682. *Photochemical Transformations. Part XIV.* Some Analogues of Isophotosantonic Lactone.*

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The previously discovered rearrangement of α-santonin to isophoto-α-santonic lactone has been shown to be a general phenomenon. β-Santonin, 6-epi-α-santonin, 6-epi-β-santonin, artemisin acetate, 6-epi-8-epiartemisin acetate, and 8-epiartemisin acetate all undergo the corresponding rearrangements. With the aid of *X*-ray crystallography the stereochemistry of this transformation has been elucidated. Differential hydrogenation or hydrogenolysis reactions in these compounds have been observed depending upon the quasi-equatorial or quasi-axial character of the alkyl-oxygen atom of the lactone ring.

Some years ago Barton, de Mayo, and Shafiq [1] reported that the rearrangement product of α-santonin (I),† produced by irradiation in aqueous acetic acid and generally known as " isophotosantonic lactone," has the constitution (II). We have been concerned, on the one hand, to generalise this reaction and to explore its usefulness in synthesis and, on the other, to determine the stereospecificity and stereochemistry of the change. The results reported in preliminary form [2] have shown that the rearrangement is indeed a general one in sesquiterpenoid chemistry, whilst an example in the steroid series has also been forthcoming.[3] The results described in the present paper give details of our work on analogues and derivatives of santonin. We have shown that the rearrangement is in every case highly stereospecific.

Irradiation of β-santonin [the 11-epimer of (I)], of 6-epi-α-santonin (XIX), and of 6-epi-β-santonin (XX) gave in each case one stereoisomer of isophoto-α-santonic lactone (II). In the sequel these compounds are assigned the stereochemistry shown in (VIII), (XIII), and (XV), respectively. None of the bonds attached to C-6, C-7, and C-11 in santonin and its epimers confers any absorption in the 300 mμ region of the ultraviolet spectrum and, therefore, these bonds cannot be altered in the rearrangement. The asymmetric centres at positions 1 and 10 are more difficult to define by ordinary chemical methods. The hydrogen at C-1 in compound (II) has been formulated as β on the basis

* Part XIII, *J.*, 1962, 1967.
† The configuration at C-11 is discussed below.

[1] Barton, de Mayo, and Shafiq, *J.*, 1957, 929.
[2] Barton, *Proc. Chem. Soc.*, 1958, 61; *Helv. Chim. Acta*, 1959, **42**, 2604.
[3] Barton and Taylor, *J.*, 1958, 2500.

of optical rotatory dispersion measurements [4] but, if the acid-catalysed rearrangement of lumisantonin to isophoto-α-santonic lactone involves inversion at every stage, then the stereochemistry of lumisantonin [5] would define the stereochemistry of isophoto-α-santonic lactone as that already written into (II). Clearly some more definitive evidence was needed.*

On hydrogenation isophoto-α-santonic lactone gave an " unstable " dihydro-derivative (V),[1] readily isomerised to a more stable isomer (VI; R = X = H). This more stable isomer was acetylated with sodium acetate–acetic anhydride, to give the derivative (VI; R = Ac, X = H) and then brominated to the monobromo-derivative (VI; R = Ac, X = Br). This compound crystallised well and was used by Asher and Sim [6] for an *X*-ray analysis. This defined completely the stereochemistry of the molecule as already written into (VI; R = Ac, X = Br). The stereochemistry of the precursor (V) is thus as indicated, and isophoto-α-santonic lactone (II) has, indeed, the " theoretical " stereochemistry. In addition, the *X*-ray work shows that the configuration at C-11 in (VI; R = Ac, X = Br) is α-methyl, and not β-methyl as generally accepted hitherto for α-santonin.[7,8] Reduction of the bromo-ketone (VI; R = Ac, X = Br) with chromous chloride gave back its precursor (VI; R = Ac, X = H). Epimerisation at C-11 does not, therefore, occur during bromination. Furthermore, hydrogenation of isophoto-β-santonic lactone gave, after epimerisation at C-4, the dihydro-derivative (VII). Acetylation of this compound gave an acetate which was not identical with the ketone (VI; R = Ac, X = H). Epimerisation at C-11 in the acetylation process is thus also excluded, and the configuration of α-santonin must be as written in the formulæ given in this paper. Interestingly enough,[7] treatment of dihydroisophoto-α-santonic lactone (VI; R = X = H) with potassium t-butoxide gave the β-santonin derivative (VII). We also prepared the *p*-bromophenylhydrazone of the ketone (VI; R = X = H) but, owing to twinning, it was not suitable for *X*-ray crystallography.

With the stereochemical problems finally settled it is now possible to discuss the further reactions of this group of compounds. Mild acid-catalysed dehydration of the keto-alcohol (VI; R = X = H) furnished an anhydro-compound assigned, on the basis of its ultraviolet and infrared spectra, the constitution (IX). Hydrogenation gave the saturated cyclopentanone (X), characterised as its 2,4-dinitrophenylhydrazone. Dehydration of the β-santonin derivative (VIII) with thionyl chloride gave the non-conjugated anhydro-derivative (XI); more vigorous acid-treatment gave the conjugated dienone (XII). The same dienone was formed by treating 6-epi-isophoto-β-santonic lactone (XV) under the same conditions. In the α-santonin series the same relations were observed. Acid-catalysed dehydration of isophoto-α-santonic lactone (II) gave the same conjugated dienone (XIV) as did isophoto-6-epi-α-santonic lactone (XIII). The dienone (XIV) was obtained earlier [1] as an oil, but we have now been able to crystallise it.

