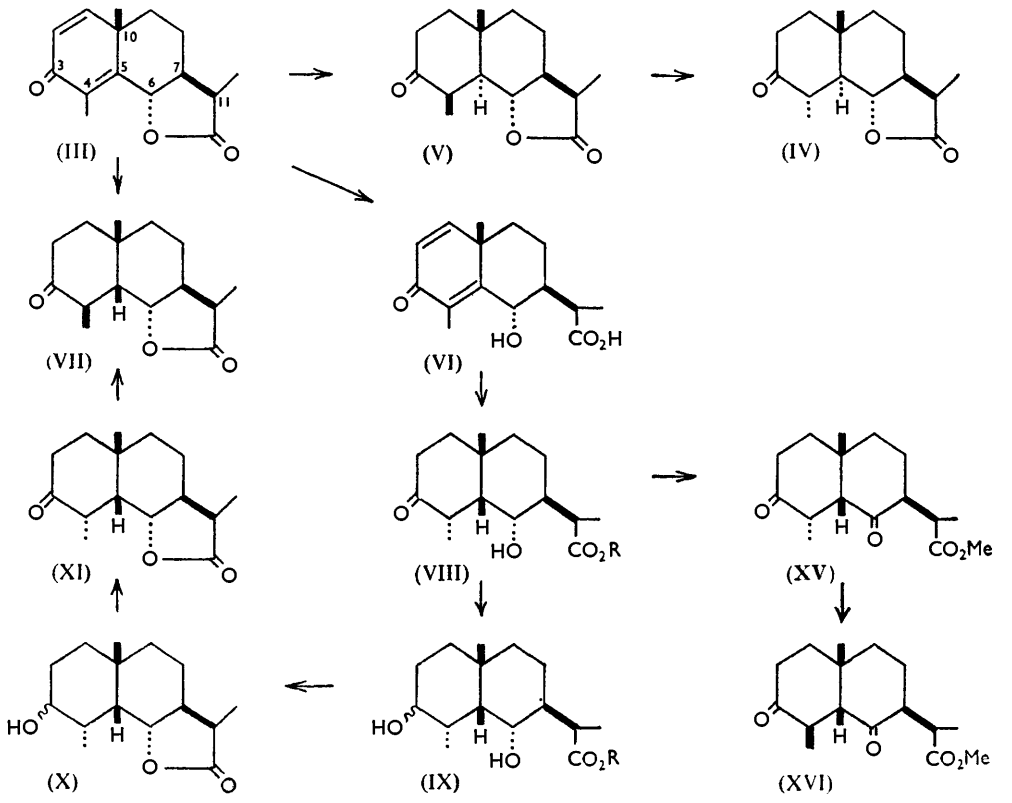
Hydrogenation of santonin [3] (III) affords three stereoisomeric tetrahydrosantonins. Two of these, α- (IV) and γ-tetrahydrosantonin (V), are based on *trans*-decalin [4,5] whilst the third, the β-isomer, more conveniently obtained by the hydrogenation of sodium santoninate (as VI), has a *cis*-ring fusion. We have confirmed the homogeneity of these compounds.

Cocker and McMurry [4] showed that the configuration of the 4-methyl group in the hydrogenation product of sodium santoninate was different from that in β-tetrahydrosantonin. This we have confirmed by showing that reduction of methyl β-tetrahydrosantoninate by lithium aluminium hydride gives a different triol from that afforded by β-tetrahydrosantonin. Now β-tetrahydrosantonin cannot be epimerised by perchloric–acetic acid. We therefore formulate it as the equatorial 4β-methyl isomer (VII), methyl tetrahydrosantoninate being the 4α-methyl compound (VIII; R = Me). These configurations are the opposite to those tentatively assigned by Cocker and McMurry.[4] Our

* Part VIII, *J.*, 1957, 150.

[1] Barton, *Experientia*, 1955, Suppl. II, p. 121.
[2] Barnes and Barton, *J.*, 1953, 1419.
[3] For stereochemistry see Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Abe and Sumi, *ibid.*, 1955, 253; Bruderer, Arigoni and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858; Sumi, *Pharm. Bull.*, 1956, **4**, 158; further refs. are given in *Ann. Reports*, 1954, **51**, 208; 1955, **52**, 191.
[4] Cocker and McMurry, *J.*, 1956, 4549; and references there cited.
[5] Kovács, Herout, Horák, and Šorm, *Chem. Listy*, 1955, **49**, 1856; *Coll. Czech. Chem. Comm.*, 1956, **21**, 225; Tahara, *J. Org. Chem.*, 1956, **21**, 422; and references there cited.

views are supported by the fact that reduction of the ester (VIII; R = Me) with potassium borohydride gave a dihydroxy-ester (IX; R = Me) which, on hydrolysis to the acid and pyrolysis, furnished the hydroxy-lactone (X). Cautious oxidation of the latter gave a keto-lactone (XI), conveniently designated δ-tetrahydrosantonin, which was at once converted into β-tetrahydrosantonin (VII) on gentle treatment with perchloric–acetic acid. If one accepts a two-chair conformation for (VII) and (XI) then the $C_{(4)}$-configurations follow. The difficulty is to rationalise the preferred 4α-configuration of compounds (VIII; R = H or Me). The simplest explanation is that these have a boat-chair conformation (as XII), which is more stable than either of the two-chair conformations (XIII) and (XIV). The conformation (XIV) is obviously destabilised by the axial 4-methyl group interacting with the axial 7- and 9-hydrogen atoms. Conformation (XIII) must be destabilised by 1 : 3-interaction of the 4β-methyl group with the 6α-hydroxyl group: this is equivalent to the corresponding 1 : 3-diaxial interaction within a *cyclo*hexane ring. Although conformation (XII) is destabilised by the usual 1 : 2-interactions within a boat conformation the trigonal 3-carbonyl group minimises interactions with the axial 7- and 9-hydrogen atoms. An analogous situation has been discussed recently.[6] The destabilising 1 : 3-interaction in conformation (XIII) referred to above does not apply to the same



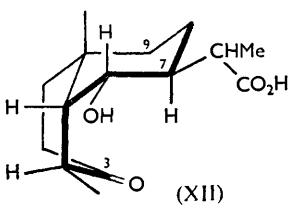
degree in β-tetrahydrosantonin (VII). This is because, according to models, the *trans*-fused γ-lactone ring pulls away the alkyl-oxygen atom from its interaction with the 4β-methyl group.

