65.   *Synthesis in the Santonin Series.   Part IV.* A Synthesis of the 7α(H)-3-Oxoeudesm-4-en-12-oic and 7β(H)-3-Oxoeudesm-4-en-12-oic Acids based on a Method of Oxidation of a Methylene to a Carboxyl Group.*

By R. Howe, F. J. McQuillin, and R. W. Temple.

The sequence, $>C=CH_2 \longrightarrow >C\overset{O}{\overset{\diagdown}{-}}CH_2 \longrightarrow >CH\cdot CHO \longrightarrow >CH\cdot CO_2H$, has been developed as a method of oxidation of the terpenoid *iso*propenyl group, and has been applied to the synthesis of (−)-2-oxo-*p*-menthan-9-oic acid and of the two (+)-7α(H)-3-oxoeudesm-4-en-12-oic and two (+)-7β(H)-3-oxoeudesm-4-en-12-oic acids epimeric at $C_{(11)}$. The former pair have been related directly to the corresponding acids obtained by reduction of (−)-α- and (−)-β-santonin. A method is described for converting an acid from the 7β(H)- to the 7α(H)-series. Observations are reported on the preferential oxidation at an olefinic and a carboxyl group by respectively perbenzoic and monoperphthalic acid.

A METHOD of oxidation of a terpenoid *iso*propenyl substituent to a propionic acid residue as a synthetic route to 3-oxoeudesm-4-en-12-oic acids was described earlier.[1] Some of the stereochemical problems involved in this approach to santonin and related substances were resolved in the synthesis of (+)-α-cyperone.[2] Meantime also Abe *et al.*[3] fruitfully explored a different route to the synthesis of (±)-α-santonin which we also outlined.[4] To obtain the natural (−)-α- or (−)-β-isomers, however, this method involves optical resolution.[3] Our original approach continued therefore to be of interest as a method of interrelating optically active terpenes and as a potentially general method of carrying out the oxidation, $>C=CH_2 \longrightarrow >CH\cdot CO_2H$.

In our earlier experiments [1] oxidation of a terminal methylene to a carboxyl group was illustrated by the hydrogenolysis of (−)-dihydrocarvone 8 : 9-oxide (II), using Raney nickel, and oxidation of the derived diol (III) to (−)-2-oxo-*p*-menthan-9-oic acid (VIII). We later found it more convenient to hydrogenate (Raney nickel, pressure) (+)-carvone 8 : 9-oxide (VI) directly to the diol (III), though mild conditions (palladised barium carbonate) lead to the epoxy-dihydro-ketone (II). The same method has also been applied to (+)-limonene dioxide (X) which by hydrogenolysis and oxidation gives (+)-2-oxo-*p*-menthan-9-oic acid (XII), the enantiomorph of the previous acid [1] (VIII).

Hydrogenolysis of the epoxy-group in these instances is not, however, unidirectional. Newman, Underwood, and Renoll [5] give examples of fission of monoalkyl-substituted

* Part III, *J.*, 1953, 4060.

[1] Clemo and McQuillin, *J.*, 1952, 3839.
[2] McQuillin, *J.*, 1955, 528; Howe and McQuillin, *J.*, 1955, 2423.
[3] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1954, **30**, 116, 119.
[4] McQuillin, *Chem. and Ind.*, 1954, 311.
[5] Newman, Underwood, and Renoll, *J. Amer. Chem. Soc.*, 1949, **71**, 3362.

ethylene oxides at Raney nickel to the primary alcohol. In examples such as (II), (VI), or (X) the additional alkyl substituent will impede a nucleophilic reductive process at the tertiary centre. The diols obtained from hydrogenolysis contained material which was not oxidisable to the required acid and which we consider to be tertiary alcohols, *e.g.*, (IV); even under the mildest conditions material was also lost by complete removal of epoxy-oxygen; this has been noted in other instances.[6]
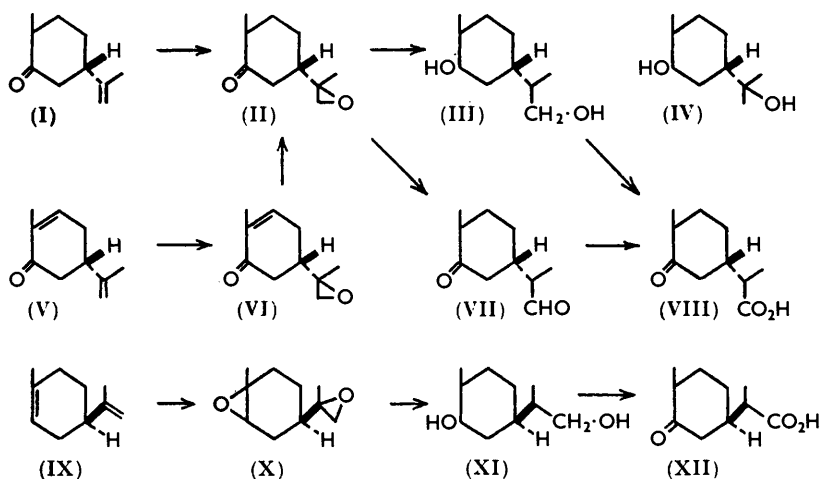
These results led us to examine as an alternative the known epoxy $\longrightarrow$ oxo rearrangement induced by Lewis acids. In the initial experiments using magnesium bromide in ether,[7] made before the use of boron trifluoride [8] had become general, we obtained from (—)-dihydrocarvone oxide (II) a bromohydrin, or by removal of solvent and further heating the required (—)-aldehyde (VII). The oxide $\longrightarrow$ bromohydrin sequence must be reversible by solvolysis (*a*). In absence of solvent intramolecular complex formation will replace solvation and provide the geometrical arrangement (*b*) necessary for rearrangement. The use of boron trifluoride–ether complex in benzene gave, however, a more convenient route to the aldehyde (VII) in good yield, and to the required acid (VIII).
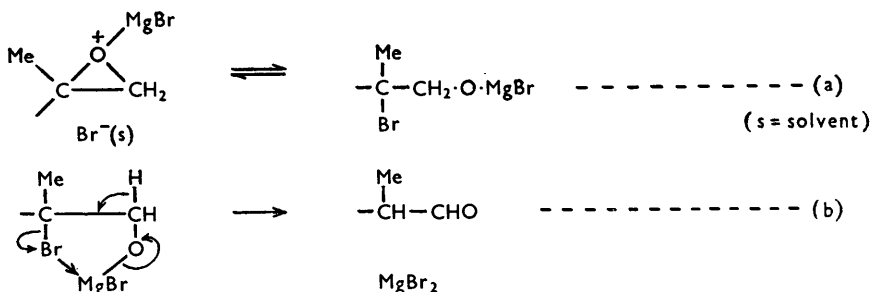

