454. *Sesquiterpenoids. Part XII.* Further Investigations on the Chemistry of Pyrethrosin.*

By D. H. R. Barton, O. C. Böckman, and P. de Mayo.

Further work on the chemistry of pyrethrosin has confirmed the presence of a 1,2-epoxide and of a ten-membered carbocycle. As a result of further degradations the positions of the acetoxyl residue and of the alkyl-oxygen atom of the γ-lactone function, assigned in an earlier paper, have been interchanged, but the constitution proposed before for pyrethrosin has been confirmed in every other detail.

The acid-catalysed cyclisation of pyrethrosin has been investigated and the stereochemistry of some of the centres of asymmetry in the molecule defined.

In an earlier part of this series [1] the constitution (I) was proposed for pyrethrosin, the sesquiterpenoid lactone from "pyrethrum." Pyrethrosin was the first sesquiterpenoid shown to have a ten-membered carbocyclic ring and its ready cyclisation made it of obvious importance in the biogenesis of other bicyclic sesquiterpenoids.[2] Since the appearance of our paper a considerable number of sesquiterpenoids containing a ten-membered ring have been discovered [3,4] and the biogenetic implications [1,2,5] of this type of structure now appear to be generally accepted.[6] The present paper reports a more detailed study of the reactions

* Part XI, *J.*, 1958, 4518.

[1] Barton and de Mayo, *J.*, 1957, 150.

[2] See also Barton and de Mayo, *Quart. Rev.*, 1957, **11**, 189.

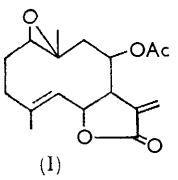
[3] *Inter al.*, Suchy, Horak, Herout, and Šorm, *Chem. and Ind.*, 1957, 894; Ognjanov, Ivanov, Herout, Horak, Pliva, and Šorm, *Coll. Czech. Chem. Comm.*, 1958, **23**, 2033; Herout and Šorm, *Chem. and Ind.*, 1959, 1067; and many other papers by Herout, Šorm, and their collaborators.

[4] Bhattacharyya, Kelkar, and Rao, *Chem. and Ind.*, 1958, 1359; 1959, 1069.

[5] Ruzicka, *Experientia*, 1953, **9**, 357.

[6] Henrickson, *Tetrahedron*, 1959, **7**, 82.

of pyrethrosin. The constitution (I) originally proposed has been confirmed except that the position of attachment of the lactone ring has been shown to be as in (II). The latter, then, is the correct constitution of pyrethrosin and will be used in the sequel.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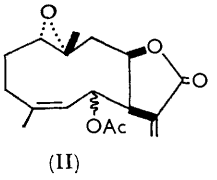
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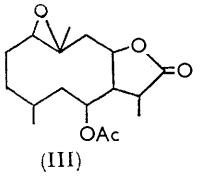
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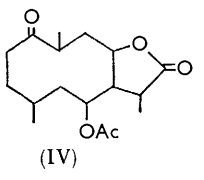
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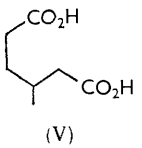
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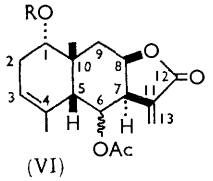
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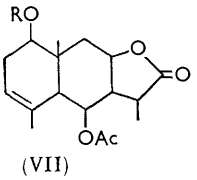
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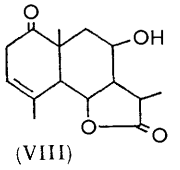

(VIII)

Hydrogenation of pyrethrosin gave a mixture of stereoisomeric tetrahydropyrethrosins (III), one of which was isolated by fractional crystallisation. On treatment with boron trifluoride in ethereal solution this rearranged [7] to give a ketone (IV). This reaction confirms the presence of the 1,2-epoxide grouping, a feature already inferred on the basis of more circumstantial evidence.

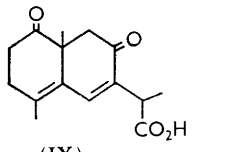
The presence of the ten-membered carbon ring was confirmed in the following way. The stereoisomeric mixture of tetrahydropyrethrosins (see above) was oxidised with aqueous chromic–sulphuric acid to β-methyladipic acid (V). This was identified by paper chromatography and by pyrolysis of the calcium salt to give 3-methylcyclopentanone, isolated as its 2,4-dinitrophenylhydrazone. Because a mixture of stereoisomers was used the product was not, of course, optically pure.

The position of the lactone ring was hitherto assigned [1] on the basis of the following evidence. Cyclisation of pyrethrosin with acetic anhydride–toluene-*p*-sulphonic acid gave a cyclopyrethrosin acetate [now to be formulated as (VI; R = Ac)]. Selective hydrogenation followed by controlled hydrolysis afforded an acetoxy-alcohol [now to be formulated as (VII; R = H)] which on oxidation by chromic acid furnished an acetoxy-ketone. Alkaline hydrolysis of this ketone gave two main products. One of these (m. p. 169—172°) could be reacetylated to give back the starting ketone and therefore had the lactone ring in the original position. The other product (m. p. 255—260°), more easily purified by crystallisation, was shown to have structure (VIII) because on oxidation by chromic acid followed by mild treatment with base it gave the conjugated dienone (IX), a substance whose constitution and stereochemistry were rigidly defined by an alternative preparation from ψ-santonin. Oxidation of the ketol, m. p. 169—172°, followed by mild treatment with base also developed ultraviolet absorption indicative of a compound (IX) although the small amount of material available at that time [1] prevented its isolation. We have now been able to repeat these experiments on a larger scale. Oxidation of the more easily available ketol, m. p. 255—260°, gave a crystalline diketone (X) showing no high-intensity ultraviolet absorption. On mild treatment with base this gave the spectrum of the dienone (IX), in confirmation of our earlier results.[1] On the other hand, oxidation of the ketol, m. p. 169—172°, gave a non-crystalline product which showed no high-intensity ultraviolet absorption and gave no dienone maximum on treatment with alkali. Our earlier observation on the ketol of m. p. 169—172° is, therefore, in error. The lower-melting ketol must now be represented as (XI; R = H). Since it is this compound which can be reacetylated to its precursor and thus related directly to pyrethrosin, the position of the