Cautious oxidation of methyl β-tetrahydrosantoninate (VIII; R = Me) gave a

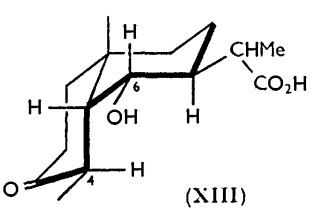
[6] Barton, Lewis, and McGhie, *J.*, 1957, 2907; see also Nace and Turner, *J. Amer. Chem. Soc.*, 953, **75**, 4063.

diketoester (XV) conveniently designated methyl β_1-3 : 6-dioxoeudesmanoate.* Reduction of the esters (VIII; R = Me) and (XV) with lithium aluminium hydride gave the same triol, confirming the assumption that inversion had not taken place. Nevertheless ester (XV) was very easily changed on chromatography over alumina or by piperidine into methyl β_2-3 : 6-dioxoeudesmanoate. This was shown to be compound (XVI), on the following evidence. First, the diketones (XV) and (XVI) gave different monoximes with pyridine–hydroxylamine hydrochloride. The 3-carbonyl group is, of course, much less hindered than the 6-group, so that the selective oximation must be at position 3. The oxime from ketone (XV) was stable under the conditions required to isomerise the parent (XV) to (XVI). The isomerisation must, therefore, involve at least inversion at $C_{(4)}$. Isomerisation of the diketone (XV) with triethylamine in deuterium oxide–dioxan gave an isomer (XVI) containing only one atom of deuterium. The rearrangement, therefore, in fact involves only the $C_{(4)}$-centre. The instability of the 4α-methyl group in compound (XV) compared with its stability in compound (VIII; R = Me) is comprehensible if one notes that oxidation of the 6α-hydroxyl to a ketone group removes in large part the destabilising 1 : 3-interaction in (XIII) referred to above. The stereochemisty of (XIII) then becomes the more stable arrangement as already implied in formula (XVI).

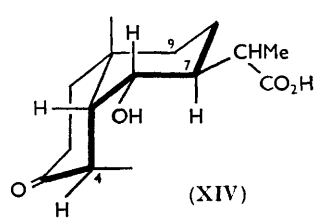
Further stereoisomers of methyl 3 : 6-dioxoeudesmanoate were obtained as follows. Dihydrosantonin [7] (XVII), best prepared by selective hydrogenation with Raney nickel in benzene,[8] was converted, by hydrolysis into the hydroxy-acid (XVIII), methylation, and oxidation with pyridine–chromium trioxide, into the unsaturated diketone (XIX). This was also obtained by oxidation of the diketone (XV) with selenium dioxide. Reduction with activated zinc dust in methanol afforded methyl γ-3 : 6-dioxoeudesmanoate (XX), readily converted by piperidine into the α-isomer (XXI). The latter compound was also



(XII)



(XIII)



(XIV)

obtained by reduction of the unsaturated diketone (XIX) with zinc dust and acetic acid. The assignment of configurations (XX) and (XXI) is based upon the concept of enol protonation from the less hindered α-side of the molecule,[9] upon the fact that (XXI) is the most stable of all the diketo-esters here reported (see below), and upon the certain identity of our ester (XXI), m. p. 79—81°, $[\alpha]_D$ −73°, with a diketo-ester, m. p. 81—82°, $[\alpha]_D$ −64°, prepared recently by Matsumura, Iwai, and Ohki [10] from α-tetrahydrosantonin (IV).

A fifth isomer, methyl ν-3 : 6-dioxoeudesmanoate, was isolated (after esterification) in about 10% yield from controlled alkali-treatment of the ester (XV) or (XVI) and by similar treatment of dihydrosantonin (XVII). Vigorous alkali-treatment converted the ν-diketo-ester into the α-isomer (XXI). The ν-diketo-ester is tentatively regarded as (XXII), with the diequatorial conformation (XXIII). The diminution of axial hydrogen–hydrogen interactions on the concave side of the molecule, as compared with (XVI) [conformation corresponding to (XIII)], would explain its greater stability.

The rates of oxidation of these and other diketones (I) by selenium dioxide were measured spectrophotometrically in acetic acid–dioxan at 65° (Table 1). For any pair of

* We are now adopting the convenient nomenclature proposed by Cocker and Cahn (*Chem. and Ind.*, 1955, 384; cf. Barton and de Mayo, *J.*, 1957, 150).