A point of interest arose in the preparation of dihydrocarvone oxide (II). Peracid may, in principle, react at the olefinic centre, or, by attack at the carbonyl group, lead to the

    [6] Cf. Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, 1944, **27**, 513; Plattner, Furst, Koller, and Kuhn, *ibid.*, 1954, **37**, 258.
    [7] Bedos, *Compt. rend.*, 1929, **189**, 255; Tiffeneau and Tchoubar, *ibid.*, 1938, **207**, 918, and later papers; Stoll and Commarmont, *Helv. Chim. Acta*, 1948, **31**, 1077; Bachmann, Horwitz, and Warzynski, *J. Amer. Chem. Soc.*, 1953, **75**, 3268; House, *ibid.*, 1955, **77**, 3070, 5083.
   [8] Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Heusler and Wettstein, *ibid.*, 1953, **36**, 398; Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.

well-known ketone ⟶ lactone cleavage of the ring.[9] In the previous work,[1] using perbenzoic acid in chloroform, epoxidation was established as the main rapid reaction. Subsequently, monoperphthalic acid in ether was used with dihydrocarvone, and consumption of peracid was found extremely slow in a reaction leading to an unsaturated lactone as main product, and to the required oxide (II) in only small yield. The lactone, which on analogy [10] is regarded as (XIII), was characterised as a methyl ester, $[\alpha]_D$ +3·7°, which adsorbed one molecular equivalent of hydrogen on catalytic reduction. A corresponding lactone diol, $[\alpha]_D$ +71°, regarded as (XIV), was later isolated in small amount from the residues of oxidation of (−)-dihydrocarvone with perbenzoic acid in chloroform.

(XIII)   (XIV)
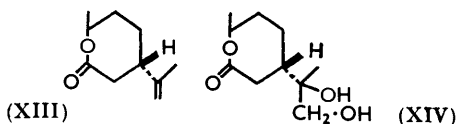
The relatively slow epoxidation of olefins by monoperphthalic acid in ether is well known. Differential reactivity, in comparison with perbenzoic acid, favouring attack at a carbonyl group has not to our knowledge previously been noted. The ketone ⟶ lactone fission is known to be acid-catalysed; [11] the acid strength of phthalic (pK_a 3·0) in comparison with benzoic acid (pK_a 4·7), which will respectively be present as reaction products, may therefore be a factor; the peracids themselves are weak.[12] Consideration of the reaction sequences (i) and (ii) suggests, however, that the basicity of the solvent may be more important: monoperphthalic acid is commonly used in ether solution.

In the previous experiments,[1] (−)-2-oxo-*p*-menthan-9-oic acid (VIII) was used (as the methyl ester) in condensation with diethylmethyl-3-oxopentylammonium iodide to give a dextrorotatory product shown to have the structure of a 3-oxoeudesm-4-en-12-oic acid, the stereochemistry of which was not determined. Parallel work with (±)-methyl 2-oxo-*p*-menthan-9-oate was later described by Abe *et al.*[13] Alkylation of a 5-substituted 2-methyl*cyclo*hexanone in this way was, however, found by the Japanese authors, and shown also in other work [2,14] to lead to the undesired 7β(H)-eudesmane derivative as the
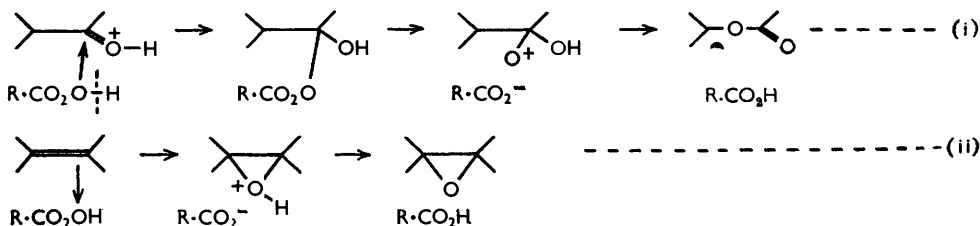
principal product. The oxidative sequence, oxide ⟶ aldehyde ⟶ acid, was therefore applied to (+)-α-cyperone (XVa), which we had previously synthesised,[2] and to the synthetic hydroxy-ketone [2,14] (XVIa) as sterically pure representatives of the 7α(H)- and 7β(H)-eudesmane series.

The required oxides (XVb) and (XVIb) were obtained in high yield by using perbenzoic acid in chloroform; in one experiment with insufficient cooling, (+)-α-cyperone gave largely the crystalline diol (XVII).

[9] Cf. Burckhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 821, 1434.

[10] Baeyer and Villiger, *Ber.*, 1899, **32**, 3625; cf. Murray, Johnson, Pederson, and Ott, *J. Amer. Chem. Soc.*, 1956, **78**, 981.

[11] Friess, *J. Amer. Chem. Soc.*, 1949, **71**, 2571; Doering and Speer, *ibid.*, 1950, **72**, 5515; Doering and Dorfmann, *ibid.*, 1953, **75**, 5595.

[12] Emmons and Pagano, *ibid.*, 1955, **77**, 89; Phillips, Frostick, and Starcher, *ibid.*, 1957, **79**, 5982.

[13] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1952, **28**, 425; *J. Amer. Chem. Soc.*, 1953, **75**, 2567.

[14] Howe and McQuillin, *J.*, 1958, 1194.