[7] House *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 1235; and many later papers; Henbest and Wrigley, *J.*, 1957, 4596, 4765.

lactone ring in the latter must be as in (II), not (I). The designation [1] " 11-iso "- for the ketol, m. p. 255—266°, is no longer justified.

Because of the importance of this conclusion we undertook further experiments to place the position of the lactone ring beyond question. The hydrogenation and selective hydrolysis of cyclopyrethrosin acetate (VI; R = Ac) to (VII; R = H) has already been referred to above. The ketone (XI; R = Ac) obtained from this by chromic acid oxidation (see above) was first selected for further study. We found that treatment with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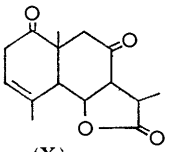
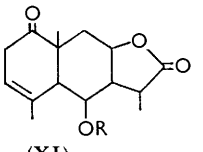
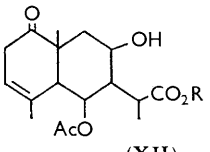

(X)


(XI)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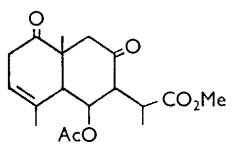
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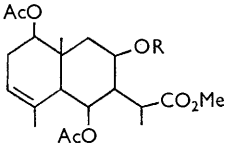
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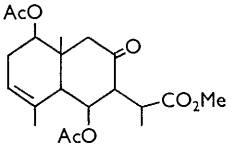
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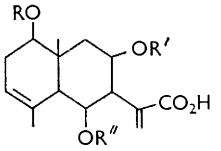

(XVI)

aqueous-ethanolic sodium hydrogen carbonate under controlled conditions gave an acid (XII; R = H) which with diazomethane afforded the methyl ester (XII; R = Me). Oxidation of the latter with chromic acid furnished a crystalline diketone (XIII) which on mild treatment with base gave the dienone (IX), fully characterised as in our earlier work [1] as the methyl ester bis-2,4-dinitrophenylhydrazone. Similarly dihydrocyclopyrethrosin acetate (VII; R = Ac) gave the desired methyl ester (XIV; R = H) which on oxidation afforded a crystalline diketone (XV). On mild treatment with base this likewise gave the characteristic dienone ultraviolet absorption spectrum. The methyl ester (XIV; R = H) was further converted into its toluene-*p*-sulphonate (XIV; R = toluene-*p*-sulphonyl) which when heated with pyridine and piperidine furnished a lactone stereoisomeric with (VII; R = Ac). Further reference to this compound is made below.

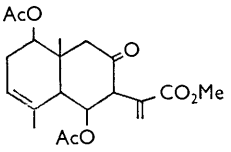
We have continued our study [1] of the influence of acidic reagents on pyrethrosin.[8] Treatment of pyrethrosin with aqueous sodium hydrogen carbonate and then with an excess of aqueous hydrochloric acid gave an acetoxy-acid (XVI; R = R′ = H, R″ = Ac) affording the triacetate (XVI; R = R′ = R″ = Ac) with pyridine–acetic anhydride. This triacetoxy-acid was also obtained by hydrolysis of cyclopyrethrosin acetate (VI; R = Ac) with an excess of sodium hydrogen carbonate solution. In contrast, hydrolysis under controlled conditions gave the diacetoxy-acid (XVI; R = R″ = Ac, R′ = H) which on methylation with diazomethane followed by oxidation with chromium trioxide afforded the crystalline diacetoxy-ketone (XVII). Mild treatment with alkali produced the usual dienone spectrum [as (IX)].

Treatment of pyrethrosin with boron trifluoride–ether complex and then with water gave the diol (XVIII; R = H) converted into the acetate (XVIII; R = Ac) on acetylation. The constitution of the diol was established by oxidation with chromic acid to the hydroxy-ketone (XIX) of established structure.[1] Digestion with acetic anhydride–toluene-*p*-sulphonic acid afforded cyclopyrethrosin acetate (VI; R = Ac). The diacetate (XVIII; R = Ac) also gave diene-lactone (VI; R = Ac) on treatment with pyridine and thionyl chloride. Hydrogenation of the monoacetate (XVIII; R = Ac) gave a dihydro-derivative which, with the same dehydrating agent, furnished dihydrocyclopyrethrosin acetate (VII; R = Ac).

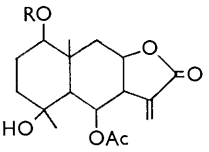
We have also been able to make experiments which shed some light on the stereochemistry of the pyrethrosin molecule. It can be shown that the stereochemistry of

[8] Cf. Rose and Haller, *J. Org. Chem.*, 1937, **2**, 484.