[7] Cusmano, *Annalen*, 1913, **400**, 332.
[8] Cf. Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[9] Zimmermann, *J. Org. Chem.*, 1955, **20**, 549; *J. Amer. Chem. Soc.*, 1956, **78**, 1168.
[10] Matsumura, Iwai, and Ohki, *J. Pharm. Soc. Japan*, 1955, **75**, 1043.

stereoisomeric ketones, that with the *cis*-configuration of eliminated hydrogen atoms is oxidised faster than that with the *trans*-arrangement. With one exception *all* the *cis*-compounds studied are oxidised faster than the *trans*-compounds. These results support Barnes and Barton's empirical rule,[2] but do not, of course, disprove reaction through the enol *provided* that the *cis*-compounds enolise faster than their *trans*-isomers. In order to

TABLE 1.*

Compound	No.	Relative configuration	Hours required for x% oxidation: x = 20%	30%	40%	50%
Methyl α-3 : 6-dioxoeudesmanoate (XXI)	1	*trans*	(4% in 120 hr.)			
3β-Acetoxylanostane-7 : 11-dione	2	*trans*	(9% in 120 hr.)			
Methyl 3β-acetoxy-12 : 19-dioxo-18α-oleanan-28-oate	3	*trans*	(10% in 120 hr.)			
Methyl β_2-3 : 6-dioxoeudesmanoate (XVI)	4	*trans*	32	52	77	120
Methyl 3β-acetoxy-12 : 19-dioxo-18β-oleanan-28-oate	5	*cis*	31	62	115	—
3β-Acetoxyergost-22-ene-7 : 11-dione	6	*trans*	28	48	84	120
Methyl ν-3 : 6-dioxoeudesmanoate (XXII)	7	*cis*	20	35	100	—
Methyl γ-3 : 6-dioxoeudesmanoate (XX)	8	*cis*	8	12	18	25
Cholestane-3 : 6-dione	9	*cis*	4	7	11	18
Methyl β_1-3 : 6-dioxoeudesmanoate (XV)	10	*cis*	4	7	10	14
3β-Acetoxyeuphane-7 : 11-dione	11	*cis* † (?)	3	6	9	12

* See p. 5050 for details of conditions referred to in this and other Tables.
† See Knight and McGhie, *Chem. and Ind.*, 1953, 920; 1954, 24.

examine this the rates of bromination of most of the diketones of Table 1 were determined in acetic acid containing sodium acetate at 30° (Table 2). The tendency for the relative rates for the various diketones to run parallel in the two reactions supports the idea that

TABLE 2.

Compound no.	Hours required for consumption of x mol. of Br_2: x = 0·2	0·4	0·6	0·8
2	45	*ca.* 240	—	—
3	45	*ca.* 240	—	—
5	15	27	42	70
6	20	45	200	—
7	29	54	83	122
9	4	8	14	20
10	6	12	35	—
11	4	9	16	24

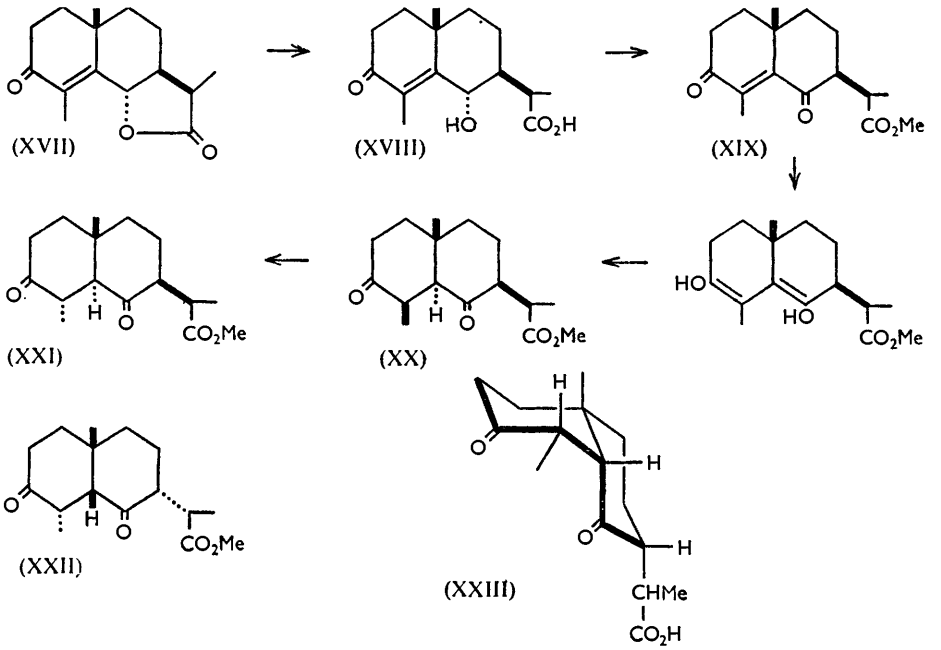
enolisation may be involved in oxidation by selenium dioxide as in bromination.

Now, the concentration of selenium dioxide might influence the rate partly by acid-catalysis of enolisation,[11] since (at least in aqueous solution) selenious acid (K_1 = $2{\cdot}4 \times 10^{-3}$) [12] is more than a hundred times stronger than acetic acid ($K = 1{\cdot}75 \times 10^{-5}$).[13] To estimate approximately the effect of selenious acid in catalysing enolisation, the rate of isomerisation of methyl β_1-3 : 6-dioxoeudesmanoate (XV) to the β_2-isomer (XVI) was measured polarimetrically at 65° in dioxan–acetic acid containing varying concentrations of chloroacetic acid ($K = 1{\cdot}36 \times 10^{-3}$) [14] which in water is about half as strong (see above) as selenious acid. The rates of isomerisation (Table 3) increased with the concentration of chloroacetic acid, but the rate of oxidation (Table 4) was much faster than that of isomerisation at equivalent acid concentration. This means either that the oxidation proceeds by a molecular mechanism or that the protonation of the enol of (XV) proceeds much faster to give back (XV) than to give (XVI). From the concept of proton-approach from the less hindered side of the enol [9] the latter is possible.

In order to avoid complications arising from the acidity of the selenious acid, further

[11] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 557.
[12] Hagisawa, *Bull. Inst. Phys. Chem. Res. Tokyo*, 1939, **18**, 648; *Chem. Abs.*, 1940, **34**, 4965.
[13] Harned and Ehlers, *J. Amer. Chem. Soc.*, 1933, **55**, 652.
[14] Ives and Pryor, *J.*, 1955, 2104.

experiments on the β_1-diketo-ester were run at 30° in aqueous acetic acid buffered with sodium acetate. The rate of oxidation was reduced by the addition of sodium acetate



(Table 5). This is in agreement with a rate-determining attack by an electrophilic species upon an enol.

