25. *Sesquiterpenoids. Part VIII.* The Constitution of Pyrethrosin.*

By D. H. R. Barton and P. de Mayo.

The monocarbocyclic sesquiterpenoid lactone pyrethrosin contains two ethylenic linkages, an acetate residue, and an oxide ring. It readily undergoes cyclisation reactions on chromic acid oxidation or on acid-catalysed acetylation. Cyclised pyrethrosin derivatives have been correlated with ψ-santonin. On the basis, mainly, of this correlation a constitution with a ten-membered carbon ring has been deduced for pyrethrosin.

The sesquiterpenoid lactone pyrethrosin, $C_{17}H_{22}O_5$, was first isolated by Thoms [1] from *Chrysanthemum cinerariaefolium*. Chemical studies of this interesting compound were initiated by Haller and his collaborators [2,3,4] with results which can be briefly summarised as follows. Pyrethrosin consumes two mols. of alkali, one for the opening of a lactone ring, the other for the hydrolytic removal of an acetate residue. Hydrogenation proceeds

* Part VII, *J.*, 1956, 142.

[1] Thoms, *Ber. deut. pharm. Ges.*, 1891, **1**, 241; see also Chou and Chu, *Chinese J. Physiol.*, 1934, **8**, 167.

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

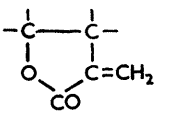
[3] Schechter and Haller, *J. Amer. Chem. Soc.*, 1939, **61**, 1607.

[4] *Idem, ibid.*, 1941, **63**, 3507.

in two stages: mild hydrogenation gives a dihydro-derivative, more vigorous hydrogenation a tetrahydro-compound. Oxidation with chromic acid gives a dehydropyrethrosin: although this might be taken as indicative of a secondary hydroxyl function, pyrethrosin could not be acetylated (cf. below). Zinc-dust distillation of pyrethrosin affords an azulene, pyrethrazulene, whose constitution is as yet uncertain.

Pyrethrosin is a by-product in the preparation of pyrethrum extract. Our own studies on this compound were only made possible through the generosity of Dr. William Mitchell of Messrs. Stafford Allen and Sons, Ltd., in providing us with an adequate supply of the purified material.

Pyrethrosin showed infrared bands (in Nujol) at 1760 (γ-lactone), 1735 and 1242 (true acetate residue; cf. ref. 5), and 1670 and 1650 cm.$^{-1}$ (two ethylenic linkages). Pyrethrosin showed no hydroxyl band in the infrared spectrum and could not be acetylated under basic conditions. The absence of the hydroxyl function was confirmed by equilibration with deuterium oxide, no deuterium being introduced into the molecule. Selective hydrogenation of pyrethrosin over palladised charcoal gave two stereoisomeric dihydro-derivatives, separated by chromatography. The minor product, *iso*dihydropyrethrosin, corresponded in m. p. to Rose and Haller's[2] dihydro-derivative. The complete purity of these two stereoisomers cannot be guaranteed as they are very difficult to separate, but this does not affect the structural argument with regard to pyrethrosin. The major hydrogenation product, dihydropyrethrosin, showed infrared bands (in Nujol) at 1773 (γ-lactone), 1726 and 1242 (acetate residue), and 1673 cm.$^{-1}$ (ethylenic linkage). A comparison of the ultraviolet absorption curves of pyrethrosin and dihydropyrethrosin established that an αβ-unsaturated lactone function had been saturated during hydrogenation. The ultraviolet absorption characteristics of *iso*dihydropyrethrosin showed the same relation to those of pyrethrosin. Ozonolysis of pyrethrosin gave formaldehyde as well as acetic acid and a little formic acid. Similar ozonolysis of dihydropyrethrosin furnished a negligible amount of formaldehyde. The lactonic function of pyrethrosin can therefore be defined as in partial formula (I).



(I)