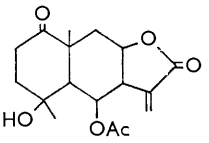
cyclopyrethrosin (VI; R = H) is probably as already represented in (VI; R = H). The absolute configuration (β) at position 10 is, of course, already established by our earlier work.[1] Treatment of dihydrocyclopyrethrosin (VII; R = H) with toluene-*p*-sulphonyl chloride in pyridine gave the expected toluene-*p*-sulphonate (VII; R = toluene-*p*-sulphonyl). The corresponding methanesulphonate was prepared in the same way. Heating either of these derivatives with collidine gave a non-conjugated diene. This compound is formulated as (XX) because it showed a strong infrared band at 893 cm.$^{-1}$ (>C=CH$_2$) which disappeared on conversion into the monoepoxide on treatment with perphthalic acid. There is excellent precedent [9] to show that this rearrangement requires that the 1-hydroxyl group be equatorial, an assignment in agreement with its lightly hindered nature.[1]



(XVII)



(XVIII)



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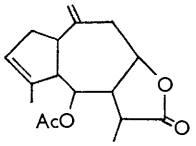

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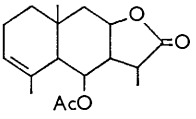
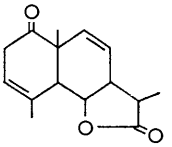


(XXI)



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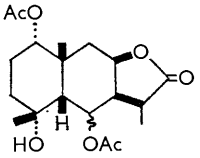

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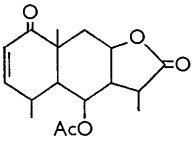

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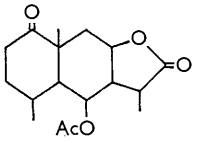

(XXV)

For purposes of molecular-rotation comparison the ketone (XI; R = Ac) was converted into the thioketal with ethanedithiol and then desulphurised to give the deoxo-compound (XXI). The $[M]_D$ of this substance showed that the hydroxyl of dihydrocyclopyrethrosin acetate (VII; R = H) made a contribution of +60 $[M]_D$ units. The analogous contributions for the groups OAc and OBz [based on the newly prepared benzoate (VII; R = Bz)] can be calculated to be +35° and +206°. Prior correlation [10] requires that, if the 10-methyl group is β, then the 1-hydroxyl group in (VII; R = H) must be α in order that these contributions to the $[M]_D$ shall pertain. The 1-hydroxyl group can only be both equatorial and α if the ring fusion of the decalin system is *cis*. The stereochemistry at positions 1, 5, and 10 of cyclopyrethrosin (VI; R = H) is thus established.

The configurations at positions 7 and 8 were next investigated. For this purpose the ketol (VIII) was converted into its benzoate which was then pyrolysed in the gas phase under (unimolecular) *cis*-elimination conditions.[11] This gave an olefin which showed three vinyl hydrogen atoms on examination by nuclear magnetic resonance.* It must, therefore, be formulated as (XXII). There is adequate precedent [11,12] to suggest that such a clear

* We are much indebted to Dr. L. M. Jackman of this Department for the measurement and for helpful discussion.

[9] Barton, *Experientia*, 1950, **6**, 316; Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1952, **74**, 2694.
[10] Klyne and Stokes, *J.*, 1954, 1979.
[11] Barton, *J.*, 1949, 2174.
[12] Barton and Rosenfelder, *J.*, 1949, 2459.

elimination away from position 7 is only possible if the 7-hydrogen atom and the 8-hydroxyl group of (VIII) are *trans* to each other.

The formation of an 8-epi-lactone (VII; R = Ac) has already been described above. The formation of both 8-lactones is only possible, chair conformations being accepted, if the $C_{(7)}$-side-chain is equatorial and thus β as in all other sesquiterpenoid lactones whose stereochemistry at this centre has been established.

The results described in the present paper could, in principle, give information about the stereochemistry at position 4 in compound (XVIII; R = Ac) and its dihydro-derivative (XXIII). Dehydration of both of these with thionyl chloride–pyridine furnished exclusively the endocyclic olefins. Analogy [13] suggests that this is only possible if the 4-hydroxyl group is axial; if a chair conformation is retained this hydroxyl group would then be α in orientation. With this fact and with the established stereochemical configurations (see above) in mind one can deduce the configuration of the endocyclic ethylenic linkage of pyrethrosin provided, of course, that the acid-catalysed cyclisations are truly stereospecific.[14] Thus a 4α-hydroxyl group in (XVIII; R = Ac) or in (XXIII) would indicate a *cis*-configuration, a 4β-hydroxyl group would indicate a *trans*-configuration for the double bond. In fact, we do not consider that a final conclusion can be reached with the evidence available. In an earlier paper [1] we showed that the thionyl chloride–pyridine dehydration of the ketone (XIX) gave exclusively the exocyclic olefin in spite of the fact that the 4-hydroxyl group is of the same configuration as in (XVIII; R = Ac) and (XXIII). Since a ketone group is more likely to cause conformational anomalies and electronic disturbance than a non-enolic acetoxyl group we believe that the results of the present paper may have more significance than those reported earlier.[1] We, therefore, favour, but with considerable reserve, a *cis*-configuration for the endocyclic linkage of pyrethrosin [see (II)]. The configuration of the centre of asymmetry at position 6 is at present unknown.

We describe in the Experimental section a convenient isomerisation of the ketone (XI; R = Ac) to its conjugated form (XXIV), and hydrogenation of the latter to the saturated derivative (XXV).

Experimental

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$, ultraviolet absorption spectra to EtOH solutions, and infrared absorption spectra to Nujol mulls. For chromatographic elutions the term " light petroleum " refers to the fraction of b. p. 40—60°; for all other purposes this term implies the fraction of b. p. 60—80°. The alumina for chromatography was acid-washed, neutralised, and standardised according to Brockmann's method.[15] Silica gel for chromatography was supplied by Messrs. B.D.H. Microanalyses were carried out by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their respective associates.