TABLE 3.

Molarity of chloroacetic acid	Hours reqd. for x% of isomerisation of 0·02M-diketone in dioxan–acetic acid containing chloroacetic acid					
	x = 20%	30%	40%	50%	60%	70%
0·0	13	22	33	48	69	100
0·4	7	12	17	22	28	39
0·8	4	7	9	12	15	19

TABLE 4.

Hours reqd. for x% of oxidation of 0·02M-diketone in dioxan–acetic acid containing 0·2M-selenium dioxide		
x = 60%	80%	100%
2	5	26

TABLE 5.

Concn. (w/v) of sodium acetate dihydrate	Hours reqd. for x% of oxidation of 0·01M-diketone by 0·1M-selenium dioxide				
	x = 20%	30%	40%	50%	60%
2·5	8	16·5	25	34·5	44
5·0	11	20·5	30	44	84
10·0	19	37	74	—	—

In preliminary experiments in the buffered medium we showed that the oxidation rate was of the first order in both diketone and selenium dioxide. This behaviour is in contrast to bromination [11] and could be construed as support for the molecular mechanism.

It is clear then that, whilst the present experiments confirm the apparent stereospecificity of these selenium dioxide oxidations, they do not provide a final definition of the mechanism involved. Indeed, both possible mechanisms may be involved, molecular attack by the selenium dioxide residue being more important for the *cis*-diketones, whilst attack on the enol may be mandatory for the *trans*-isomers.

Experimental

Unless otherwise noted, ultraviolet spectra were measured for EtOH and optical rotations for $CHCl_3$ solutions.

Dihydrosantonin (XVII).—Santonin (2·0 g.) in dry benzene (100 ml.) was hydrogenated at room temperature and pressure over Raney nickel (1·5 g.). After about 1 hr. absorption of hydrogen ceased at 1 mol., and the catalyst and solvent were removed. Recrystallisation of the semisolid residue from ether–light petroleum (b. p. 60—80°) or from carbon tetrachloride–light petroleum gave dihydrosantonin (XVII) (1·7 g.), m. p. 101—102°, $[\alpha]_D$ +79° (*c* 1·42), $\lambda_{max.}$ 244 mμ (ε 14,700), $\nu_{max.}$ (in CCl_4) 1795 (γ-lactone), 1680 and 1628 cm.$^{-1}$ (αβ-unsaturated ketone): lit.,[10] m. p. 99°, $[\alpha]_D$ +75° (in EtOH).

The semicarbazone, recrystallised from ethanol, had m. p. 237—238° (decomp.), $[\alpha]_D$ +201° (*c* 1·12), $\lambda_{max.}$ 269 mμ (ε 27,800) [lit.,[10] m. p. 243° (decomp.)].

Tetrahydrosantonins.—(*a*) Santonin (4·0 g.) in ethyl acetate (120 ml.) was hydrogenated at room temperature and pressure in the presence of 1% palladium–calcium carbonate (1·8 g.). After 90 min. absorption of hydrogen ceased with the consumption of 2 mols. The product was crystallised from aqueous acetone and then from methanol, to give γ-tetrahydrosantonin (V) (628 mg.), m. p. 146—147°, $[\alpha]_D$ +64° (*c* 1·36) (Found: C, 71·8; H, 8·8. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9%).

The α- and β-tetrahydrosantonin in the combined mother-liquors were separated as described by Wienhaus and Oettingen,[15] by hydrolysis with alkali and preferential re-lactonisation of the α-isomer with dilute acid. The resulting α-tetrahydrosantonin (IV) (773 mg.), after several recrystallisations from ethanol, had m. p. 154—155°, $[\alpha]_D$ +28° (*c* 1·45), $\nu_{max.}$ (in CCl_4) 1785 (γ-lactone) and 1710 cm.$^{-1}$ (*cyclo*hexanone).

In a typical experiment in which the product was treated with alkali directly, the yield of α-tetrahydrosantonin was 35—40%.

(*b*) β-Tetrahydrosantonin (VII) was conveniently obtained by the following procedure. Santonin (5·0 g.) was dissolved in 0·1N-sodium hydroxide (250 ml.) by warming and the solution was then hydrogenated at room temperature and pressure over Adams catalyst (0·5 g.). After 3 hr. absorption of hydrogen ceased with the uptake of 2 mols. The filtered solution was brought to pH 3 with dilute sulphuric acid and then heated on a steam-bath for ½ hr., to lactonise the easily lactonised acids. The cooled solution was extracted with ether, which was washed with 5% aqueous sodium carbonate till neutral. The carbonate layers were acidified and extracted with ether. After treatment with diazomethane the product crystallised from acetone–light petroleum (b. p. 60—80°), giving methyl β-tetrahydrosantoninate (VIII; R = Me) (3·47 g.), m. p. 158—160°, $[\alpha]_D$ +26° (*c* 1·49), $\lambda_{max.}$ 274 mμ (ε 24) (Found: C, 68·3; H, 9·2. Calc. for $C_{16}H_{26}O_4$: C, 68·05; H, 9·3%).

A sample of methyl β-tetrahydrosantoninate, m. p. 161—161·5°, $[\alpha]_D$ +26°, was separated into eleven fractions by chromatography on silica gel in 1 : 9 ether–benzene. All fractions had the same m. p. and rotation (±1°) as the original sample. The first and the last fraction, and intermediate fractions, showed no depression in mixed m. p.

The neutral material in the original ether extract that had been washed with sodium carbonate crystallised from aqueous methanol. The resulting α-tetrahydrosantonin (IV) (240 mg.), recrystallised from ethanol, had m. p. 153—155°, $[\alpha]_D$ +28° (*c* 1·42).