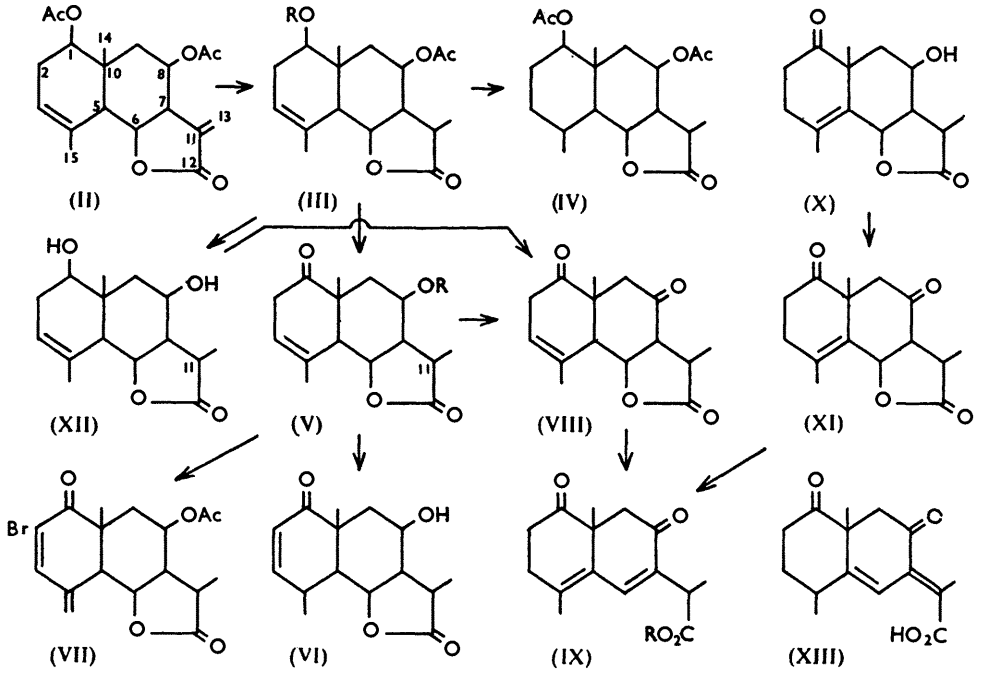
The most significant single experiment for the elucidation of the constitution of pyrethrosin resulted from an attempt to acetylate the compounds under acid conditions. Treatment with acetic anhydride and toluene-*p*-sulphonic acid under reflux gave in good yield a crystalline *cyclo*pyrethrosin acetate, $C_{19}H_{24}O_6$. Evidence outlined in the sequel shows this compound to have the constitution (II).*

The ultraviolet absorption spectrum of the cyclised product (II) showed the retention of the αβ-unsaturated lactone system; this was confirmed by the formation of formaldehyde on ozonolysis. Hydrogenation over palladised charcoal afforded a single dihydro-derivative (III; R = Ac), further hydrogenated to a saturated tetrahydro-compound (IV). The dihydro-compound did not give a significant amount of formaldehyde on ozonolysis. Treatment of the diacetate (III; R = Ac) with aqueous sodium hydrogen carbonate gave *cyclo*pyrethrosin (III; R = H), oxidised by chromic acid to the keto-acetate (V; R = Ac). This showed infrared bands (in chloroform) at 1777 (γ-lactone), 1727 and 1254 (acetate), 1710 (*cyclo*hexanone), and 1655 cm.$^{-1}$ (isolated ethylenic linkage). Its precursor (III; R = H) similarly showed bands (in chloroform) at 1770 (γ-lactone), 1727 and 1254 (acetate), and 1650 cm.$^{-1}$ (isolated ethylenic linkage). That the ethylenic linkage of the ketone (V; R = Ac) was placed βγ with respect to the keto-group was shown as follows.

* In the Experimental section we have used the santanic acid nomenclature which we originally proposed (quoted by Dauben and Hance [6]) and which has found some acceptance.[6, 7] For alternative nomenclature proposals see Cocker and Cahn,[8] and Abe and Sumi.[9]

[5] Barton and de Mayo, *J.*, 1956, 142.
[6] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[7] Kovács, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1956, **21**, 225.
[8] Cocker and Cahn, *Chem. and Ind.*, 1955, 384.
[9] Abe and Sumi, *ibid.*, 1955, 253.

First, treatment with base gave, amongst other products (see below), a conjugated αβ-unsaturated ketone (VI). Secondly, bromination followed by dehydrobromination furnished a conjugated bromo-dienone (VII) of characteristic ultraviolet absorption spectrum ($\lambda_{max.}$ 286 mμ, ε 15,200). The position of this maximum excludes a homoannular conjugated structure.