Tetrahydropyrethrosin (III).—Pyrethrosin (4 g.) in ethyl acetate (150 ml.) was hydrogenated over platinum oxide (2 g.) until saturated. On digestion with ether the product gave in poor yield *tetrahydropyrethrosin* (III). Recrystallised from ethyl acetate–light petroleum this had m. p. 130—131°, $[\alpha]_D$ −44° (*c* 1·07), $\lambda_{max.}$ 208 mμ (ε 400) (Found: C, 66·0; H, 8·6. $C_{17}H_{26}O_5$ requires C, 65·8; H, 8·4%). Schechter and Haller [16] describe a tetrahydropyrethrosin of m. p. 231—232°.

Isotetrahydropyrethrosin (IV).—Tetrahydropyrethrosin (2·5 g.) in dry benzene (2·0 ml.) was treated with boron trifluoride–ether complex (7·0 ml.) and left overnight at 0°. The product was filtered in benzene–ether (1 : 1) through silica gel (31 g.). Crystallisation from ethyl acetate–light petroleum then afforded *isotetrahydropyrethrosin* (IV), m. p. 210—212°, $[\alpha]_D$ +23° (*c* 1·00) (Found: C, 66·1; H, 8·1. $C_{17}H_{26}O_5$ requires C, 65·8; H, 8·4%). The compound gave a positive Zimmermann test.

[13] Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.
[14] Stadler, Eschenmoser, Schinz, and Stork, *Helv. Chim. Acta*, 1957, **40**, 2191.
[15] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.
[16] Schechter and Haller, *J. Amer. Chem. Soc.*, 1939, **61**, 1607.

Characterisation of β-Methyladipic Acid as an Oxidation Product of Tetrahydropyrethrosin.—(*a*) β-Methyladipic acid (500 mg.) (kindly supplied by Dr. J. A. Elvidge, Imperial College) was ground with calcium hydroxide (600 mg.) and a few drops of water in a mortar to furnish a slurry. This was dried in a desiccator, powdered, and pyrolysed at 350—400° in a U-tube in a slow stream of nitrogen. The gas stream was passed into aqueous-ethanolic 2,4-dinitrophenylhydrazine. The precipitate formed was collected and chromatographed over bentonite–Celite.[17] Elution with chloroform and crystallisation from ethyl acetate–light petroleum furnished racemic 3-*methylcyclopentanone* 2,4-*dinitrophenylhydrazone*, m. p. 117—119° (Found: C, 51·8; H, 5·0; N, 20·7. $C_{12}H_{14}N_4O_4$ requires C, 51·8; H, 5·1; N, 20·2%).

(*b*) Tetrahydropyrethrosin (total hydrogenation product; 1·0 g.) was refluxed with aqueous chromic–sulphuric acid [75 ml.; solution prepared by dissolving chromium trioxide (33 g.) in water (200 ml.) and concentrated sulphuric acid (20 ml.)] for 105 min. The excess of chromic acid was destroyed with sulphur dioxide, and the solution saturated with sodium sulphate and then continuously extracted for 15 hr. with chloroform. This gave a gum (367 mg.). Paper chromatography on Whatman No. 1 paper, development with propan-1-ol (25 ml.)–2N-aqueous ammonia (7 ml.), and spraying with Bromocresol Green in ethanol–formaldehyde [18] showed the presence of β-methyladipic acid (R_F 0·19). The product (350 mg.) was ground with calcium hydroxide (420 mg.), then pyrolysed and further processed as described under (*a*) above. This gave partly racemic 3-methylcyclopentanone 2,4-dinitrophenylhydrazone, m. p. 114—124°, $[\alpha]_D$ −9° (*c* 0·45) (Found: C, 51·4; H, 5·1; N, 20·5%), undepressed in m. p. on admixture with racemic material as described under (*a*) and of identical infrared spectrum ($CHCl_3$ solution). For comparison, pulegone was oxidised as under (*b*) to give (+)-β-methyladipic acid which on cyclisation gave (+)-3-methylcyclopentanone 2,4-dinitrophenylhydrazone, m. p. 137—139°, $[\alpha]_D$ +35° (*c* 0·88), with an identical infrared spectrum (in $CHCl_3$) with that of the materials described under (*a*) and (*b*). The (+)- and (±)-2,4-dinitrophenylhydrazones were mixed in such proportions as to give a product of $[\alpha]_D$ +9°. This had the same m. p. as the material described under (*b*).

Hydrolysis of 6-*Acetoxy*-1-*oxoeudesm*-3-*en*-8,12-*olide* (XI; R = Ac).—The acetoxy-ketone (4·0 g.) in ethanol (20 ml.) was added to aqueous 0·8N-sodium hydroxide (120 ml.) previously heated on the steam-bath to 90° and the heating was continued for 15 min. After rapid cooling, the solution was acidified with aqueous 2N-sulphuric acid and left at room temperature overnight. Thorough extraction with chloroform afforded a gum which, on digestion with ethyl acetate, gave 8-hydroxy-1-oxoeudesm-3-en-6,12-olide (17%), m. p. (from ethyl acetate–ethanol–chloroform) 260—265° (Barton and de Mayo [1] recorded m. p. 255—260°). The residual material was chromatographed over silica to give 6-hydroxy-1-oxoeudesm-3-en-8,12-olide, m. p. 169—172°.