Hydrolysis of the methyl ester gave β-tetrahydrosantoninic acid (VIII; R = H), which formed crystals from acetone–light petroleum (b. p. 60—80°) with m. p. 193—194° (heated from 170°) and $[\alpha]_D$ +12° (*c* 2·00). The acid (80 mg.) was heated at 200°/16 mm. for 10 min. A solution of the product in ether was washed with 5% aqueous sodium carbonate, the ether was evaporated, and the product recrystallised from ether–light petroleum (b. p. 40—60°). β-Tetrahydrosantonin (VII) melted at 89—90°, resolidified, and melted again at 100—102°, and had $[\alpha]_D$ +7° (*c* 1·11), $\nu_{max.}$ (in CCl_4) 1785 (γ-lactone) and 1718 cm.$^{-1}$ (*cyclo*hexanone).

β-Tetrahydrosantonin (29·2 mg.) in acetic acid (3·0 ml.) was treated with 70% perchloric acid (4 drops) overnight at room temperature. There was no change in rotation. The solution was heated on the steam-bath for 1 hr. (again no change in rotation) and then worked up in the usual way, to give back β-tetrahydrosantonin (m. p. and mixed m. p.).

(*c*) δ-Tetrahydrosantonin (XI) was prepared in the following way. Methyl β-tetrahydrosantoninate (see above; 360 mg.) in methanol (8·0 ml.) was treated with potassium borohydride

[15] Wienhaus and Oettingen, *Annalen*, 1913, **397**, 219.

(36 mg.) in water (2·0 ml.) and left at room temperature for 1 hr. Dilution with water, filtration, and crystallisation from acetone–light petroleum (b. p. 60—80°) gave *methyl* 3ξ : 6α-*dihydroxy*-4β : 5β : 6β(H)-*eudesmanoate* (IX) (225 mg.), m. p. 135—136°, $[\alpha]_D$ +17° (*c* 2·34), +11° (*c* 2·18 in MeOH) (Found: C, 67·7; H, 9·85. $C_{16}H_{28}O_4$ requires C, 67·55; H, 9·95%). This ester diol (375 mg.) was saponified by refluxing for 1 hr. with 5% potassium hydroxide in methanol (12 ml.) and water (8 ml.). The acidic product (350 mg.), without purification, was heated at 200—210°/1·5 mm. for 5 min., to give a glass (329 mg.). Crystallisation from acetone–light petroleum (b. p. 60—80°) gave 3ξ-hydroxy-4β : 5β : 6β(*H*)-eudesman-6 : 13-olide (X) (205 mg.), m. p. 156—157°, $[\alpha]_D$ +39° (*c* 1·46) (Found: C, 71·7; H, 9·65. Calc. for $C_{15}H_{24}O_3$: C, 71·4; H, 9·6%). For this compound Cocker and McMurry [4] recorded m. p. 153—154°, $[\alpha]_D$ +37°. Potassium dichromate (181 mg.) in acetic acid (8·0 ml.) and water (2·0 ml.) was added to a solution of this hydroxy-lactone (300 mg.) in acetic acid (10·0 ml.) at 20° and left at this temperature for 4 hr. Dilution with water, extraction into ether, and washing with saturated aqueous sodium hydrogen carbonate solution and finally with water gave, on evaporation *in vacuo* at room temperature, a solid residue (170 mg.). Crystallisation from acetone–light petroleum (b. p. 40—60°) at room temperature or lower gave three crops of unchanged starting material (m. p. and mixed m. p.). Crystallisation of the residue from ether at −80° afforded the desired δ-*tetrahydrosantonin* (XI) (71 mg.), m. p. (plates) 119—120°, depressed on admixture with β-tetrahydrosantonin, $[\alpha]_D$ −30° (*c* 1·36 and 1·08 in EtOH), $\nu_{max.}$ (in Nujol) 1765 (γ-lactone) and 1705 cm.$^{-1}$ (*cyclo*hexanone) (Found: C, 72·1; H, 8·9. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). The infrared spectra of δ- and β-tetrahydrosantonins were different in the " finger-print " region. δ-Tetrahydrosantonin (28 mg.) was treated with perchloric acid, as described above for β-tetrahydrosantonin. The rotation at once changed at room temperature to $[\alpha]_D$ +15° (*c* 2·79 in acetic acid), identical with that of β-tetrahydrosantonin in the same solvent. Working up as above gave β-tetrahydrosantonin (23·6 mg.), identified by m. p., mixed m. p. and rotation {$[\alpha]_D$ +10° (*c*, 0·99 in EtOH)}.

The action of perchloric–acetic acid on 3ξ-hydroxy-4β : 5β : 6β(H)-eudesman-6 : 13-olide was also investigated. During 11 hr. at room temperature the rotation changed from +50° to +96°. Working up the acetic acid solution gave the corresponding acetate, identified with an authentic specimen (prepared by acetylation with pyridine–acetic anhydride overnight at room temperature) by m. p., mixed m. p., and rotation. The authentic specimen had m. p. 153—154°, $[\alpha]_D$ +72° (*c* 1·45), +92° (*c* 1·16 in acetic acid), in agreement with constants {m. p. 151—152°, $[\alpha]_D$ +71° (*c* 0·9)} recorded by Cocker and McMurry.[4]

(*d*) The conversion of γ- into α-tetrahydrosantonin was effected as follows. The γ-isomer (80 mg.) was dissolved in N-potassium hydroxide (2 ml.) on a steam-bath in 30 min. After acidification and a further 30 minutes' heating the solution was cooled. Recrystallisation of the precipitate from ethanol yielded α-tetrahydrosantonin (IV) (25 mg.), m. p. and mixed m. p. 153—154°, $[\alpha]_D$ +27° (*c* 1·05).