Henbest, Meakins, Nicholls, and Taylor [15] have drawn attention to a CH stretching frequency in the 3000 cm.$^{-1}$ region in the spectra of suitably substituted oxirans and in the present work we made a similar observation. The oxides (II), (XVb), and (XVIb), showed strong bands at 3034, 3016, and 3050 cm.$^{-1}$ respectively, and rearrangement of (+)-α-cyperone oxide (XVb) was conveniently followed by fall in absorption at 3016 cm.$^{-1}$ and development of the aldehyde band at 2700 cm.$^{-1}$ Treatment with a half-molar proportion of boron trifluoride–ether complex in benzene for 2 hr. gave a satisfactory result. A catalytic amount of boron trifluoride, on the other hand, rapidly converted the ketol oxide

(XV), (XVI); R = (a) CMe:CH$_2$, (b) C̄Me·CH$_2$, (c) CHMe·CHO, (d) CHMe·CO$_2$H.
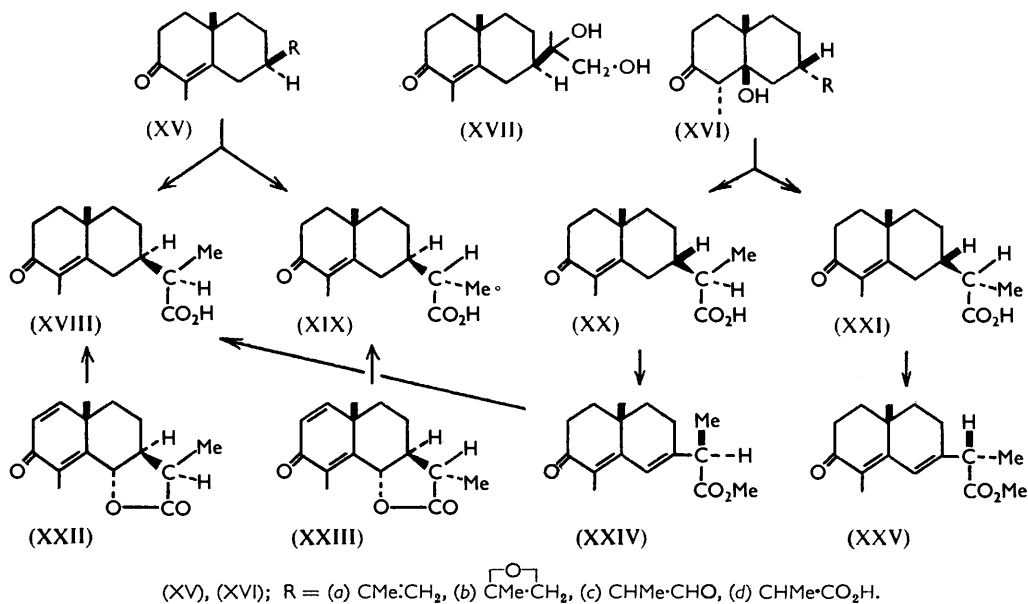
(XVIb) into the corresponding 11-epimeric aldehydes (XVIc) which were not separated. The aldehydes (XVc) and (XVIc) were oxidised by chromic acid and potassium permanganate respectively to the mixed 11-epimeric acids (XVd) and (XVId).

In agreement with the 5 : 10-*cis*-formulation of the hydroxy-ketone (XVIa), previously deduced on other grounds,[2,14] the crystalline hydroxy-acid (XVId) failed to lactonise when heated alone or with acetic anhydride. It could be dehydrated by refluxing aqueous-alcoholic potassium hydroxide, or, more conveniently with a little toluene-*p*-sulphonic acid in toluene. The 11-epimeric dehydro-acids were separated to give an acid, m. p. 121°, [α]$_D$ +90°, from benzene–light petroleum, and a second acid which crystallised from dilute acetic acid as a monohydrate, m. p. 78°, [α]$_D$ +208°. The former corresponds to the acid, m. p. 121°, [α]$_D$ +91°, obtained by Abe *et al.*[16] by resolution of a (±)-synthetic acid and related by them to (+)-α-desmotroposantonin. In accord with the configuration for (—)-α-santonin deduced by Woodward and Yates,[17] our acid of m. p. 121° may be given the configuration (XXI). The hydrated acid, m. p. 78°, therefore has configuration (XX); a corresponding (±)-acid was described as having m. p. 125° (anhydrous) by Abe and his co-workers,[13] but it was not resolved.

From (+)-α-cyperone one of the corresponding pair of acids could readily be isolated, having m. p. 126°, [α]$_D$ +126°, and after rigorous crystallisation was obtained with m. p.

[15] Henbest, Meakins, Nicholls, and Taylor, *J.*, 1957, 1459.
[16] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1416.
[17] Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Corey, *J. Amer. Chem. Soc.*, 1955, **77**, 1044; Cocker and Edward, *Chem. and Ind.*, 1955, 41; cf., however, Abe, Miki, Sumi, and Toga, *ibid.*, 1956, 953; Cocker and McMurry, *ibid.*, 1956, 1430.

133°, $[\alpha]_D$ +130° (methyl ester, $[\alpha]_D$ +129°). The more soluble epimer was separated only with some difficulty and obtained having m. p. 105°, $[\alpha]_D$ +114° (methyl ester $[\alpha]_D$ +100°). Two corresponding racemic acids, m. p. 133° and 145°, described by Abe and his co-workers [3,18] were not resolved but were related respectively to the α- and the β-santonin series. We have directly related our (+)-synthetic acids, m. p. 133° and 105°, to (—)-α- and (—)-β-santonin respectively.

Bruderer, Arigoni, and Jeger,[19] in relating the stereochemistry of (—)-α-santonin to that of the cyperones, described the reduction of (—)-α-santonin (XXII) to an acid (XVIII), m. p. 124°, $[\alpha]_D$ +11·4° (methyl ester $[\alpha]_D$ +90°), by means of lithium in ammonia. We have repeated this preparation, and, through the kindness of Professor Jeger, we have been able to show that the acid, which we obtained having m. p. 126°, $[\alpha]_D$ +114° (methyl ester $[\alpha]_D$ +98°), gives an undepressed melting point with, and the same infrared spectrum as, the earlier Swiss preparation, also the same spectrum as our synthetic acid of m. p. 133°. This synthetic product may therefore be given the configuration (XVIII); it seems likely that the acid from reduction of (—)-α-santonin retains a small amount of a persistent lævorotatory impurity.