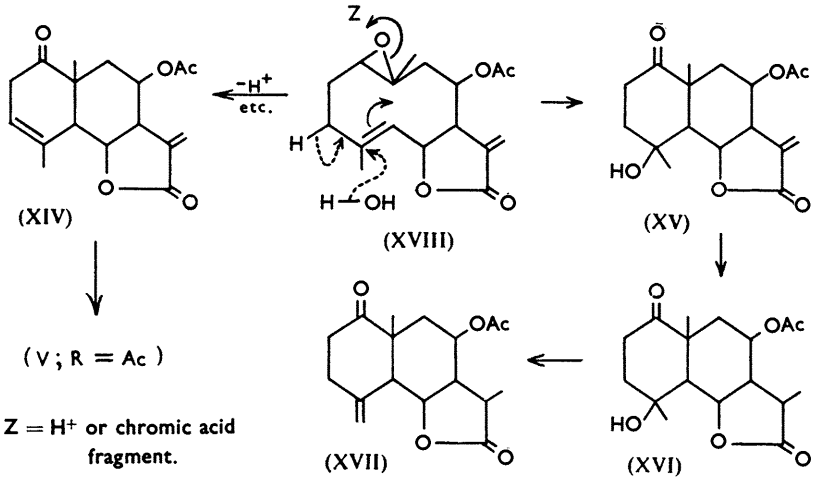
The other products formed by the action of base on the keto-acetate (V; R = Ac) were identified as the hydroxy-ketones (V; R = H) stereoisomeric at $C_{(11)}$. Acetylation of one of these hydroxy-ketone (m. p. 169—172°) gave back the starting acetate (V, R = Ac), whereas acetylation of its stereoisomer, m. p. 255—260°, gave a new acetate (V; R = Ac and with $C_{(11)}$ inverted). Both hydroxy-ketones on oxidation with chromic acid gave diketones (VIII). These were not isolated but both were characterised by the appearance of a strong absorption maximum at 305 mμ on very mild treatment with base. The more readily available hydroxy-ketone, m. p. 255—260°, was oxidised, then treated with alkali, and the product (IX; R = H), responsible for the 305 mμ absorption, was characterised as its highly crystalline bis-2 : 4-dinitrophenylhydrazone and as the methyl ester of the latter. The same bis-2 : 4-dinitrophenylhydrazone, characterised further as the methyl ester, was obtained by oxidation of ψ-santonin [6,10,11] (X) (for a summary of earlier work by Cocker and his collaborators see Simonsen and Barton [12]) to the diketone (XI), followed by treatment with base and then with the 2 : 4-dinitrophenylhydrazine reagent exactly as for the pyrethrosin derivatives. The bis-2 : 4-dinitrophenylhydrazone of the diketone (IX; R = H) was also obtained by hydrolysis of the diacetate (III; R = Ac) to the diol (XII) followed by conversion into the diketone (VIII) and processing as before. We do not consider that these identities necessarily provide information upon

[10] Chopra, Cocker, Goss, Edward, Hayes, and Hutchison, *J.*, 1955, 586; Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828; and references there cited.

[11] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 2451; Dauben, Hance, and Mayes, *ibid.*, p. 4609; and references there cited.

[12] Simonsen and Barton, " The Terpenes," Vol. III, Cambridge Univ. Press, 1952.

the $C_{(11)}$ configuration in the diol (XII) or provide a correlation between the $C_{(11)}$ configuration of ψ-santonin [10] and that of compounds described in the present paper, for acid-catalysed equilibration of the bis-2 : 4-dinitrophenylhydrazone of (IX; R = H) with that of (XIII) is possible. When coupled with evidence already cited as to the positions of the ethylenic linkages, the identities do, however, establish the constitution of *cyclo*pyrethrosin acetate as (II).



Reference has already been made to the experiments of Rose and Haller [2] on the chromic acid oxidation of pyrethrosin. We have found that this oxidation is strongly acid-catalysed but that it will proceed under very mild conditions, even with sodium dichromate in aqueous acetic acid at room temperature. Two crystalline products were isolated. The first of these, $C_{17}H_{20}O_5$, is very probably identical with Rose and Haller's dehydropyrethrosin : [2] it showed infrared bands (in Nujol) at 1777 (γ-lactone), 1723 and 1251 (acetate), 1703 (*cyclo*hexanone), and 1667 and 1650 cm.$^{-1}$ (ethylenic linkages) and had the ultraviolet absorption spectrum of an $\alpha\beta$-unsaturated lactone; on selective hydrogenation it gave the acetoxy-ketone (V; R = Ac) and must therefore be formulated as (XIV). The second oxidation product had the composition $C_{17}H_{22}O_6$ and showed infrared bands (in Nujol) at 1760 (γ-lactone), 1747 and 1215 (acetate), 1705 (*cyclo*hexanone), and 1677 cm.$^{-1}$ (ethylenic linkage); the ultraviolet absorption spectrum indicated the retention of the $\alpha\beta$-unsaturated lactone system; the compound must be formulated as the hydroxy-ketone (XV). Hydrogenation afforded a saturated product (XVI) smoothly dehydrated by thionyl chloride and pyridine to the exocyclic methylene compound (XVII).

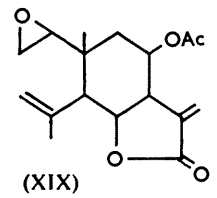
C-Me *Determinations.*

Compound	No. of *C*-Me	Found (%)	Theor. (%)
Pyrethrosin	3	14·05	14·7
1 : 8-Diacetoxysanta-3 : 11(13)-dien-6 : 12-olide (II)	4	16·15	17·2
1 : 8-Diacetoxysant-3-en-6 : 12-olide (III)	5	18·8	21·45
8-Acetoxy-1-oxosanta-3 : 11(13)-dien-6 : 12-olide (XIV)	3	14·8	14·8
8-Acetoxy-1-oxosant-3-en-6 : 12-olide (V; R = Ac)	4	18·3	19·6
8-Acetoxy-4-hydroxy-1-oxosant-11(13)-en-6 : 12-olide (XV)	3	13·35	14·0
8-Acetoxy-4-hydroxy-1-oxosantan-6 : 12-olide (XVI)	4	18·7	18·5
8-Acetoxy-1-oxosant-4(15)-en-6 : 12-olide (XVII)	3	14·15	14·7