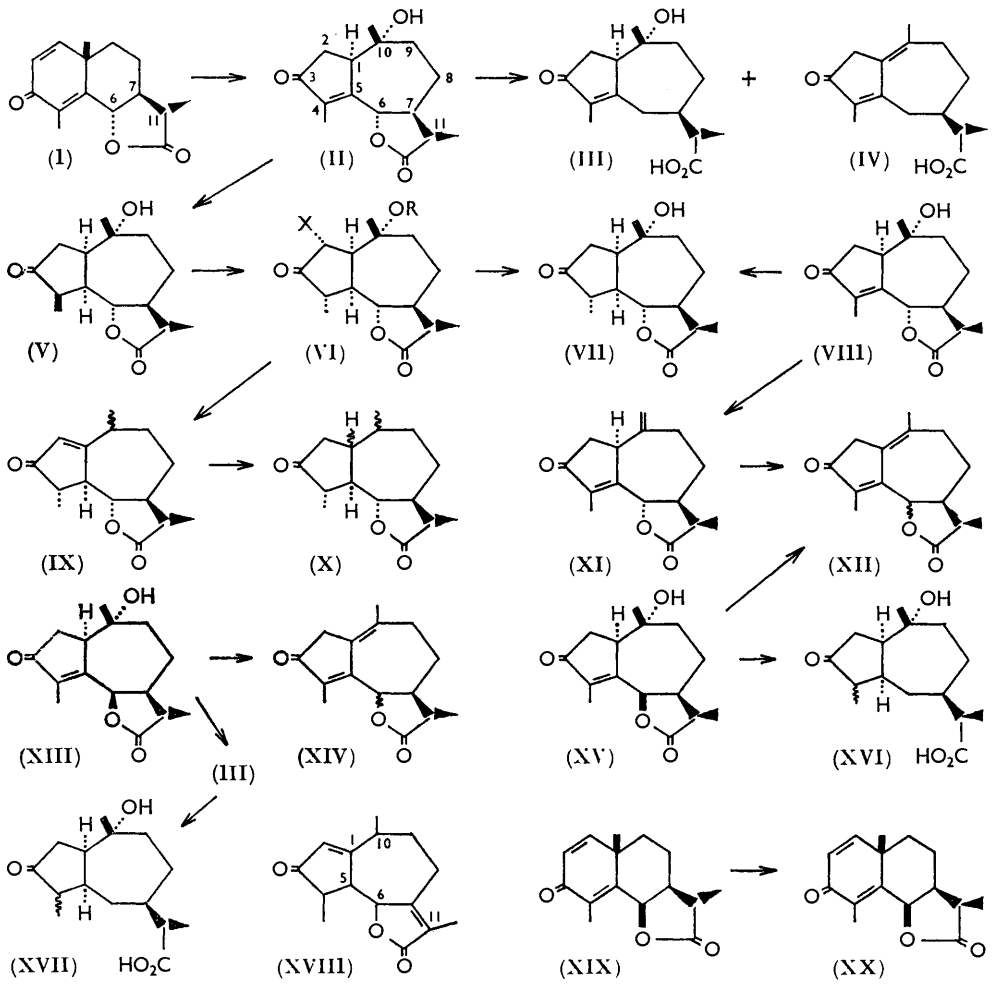
Other interesting chemical facts discovered incidentally to this work were as follows. Treatment of either isophoto-α- or isophoto-β-santonic lactone with sodium acetate in acetic acid under reflux gave an optically inactive product which we designate as allo-anhydroisophotosantonic lactone. This compound has ultraviolet and infrared spectra indicative of formula (XVIII). The formation of this compound is easily understood in the following, or equivalent, terms: (*a*) Vinylogous β-elimination to the 4,1(10)-dienones; (*b*) isomerisation to the 1,5-dienones; (*c*) further isomerisation to the 1,6-dienones; (*d*) prototropic shift to the final dienone (XVIII). Vinylogous β-elimination of the alkyl

* We acknowledge helpful discussions that we have had at intervals for some years past with Professor R. B. Woodward (Harvard). Professor Woodward has always advocated the correct configuration at C-1 for (II) and thus stimulated us to more definitive work.

[4] Djerassi, Osiecki, and Herz, *J. Org. Chem.*, 1957, **22**, 1361.
[5] Barton and Gilham, *J.*, 1960, 4596; see also de Mayo and Reid, *Quart. Rev.*, 1961, **15**, 393.
[6] Asher and Sim, *Proc. Chem. Soc.*, 1962, 111.
[7] See Cocker and McMurry, *Tetrahedron*, 1960, **8**, 181.
[8] Contrast, however, Miki, *J. Pharm. Soc. Japan*, 1955, **75**, 416.

oxygen of the lactone from (XVIII) would furnish the 1,5,7(11)-trienone, both asymmetric centres of which would be α or vinylogously α to the ketone. The racemic character of the final product would thus be explained.