8-Hydroxy-1-oxoeudesm-3-en-6,12-olide (34 mg.) in " AnalaR " acetone (4 ml.) and alcohol-free chloroform (1 ml.) was treated with 50% v/v sulphuric acid (1 ml.) previously mixed with chromium trioxide (9 mg.) in water (0·6 ml.) at room temperature for 10 min. Dilution with water and extraction into chloroform gave 1,8-*dioxoeudesm*-3-*en*-6,12-*olide* (X). Recrystallised from ethyl acetate–light petroleum this had m. p. 180° (decomp.), $[\alpha]_D$ +192° (*c* 0·70) (Found: C, 68·5; H, 6·7. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Treatment in ethanol solution with a drop of aqueous N-sodium hydroxide brought out a band, $\lambda_{max.}$ 305 mμ (ε 13,000), in agreement with the results of Barton and de Mayo.[1]

6-Hydroxy-1-oxoeudesm-3-en-8,12-olide, oxidised in the same way, gave a gum. This gave no ultraviolet maximum in ethanolic alkali near 300 mμ (cf. Barton and de Mayo [1]).

Methyl 6-*Acetoxy*-8-*hydroxy*-1-*oxoeudesm*-3-*en*-12-*oate* (XII; R = Me) *and Derived Compounds.*—6-Acetoxy-1-oxoeudesm-3-en-6,12-olide (XI; R = Ac) (339 mg.) was refluxed on the steam-bath for 30 min. with sodium hydrogen carbonate (95 mg.) in water (7 ml.) and ethanol (10 ml.). The solution was cooled and aqueous 0·1N-hydrochloric acid (10·6 ml.) was added slowly with agitation. Extraction into chloroform and evaporation at room temperature *in vacuo* gave a gum. This was treated with an excess of ethereal diazomethane. The product, crystallised from ethyl acetate–light petroleum, afforded *methyl* 6-*acetoxy*-8-*hydroxy*-1-*oxoeudesm*-3-*en*-12-*oate* (XII; R = Me), m. p. 162—164°, $[\alpha]_D$ +29° (*c* 1·10) (Found: C, 63·8; H, 7·6. $C_{18}H_{26}O_5$ requires C, 63·9; H, 7·7%). This ester (106 mg.) in acetic acid (15 ml.) containing sodium dichromate (120 mg.) was left at room temperature for 8 hr. Dilution with water,

[17] Elvidge and Whalley, *Chem. and Ind.*, 1955, 584.

[18] *Inter al.*, Duncan and Porteous, *Analyst*, 1953, **78**, 641; Isherwood and Hanes, *Biochem. J.*, 1953, **55**, 824; Reid and Lederer, *ibid.*, 1951, **50**, 60.

reduction of the excess of oxidant with sulphur dioxide, and extraction into chloroform furnished *methyl 6-acetoxy-1,8-dioxoeudesm-3-en-12-oate* (XIII). Recrystallised from ethyl acetate–light petroleum this had m. p. 134—136°, $[\alpha]_D$ −16° (*c* 1·27) (Found: C, 64·3; H, 7·6. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·2%). This diketone (32 mg.) in ethanol (1 ml.) was treated with aqueous N-sodium hydroxide (0·5 ml.) at room temperature [ultraviolet control of band at 305 mμ (ε 12,000)]. After 3 min. 2,4-dinitrophenylhydrazine (63 mg.) in aqueous 6N-sulphuric acid (6 ml.) was added and the suspension heated on the steam-bath for 4·5 hr. The precipitate was collected and chromatographed over bentonite–Celite. Elution with chloroform–ethanol (14 : 1) gave a crystalline acid which on treatment with excess of ethereal diazomethane, afforded the bis-2,4-dinitrophenylhydrazone of methyl 1,8-dioxoeudesma-4,6-dien-12-oate identical (m. p., mixed m. p., crystal form, $[\alpha]_D$, ultraviolet and infrared spectra) with authentic material obtained earlier [1] from ψ-santonin.

Methyl 1,6-Diacetoxy-8-hydroxyeudesm-3-en-12-oate (XIV; R = H) *and Derived Compounds.*—1,6-Diacetoxyeudesm-3-en-8,12-olide (469 mg.) in water (10 ml.) and ethanol (7 ml.) was refluxed on the steam-bath with sodium hydrogen carbonate (114 mg.) for 1 hr. The solution was cooled and neutralised with aqueous 0·1N-hydrochloric acid (10 ml.). Extraction into chloroform, careful evaporation, and methylation as above, gave methyl *1,6-diacetoxy-8-hydroxyeudesm-3-en-12-oate* (XIV; R = H). Recrystallised from ethyl acetate–light petroleum this had m. p. 135—137°, $[\alpha]_D$ −3° (*c* 1·00) (Found: C, 62·7; H, 8·1; Ac, 23·6. $C_{20}H_{30}O_7$ requires C, 62·8; H, 7·9; Ac, 22·6%). This compound (74 mg.) was left at room temperature for 8 hr. with acetic acid (9 ml.) containing sodium dichromate (54 mg.). Working up as in the section above and crystallisation from ethyl acetate–light petroleum gave *methyl 1,6-diacetoxy-8-oxoeudesm-3-en-12-oate* (XV), m. p. 113—116°, $[\alpha]_D$ −19° (*c* 0·69) (Found: C, 63·3; H, 7·6; Ac, 22·0. $C_{20}H_{28}O_7$ requires C, 63·1; H, 7·5; Ac, 22·6%). On addition of a drop of aqueous N-sodium hydroxide to an ethanolic solution the usual band at 305 mμ (ε 15,600) appeared.