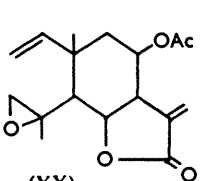
In agreement with its formulation the latter showed infrared bands (in Nujol) at 1770 (γ-lactone), 1723 and 1254 (acetate), 1707 (*cyclo*hexanone), and 1647 and 890 cm.$^{-1}$ (exocyclic methylene). Also Mr. J. M. L. Cameron kindly determined the *C*-Me values for many of the compounds described in this paper (see Table); in so far as all determinations

are in excellent agreement with the constitutions proposed we direct attention only to the presence of three *C*-Me groups in (XV) and (XVII) and of four in (XVI). The direction of the elimination of water from the hydroxy-ketone (XVI) no doubt indicates that the hydroxyl group has the equatorial conformation.[13]

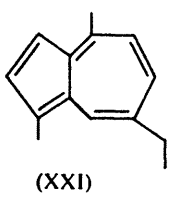
The constitution of pyrethrosin itself can now be discussed. Pyrethrosin contains one γ-lactone function, one acetate residue, and two ethylenic linkages. The remaining oxygen atom must be ethereal because it is not present as a hydroxyl or, from the infrared data, as a carbonyl group. From the composition $C_{17}H_{22}O_5$ the molecule must, therefore, be monocarbocyclic. The formation of *cyclo*pyrethrosin acetate (II) must, therefore, involve the opening of the ethereal ring by the acetylium ion and formation of a new carbon–carbon bond through interaction with an ethylenic linkage. The position of the additional acetate residue of *cyclo*pyrethrosin acetate (II) should indicate one terminus of the ethereal oxygen ring, whilst the position of the newly formed carbon–carbon bond should mark the other. The conditions of formation of the diacetate (II) are rather drastic and therefore might not justify firm conclusions. The conditions for the cyclisation during chromic acid oxidation are, in contrast, remarkably mild. They demonstrate that one terminus of the oxide ring must be at $C_{(1)}$. The ethylenic linkage which interacts with the opening oxide ring in the generation of the new carbon–carbon bond must be at $C_{(3)}$–$C_{(4)}$ or at $C_{(4)}$–$C_{(5)}$ in order to explain the formation of the 4-hydroxy-compound (XV). We are left then with two constitutions (XVIII) and (XIX) for pyrethrosin. Clearly the latter is



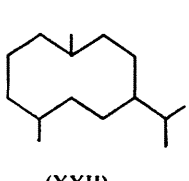
(XIX)



(XX)



(XXI)



(XXII)

unacceptable since dihydropyrethrosin contains no methylene grouping (=CH_2) and, further, there is no reason to suppose that a compound (XIX) would show the remarkable cyclisation on chromic acid oxidation. The facility of ring closure is reminiscent only of caryophyllene. On these grounds we prefer structure (XVIII) which offers an adequate explanation for all the known experimental facts.

A further alternative formula (XX) for pyrethrosin in which one terminus of the oxide ring is *not* indicated by the carbonyl group produced on oxidation is even less probable. The resultant tertiary alcohol, or chromate ester, would be required to undergo an elimination reaction under extremely mild conditions. The formula (XX) is decisively excluded by the absence of a methylene grouping (=CH_2) in dihydropyrethrosin acetate.

It will now be seen that the formation of an azulene from pyrethrosin [4] is a misleading indication of its carbon skeleton. A similar misleading observation was made in the early stages of our own work when we found that the major dehydrogenation product of dihydro-*cyclo*pyrethrosin acetate (II) is chamazulene (XXI).[14] Clearly the $C_{(1)}$ oxygenated function in the acetate (II) initiates a rearrangement during dehydrogenation, thus avoiding the relatively difficult elimination of the angular methyl group.

The constitution (XVIII) of pyrethrosin may be of some biogenetic significance [15] since if one writes a ten-membered carbon ring as in (XXII), it is possible by establishing different bonds across the ring to construct the carbon skeletons of most of the bicyclic sesquiterpenoids. The cyclisation reactions of pyrethrosin itself already illustrate this point experimentally.

[13] Barton, *Experientia*, 1955, Suppl. II, p. 121; Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.

[14] Meisels and Weizmann, *J. Amer. Chem. Soc.*, 1953, **75**, 3865; Šorm, Herout, and Takeda, *Chem. Listy*, 1954, **48**, 281; Novak, Šorm, and Sicher, *ibid.*, p. 1648.

[15] Cf. Ruzicka, *Experientia*, 1953, **9**, 357.

We are now working on the stereochemistry of the pyrethrosin molecule and on further aspects of its ready cyclisation.

Experimental

M. p.s marked (K) were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ are in $CHCl_3$; ultraviolet absorption spectra were determined in EtOH on the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his colleagues. The alumina for chromatography was acid-washed, neutralised, and standardised according to Brockmann's method.[16] Unless stated to the contrary the light petroleum used was of b. p. 40—60°. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates.