The behaviour of the 6-epi-isophoto-α- and -β-santonic lactones on hydrogenation was quite different from that of the normal series. Hydrogenation of the 6-epi-α-compound (XIII) gave (1 mol. uptake) an unsaturated acid (III), isolated as its 2,4-dinitrophenylhydrazone. The same compound [together with the conjugated dieneone (IV)] was obtained on reduction of the normal isophoto-α-santonic lactone (II) with zinc dust and



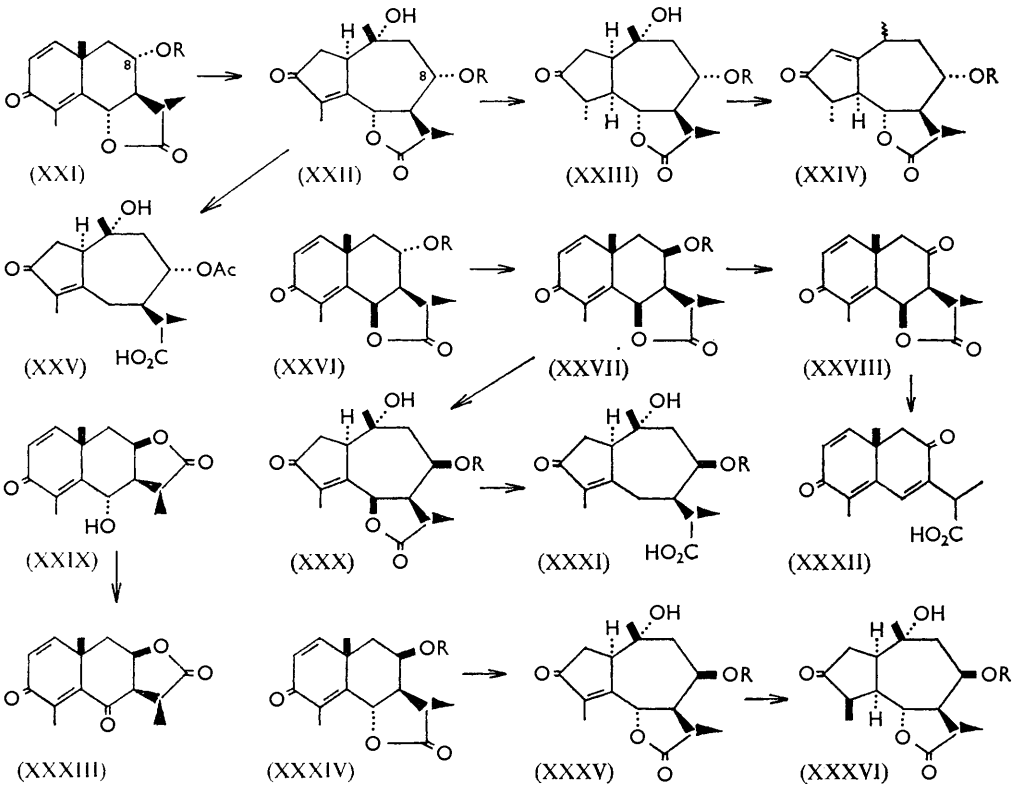
acetic acid. Hydrogenation of the 6-epi-α-compound (XIII) with 2 mols. uptake gave the saturated keto-acid (XVII). Similar hydrogenation of the 6-epi-β-compound (XV) afforded the saturated keto-acid (XVI). Clearly when the alkyl-oxygen of the lactone is quasi-axial in character, as it is in the 6-epi-series, hydrogenolysis precedes saturation of the 4,5-ethylenic linkage. When, however, this structural feature has quasi-equatorial character normal hydrogenation is faster than hydrogenolysis. Professor Wesley Cocker (Trinity College, Dublin) has kindly told us of his experiments in the desmotroposantonin series where a similar effect is operative.[9]

[9] See also Dauben, Hayes, Schwarz, and McFarland, *J. Amer. Chem. Soc.*, 1960, **82**, 2232.

Having the two 6-epi-α- and -β-santonins available we were interested to examine their relative stabilities. Contrary to expectation [7] the α-santonin compound (XIX) was smoothly isomerised to the β-isomer (XX) on treatment with potassium t-butoxide at room temperature.

Many of the naturally occurring guaianolides have oxygen substituents at both positions 6 and 8. The obvious starting material for the partial synthesis of such compounds, by means of our photochemical rearrangement, is artemisin (XXI; R = H), a congener of α- and β-santonin. On irradiation artemisin acetate (XXI; R = Ac) gave isophotoartemisic lactone acetate (XXII; R = Ac) in poor yield (5%). This keto-lactone was characterised as its 2,4-dinitrophenylhydrazone. On hydrogenation it gave a dihydroderivative (XXIII; R = Ac) which on acid-catalysed dehydration afforded anhydrodihydroisophotoartemisic lactone acetate (XXIV; R = Ac). Although hydrogenation of the lactone (XXII; R = Ac) proceeded as we expected (see above) without hydrogenolysis, the corresponding acid (XXV) was easily obtained by chromous chloride reduction.