Methyl 1,6-diacetoxy-8-hydroxyeudesm-3-en-12-oate (157 mg.) in dry pyridine (2 ml.) containing toluene-*p*-sulphonyl chloride (351 mg.) was left at room temperature for 3 days. Crystallisation of the product from ethyl acetate–light petroleum gave the desired *toluene-p-sulphonate* (XIV; R = toluene-*p*-sulphonyl), m. p. 156—158°, $[\alpha]_D$ +25° (*c* 1·10) (Found: C, 60·2; H, 7·0. $C_{27}H_{36}O_9S$ requires C, 60·4; H, 6·7%). This toluene-*p*-sulphonate (99 mg.) in pyridine (7 ml.) containing piperidine (0·2 ml.) was refluxed overnight. Crystallisation of the product from ethyl acetate–light petroleum gave *1,6-diacetoxyeudesm-3-en-8α,12-olide*, m. p. 168—170°, $[\alpha]_D$ +92° (*c* 1·04) (Found: C, 65·4; H, 7·4. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%). The compound showed an infrared band at 1770 cm.$^{-1}$ (γ-lactone) and gave a pronounced m. p. depression on admixture with dihydrocyclopyrethrosin acetate of m. p. 183—185°.[1]

6-Acetoxy-1,8-dihydroxyeudesma-3,11(13)-dien-12-oic Acid (XVI; R = R′ = H, R″ = Ac) *and Related Compounds.*—(*a*) Pyrethrosin (1 g.) in ethanol (40 ml.) and water (20 ml.) was heated on the steam-bath for 1·5 hr. with saturated aqueous sodium hydrogen carbonate (30 ml.). The solution was acidified with 2N-hydrochloric acid and evaporated to 4 ml. on the steam-bath *in vacuo*. Extraction with chloroform gave a gum which was chromatographed over silica gel (7 g.). Elution with ether and crystallisation from ethanol–light petroleum gave *6-acetoxy-1,8-dihydroxyeudesma-3,11(13)-dien-12-oic acid* (XVI; R = R′ = H, R″ = Ac), m. p. 223—226°, $[\alpha]_D$ +32° (*c* 1·07 in EtOH) (Found: C, 62·8; H, 7·6; Ac, 13·6. $C_{17}H_{24}O_6$ requires C, 63·0; H, 7·5; Ac, 13·3%). Treatment with pyridine–acetic anhydride overnight at room temperature furnished *1,6,8-triacetoxyeudesma-3,11(13)-dien-12-oic acid* (XVI; R = R′ = R″ = Ac). Recrystallised from ethyl acetate–light petroleum this had m. p. 176—178°, $[\alpha]_D$ +33° (*c* 0·52) (Found: C, 61·7; H, 6·9; Ac, 32·6. $C_{21}H_{28}O_8$ requires C, 61·7; H, 6·9; Ac, 31·6%). This triacetate (50 mg.) in chloroform (20 ml.) was treated with ozone at −65° for 1·5 hr. Decomposition of the ozonide with water and steam-distillation into aqueous dimedone gave the formaldehyde derivative (35 mg.), identified by m. p. and mixed m. p. The corresponding control gave less than 3 mg. of this derivative.

(*b*) Pyrethrosin (1 g.) in ethanol (35 ml.) and water (25 ml.) was refluxed on the steam-bath for 3·5 hr. with saturated aqueous sodium hydrogen carbonate (25 ml.). The solution was concentrated *in vacuo* to 50 ml. and filtered through Amberlite I.R.-120 (50 g.; acid form). The column was washed with water (500 ml.), and the combined eluates were evaporated to a gum. A portion (65 mg.) was heated with N-hydrochloric acid (6 ml.) on the steam-bath for 10 min. ($[\alpha]_D$ change from +16° to +40°). Concentration at room temperature *in vacuo* and ether

extraction gave 6-acetoxy-1,8-dihydroxyeudesma-3,11(13)-dien-12-oic acid identical with the material described under (*a*) above.

(*c*) 1,6-Diacetoxyeudesma-3,11(13)-dien-8,12-olide (cyclopyrethrosin acetate) (VI; R = Ac) (300 mg.) in ethanol (12 ml.) and water (10 ml.) was refluxed on the steam-bath for 1 hr. with saturated aqueous sodium hydrogen carbonate solution (8 ml.). Filtration through Amberlite IR-120 (15 g.; acid form) and processing as under (*b*) gave 6-acetoxy-1,8-dihydroxyeudesma-3,11(13)-dien-12-oic acid, identical with material described under (*a*) above. The identity was confirmed by acetylation to the 1,6,8-triacetate.

(*d*) 1,6-Diacetoxyeudesma-3,11(13)-dien-8,12-olide (VI; R = Ac) (319 mg.) in ethanol (9 ml.) and water (15 ml.) containing sodium hydrogen carbonate (100 mg.) was refluxed on the steam-bath for 2 hr. The solution was concentrated *in vacuo*, acidified with 2N-hydrochloric acid, and extracted with chloroform, to furnish 1,6-*diacetoxy*-8-*hydroxyeudesma*-3,11(13)-*dien*-12-*oic acid* (XVI; R = R″ = Ac, R′ = H) (105 mg.). Recrystallised from ethyl acetate–light petroleum this had m. p. 188—201°, $[\alpha]_D$ +39° (*c* 0·62) (Found: C, 62·7; H, 6·9; Ac, 23·1. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·1; Ac, 23·4%). Acetylation in the usual way gave the 1,6,8-triacetate described under (*a*). The 1,6-diacetoxy-acid (240 mg.), on treatment with excess of diazomethane, gave a neutral gum. This, left for 10 hr. in acetic acid (30 ml.) containing sodium dichromate (180 mg.), afforded *methyl* 1,6-*diacetoxy*-8-*oxoeudesma*-3,11(13)-*dien*-12-*oate* (XVII), m. p. 165—169° (from ethyl acetate–light petroleum), $[\alpha]_D$ +3° (*c* 0·86) (Found: C, 63·2; H, 7·0. $C_{20}H_{26}O_7$ requires C, 63·5; H, 7·0%). Addition of one drop of aqueous N-sodium hydroxide to an ethanolic solution gave the usual band at 305 mμ (ε 11,300).