Pyrethrosin (XVIII).—Pure pyrethrosin, supplied by Dr. W. Mitchell, was unchanged after repeated crystallisation from ethanol, ethyl acetate, aqueous dioxan, or benzene–light petroleum. It collapsed to a glass at 198—200° if inserted into a tube at 180°, but did not become liquid below 360°. Similar behaviour was noted for all substances containing the conjugated exocyclic methylene group. In agreement with Rose and Haller,[2] pyrethrosin had $[\alpha]_D$ −31° (*c* 1·73). The identity of pyrethrosin used in our work was confirmed by direct comparison with a specimen kindly supplied by Professor N. L. Drake of the University of Maryland through the courtesy of Dr. H. L. Haller. Pyrethrosin gave no colour with tetranitromethane or in the Zimmermann test; it had $\lambda_{max.}$ 204 (ε 14,600), 210 (ε 12,200), 220 (ε 6000), and 230 mμ (ε 1700) (Found: C, 66·75; H, 7·35. Calc. for $C_{17}H_{22}O_5$: C, 66·6; H, 7·25%).

Ozonolysis of Pyrethrosin.—(*a*) Pyrethrosin (200 mg.) in chloroform (20 ml.; washed and dried) was ozonised at 0° for 1·5 hr. Decomposition of the ozonide with water, steam-distillation of the volatile acids, conversion into the *p*-bromophenacyl esters, and chromatography over alumina (5 g.; grade 4) gave *p*-bromophenacyl acetate (26 mg., 16%) and *p*-bromophenacyl formate (5 mg., 3%), both identified by m. p., mixed m. p., and infrared spectra. Boiling pyrethrosin with water for five times as long as required for the steam-distillation afforded (titration) no volatile acid.

(*b*) Pyrethrosin (46 mg.) was ozonised as under (*a*). Treatment of the distillate with dimedone (100 mg.) followed by removal of the chloroform gave the formaldehyde–dimedone compound (13·5 mg., 34%), identified by m. p. and mixed m. p.

Deuterium Equilibration.—Pyrethrosin (100 mg.) in pure dioxan (1·5 ml.) was treated with pure deuterium oxide (0·5 ml.) on the steam-bath for 5 min. Further addition of deuterium oxide (0·5 ml.) induced crystallisation. After cooling, the pyrethrosin was collected and thoroughly dried *in vacuo*. Combustion and deuterium analysis kindly carried out by Dr. G. Eglinton and his colleagues showed only 0·10% of D_2O in the water.

Hydrogenation of Pyrethrosin.—Pyrethrosin (294 mg.) in ethyl acetate (5 ml.) was hydrogenated over palladised charcoal (5%; 50 mg.) (uptake, 1 mol.). Chromatography of the product over alumina (10 g.; grade 4) afforded on elution with benzene–light petroleum (1 : 1) *dihydropyrethrosin*, m. p. 156—159°, $[\alpha]_D$ −23° (*c* 0·98) (Found: C, 66·35; H, 7·75. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%). Further elution with benzene furnished *iso*dihydropyrethrosin, m. p. 205—208°, $[\alpha]_D$ −76° (*c* 0·89), corresponding to the " dihydrochrysanthin," m. p. 205—208°, of Rose and Haller.[2] Both dihydro-compounds showed $\lambda_{max.}$ 205 mμ (ε 6200) and gave no colour with tetranitromethane. The difference curve between pyrethrosin and dihydropyrethrosin has λ 210 (ε 7500), 220 (ε 4500), 230 (ε 1400), and 240 mμ (ε 500), indicative of an αβ-unsaturated ester, acid, or lactone. Ozonolysis of dihydropyrethrosin (90 mg.) as above gave the formaldehyde–dimedone compound (5 mg., 6%), identified by m. p. and mixed m. p.

Hydrogenation of pyrethrosin in ethanol over platinum resulted in a rapid uptake of 2 mols. of hydrogen.

Cyclisation of Pyrethrosin.—Pyrethrosin was recovered unchanged after treatment with pyridine–acetic anhydride or refluxing acetic anhydride–anhydrous sodium acetate (1 hr.).

Pyrethrosin (500 mg.) in acetic anhydride (16 ml.) was refluxed with toluene-*p*-sulphonic acid for 1 hr. Decomposition of the excess of anhydride and isolation in the usual way followed by filtration of the product in benzene–light petroleum (7 : 3) through alumina (8 g.; grade 4) gave 1 : 8-*diacetoxysanta*-3 : 11(13)-*dien*-6 : 12-*olide* (cyclo*pyrethrosin acetate*) (II), m. p. *ca.* 175°, [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +60° (*c* 1·41), λ 205 (ε 9500), 210 (ε 8300), 220 (ε 3700), and 230 mμ (ε 900) (Found: C, 65·4; H, 7·15; Ac, 22·2. $C_{19}H_{24}O_6$

[16] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

requires C, 65·5; H, 6·95; Ac, 24·7%). It gave a yellow colour with tetranitromethane. Ozonolysis of the diacetate (100 mg.) in chloroform (20 ml.) at 0° for 3 hr., followed by steam distillation, etc., gave the formaldehyde–dimedone compound (31 mg., 37%) and the *p*-bromophenacyl esters of acetic acid (34 mg., 23%) and formic acid (4 mg., 6%).