In order to correlate artemisin with geigerin [10] an 8β-configuration for oxygen is required. The following approach ultimately led to success.[10] Artemisin was converted



into 6-epi-artemisin [11] (XXVI; R = H) and thence into the methanesulphonate (XXVI; R = Me·SO_2). Treatment of the latter with dilute aqueous base must involve intramolecular attack of carboxylate anion upon C-8 with inversion of configuration. In the event, acidification furnished the desired 6-epi-8-epiartemisin (XXVII; R = H), readily

[10] Barton, Miki, Pinhey, and Wells, *Proc. Chem. Soc.*, 1962, 112. Hamilton, McPhail, and Sim, *Proc. Chem. Soc.*, 1960, 278; Barton and Pinhey, *Proc. Chem. Soc.*, 1960, 279.

[11] Sumi, *J. Amer. Chem. Soc.*, 1958, **80**, 4869.

converted into its acetate (XXVII; R = Ac). The position of the lactone ring as terminal at (C-6 rather than C-8) was proved by oxidation of 6-epi-8-epiartemisin (XXVII; R = H) to the saturated ketone (XXVIII). On very mild treatment with base this showed (ultraviolet spectrum) the expected formation of an extended dienone system (XXXII). Analogous experiments in the artemisin series have been reported previously.[11,12]

Irradiation of 6-epi-8-epiartemisin acetate gave the corresponding isophoto-compound (XXX; R = Ac) in good yield. As expected (see above), hydrogenolysis of this compound preceded hydrogenation and the appropriate carboxylic acid (XXXI; R = Ac) was formed.

Artemisin was also converted into its methanesulphonate (XXI; R = Me·SO_2) and then treated with dilute aqueous alkali. Acidification afforded the desired 8-epiartemisin (XXXIV; R = H), characterised as its acetate (XXXIV; R = Ac), as well as the corresponding compound with the lactone ring closed on to C-8 (XXIX). The constitution of the latter was proved by oxidation to the conjugated ketone (XXXIII).

The usual photochemical rearrangement of 8-epiartemisin acetate (XXXIV; R = Ac) gave 8-epi-isophotoartemisic lactone acetate (XXXV; R = Ac). As expected, hydrogenation of this compound preceded hydrogenolysis and a dihydro-derivative (XXXVI; R = Ac) was formed in high yield. The unstable configuration at C-4 in this particular dihydro-derivative is assigned on molecular-rotation grounds. Reduction of 8-epi-isophotoartemisic lactone acetate (XXXV; R = Ac) with chromous chloride gave the same carboxylic acid (XXXI) as was obtained earlier (see above) from the 6-epi-8-epi-compound by hydrogenolysis. This experiment, incidentally, confirms the attachment of the lactone ring at position 6 in 8-epiartemisin (XXXIV; R = H).

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, and infrared absorption spectra to $CHCl_3$ solutions. All irradiations were carried out over a bare mercury-arc lamp in Pyrex apparatus.[1] Light petroleum refers to the fraction of b. p. 60—80°.

Dihydroisophoto-α-santonic Lactone.—(*a*) *Unstable isomer.* Isophoto-α-santonic lactone (360 mg.) in ethanol (20 ml.) was hydrogenated over 10% palladised charcoal (150 mg.) until saturated (1·2 mol. uptake). Crystallisation of the product from ethyl acetate–light petroleum (b. p. 60—80°) gave the dihydro-compound (V), m. p. 158—160°, $[\alpha]_D$ −46° (*c* 0·70). Barton, de Mayo and Shafiq [1] recorded m. p. 135—138°, $[\alpha]_D$ −46°.

(*b*) *Stable isomer.* When kept in 1% ethanolic potassium hydroxide at room temperature for 2 hr. the unstable isomer gave the more stable dihydroisophoto-α-santonic lactone (VI; R = X = H) in quantitative yield. Recrystallised from ethyl acetate this had m. p. 150—152°, $[\alpha]_D$ +39° (*c* 2·49), $\nu_{max.}$ 3415 (OH), 1762 (γ-lactone), and 1735 (cyclopentanone) $cm.^{-1}$ (Found: C, 67·55; H, 8·15. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%).

(*c*) *Derived acetate.* Either the stable or the unstable dihydro-lactone (150 mg.), anhydrous sodium acetate (30 mg.), and acetic anhydride (5 ml.) were refluxed for 3 hr. The solution was poured on ice, extracted into methylene dichloride, and worked up in the usual way. Crystallisation from ethyl acetate–light petroleum gave the more stable *dihydroisophoto-α-santonic lactone acetate* (VI; R = Ac, X = H), m. p. 165—167°, $[\alpha]_D$ −26° (*c* 1·13), $\nu_{max.}$ 1772 (γ-lactone) and 1735 (superimposed acetate and cyclopentanone) (Found: C, 66·35; H, 7·85. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