Reduction of (—)-β-santonin (XXIII) by lithium in ammonia led to an isomeric acid (XIX), m. p. 117°, $[\alpha]_D$ +111°. This showed characteristic differences in infrared absorption from the α-santonin acid (XVIII) and by this means separation of our synthetic acids could be followed. This separation was difficult; our purest preparation showed all the infrared bands characteristic of the β-santonin acid (XIX) and closely similar optical rotation, $[\alpha]_D$ +114°, but the melting point has not been raised beyond 105°. This second synthetic acid, however, clearly agrees closely with a structure (XIX).

The 7α(H)- and 7β(H)-series of 3-oxoeudesm-4-en-12-oic acids were interrelated by the method of partial reduction of a 4 : 6-dien-3-one applied earlier to (+)-β-cyperone.[20] The methyl ester of the acid (XX), m. p. 78°, $[\alpha]_D$ +208°, on bromination with *N*-bromo-succinimide and dehydrobromination with collidine (cf. Clemo and McQuillin [1]) gave a dienoic ester (XXIV). This, on half-hydrogenation in benzene with a modified Lindlar [21] catalyst and then hydrolysis, gave an acid, m. p. 123°, $[\alpha]_D$ +130°, identical in infrared absorption with the synthetic acid (XVIII) from (+)-α-cyperone, and different from the 7β(H)-acid (XXI), m. p. 121°, $[\alpha]_D$ +90°. This interconversion is in agreement with the configurations assigned and relates the two series of synthetic acids.

Complete hydrogenation of the dienoic ester (XXIV), $[\alpha]_D$ +392°, gave a tetrahydro-ester, $[\alpha]_D$ +23·7° which, however, is probably a mixture of 5α(H)- and 5β(H)-isomers. The isomeric acid (XXI), m. p. 121°, $[\alpha]_D$ +90°, gave a corresponding dienoic ester (XXV), $[\alpha]_D$ +201°, and a tetrahydro-derivative, $[\alpha]_D$ —12·6°.

A point of interest arose in connexion with the hydrogenation of the 7β(H)-eudesmenoic acids (XX) and (XXI). The former with palladised charcoal in alcohol gave a product, m. p. 126°, $[\alpha]_D$ +16·8°; the latter failed to absorb hydrogen and was recovered. The reduction product, m. p. 126°, is regarded as the *cis*-ring-fused acid (XXVI) which represents a stable configuration; *trans*-reduction will be strongly impeded by the 7α-substituent (cf. ref. 14). The non-reduction of the acid (XXI) is clearly related to the orientation of the carboxyl group, the bulk of which is known to impede catalytic reduction.[22]

The oxidative sequence, $>$C=CH$_2$ ⟶ oxide ⟶ aldehyde ⟶ acid, has analogy with, *e.g.*, the ozonolysis of longifolene to a C_{15} acid noted by Naffa and Ourisson [23] who record other examples. The mechanism may be similar. Our method was suggested by a

[18] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1422.
[19] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858.
[20] Howe and McQuillin, *J.*, 1956, 2670.
[21] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[22] Cf. Dauben, Tweit, and MacLean, *J. Amer. Chem. Soc.*, 1955, **77**, 48; Wieland, Ueberwasser, Heusler, and Wettstein, *Helv. Chim. Acta*, 1958, **41**, 74.
[23] Naffa and Ourisson, *Bull. Soc. chim. France*, 1954, 1115.

biogenetic speculation [1] which regarded, for example, the various members of the eudesmane group as representing differing states of oxidation of a common precursor. The recognition that cholesterol [24] and also simpler terpenes [25] arise from acetate units *via* mevalonic acid lends point to this view. Reconsideration of the eudesmane series in these terms (XXVII) indicates that oxygenation at positions 3 and/or 12 probably does involve a subsequent oxidative step; the demethylation of lanosterol [24] and the origin of the carboxyl group of

(XXVI)   (XXVII)
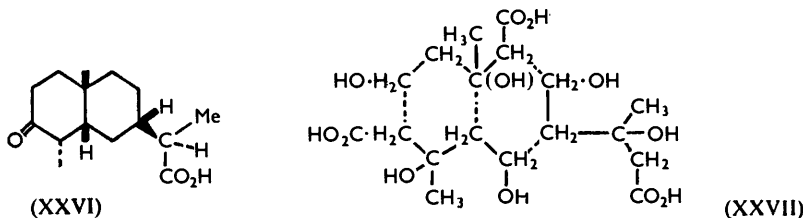
eburicoic acid [26] are precedents. The 6α- and/or 8α-hydroxylation characteristic of the santonins and alantolactone,[27] on the other hand, may clearly arise from the mevalonic acid unit. The structure of pyrethrosin [28] also fits into this scheme and is interesting in relation to the oxygenation of *pseudo*santonin at position 1.

In naming the epimeric eudesmenoic acids (cf. Experimental section) the configuration at position 11 has been indicated by giving the 11-hydrogen substituent the appropriate α- or β-designation, with the convention that the formulæ are drawn as in (XVIII)—(XXI).

EXPERIMENTAL

$[\alpha]_D$ and $\lambda_{max.}$ values refer to solutions in chloroform and ethyl alcohol respectively. Infrared absorption was determined in liquid film (0·01 mm.) or, for solids, in a potassium bromide disc.