1 : 8-*Diacetoxysant*-3-*en*-6 : 12-*olide* (III) *and its Derivatives*.—1 : 8-Diacetoxysanta-3 : 11(13)-dien-6 : 12-olide (94 mg.) in ethyl acetate (5 ml.) was hydrogenated over palladised charcoal (5%; 30 mg.) (1 mol. uptake), to give 1 : 8-*diacetoxysant*-3-*en*-6 : 12-*olide*, m. p. 183—185° [from ethyl acetate–light petroleum (b. p. 60—80°), $[\alpha]_D$ +74° (*c* 0·77) (Found : C, 65·25; H, 7·15. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%). Ozonolysis gave no significant quantity of formaldehyde. Hydrogenation of this compound (204 mg.) in acetic acid (5 ml.) over platinum (1 mol. uptake) gave 1 : 8-*diacetoxysantan*-6 : 12-*olide* (IV), m. p. 221—223° [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +24° (*c* 0·98) (Found : C, 64·7; H, 7·7. $C_{19}H_{28}O_6$ requires C, 64·75; H, 8·0%). The compound gave no colour with tetranitromethane.

1 : 8-Diacetoxysant-3-en-6 : 12-olide (350 mg.) in ethanol (20 ml.) and water (20 ml.) was heated on the steam-bath, and aqueous sodium hydrogen carbonate (saturated; 20 ml.) added. The heating was continued for 3 hr. Acidification and extraction with chloroform afforded 8-*acetoxy*-1-*hydroxysant*-3-*en*-6 : 12-*olide* (III; R = H) (280 mg.), m. p. 207—208° [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +95° (*c* 0·64) (Found : C, 66·25; H, 7·95. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%). Treatment of this hydroxy-acetate (165 mg.) with chromic acid in 0·05N-acetic acid (50 ml.) at room temperature for 30 min. (optimum time as determined by previous experiments) gave 8-*acetoxy*-1-*oxosant*-3-*en*-6 : 12-*olide* (V; R = Ac), m. p. 164—165° [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +123° (*c* 1·10) (Found : C, 66·8; H, 7·1. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%), which gave a positive Zimmermann test.

Chromic Acid Oxidation of Pyrethrosin.—(*a*) Pyrethrosin (39·6 mg.) in acetic acid containing chromic acid (0·07N; 15 ml.) consumed 4 equivs. of oxygen in less than 15 min. Pyrethrosin (56 mg.) in acetic acid containing sodium dichromate (0·25N; 10 ml.) consumed 2 equiv. in 3 hr.

(*b*) Pyrethrosin (100 mg.) in acetic acid containing sodium dichromate (0·1N; 20 ml.) was left overnight at room temperature (consumption of 1·6 equiv.). Isolation of the product in the usual way and chromatography over alumina (1·5 g.; grade 3) afforded, on elution with ether–benzene (1 : 4), 8-*acetoxy*-4-*hydroxy*-1-*oxosant*-11(13)-*en*-6 : 12-*olide* (XV), m. p. *ca.* 180—185° [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ −82° (*c* 0·96), $\lambda_{max.}$ 206 (ε 8100), 210 (ε 8000), 220 (ε 4000), and 230 mμ (ε 750) (Found : C, 63·0; H, 6·8. $C_{17}H_{22}O_6$ requires C, 63·35; H, 6·9%), which gave a positive Zimmermann test. Hydrogenation of this hydroxy-ketone (250 mg.) in ethyl acetate (5 ml.) over palladised charcoal (5%) (uptake of 1 mol.) gave 8-*acetoxy*-4-*hydroxy*-1-*oxosantan*-6 : 12-*olide* (XVI), m. p. 169—171° [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ −34° (*c* 1·07) (Found : C, 62·9; H, 7·45. $C_{17}H_{24}O_6$ requires C, 62·95; H, 7·45%).

(*c*) Pyrethrosin (117 mg.) in aqueous 20% v/v acetic acid containing sodium dichromate (0·08N) was left at room temperature for 16 hr. (consumption of 2 equiv. of oxygen). Chromatography over silica (3 g.) and elution with ether–benzene (9 : 1) gave, first, the hydroxy-ketone described under (*b*) (3 mg.) and then 8-acetoxy-1-oxosanta-3 : 11(13)-dien-6 : 12-olide (XIV) (7 mg.) (see below), identified by m. p. and mixed m. p.