(*d*) *Derived* p-*bromophenylhydrazone.* Either of the dihydroisophoto-α-santonic lactones (see above; 280 mg.) in ethanol (4 ml.) containing *p*-bromophenylhydrazine hydrochloride (280 mg.) and pyridine (4 drops) was kept at 60—70° for 1½ hr. On cooling, the p-*bromophenylhydrazone* separated. It was recrystallised from ethanol as pale yellow needles, m. p. 210—220° (decomp.), $[\alpha]_D$ +93° (*c* 0·88), $\lambda_{max.}$ 284 mμ (ε 22,400), $\nu_{max.}$ (in Nujol) 1775 (γ-lactone) and 1600 (C=N) $cm.^{-1}$ (Found: C, 58·1; H, 6·65. $C_{21}H_{27}BrN_2O_3$ requires C, 57·9; H, 6·25%).

Bromodihydroisophoto-α-santonic Lactone Acetate (with Mr. R. J. Wells).—Dihydroisophoto-α-santonic lactone acetate (VI; R = Ac, X = H) (200 mg.) in acetic acid (2 ml.) was

[12] Barton, Bernasconi, and Klein, *J.*, 1960, 511.

treated with bromine (120 mg.) in the same solvent (0·85 ml.) with addition of a 50% solution (1 drop) of hydrobromic acid in acetic acid at room temperature until decolorised (3 min.). Working-up in the usual way and crystallisation from methylene dichloride–light petroleum gave 2-*bromodihydroisophoto-α-santonic lactone acetate* (VI; R = Ac, X = Br) (70 mg.), m. p. 117—118° (decomp.), $[\alpha]_D$ −33° (*c* 1·00), $\nu_{max.}$ 1776 (γ-lactone), 1745 (α-bromocyclopentanone), and 1735 (shoulder; acetate) cm.$^{-1}$ (Found: C, 52·5; H, 6·4. $C_{17}H_{23}BrO_5$ requires C, 52·7; H, 6·0%).

The bromo-lactone (VI; R = Ac, X = Br) (40 mg.) in " AnalaR " acetone (2 ml.) was treated under nitrogen with M-chromous chloride in N-hydrochloric acid (3 ml.) overnight at room temperature. Crystallisation from ethyl acetate–light petroleum gave the acetate (VI; R = Ac, X = H) (25 mg.), identified by m. p., mixed m. p., and $[\alpha]_D$.

Reduction of Isophoto-α-santonic Lactone with Zinc Dust.—Isophoto-α-santonic lactone (528 mg.) and zinc dust (2·8 g.) were refluxed in acetic acid (20 ml.) for 13 hr. The product was separated into acidic and neutral (negligible) fractions. Chromatography of the acid fraction over silica gel and elution with benzene–ether furnished the carboxylic acid (IV) (290 mg.). Crystallised from benzene–ether–light petroleum this had m. p. 106—108°, $[\alpha]_D$ +112° (*c* 0·90), $\lambda_{max.}$ 305 mμ (ε 16,400), $\nu_{max.}$ (in Nujol) 3175 and 2570 (CO_2H), 1720 (CO_2H and cyclopentenone), and 1637 and 1577 (conjugated C:C) cm.$^{-1}$ (Found: C, 72·85; H, 8·2. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). The derived 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as deep red needles, m. p. 232°, $\lambda_{max.}$ 417 mμ (ε 27,600 in $CHCl_3$) (Found: C, 58·3; H, 5·3; N, 12·4. $C_{21}H_{24}N_4O_6$ requires C, 58·85; H, 5·65; N, 13·15%).

Elution with ether–acetone gave an oil (69 mg.) with $\lambda_{max.}$ 243 (ε 11,000) and 306 mμ (ε 1600). This afforded the 2,4-*dinitrophenylhydrazone* of the acid (III), which crystallised as red needles (from chloroform–ethanol), m. p. 229—233°, $\lambda_{max.}$ 395 mμ (ε 28,600 in $CHCl_3$) (Found: C, 56·55; H, 5·7; N, 12·4. $C_{21}H_{26}N_4O_7$ requires C, 56·5; H, 5·85; N, 12·55%). The same compound was formed in the following way. 6-Epi-isophoto-α-santonic lactone (see below) (266 mg.) in ethanol (50 ml.) was hydrogenated over 10% palladised charcoal (250 mg.). After uptake of 1 mol. the hydrogenation rate slowed markedly and the reaction was interrupted. The product was acidic [$\lambda_{max.}$ 243 mμ (ε 12,500)], the neutral fraction being negligible. The 2,4-dinitrophenylhydrazone derived from the acidic fraction was shown to be identical with that from the acid (III) (see above) by m. p., mixed m. p., and ultraviolet and infrared spectra.

6-Epi-isophoto-α-santonic lactone (529 mg.) in ethanol (100 ml.) was hydrogenated over 10% palladised charcoal (500 mg.) until saturated (2 mol.). The product was separated into acidic (439 mg.) and neutral (68 mg.) fractions. Chromatography of the former over silica gel and crystallisation from chloroform–hexane gave the saturated *keto-acid* (XVII), m. p. 184—187°, $\nu_{max.}$ 3330 (CO_2H and HO), 1730 (cyclopentanone), and 1685 (CO_2H) cm.$^{-1}$ (Found: C, 66·95; H, 9·1. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%).