Oxidation of (—)-*Dihydrocarvone with Monoperphthalic Acid.*—(—)-Dihydrocarvone (20 g.) in ether (80 c.c.) was treated with monoperphthalic acid (24·5 g.) in ether (450 c.c.) at 0°. After 6 days the peracid was consumed and the product, isolated after washing with sodium hydrogen carbonate solution and water, gave recovered (—)-dihydrocarvone (4 g.) followed by material (7·5 g.), b. p. 105—116°/5 mm. The latter gave the semicarbazone of (—)-dihydrocarvone oxide, m. p. 188° (cf. Clemo and McQuillin [1]) in small yield. It was refractionated to give the *lactone*, b. p. 93—95°/2 mm., n_D^{20} 1·4735, of 6-hydroxy-3-*iso*propenylheptanoic acid (Found: C, 71·7; H, 9·9. $C_{10}H_{16}O_3$ requires C, 71·4; H, 9·5%). Hydrolysis by methanolic aqueous potassium hydroxide followed by esterification gave (+)-*methyl* 6-*hydroxy*-3-iso*propenyl-heptanoate*, b. p. 84—86°/0·2 mm., n_D^{20} 1·4595, $[\alpha]_D$ +3·7° (*c* 2·6) (Found: C, 66·1; H, 10·3. $C_{11}H_{20}O_2$ requires C, 66·0; H, 10·0%). Hydrogenated in alcohol over platinum the ester absorbed one mol. of hydrogen. Residues from oxidation of (—)-dihydrocarvone with perbenzoic deposited material of m. p. 103° (from benzene), $[\alpha]_D$ +71° (*c* 3·2) (Found: C, 59·8; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·5; H, 8·5%), regarded as the 6-*lactone* of 6-hydroxy-3-(1 : 2-di-hydroxy-1-methylethyl)heptanoic acid.

(+)-2-*Oxo*-p-*menth*-6-*ene* 8 : 9-*Oxide.*—(+)-Carvone (23·5 g.) with perbenzoic acid (21 g.) in chloroform (400 c.c.) for 14 hr. at 20° gave (+)-2-oxo-*p*-menth-6-ene 8 : 9-oxide (VI) (21·4 g.), b. p. 128—132°/16 mm., $[\alpha]_D$ +37·6° (*c* 5·1) (Found: 71·9; H, 8·8. Calc. for $C_{10}H_{14}O_2$: C, 72·2; H, 8·4%). The *semicarbazone* formed prisms, m. p. 155°, from methanol (Found: C, 58·8; H, 8·0. $C_{11}H_{17}O_2N_3$ requires C, 59·2; H, 7·7%). Excess of reagent gave a *semicarbazidosemi-carbazone*, m. p. 137° (from methanol) (Found: C, 48·2; H, 7·9. $C_{12}H_{22}O_3N_6$ requires C, 48·3; H, 7·4%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 181° (from ethyl acetate), corresponded with a derivative of 2-oxo-*p*-menth-6-ene 8 : 9-diol (Found: C, 53·1; H, 5·6. $C_{16}H_{20}O_6N_4$ requires C, 52·8; H, 5·5%).

[24] Cf. Bloch, *Vitamins and Hormones*, 1957, **15**, 119.
[25] Birch, English, Massy-Westrop, and Smith, *J.*, 1958, 369.
[26] Dauben, Ban, and Richards, *J. Amer. Chem. Soc.*, 1957, **79**, 968.
[27] Tsuda, Tanabe, Iwai, and Funakoshi, *ibid.*, p. 5721.
[28] Barton and Mayo, *J.*, 1957, 150.

Hydrogenation of (+)-*Carvone Oxide.*—The oxide (5 g.) in ethanol (35 c.c.) with palladium–barium carbonate was reduced at 100 lb./sq. in. for 20 hr. to give (−)-dihydrocarvone oxide (3·4 g.), b. p. 108—110°/3 mm. (Found: C, 71·4; H, 9·8. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·5%), identified as the semicarbazone, m. p. 187° (cf. Clemo and McQuillin [1]) (Found: C, 58·8; H, 8·7. Calc. for $C_{11}H_{19}O_2N_3$: C, 58·6; H, 8·4%).

(−)-α-(4-*Methyl*-3-*oxocyclohexyl*)*propionic Acid* (VIII).—(+)-Carvone oxide was hydrogenated at 80 atm. for various periods at 20° and at 80°. Brief reduction (∼2 hr.) at 80° appeared to be optimal for production of *p*-menthane-2 : 9-diol, as estimated by the yield of acid on oxidation, but over-reduction to menthols could not be avoided. The diol fraction, oxidised as described by Clemo and McQuillin,[1] gave (−)-methyl α-(4-methyl-3-oxo*cyclo*hexyl)propionate, b. p. 78—81°/0·2 mm., n_D^{20} 1·4653, $[\alpha]_D$ −8·3° (*c* 2·8).

(+)-α-(4-*Methyl*-3-*oxocyclohexyl*)*propionic Acid* (XII).—(+)-Limonene dioxide (14 g.),[29] b. p. 115—118°/20 mm., $[\alpha]_D$ +49·5° (*c* 5·0), obtained in 85% yield by using perbenzoic acid in chloroform, was hydrogenated in ethanol (100 c.c.) at 90°/80 atm. with Raney nickel for 2·5 hr., to give 4·5 g. of material of b. p. 95—100°/0·2 mm., followed by *p*-menthane-2 : 9-diol (8 g.), b. p. 100—105°/0·2 mm. (Found: C, 69·9; H, 11·1. Calc. for $C_{10}H_{20}O_2$: C, 69·8; H, 11·6%). This diol was oxidised with potassium permanganate and the acidic product esterified to give (+)-*methyl* α-(4-*methyl*-3-*oxocyclohexyl*)*propionate*, b. p. 73—75°/0·2 mm., n_D^{20} 1·4616, $[\alpha]_D$ +10·9° (*c* 2·7) (Found: C, 66·5; H, 9·1. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%).