(*d*) Pyrethrosin (2·7 g.) in 85% aqueous acetic acid containing sodium dichromate (180 ml.; 0·35N) was treated with 6N-sulphuric acid (70 ml.) (consumption of 2 equiv. of oxygen in 8 min. at room temperature). Chromatography over silica and elution with benzene–ether (19 : 1) gave 8-*acetoxy*-1-*oxosanta*-3 : 11(13)-*dien*-6 : 12-*olide* (XIV) (300 mg.), m. p. *ca.* 175° [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +103° (*c* 0·76), $\lambda_{max.}$ 208 (ε 8900), 210 (ε 8600), 220 (ε 3000), and 230 mμ (ε 300) (Found : C, 67·45; H, 6·5. $C_{17}H_{20}O_5$ requires C, 67·05; H, 6·65%). Hydrogenation of this keto-acetate (85 mg.) in ethyl acetate (5 ml.) over palladised charcoal (5%) gave 8-acetoxy-1-oxosant-3-en-6 : 12-olide, identical {m. p., mixed m. p., and rotation, $[\alpha]_D$ +126° (*c*, 0·97)} with material prepared as described above.

8-*Acetoxy*-1-*oxosant*-4(15)-*en*-6 : 12-*olide* (XVII).—8-Acetoxy-4-hydroxy-1-oxosantan-6 : 12-olide (65 mg.) in dry pyridine (5 ml.) was treated at 0° with thionyl chloride (0·4 ml.) for 5 min. Addition of water, extraction into chloroform, and working up in the usual way gave, after filtration in benzene–ether (9 : 1) through silica, 8-*acetoxy*-1-*oxosant*-4(15)-*en*-6 : 12-*olide*, m. p. 140—143° (from ethyl acetate–ether–light petroleum), $[\alpha]_D$ +64° (*c* 0·91) (Found : C, 66·7; H, 7·4. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%).

Hydrolysis of 8-*Acetoxy*-1-*oxosant*-3-*en*-6 : 12-*olide*.—(*a*) The ketone (64 mg.) in aqueous 1·0N-sodium hydroxide (2 ml.) was heated on the steam-bath for 15 min. Acidification, extraction with chloroform, chromatography over silica, and elution with benzene–ether (9 : 1) gave 8-*hydroxy*-1-*oxosant*-2-*en*-6 : 12-*olide* (VI), m. p. 164—165° [from ethyl acetate–light petroleum (b. p. 60—80°)] (depressed to 130—145° on admixture with starting material), $[\alpha]_D$ +142° (*c* 0·64), $\lambda_{max.}$ 230 mμ (ε 10,400) (Found : C, 67·9; H, 7·55. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). It should be noted that the position of the lactone ring is not proved and that, apart from analogy (see text), this compound could be the 6-hydroxy-8 : 12-olide. Elution with benzene–ether (7 : 3) gave 8-*hydroxy*-1-*oxo*-11-iso*sant*-3-*en*-6 : 12-*olide* (V), m. p. 255—260° (decomp.) [from ethyl acetate–light petroleum (b. p. 60—80°)], $[\alpha]_D$ +256° (*c* 0·82) (Found : C, 68·3; H, 7·35. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%), which showed no high-intensity selective ultraviolet absorption and with pyridine–acetic anhydride overnight at room temperature furnished the 8-*acetate*, m. p. 190—191° [from ethyl acetate–light petroleum (b. p. 60—80°)] $[\alpha]_D$ +234° (*c* 0·76) (Found : C, 66·35; H, 7·15. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%).

(*b*) In a similar experiment with 300 mg. of the ketone the total hydrolysis product was crystallised from ethyl acetate, whereby the very insoluble hydroxy-ketone, m. p. 255—260°, was readily removed. The residual material was chromatographed over silica. Elution with benzene–ether (4 : 1) gave 8-*hydroxy*-1-*oxosant*-3-*en*-6 : 12-*olide*, m. p. 169—172° [from ethyl acetate–light petroleum (b. p. 60—80°)] (mixed m. p. with starting material 135—140°), $[\alpha]_D$ +121° (*c* 0·93) (Found : C, 68·35; H, 7·4. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). The compound showed no high-intensity ultraviolet absorption and with pyridine–acetic anhydride gave back 8-acetoxy-1-oxosant-3-en-6 : 12-olide (m. p. and mixed m. p.).

8-*Acetoxy*-2-*bromo*-1-*oxosanta*-2 : 4(15)-*dien*-6 : 12-*olide* (VII).—8-Acetoxy-1-oxosant-3-en-6 : 12-olide (143 mg.) in chloroform (20 ml.) containing bromine (3 mol.) was left at room temperature for 1 hr. The solvent and excess of bromine were removed *in vacuo* and the residue refluxed with pyridine (5 ml.) for 1 hr. The product was filtered in benzene–ether (9 : 1) through alumina, to give 8-*acetoxy*-2-*bromo*-1-*oxosanta*-2 : 4(15)-*dien*-6 : 12-*olide*, m. p. 235—236° (decomp.) (from ethyl acetate–light petroleum), $[\alpha]_D$ +306° (*c* 1·94), $\lambda_{max.}$ 286 mμ (ε 15,200) (Found : C, 53·0; H, 4·85; Br, 20·7. $C_{17}H_{19}O_5Br$ requires C, 53·25; H, 5·0; Br, 20·85%).