Anhydrodihydroisophoto-α-santonic Lactone.—The more stable dihydroisophoto-α-santonic lactone (VI; R = X = H) (703 mg.) in perchloric acid (60%)–acetic acid (1 : 4; 20 ml.) was kept at room temperature for 22 hr. (ultraviolet-absorption control). After dilution with water and extraction in the usual way the product was crystallised from ethanol, to give *anhydrodihydroisophoto-α-santonic lactone* (IX) as prisms, m. p. 151—155°, $[\alpha]_D$ +20° (*c* 1·26), $\lambda_{max.}$ 227 mμ (ε 11,800), $\nu_{max.}$ 1765 (γ-lactone), 1697 (cyclopentenone), and 1603 (conjugated C:C) cm.$^{-1}$ (Found: C, 72·3; H, 8·0. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

Hydrogenation of this unsaturated ketone (237 mg.) in ethanol (70 ml.) over 5% palladised charcoal (400 mg.) gave the saturated *dihydro-derivative* (X), which crystallised from chloroform–ethanol as rhomboid plates, m. p. 195—200°, $[\alpha]_D$ +56° (*c* 1·49), $\nu_{max.}$ 1760 (γ-lactone) and 1730 (cyclopentenone) cm.$^{-1}$ (Found: C, 72·1; H, 8·75. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·85%). The desired 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as yellow needles, m. p. 217—228°, $\lambda_{max.}$ 363 mμ (ε 23,400 in $CHCl_3$) (Found: C, 58·6; H, 5·45; N, 12·9. $C_{21}H_{26}N_4O_6$ requires C, 58·6; H, 6·1; N, 13·0%).

Conjugated Anhydroisophoto-α-santonic Lactone (XIV).—Isophoto-α-santonic lactone (1·2 g.) in perchloric acid (60%)–acetic acid (1 : 9; 50 ml.) was heated at 70° for 3½ hr. (ultraviolet control of the developing band at 305 mμ). The mixture was poured into water and worked up in the usual way, and the product was chromatographed over alumina (grade III; 15 g.). Elution with benzene gave the conjugated *anhydroisophoto-α-santonic lactone* (XIV). This crystallised from methanol as prisms (106 mg.), m. p. 93—95°, $[\alpha]_D$ +2 (*c* 3·18), $\lambda_{max.}$ (ε 13, 700), $\nu_{max.}$ 1755 (γ-lactone), 1685 (C=O), and 1660 and 1598 (conjugated C:C) cm.$^{-1}$ (Found: C, 72·9;

H, 7·4; *C*-Me, 17·7. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·4; 3*C*-Me, 18·3%). Barton, de Mayo, and Shafiq [1] did not obtain this compound in crystalline form.

The same conjugated dienone was obtained when isophoto-6-epi-α-santonic lactone (see below) was treated with acid in the same way (m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum).

Alloanhydroisophotosantonic Lactone (XVIII).—Either isophoto-α- or -β-santonic lactone (1·06 g.) in acetic acid (40 ml.) containing anhydrous sodium acetate (4·1 g.) was refluxed for 4 days (ultraviolet control of the developing maximum at 224 mμ). The solution was poured into water and worked up in the usual way and the neutral product was chromatographed over alumina (Grade III). Elution with benzene–ether and with ether, crystallisation from chloroform–hexane, and sublimation *in vacuo* gave *alloanhydroisophotosantonic lactone* (XVIII), m. p. 138—140°, $[\alpha]_D$ ±0°, $\lambda_{max.}$ 224 mμ (ε 26,900), $\nu_{max.}$ 1757 (conjugated γ-lactone), 1705 (cyclopentenone), and 1673 and 1612 (conjugated C:C) cm.$^{-1}$ (Found: C, 73·2; H, 7·35. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The derived 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as bright red needles, m. p. 214—216°, $\lambda_{max.}$ 384 mμ (ε 28,700 in $CHCl_3$) (Found: C, 58·9; H, 5·2; N, 13·05. $C_{21}H_{22}N_4O_6$ requires C, 59·15; H, 5·2; N, 13·15%).

Isophoto-β-santonic Lactone (VIII).—β-Santonin (6·0 g.) in aqueous 45% acetic acid (300 ml.) was irradiated under reflux in a nitrogen atmosphere until the rotation had reached +30°. The neutral product was chromatographed over alumina (grade III; 60 g.). Elution with benzene–acetone (9 : 1) gave unchanged β-santonin. Further elution with benzene–acetone (4 : 1) afforded isophoto-β-santonic lactone (VIII) (1·64 g.). This crystallised from ethyl acetate as plates, m. p. 154—157°, $[\alpha]_D$ +207° (*c* 1·36), $\lambda_{max.}$ 240 mμ (ε 12,900), $\nu_{max.}$ 3400 (OH), 1770 (γ-lactone), 1697 (cyclopentenone), and 1635 (conjugated C:C) cm.$^{-1}$ (Found: C, 68·1; H, 7·45; *C*-Me, 16·2. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65; 3*C*-Me, 17·05%). The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as orange-red plates, m. p. 261—264°, $\lambda_{max.}$ 385 mμ (ε 22,600 in $CHCl_3$) (Found: C, 57·0; H, 5·3; N, 12·55. $C_{21}H_{24}N_4O_7$ requires C, 56·75; H, 5·45; N, 12·6%).