Rearrangement of (−)-*Dihydrocarvone Oxide.*—(i) *By magnesium bromide.* Mercuric bromide (21·6 g.) was added to a suspension of magnesium powder (3 g.) in dry ether (300 c.c.) and benzene (100 c.c.), and the mixture refluxed (2 hr.), filtered, and made up to 400 c.c. To this solution (320 c.c.), (−)-dihydrocarvone oxide (5 g.) was added in ether (30 c.c.) and the whole refluxed for 2·5 hr. Recovery gave a bromohydrin (3 g.), b. p. 123—125°/0·4 mm., n_D^{20} 1·5117, regarded as 2-*bromo*-2-(3-*oxo*-4-*methylcyclohexyl*)*propan*-1-*ol* (Found: C, 48·2; H, 7·0. $C_{10}H_{17}O_2Br$ requires C, 48·2; H, 6·8%). Alternatively the benzene and ether were removed by distillation and the residual magnesiobromo-complex heated on the water-bath for 1 hr. Recovery then gave (−)-α-(3-*oxo*-4-*methylcyclohexyl*)*propionaldehyde* (3·1 g.), b. p. 72—75°/0·2 mm., n_D^{20} 1·4765, $[\alpha]_D$ −22·3° (*c* 2·5) (Found: C, 71·7; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%).

(ii) *By boron trifluoride.* (−)-Dihydrocarvone oxide (3 g.) in dry benzene (50 c.c.) with boron trifluoride–ether complex (2·5 g.) was kept for 0·5 hr. and then recovered, after treatment with sodium hydrogen carbonate solution, to give the aldehyde (VII) as above.

(−)-α-(3-*Oxo*-4-*methylcyclohexyl*)*propionic Acid* (VIII).—The foregoing aldehyde (0·8 g.), oxidised with the theoretical amount of potassium permanganate in water, gave the acid, isolated as the methyl ester (0·6 g.), b. p. 80°/0·1 mm., n_D^{20} 1·4638, $[\alpha]_D$ −13·3° (*c* 2·7) (Found: C, 66·3; H, 9·3. Calc. for $C_{11}H_{18}O_3$: C, 66·7; H, 9·1%) (2 : 4-dinitrophenylhydrazone, m. p. 169°) (cf. Clemo and McQuillin [1]).

11 : 12-*Epoxy*-5β-*hydroxy*-4β : 7β(H)-*eudesman*-3-*one* (XVIb).—(−)-5β-Hydroxy-4β : 7β(H)-eudesm-11-en-3-one (XVIa) (9·4 g.) in chloroform (50 c.c.) with perbenzoic acid (5·75 g.) in chloroform (115 c.c.) overnight at 0° gave (−)-11 : 12-*epoxy*-5β-*hydroxy*-4β : 7β(H)-*eudesman*-3-*one* (XVIb), m. p. 162°, $[\alpha]_D$ −51·3° (*c* 0·9), prisms (from benzene–light petroleum) (Found: C, 71·4; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%).

(−)-5β-*Hydroxy*-3-*oxo*-4β : 7β(H)-*eudesman*-12-*al* (XVIc).—The epoxide above (5 g.) in dry benzene (250 c.c.) was treated with boron trifluoride–ether complex (0·5 g.) in benzene (25 c.c.) with stirring. After 8 min. 10% sodium hydrogen carbonate solution (50 c.c.) was added. The product isolated from the washed and dried benzene solution crystallised from benzene–light petroleum as prisms (4 g.), m. p. 126—127°, $[\alpha]_D$ −53·3° (*c* 1·3), of (−)-5β-*hydroxy*-3-*oxo*-4β : 7β(H)-*eudesman*-12-*al* (Found: C, 71·2; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%).

(−)-5β-*Hydroxy*-3-*oxo*-4β : 7β(H)-*eudesman*-12-*oic Acid* (XVId).—The aldehyde above (6 g.) in acetone (60 c.c.) was treated with a solution of sodium carbonate (2·5 g.) in water (15 c.c.), followed by potassium permanganate (2·5 g.) in water (60 c.c.) with stirring during 1·5 hr. After a further 0·5 hr. the manganese dioxide was dissolved by means of sulphur dioxide, and organic material was isolated in chloroform. Extraction with sodium hydrogen carbonate solution and recovery of acidic material (5·2 g.) gave (−)-5β-*hydroxy*-3-*oxo*-4β : 7β(H)-*eudesman*-12-*oic acid* (XVId), m. p. 137—139° (from benzene–light petroleum), $[\alpha]_D$ −49·5° (*c* 0·9) (Found: C, 67·6; H, 9·3. $C_{15}H_{24}O_4$ requires C, 67·2; H, 9·0%).

[29] Prileshajew, *Ber.*, 1909, **42**, 4811.

Dehydration of (−)-5β-*Hydroxy*-3-*oxo*-4β : 7β(H)-*eudesman*-12-*oic Acid.*—(i) The hydroxy-acid (0·5 g.) with 4% methanolic hydrogen chloride (25 c.c.), after refluxing, afforded the 11 epimeric methyl 3-oxo-7β(H)-eudesm-4-en-12-oates, b. p. 130—132°/0·1 mm., n_D^{20} 1·5145, $[\alpha]_D$ +109° (*c* 4·5) (Found: C, 72·5; H, 9·2. Calc. for $C_{16}H_{24}O_3$: C, 72·6; H, 9·1%) [2 : 4-dinitrophenylhydrazone, m. p. 167° (cf. Clemo and McQuillin [1]) (Found: C, 59·0; H, 6·3. Calc. for $C_{22}H_{26}O_6N_4$: C, 59·4; H, 6·3%)]. Hydrolysed by methanolic potassium hydroxide under nitrogen, this methyl ester afforded the mixed acids, $[\alpha]_D$ +131° (*c* 1·9). (ii) The hydroxy-acid (5 g.) in toluene (50 c.c.) with toluene-*p*-sulphonic acid (0·1 g.) was heated until the optical rotation had reached a maximum value. The recovered acid, $[\alpha]_D$ +140° (*c* 1·4), was chromatographed on silica gel and eluted with benzene–ether (20 : 1), to give (+)-3-*oxo*-7β : 11β(H)-*eudesm*-4-*en*-12-*oic acid* (XXI), m. p. 121—122°, $[\alpha]_D$ +90° (*c* 3·08), $\lambda_{max.}$ 250 mμ (log ε 4·13), after crystallisation from benzene–light petroleum (Found: C, 72·2; H, 9·0. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). The *oxime*, m. p. 187—188°, $[\alpha]_D$ +61·2° (*c* 1·0 in EtOH), crystallised from aqueous methanol (Found: C, 67·6; H, 8·7. $C_{15}H_{23}O_3N_3$ requires C, 67·9; H, 8·7%). Diazomethane gave the *methyl ester*, b. p. 130°/0·1 mm., n_D^{20} 1·5156, $[\alpha]_D$ +57·4° (*c* 4·4), which crystallised as prisms, m. p. 47° (Found: C, 72·4; H, 9·1. $C_{16}H_{24}O_3$ requires C, 72·6; H, 9·1%). The remaining non-crystalline acid from chromatography was treated with dilute acetic acid and then gave (+)-3-*oxo*-7β : 11α(H)-*eudesm*-4-*en*-12-*oic acid monohydrate* (XX), prisms, m. p. 78°, $[\alpha]_D$ +208° (*c* 1·9), $\lambda_{max.}$ 251 mμ (log ε 4·17) (Found: C, 67·2; H, 9·2. $C_{15}H_{22}O_3,H_2O$ requires C, 67·2; H, 9·0%). The *methyl ester* formed an oil, b. p. 130°/0·1 mm., n_D^{20} 1·5185, $[\alpha]_D$ +176° (*c* 2·4) (Found: C, 72·6; H, 9·4%).