Methyl β_1-3 : 6-*Dioxoeudesmanoate* (XV).—Methyl β-tetrahydrosantoninate (VIII; R = Me) (1·5 g.) in acetic acid (3 ml.) and benzene (3 ml.) was treated with sodium dichromate dihydrate (550 mg.) in acetic acid (5 ml.). After 12 hr. at room temperature the product was isolated with ether and crystallised from acetone–light petroleum (b. p. 60—80°). The β_1-*diketo-ester* (XV) (794 mg.) had m. p. 94—95°, $[\alpha]_D$ −63° (*c* 1·35) (Found, after sublimation: C, 68·9; H, 9·1. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

The *oxime*, prepared in pyridine at room temperature, separated from ethanol–ether in needles, m. p. 153—154°, $[\alpha]_D$ −112° (*c* 1·03) (Found: C, 65·3; H, 8·6; N, 4·9. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·55; N, 4·75%).

Methyl β_2-3 : 6-*Dioxoeudesmanoate* (XVI).—Chromatography of the β_1-diketo-ester (100 mg.) in benzene on untreated (alkaline) alumina and crystallisation of the product from acetone–light petroleum (b. p. 60—80°) gave the β_2-*diketo-ester* (XVI) (82 mg.), m. p. 127—128°, $[\alpha]_D$ −141° (*c* 1·56) (Found: C, 68·1; H, 8·6. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

Chromatography of the residue from the mother-liquors of the β_1-diketo-ester (above) gave the β_2-isomer (300 mg.), m. p. and mixed m. p. 125—126°, $[\alpha]_D$ −138° (*c* 1·02).

The β_2-diketo-ester was also made directly from methyl β-tetrahydrosantoninate in good yield, by carrying out the oxidation as above on the steam-bath.

The *monoxime*, prepared in pyridine at room temperature, crystallised from ethanol–ether, m. p. 164—165°, depressed on admixture with β_1-oxime (see above), $[\alpha]_D$ +12° (*c* 1·51) (Found: C, 65·0; H, 8·2; N, 5·0. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·55; N, 4·75%).

Action of Piperidine on Methyl β_1-3 : 6-*Dioxoeudesmanoate* (XV) *and its Oxime.*—Piperidine (0·2 ml.) was added to a solution of the β_1-diketo-ester (0·5 mmole) in dioxan (24·8 ml.). The solution was heated in a stoppered flask jacketed with methanol vapour (65°), and the change in rotation was followed. After 68 hr. isomerisation was complete ($[\alpha]_D$ $-61° \longrightarrow -138°$). The product was crystallised from acetone–light petroleum (b. p. 60—80°), to yield the β_2-diketo-ester (XVI) (95 mg.), identified by m. p., mixed m. p., and rotation.

Under identical conditions a solution of the β_1-diketo-ester monoxime maintained a constant rotation. After 72 hr. the solute was isolated; crystallisation from ethanol–ether gave the unchanged monoxime (92 mg.), identified by m. p., mixed m. p., and rotation. The β_1-oxime was stable also to alkaline alumina.

Isomerisation of Methyl β_1-3 : 6-*Dioxoeudesmanoate* (XV) *in Presence of Deuterium Oxide.*—All organic solvents, except "AnalaR" acetone, had been freshly distilled from sodium. Triethylamine (5 ml.) was added to a solution of the β_1-diketo-ester (XV) (1·4 g.) in 1 : 19 deuterium oxide–dioxan (80 ml.). The solution was heated in a stoppered flask at the temperature of refluxing methanol. After 72 hr. the rotation indicated 75% of isomerisation to the β_2-isomer, and the solvents were evaporated *in vacuo* to a crystalline residue. Part of this was removed and rapidly recrystallised from acetone–light petroleum (b. p. 60—80°), yielding crystals (*A*), m. p. and mixed m. p. with β_2-diketo-ester (XVI) 126—127°, $[\alpha]_D$ −138° (*c* 1·53). The rest of the product (*B*) after exhaustive drying *in vacuo* had $[\alpha]_D$ −122°, indicating 88% of β_2-isomer.

The samples were analysed for deuterium by Dr. G. Eglinton and his associates by complete combustion and measurement of the intensity of the O–D stretching vibration in the resulting water. The results, expressed in atoms of deuterium per mole, were: *A* (recrystallised) 1·0, 1·0; *B* (not recrystallised) 1·3.

Methyl ν-3 : 6-*Dioxoeudesmanoate* (XXII).—(a) *Isomerisation of* β_2-*diketo-ester.* The β_2-diketo-ester (XVI) (500 mg.) was boiled for 2 hr. in 10% sodium hydroxide solution (5 ml.). The oily mixture of acids, extracted with chloroform from the acidified solution, was esterified with diazomethane. Crystallisation of the product from acetone–light petroleum (b. p. 60—80°) gave the ν-*diketo-ester* (XXII) (50 mg.), m. p. 182—184°. After several recrystallisations the ester had m. p. 188—189°, $[\alpha]_D$ +64° (*c* 1·36) (Found: C, 68·3; H, 8·70. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

(b) *Isomerisation of* β_1-*diketo-ester* (XV). The β_1-diketo-ester (1 g.), dissolved in the minimum amount of methanol, was mixed with potassium carbonate (5 g.) in 50% aqueous methanol (250 ml.). After 90 minutes' boiling the acidic product was esterified with diazomethane. Crystals (90 mg.) separated from acetone–light petroleum (b. p. 60—80°) and on recrystallisation had m. p. and mixed m. p. with the ν-diketo-ester 187—188°. The material in the mother-liquors was chromatographed on alumina. The first fractions eluted with benzene gave pure ν-diketo-ester (XXII) (30 mg.) after two recrystallisations. Later benzene fractions, on recrystallisation, yielded slightly impure β_2-diketo-ester (12 mg.), m. p. and mixed m. p. 118—122°, $[\alpha]_D$ −129° (*c* 0·5).