Dihydroisophoto-β-santonic Lactone (VII).—(*a*) *By hydrogenation.* Isophoto-β-santonic lactone (1·06 g.) in ethanol (100 ml.) was hydrogenated over 10% palladised charcoal (500 mg.) (1 mol. uptake). Crystallisation of the product from ethanol gave *dihydroisophoto-β-santonic lactone* (VII) as hexagonal plates, m. p. 220—225°, $[\alpha]_D$ +123° (*c* 1·01), $\lambda_{max.}$ 293 mμ (ε 28), $\nu_{max.}$ 3400 (OH), 1758 (γ-lactone), and 1730 (cyclopentanone) cm.$^{-1}$ (Found: C, 67·5; H, 8·15. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%). Acetylation as for the α-analogue (VI; R = X = H) (see above) gave the *acetate*. Crystallised from ethyl acetate this had m. p. 181—191°, $[\alpha]_D$ +42° (*c* 0·97) (Found: C, 66·2; H, 7·85. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

(*b*) *By isomerisation.* The more stable dihydroisophoto-α-santonic lactone (VI; R = X = H) (380 mg.) in benzene (80 ml.) made 0·25N with potassium t-butoxide was refluxed for 1 hr. The solution was acidified with aqueous 2N-sulphuric acid and worked up in the usual way. Crystallisation of the product from ethanol gave dihydroisophoto-β-santonic lactone (m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum).

Non-conjugated Anhydroisophoto-β-santonic Lactone (XI).—Isophoto-β-santonic lactone (504 mg.) in pyridine (30 ml.) was treated with thionyl chloride (0·65 ml.) at 0° for 10 min. The product was chromatographed over silica gel (20 g.) and eluted with benzene. Crystallisation from benzene gave the non-conjugated *anhydroisophoto-β-santonic lactone* (XI) as plates, m. p. 186—190°, $[\alpha]_D$ +446° (*c* 1·13), $\lambda_{max.}$ 236 mμ (ε 13,400), $\nu_{max.}$ 1770 (γ-lactone), 1697 (cyclopentenone), 1640 (conjugated C:C), and 905 (>C:CH_2) cm.$^{-1}$ (Found: C, 72·3; H, 7·4; *C*-Me, 11·65. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35; 2*C*-Me, 12·2%).

Conjugated Anhydroisophoto-β-santonic Lactone (XII).—Isophoto-β-santonic lactone (748 mg.) in 60% perchloric acid–acetic acid (1 : 9); 90 ml.) was heated on a steam-bath for 20 min. (ultraviolet control). The product, in benzene–ether (1 : 1), was filtered through alumina (grade III), to furnish the conjugated *anhydroisophoto-β-santonic lactone* (XII). Crystallised from chloroform–light petroleum this formed needles, m. p. 177—180°, $[\alpha]_D$ −180° (*c* 1·03), $\lambda_{max.}$ 312 mμ (ε 12,500), $\nu_{max.}$ 1763 (γ-lactone), 1684 (cyclopentenone), and 1650 and 1598 (conjugated C:C) cm.$^{-1}$ (Found: C, 72·9; H, 7·15. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as red needles, m. p. 260—280°, $\lambda_{max.}$ 404 mμ (ε 30,700 in $CHCl_3$) (Found: C, 59·15; H, 4·95; N, 12·95. $C_{21}H_{22}N_4O_6$ requires C, 59·15; H, 5·2; N, 13·15%).

The same doubly conjugated ketone was obtained in the following way. 6-Epi-isophoto-β-santonic lactone (XV) (see below) (740 mg.) in 60% perchloric acid–acetic acid (1 : 9; 90 ml.) was heated on the steam-bath for 25 min. (ultraviolet control). Chromatography of the product over alumina (grade III; 7 g.) gave the conjugated anhydroisophoto-β-santonic lactone (128 mg.) identical (m. p., mixed m. p., and infrared spectrum) with the compound described above.