(+)-*Methyl* 3-*Oxo*-11β(H)-*eudesma*-4 : 6-*dien*-12-*oate* (XXV).—The methyl ester of the acid, m. p. 121° (XXI), was treated with *N*-bromosuccinimide in dry carbon tetrachloride under reflux for 1·5 hr., and the derived bromo-ester heated with *sym*-collidine on the steam-bath for 3·5 hr., to give (+)-*methyl* 3-*oxo*-11β(H)-*eudesma*-4 : 6-*dien*-12-*oate*, b. p. 120°/0·05 mm., n_D^{20} 1·5478, $[\alpha]_D$ +201·7° (*c* 3·15), $\lambda_{max.}$ 296 mμ (log ε 4·28) (Found: C, 72·8; H, 8·6. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

(+)-*Methyl* 3-*Oxo*-11α(H)-*eudesma*-4 : 6-*dien*-12-*oate* (XXIV).—The methyl ester of the acid, m. p. 78° (XX), treated similarly with *N*-bromosuccinimide followed by *sym*-collidine, afforded (+)-*methyl* 3-*oxo*-11α(H)-*eudesma*-4 : 6-*dien*-12-*oate*, b. p. 125°/0·1 mm., n_D^{20} 1·5503, $[\alpha]_D$ +392° (*c* 1·07), $\lambda_{max.}$ 298 mμ (log ε 4·27) (Found: C, 73·3; H, 8·7%).

Methyl 3-*Oxoeudesman*-12-*oates.*—(i) (+)-Methyl 3-oxo-11β(H)-eudesma-4 : 6-dien-12-oate (XXV), hydrogenated with palladised charcoal in alcohol, absorbed two mols. of hydrogen to give a methyl 3-oxoeudesman-12-oate, b. p. 120°/0·1 mm., n_D^{20} 1·4908, $[\alpha]_D$ −12·6° (*c* 4·43) (Found: C, 72·6; H, 10·0. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8%). (ii) (+)-Methyl 3-oxo-11α(H)-eudesma-4 : 6-dien-12-oate (XXIV) similarly afforded a methyl 3-oxoeudesman-12-oate, b. p. 120°/0·1 mm., n_D^{20} 1·4928, $[\alpha]_D$ +23·7° (*c* 5·0) (Found: C, 72·6; H, 9·8%).

(+)-3-*Oxo*-7β(H)-*eudesman*-12-*oic acid* (XXVI).—The acid (XX), hydrogenated in alcohol with palladised charcoal, absorbed one mol. of hydrogen to give a product which was recrystallised from benzene–light petroleum and sublimed in *vacuo*, to give stout prisms, m. p. 126°, $[\alpha]_D$ +16·8° (*c* 1·64), regarded as 3-oxo-4β : 5β : 7β : 11α(H)-eudesman-12-oic acid (XXVI) (Found: C, 71·0; H, 9·4. $C_{15}H_{24}O_3$ requires C, 71·3; H, 9·5%).

(+)-11 : 12-*Epoxyeudesm*-4-*en*-3-*one* (XVb).—(+)-α-Cyperone (10·3 g.) in chloroform (150 c.c.) was treated at 2—3° with one equivalent of perbenzoic acid in chloroform (170 c.c.). Reaction was complete in 4·5 hr. The *epoxy-ketone*, isolated after washing of the solution with sodium hydrogen carbonate solution and with water, formed an oil (9 g.), b. p. 125°/0·3 mm., n_D^{20} 1·5238, $[\alpha]_D$ +108° (*c* 3·01) (Found: C, 76·6; H, 9·8. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%). After longer contact with the perbenzoic acid solution the epoxide was accompanied by (+)-11 : 12-*dihydroxyeudesm*-4-*en*-3-*one* (XVII), b. p. 130°/0·2 mm., m. p. 37° (from pentane), $[\alpha]_D$ +127·4° (*c* 2·6) (Found: C, 71·9; H, 9·2. $C_{15}H_{24}O_3$ requires C, 71·5; H, 9·5%).

(+)-*Eudesm*-4-*ene*-3 : 12-*dione* (XVc).—(+)-11 : 12-Epoxyeudesm-4-en-3-one (7·5 g.) in dry benzene (260 c.c.) was treated with boron trifluoride–ether complex (2·25 g.) and kept at the room temperature for 2·5 hr. The product, isolated after addition of sodium hydrogen carbonate solution and washing with water, formed an oil (5·5 g.), b. p. 129°/0·2 mm., n_D^{20} 1·5234, $[\alpha]_D$ +109° (*c* 2·13): it was (+)-*eudesm*-4-*ene*-3 : 12-*dione* (XVc) (Found: C, 77·0; H, 9·3. $C_{15}H_{22}O_3$ requires C, 76·9; H, 9·4%), and gave a bis-2 : 4-dinitrophenylhydrazone, m. p. 202° (Found: C, 55·0; H, 5·1. Calc. for $C_{27}H_{30}O_{88}N$: C, 54·5; H, 5·1%); Bruderer, Arigoni, and Jeger [19] give m. p. 203°.