(c) *Isomerisation of dihydrosantonin* (XVII). Dihydrosantonin (5·0 g.) was boiled in 5% aqueous potassium hydroxide (100 ml.) under nitrogen for 8 hr. After acidification to pH 3 the solution was heated on a steam-bath for 10 min. Separation of the product into neutral and acid fractions gave only a small amount of neutral fraction. The acid fraction was methylated with diazomethane and crystallised from acetone–light petroleum (b. p. 60—80°), to yield the ν-diketo-ester (XXII) (542 mg.), m. p. and mixed m. p. 186—188°.

Dihydrosantonin (500 mg.) in ethanol (20 ml.) and concentrated hydrochloric acid (1 ml.) were refluxed for 10 hr.; alkaline hydrolysis and esterification gave the ν-diketo-ester (35 mg.).

The ν-*diketo-ester monoxime*, prepared in pyridine at room temperature, separated from ethanol–ether in needles, m. p. 165—166°, $[\alpha]_D$ −29° (*c* 0·92) (Found: C, 65·1; H, 8·8; N, 5·15. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·55; N, 4·75%).

Methyl 3 : 6-*Dioxoeudesm*-4-*enoate* (XIX).—(a) *Dehydrogenation of methyl* β_1-3 : 6-*dioxoeudesmanoate* (XV). The β_1-diketo-ester (3·1 g.) was boiled with selenium dioxide (2·6 g.) in acetic acid (80 ml.) for 90 min. The chloroform extract of the diluted mixture was washed with alkali and then water. The residue from evaporation of the chloroform was boiled with precipitated silver for 1 hr. The product was chromatographed on acid-washed alumina (130 g.) in 1 : 9 benzene–light petroleum (b. p. 40—60°). The earlier fractions (total 1·02 g.),

with m. p. *ca.* 60° and $\lambda_{max.}$ 255 mμ (ε 10,500), were combined. Six recrystallisations from light petroleum (b. p. 60—80°) gave *methyl* 3 : 6-*dioxoeudesm*-4-*enoate* (XIX) as colourless needles, m. p. 64—64·5°, $[\alpha]_D$ +113° (*c* 1·64) (Found, on a sublimed sample: C, 69·0; H, 7·9. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·95%).

(b) *From dihydrosantonin* (XVII). Dihydrosantonin (1·0 g.) was dissolved in warm 0·1N-sodium hydroxide (100 ml.). The solution at 0° was brought to pH 2 with dilute sulphuric acid and immediately extracted with ether. The ethereal solution was methylated with diazomethane and then evaporated *in vacuo* at room temperature. The resulting *methyl dihydrosantoninate* crystallised from light petroleum (b. p. 60—80°) containing a trace of acetone as needles, m. p. 104—105°, $[\alpha]_D$ +149° (*c* 1·8) (Found: C, 68·2; H, 8·6. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%). Heating the methyl ester at 70° *in vacuo* for 24 hr. gave back dihydrosantonin (m. p. and mixed m. p.).

Methyl dihydrosantoninate (150 mg.) was oxidised with chromic oxide (150 mg.) in pyridine (5 ml.). After 24 hr. at room temperature the product was crystallised from light petroleum (b. p. 60—80°) containing a trace of acetone, yielding the enedione (XIX) (80 mg.), m. p. and mixed m. p. 64·5°, $[\alpha]_D$ +112° (*c* 0·57), $\lambda_{max.}$ 255 mμ (ε 10,500) and (in $CHCl_3$) 305—306 mμ (ε 110).

Methyl γ-3 : 6-*Dioxoeudesmanoate* (XX).—The enedione ester (XIX) (250 mg.) was boiled in methanol (200 ml.) with activated zinc dust (4 g.). After 8 hr. the maximum at 255 mμ had disappeared, and the cooled solution was filtered through " filter-aid," and then evaporated to dryness in the cold *in vacuo*. A solution of the residue in ether was washed with water. The oil remaining on evaporation of the ether crystallised from light petroleum containing a trace of acetone, to furnish *methyl* γ-3 : 6-*dioxoeudesmanoate* (XX) (100 mg.), m. p. (blades) 101—102°, $[\alpha]_D$ −7° (*c* 1·23) (Found: C, 68·4; H, 8·4. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

Methyl α-3 : 6-*Dioxoeudesmanoate* (XXI).—(*a*) The γ-diketo-ester (XX) (50 mg.) in dioxan (19 ml.) containing piperidine (1 ml.) was heated in a stoppered flask jacketed with refluxing methanol. After 48 hr. the initial rotation (−7°) had fallen to a constant value (−60°). Chromatography of the product on alumina and elution with 1 : 9 ether–benzene led to the α-diketo-ester (XXI), crystallising from a small volume of light petroleum (b. p. 60—80°) in needles (19 mg.), m. p. 81—82°, $[\alpha]_D$ −64° (*c* 0·9).

(*b*) The ester (XIX) (100 mg.) and zinc dust (1 g.) were boiled in acetic acid (10 ml.) for 2 hr. The isolated methyl α-3 : 6-dioxoeudesmanoate (XXI) crystallised from light petroleum in needles (40 mg.), m. p. and mixed m. p. 80—81°, $[\alpha]_D$ −64° (*c* 0·72) (Found: C, 68·6; H, 7·8. Calc. for $C_{16}H_{24}O_4$: C, 68·55; H, 8·65%).

(*c*) The ν-diketo-ester (XXII) (184 mg.) in 0·1N-sodium methoxide in methanol (25 ml.) was heated at 65° (methanol-vapour bath). After about 19 hr. the rotation became constant (−63°); the isolated product was chromatographed on silica gel (12 g.). Ether–benzene (1 : 19) eluted material that yielded pure α-diketo-ester (XXI) (7 mg.), identified by mixed m. p. and rotation.