6-*Acetoxy*-1,4-*dihydroxyeudesm*-11(13)-*en*-8,12-*olide* (XVIII; R = H) *and Derivatives.*—Pyrethrosin (250 mg.) in chloroform (4 ml.; ethanol-free) and dry benzene (15 ml.) was kept at room temperature with boron trifluoride–ether complex (1 ml.) for 7 min. The resultant gel was treated with excess of aqueous sodium hydrogen carbonate, then extracted into chloroform, and the product crystallised from ethyl acetate–light petroleum to furnish 6-*acetoxy*-1,4-*dihydroxyeudesm*-11(13)-*en*-8,12-*olide* (XVIII; R = H), m. p. 190—195°, $[\alpha]_D$ −46° (*c* 1·00) (Found: C, 63·0; H, 7·2. $C_{17}H_{24}O_6$ requires C, 63·0; H, 7·5%). Treatment with pyridine–acetic anhydride overnight at room temperature gave 1,6-*diacetoxy*-4-*hydroxeudesm*-11(13)-*en*-8,12-*olide* (XVIII; R = Ac), m. p. 167—169° (from ethyl acetate–light petroleum), $[\alpha]_D$ −38° (*c* 1·10) (Found: C, 62·6; H, 7·5; Ac, 23·7. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·2; Ac, 23·4%).

6-Acetoxy-1,4-dihydroxyeudesm-11(13)-en-8,12-olide (135 mg.) in acetic acid (40 ml.) containing sodium dichromate (120 mg.) was kept at room temperature for 4·5 hr. (optimum time). Crystallisation of the product from ethyl acetate–light petroleum gave 6-acetoxy-4-hydroxy-1-oxoeudesm-11(13)-en-8,12-olide, identical with material prepared earlier.[1] Hydrogenation of this compound, as described earlier, and the subsequent dehydration with thionyl chloride and pyridine to give the exocyclic methylene compound, were also confirmed.

The acetoxy-diol was also treated with acetic anhydride and toluene-*p*-sulphonic acid as in the cyclisation of pyrethrosin by these reagents.[1] The product was identified as cyclopyrethrosin acetate (VI; R = Ac).

1,6-Diacetoxy-4-hydroxyeudesm-11(13)-en-8,12-olide (XVIII; R = Ac) (600 mg.) in ethyl acetate (10 ml.) was hydrogenated over 10% palladised charcoal (200 mg.). One mol. of hydrogen was rapidly absorbed. Crystallisation of the product from ethyl acetate–light petroleum gave 1,6-*diacetoxy*-4-*hydroxyeudesman*-8,12-*olide*, m. p. 210—212°, $[\alpha]_D$ +24° (*c* 1·08) (Found: C, 62·1; H, 7·6. $C_{19}H_{28}O_7$ requires C, 61·9; H, 7·7%). This diacetate (109 mg.) in pyridine (5 ml.) was treated at 0° with thionyl chloride (0·5 ml.) for 5 min. The solution was poured into ice and excess of dilute hydrochloric acid, and the product was extracted into chloroform and crystallised from ethyl acetate–light petroleum to give 1,6-diacetoxyeudesm-3-en-8,12-olide (dihydrocyclopyrethrosin acetate) identical with material described earlier.[1]

8-*Benzoyloxy*-1-*oxoeudesm*-3-*en*-6,12-*olide and its Pyrolysis.*—8-Hydroxy-1-oxoeudesm-3-en-6,12-olide (300 mg.) in dry pyridine (4 ml.) was treated with benzoyl chloride (1 ml.) at room temperature for 40 hr. Filtration of the product through alumina (Grade V) in benzene–chloroform and crystallisation from ethyl acetate–light petroleum gave 8-*benzoyloxy*-1-*oxoeudesm*-3-*en*-6,12-*olide*, m. p. 231—232°, $[\alpha]_D$ +213° (*c* 1·33) (Found: C, 71·8; H, 6·7. $C_{22}H_{24}O_5$ requires C, 71·7; H, 6·6%).

The pyrolysis of this benzoate was carried out as described [19] for an analogous elimination.

[19] Barton and de Mayo, *J.*, 1954, 887.

The benzoate (450 mg.) was pyrolysed at 1 mm., the temperature of the empty tube being 550—580°. The product, in benzene–chloroform (1 : 1; 10 ml.), was filtered through alumina (grade III; 5 g.). Removal of the solvent and crystallisation from benzene–light petroleum (seeding with the original benzoate) afforded some unchanged starting material (210 mg.). Crystallisation of the remaining material from ethyl acetate–light petroleum furnished 1-*oxo-eudesma*-3,8-*dien*-6,12-*olide* (XXII) (55 mg.) as prisms, m. p. 168—170°, $[\alpha]_D$ +310° (*c* 1·02) (Found: C, 72·8; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

Derivatives of 6-*Acetoxy*-1-*hydroxyeudesm*-3-*en*-8,12-*olide* (VII; R = H).—(*a*) The acetoxy-alcohol (116 mg.) in pyridine (0·5 ml.) and acetic anhydride (0·2 ml.) was left at room temperature overnight. Crystallisation of the product from ethyl acetate–light petroleum gave back 1,6-diacetoxyeudesm-3-en-8,12-olide (dihydrocyclopyrethrosin diacetate).