3-Oxoeudesm-4-en-12-oic Acids.—(+)-Eudesm-4-ene-3 : 12-dione (5 g.) in acetic acid (40 c.c.) with chromium trioxide (1·9 g.) in water (10 c.c.) was kept overnight. The acidic product (4 g.) largely crystallised. Repeated crystallisation first from benzene–light petroleum and finally from ether gave (+)-3-oxo-11α(H)-*eudesm-4-en-12-oic acid* (XVIII), m. p. 133—134°, $[\alpha]_D$ +130° (c 1·03), λ_{max} 250 mμ (log ε 4·2) (Found: C, 71·8; H, 9·2. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%) [*methyl ester*, b. p. 125°/0·1 mm., n_D^{20} 1·5132, $[\alpha]_D$ +129° (c 0·72) (Found: C, 72·9; H, 9·3. $C_{16}H_{24}O_3$ requires C, 72·8; H, 9·1%)]. From the remaining material by means of benzene–light petroleum an acid, m. p. 95°, was obtained. Chromatography on silica gel and elution with benzene–ether (20 : 1) failed to raise the m. p. as did repeated crystallisation from benzene–light petroleum or ethyl acetate–light petroleum. Exhaustive recrystallisation from aqueous methanol removed a little of the acid (XVIII) in the less soluble fractions and finally yielded, from the more soluble, prisms, m. p. 105°, $[\alpha]_D$ +114° (c 1·7), λ_{max} 250 mμ (log ε 4·2), regarded as (+)-3-oxo-11β(H)-*eudesm-4-en-12-oic acid* (XIX) (Found: C, 71·7; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%); it gave a *methyl ester*, b. p. 125—130°/0·1 mm., n_D^{20} 1·5108, $[\alpha]_D$ +100° (Found: C, 73·1; H, 9·0. $C_{16}H_{24}O_3$ requires C, 72·8; H, 9·1%), and a *semicarbazone*, m. p. 210° (Found: C, 62·5; H, 8·2. $C_{16}H_{25}O_3N_3$ requires C, 62·5; H, 8·1%).

Lithium–Ammonia Reduction of (−)-α- *and* (−)-β-*Santonin.*—(i) Reduction of (−)-α-santonin carried out essentially as described by Bruderer, Arigoni, and Jeger [19] gave directly an acid product which largely crystallised, and gave (+)-3-oxo-11α(H)-eudesm-4-en-12-oic acid, m. p. 126° (after crystallisation from benzene–light petroleum and sublimation *in vacuo*), $[\alpha]_D$ +114° (c 3·34), λ_{max} 250 mμ (log ε 4·1) (Found: C, 72·4; H, 8·8. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·8%) {*methyl ester*, b. p. 120°/0·05 mm., n_D^{20} 1·5102, $[\alpha]_D$ +98·5° (c 4·5) (Found: C, 72·5; H, 9·2. Calc. for $C_{16}H_{24}O_3$: C, 72·8; H, 9·1%)}. (ii) (−)-β-Santonin (1 g.) in tetrahydrofuran (50 c.c.) was added to a solution of lithium (0·3 g.) in liquid ammonia (200 c.c.) with stirring and the liquid kept for 24 hr.; the ammonia had then evaporated. Acidic material (0·8 g.) was purified *via* the methyl ester which was chromatographed and hydrolysed, to give (+)-3-oxo-11β(H)-eudesm-4-en-12-oic acid, m. p. 117° (after recrystallisation from ether–light petroleum and sublimation *in vacuo*), $[\alpha]_D$ +110·5° (c 3·24), λ_{max} 250 mμ (log ε 4·15) (Found: C, 72·2; H, 8·6. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·8%) {*methyl ester*, b. p. 130°/0·1 mm., n_D^{20} 1·5132 $[\alpha]_D$ +96° (c 1·4) (Found: C, 72·7; H, 9·4. $C_{16}H_{24}O_3$ requires C, 72·8; H, 9·1%)}.

Inversion of (+)-3-Oxo-7β : 11α(H)-*eudesm-4-en-12-oic Acid* (XX) *to* (+)-3-Oxo-7α : 11α(H)-*eudesm-4-en-12-oic Acid* (XVIII).—Methyl 3-oxo-11β(H)-eudesma-4 : 6-dien-12-oate (XXIV) (1·8 g.) in benzene (25 c.c.) in presence of palladium–strontium carbonate which had been treated with lead acetate (Howe and McQuillin [14]) absorbed 1 mol. of hydrogen. Recovery gave a methyl ester (1·7 g.), b. p. 130°/0·1 mm., λ_{max} 247 (log ε 3·98) and 296 mμ (log ε 3·56), which was hydrolysed by methanolic potassium hydroxide. The acid was heated at 130°/0·1 mm., to decarboxylate residual dienone-carboxylic acid, and acidic material (1·1 g.) was then recovered and converted into the *oxime*. This formed prisms, m. p. 185° (from methanol), $[\alpha]_{5461}$ +86·7° (c 0·6 in EtOH), λ_{max} 243 mμ (log ε 4·25) (Found: C, 67·4; H, 9·0. $C_{15}H_{23}O_3N$ requires C, 67·9; H, 8·7%). The oxime was boiled in aqueous-methanolic hydrochloric acid for 4 hr., giving an acidic product (0·35 g.) which on trituration with ether–light petroleum gave (+)-3-oxo-11α(H)-eudesm-4-en-12-oic acid, m. p. 123°, $[\alpha]_D$ +126° (c 2·8), λ_{max} 250 mμ (log ε 4·14) (Found: C, 71 7; H, 9·2. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·8%). The mixed m. p. with authentic acid (XVIII) was 123°.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1.