Reductions by Lithium Aluminium Hydride.—(a) α-*Tetrahydrosantonin* (IV). The lactone (1 g.) in ether (500 ml.) was boiled with an excess of lithium aluminium hydride for 12 hr. The resulting *triol* separated from light petroleum (b. p. 60—80°) in rhomb-shaped crystals (640 mg.), m. p. 138—139°, $[\alpha]_D$ +8° (*c* 0·79) (Found: C, 70·5; H, 10·6. $C_{15}H_{28}O_3$ requires C, 70·25; H, 11·0%).

(b) *Methyl* α-3 : 6-*dioxoeudesmanoate* (XXI). The diketo-ester (60 mg.) on reduction and two recrystallisations from light petroleum ether gave a *triol*, flaky crystals (12 mg.), m. p. 135—136° [depressed on admixture with the triol from α-tetrahydrosantonin (see above)], $[\alpha]_D$ +12° (*c* 0·6) (Found: C, 70·7; H, 11·1%).

(c) β-*Tetrahydrosantonin* (VII). Reduction of the lactone gave a triol, m. p. [from ethanol–light petroleum (b. p. 40—60°)] 223—224°, $[\alpha]_D$ −41° (*c* 1·96 in EtOH), in good agreement with the constants recorded for this compound (m. p. 220°, $[\alpha]_D$ −43° in MeOH) by Cocker and McMurry.[4]

(d) *Methyl* β-*tetrahydrosantoninate* (VIII; R = Me). The ester (200 mg.) was reduced as above. The *triol* crystallised from acetone–light petroleum (b. p. 60—80°) in needles (103 mg.), m. p. 120—121°, $[\alpha]_D$ −14° (*c* 1·00) (Found: C, 69·8; H, 11·3%).

(e) *Methyl* β_1-3 : 6-*dioxoeudesmanoate* (XV). The diketo-ester (250 mg.) gave recrystallised triol (195 mg.), m. p. and mixed m. p. with the above sample from (d) 120—121°, $[\alpha]_D$ −14° (*c* 1·12) (Found: C, 70·4; H, 10·9%).

Miscellaneous Diketones.—In general the required enediones and derived saturated derivatives were prepared by published methods and had the expected physical properties.

Rate Measurements.—(a) *General.* In all experiments the appropriate blanks were run at the same time. Since the criterion of oxidation adopted was the measurement of the appearance of the appropriate ene-1 : 4-dione chromophore it was necessary to show that this gives a true measure of the rate of consumption of the selenium dioxide. This was checked in the case of the diketone (XV) by the following experiments. The rate of oxidation was determined in buffered aqueous acetic acid consisting of sodium acetate trihydrate (25 g.) in water (100 ml.) and " AnalaR " acetic acid (400 ml.). A solution of the ester (XV) (140 mg.) in the buffer (40 ml.) was mixed with selenium dioxide in the same solvent (10 ml.; containing 55·5 g. of selenium dioxide per l.) at 30° and held at this temperature. Periodically portions (5 ml.) were withdrawn, diluted with water (200 ml.), and acidified (20 ml. of 6N-hydrochloric acid). 0·05N-Sodium thiosulphate was then added, care being taken that the excess of this reagent did not exceed the recommended limit.[16] The excess of thiosulphate was then titrated with iodine. This gave the rate of consumption of selenium dioxide. The rate of development of the enedione chromophore (see XVIII) was measured on the Unicam S.P. 500 spectrophotometer as usual. Typical results are shown in Table 6.

TABLE 6. *Oxidation of* 0·01M-*ester* (XV) *by* 0·1M-*selenium dioxide.*

Reaction time (hr.)	8	23	31	48	72
SeO_2 consumed (volumetric) (%)	9·2	16·7	20·7	30·0	37·0
Enedione (XVIII) produced (spectr.) (%)	16·1	36·0	39·3	55·7	59·2

(b) *Notes on Table* 1. The standard solution of selenium dioxide contained 11·0 g./l. in 99% acetic acid. This solution (5 ml.) was added to one of the diketone (0·05 mmole) in purified dioxan (20 ml.), and the mixture was heated in a stoppered flask, jacketed with the vapour of refluxing methanol (65°). Periodically 1 ml. of the mixture was withdrawn and diluted to 10 ml. with ethanol. The optical density (kept between 0·25 and 0·5 by choice of cell-thickness or dilution) of the resulting solution was then measured at the wavelength of the maximum of the expected enedione against an appropriate blank. The extent of reaction was calculated by using $\varepsilon_{max.}$ of the pure enedione measured in the same solvent.

(c) *Notes on Table* 2. Bromine (6 mmoles) in acetic acid–carbon tetrachloride (4 : 1 by vol.) was added to a solution of the diketone (1 mmole) and anhydrous sodium acetate (2 g.) in the same solvent, bringing the total volume to 200 ml. The reaction flasks and controls were protected from light and kept in a thermostat at 30°. The consumption of bromine was determined iodometrically.

(d) *Notes on Table* 3. Methyl β_1-3 : 6-dioxoeudesmanoate (XV) (1 mmole) was dissolved in dioxan containing chloroacetic acid (none, 20 or 40 mmoles). 98% Acetic acid (10 ml.) was added, and the solution made up to 50 ml. with dioxan. The extent of isomerisation was determined by measurement of the optical rotation after various times of heating at 65°. Under the same conditions the rotation of the β_2-diketo-ester (XVI) scarcely changed.

(e) *Notes on Table* 4. The rate of development of the ene-1 : 4-dione chromophore was measured in the same mixture as used for work in Table 3, but containing selenium dioxide (10 mmoles) in place of chloroacetic acid.

(f) *Notes on Table* 5. The rate of oxidation by selenium dioxide was followed spectrophotometrically, as before, at 30°. The solvent was the buffered acetic acid mixture referred to under (a), but with variation in the concentration of sodium acetate.

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