(*b*) The acetoxy-alcohol (1·17 g.) in pyridine (15 ml.) and benzoyl chloride (2·5 ml.) was kept at room temperature for 40 hr. Crystallisation of the product from ethyl acetate–light petroleum afforded 6-*acetoxy*-1-*benzoyloxyeudesm*-3-*en*-8,12-*olide* (VII; R = Bz), m. p. 193—195°, $[\alpha]_D$ +131° (*c* 0·70) (Found: C, 69·9; H, 6·7. $C_{24}H_{28}O_6$ requires C, 69·9; H, 6·8%).

(*c*) The acetoxy-alcohol (156 mg.) in pyridine (5 ml.) containing toluene-*p*-sulphonyl chloride (415 mg.) was kept at room temperature for 3 days. Crystallisation of the product from ethyl acetate–light petroleum gave 6-*acetoxy*-1-*toluene*-p-*sulphonyloxyeudesm*-3-*en*-8,12-*olide* (VII; R = toluene-*p*-sulphonyl) (161 mg.), m. p. 175—176°, $[\alpha]_D$ +70° (*c* 0·44) (Found: C, 62·3; H, 6·4. $C_{24}H_{30}O_7S$ requires C, 62·3; H, 6·6%).

(*d*) The acetoxy-alcohol (148 mg.) in pyridine (5 ml.) containing methanesulphonyl chloride (0·5 ml.) was left overnight at room temperature. Crystallisation of the product from ethyl acetate–light petroleum furnished 6-*acetoxy*-1-*methanesulphonyloxyeudesm*-3-*en*-8,12-*olide* (VII; R = methanesulphonyl) (143 mg.), m. p. 169—170°, $[\alpha]_D$ +75° (*c* 1·10) (Found: C, 56·1; H, 6·6. $C_{18}H_{26}O_7S$ requires C, 56·0; H, 6·8%).

6-*Acetoxyguaia*-3,10(14)-*dien*-8,12-*olide* (XX).—6-Acetoxy-1-toluene-*p*-sulphonyloxyeudesm-3-en-8,12-olide (320 mg.) in collidine (5 ml.) was heated in a sealed tube at 210° overnight. Crystallisation of the product from carbon tetrachloride–light petroleum gave 6-*acetoxyguaia*-3,10(14)-*dien*-8,12-*olide* (XX) (109 mg.), m. p. 156—157°, $[\alpha]_D$ +60° (*c* 1·07) (Found: C, 70·5; H, 8·1. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%). Treatment of the corresponding methanesulphonate in the same way also afforded this diene in the same yield.

Treatment of the diene (34 mg.) in chloroform (11 ml.) with a three-fold excess of perphthalic acid for 17 hr. at room temperature gave (1·05 equiv. uptake) 6-*acetoxy*-10(14)-*epoxyguai*-3-*en*-8,12-*olide*. Recrystallised from ethyl acetate–light petroleum this had m. p. *ca.* 170°, $[\alpha]_D$ +43° (*c* 0·33) (Found: C, 67·0; H, 7·3. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%).

6-*Acetoxyeudesm*-3-*en*-8,12-*olide* (XXI).—6-Acetoxy-1-oxoeudesm-3-en-8,12-olide (XI; R = Ac) (122 mg.) was treated at room temperature for 1 hr. with ethanedithiol (0·2 ml.) and boron trifluoride–ether complex (0·2 ml.). The oily product was refluxed in dioxan (35 ml.) with Raney nickel (W4) (excess) for 20 hr. The excess of nickel was removed by filtration through Celite, and the dioxan evaporated *in vacuo*. Crystallisation of the product from ethyl acetate–light petroleum furnished 6-*acetoxyeudesm*-3-*en*-8,12-*olide* (XXI), m. p. 131—133°, $[\alpha]_D$ +80° (*c* 1·08) (Found: C, 69·8; H, 8·0. $C_{17}H_{24}O_4$ requires C, 69·8; H, 8·3%).

6-*Acetoxy*-1-*oxoeudesm*-2-*en*-8,12-*olide* (XXIV).—6-Acetoxy-1-oxoeudesm-3-en-8,12-olide (XI; R = Ac) (190 mg.) in acetic acid (8 ml.) was heated on the steam-bath with acetic anhydride (1 ml.) and aqueous 60% perchloric acid (15 min.). The product, chromatographed over silica (5 g.), and eluted with benzene, gave 6-*acetoxy*-1-*oxoeudesm*-2-*en*-8,12-*olide* (XXIV). Recrystallised from ethyl acetate–light petroleum this had m. p. 179—181°, $[\alpha]_D$ +200° (*c* 1·19), $\lambda_{max.}$ 226 mμ (ε 8700) (Found: C, 66·8; H, 7·1. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%). Hydrogenation of this compound (29 mg.) in ethyl acetate (7 ml.) over 5% palladised charcoal (90 mg.) gave (0·9 mol. uptake) 6-*acetoxy*-1-*oxoeudesman*-8,12-*olide* (XXV). Recrystallised from ethyl acetate–light petroleum this had m. p. 164—165°, $[\alpha]_D$ +60° (*c* 0·76) (Found: C, 66·5; H, 7·6. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·9%).

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