1 : 8-*Dioxosant*-4-*en*-6 : 12-*olide* (XI) (cf. ref. 6) (with Dr. E. W. WARNHOFF).—ψ-Santonin (T. and H. Smith) (2·0 g.) in " AnalaR " acetic acid (25 ml.) was treated with chromium trioxide (600 mg.) at room temperature for 6 hr. Isolation of the product in the usual way gave 1 : 8-*dioxosant*-4-*en*-6 : 12-*olide* (1·04 g.), m. p. 134—135° (from chloroform–light petroleum), $[\alpha]_D$ −137° (*c* 1·65) (Found : C, 68·4; H, 7·2. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

1 : 8-*Dioxosanta*-4 : 6-*dienoic Acid Bis*-2 : 4-*dinitrophenylhydrazone* [cf. (IX; R = H)].—(*a*) 1 : 8-Dioxosant-4-en-6 : 12-olide (100 mg.) in 2N-sodium hydroxide (3 ml.) was left at room temperature for 3 min. (preliminary experiments with spectroscopic control had shown that this time was adequate). 2 : 4-Dinitrophenylhydrazine (150 mg.) in 6N-sulphuric acid (10 ml.) was added and the solution heated on the steam-bath for 1 hr. The dark red precipitate was collected and chromatographed over bentonite–Celite.[17] Elution with chloroform–ethanol (9 : 1) gave the *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 278—279° (decomp.) (260—265° K), $\lambda_{max.}$ 265 and 367 mμ (ε 25,000 and 42,500 respectively), $\lambda_{infl.}$ 320 mμ (ε 17,000), $[\alpha]_D$ +1550° ± 50° (*c* 0·047) (Found : C, 51·75; H, 4·45; N, 17·8. $C_{27}H_{26}O_{10}N_8$ requires C, 52·1; H, 4·2; N, 18·0%). The ultraviolet absorption curve, after subtraction of the curve for acetone 2 : 4-dinitrophenylhydrazone, showed $\lambda_{max.}$ 405 mμ (ε 27,000). Treatment in chloroform–methanol with ethereal diazomethane gave the *methyl ester*, m. p. 255—258° (decomp.) (K) (from ethyl acetate) (Found : OMe, 5·0; N, 17·6. $C_{28}H_{28}O_{10}N_8$ requires 1OMe, 4·85; N, 17·6%).

(*b*) 8-Hydroxy-1-oxo-11-*iso*sant-3-en-6 : 12-olide (75 mg.) in acetic acid (20 ml.) containing chromium trioxide (40 mg.) was left at room temperature for 1·5 hr. Working up in the usual way afforded a crude crystalline product showing no high-intensity ultraviolet absorption. Addition of aqueous 4N-sodium hydroxide (1 ml.) to the product in ethanol gave a spectrum showing $\lambda_{max.}$ 305 mμ (ε 12,000). Treatment of 8-hydroxy-1-oxosant-3-en-6 : 12-olide in the same way led to essentially the same spectrum. The product from the experiment in the 11-*iso*-series was then treated with 2 : 4-dinitrophenylhydrazine as in the procedure (*a*), to give 1 : 8-dioxosanta-4 : 6-dienoic acid bis-2 : 4-dinitrophenylhydrazone, identified by m. p., mixed m. p., rotation {($[\alpha]_D$ +1400° ± 200° (*c* 0·024)}, ultraviolet and infrared absorption spectra, and methylation to the methyl ester (m. p. and mixed m. p.)

[17] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.

(*c*) 1 : 8-Diacetoxysant-3-en-6 : 12-olide (530 mg.) was treated with aqueous 1·5N-sodium hydroxide (5 ml.) on the steam-bath for 1 hr. Acidification and extraction with chloroform gave 1 : 8-*dihydroxysant*-3-*en*-6 : 12-*olide* (XII) (solvated from aqueous ethanol), m. p. 100—120° with evolution of solvent, $[\alpha]_D$ +149° (*c* 0·78 in EtOH) (Found: C, 63·65; H, 8·8. $C_{15}H_{22}O_4,H_2O$ requires C, 63·35; H, 8·5%). This compound may have the 11-*iso*-configuration. The remaining material (400 mg.) in acetic acid (50 ml.) containing chromium trioxide (500 mg.) was left for 20 min. at room temperature. Isolation of the product and treatment with sodium hydroxide and then with 2 : 4-dinitrophenylhydrazine as detailed under (*a*) gave the same bis-2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p.).

Dehydrogenation of 1 : 8-*Diacetoxysant*-3-*en*-6 : 12-*olide*.—The diacetate (1·0 g.) was heated in portions (250 mg.) with an equal weight of palladised charcoal (10%) at 320° for 30 min. The product was extracted with light petroleum and filtered through alumina (grade 5). The azulene fraction (colour) was extracted into 90% phosphoric acid and then isolated by dilution and re-extraction into light petroleum. Conversion into the trinitrobenzene adduct gave the derivative of chamazulene, identified by m. p., mixed m. p., and absorption spectrum over the range 230—750 mμ.

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