6-Epi-isophoto-α-santonic Lactone (XIII).—6-Epi-α-santonin was prepared (68%) by Ishikawa's method.[13] Recrystallised from ethyl acetate it formed plates, m. p. 103—104°, $[\alpha]_D$ −332° (*c* 1·01), $\lambda_{max.}$ 246 mμ (ε 13,900), $\nu_{max.}$ 1765 (γ-lactone), 1660 (cyclohexadienone), and 1628 and 1607 (conjugated C:C) cm.$^{-1}$ (Found: C, 73·25; H, 7·5. Calc. for $C_{15}H_{18}O_3$: C, 73·15; H, 7·25%). The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as red leaflets, m. p. 249—256°, $\lambda_{max.}$ 393 mμ (ε 30,900 in $CHCl_3$) (Found: C, 59·0; H, 5·05; N, 13·25. $C_{21}H_{22}N_4O_6$ requires C, 59·15; H, 5·2; N, 13·15%). For 6-epi-α-santonin Ishikawa [13] recorded m. p. 105°, $[\alpha]_D$ −288°. 6-Epi-α-santonin (4·5 g.) in 45% aqueous acetic acid (125 ml.) was irradiated under reflux in a nitrogen atmosphere until the rotation was −74°. The neutral product was chromatographed over alumina (grade III; 60 g.). Elution with ether–acetone (1 : 2) and crystallisation from ethyl acetate gave *6-epi-isophoto-α-santonic lactone* (XIII) as plates (24%), m. p. 180—181°, $[\alpha]_D$ −105° (*c* 1·34), $\lambda_{max.}$ 239 mμ (ε 11,600), $\nu_{max.}$ 3450 and 3365 (OH), 1770 (γ-lactone), 1702 (cyclopentenone), and 1635 (conjugated C:C) cm.$^{-1}$ (Found: C, 67·9; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). The 2,4-*dinitrophenylhydrazone* crystallised from chloro–ethanol as red needles, m. p. 232—240°, $\lambda_{max.}$ 383 mμ (ε 28,300 in $CHCl_3$) (Found: C, 56·85; H, 5·3; N, 12·75. $C_{21}H_{24}N_4O_7$ requires C, 56·75; H, 5·75; N, 12·6%).

6-Epi-β-Santonin (XX).—(*a*) *From β-santonin.* β-Santonin (10 g.) in dimethylformamide (100 ml.) containing gaseous hydrogen chloride (5%) was heated for 5 hr. on the steam-bath. The product was chromatographed over alumina (grade III; 100 g.). Elution with benzene gave *6-epi-β-santonin* (XX) (54%), which crystallised from ethyl acetate as needles, m. p. 191—192°, $[\alpha]_D$ −306° (*c* 1·00), $\lambda_{max.}$ 246 mμ (ε 14,900), $\nu_{max.}$ 1765 (γ-lactone), 1660 (cyclohexadienone), and 1625 and 1610 (conjugated C:C) cm.$^{-1}$ (Found: C, 73·15; H, 7·1. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as red plates, m. p. 282—285°, $\lambda_{max.}$ 392 mμ (ε 31,000 in $CHCl_3$) (Found: C, 59·1; H, 5·2; N, 13·3. $C_{21}H_{22}NO_6$ requires C, 59·15; H, 5·2; N, 13·15%).

(*b*) *From 6-epi-α-santonin.* 6-Epi-α-santonin (XIX) (2·0 g.) in thoroughly dried t-butyl alcohol–benzene (1 : 1; 150 ml.) containing potassium t-butoxide (0·3%) was kept at room temperature under nitrogen for 4 hr. The solution was poured into an excess of aqueous 2N-sulphuric acid and extracted into benzene. Crystallisation from ethyl acetate afforded 6-epi-β-santonin (50%), identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

6-Epi-isophoto-β-santonic Lactone (XV).—6-Epi-β-santonin (XX) (4·0 g.) in aqueous 45% acetic acid (110 ml.) was irradiated under reflux in a nitrogen atmosphere until the rotation reached −70°. The neutral product was chromatographed over alumina (grade III; 40 g.). Elution with ether–acetone mixtures furnished *6-epi-isophoto-β-santonic lactone* (XV). Recrystallised from ethyl acetate this formed prisms (24%), m. p. 200—201°, $[\alpha]_D$ −101° (*c* 1·10), $\lambda_{max.}$ 241 mμ (ε 11,700), $\nu_{max.}$ 3525 and 3400 (OH), 1770 (γ-lactone), 1699 (cyclopentenone), and 1625 (conjugated C:C) cm.$^{-1}$ (Found: C, 67·9; H, 7·45. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). The derived 2,4-*dinitrophenylhydrazone* crystallised from ethyl acetate as orange-red needles, m. p. 245—250°, $\lambda_{max.}$ 385 mμ (ε 28,100 in $CHCl_3$) (Found: C, 56·5; H, 5·6; N, 12·45. $C_{21}H_{24}N_4O_7$ requires C, 56·75; H, 5·75; N, 12·6%).

Hydrogenation of 6-Epi-isophoto-β-santonic Lactone.—6-Epi-isophoto-β-santonic lactone (528 mg.) in ethanol (100 ml.) was hydrogenated over 10% palladised charcoal (500 mg.) until saturated (2 ml. uptake). The product was separated into acidic (457 mg.) and neutral (71 mg.) fractions. The acidic fraction did not crystallise but it was identified as the acid (XVI) by conversion into the 2,4-*dinitrophenylhydrazone*. Recrystallised from chloroform–ethanol this formed yellow plates, m. p. 205—208°, $\lambda_{max.}$ 366 mμ (ε 21,600 in $CHCl_3$) (Found: C, 55·9; H, 6·45. $C_{21}H_{28}N_4O_7$ requires C, 56·25; H, 6·3%).

Isophotoartemisic Lactone Acetate (XXII; R = Ac).—Artemisin acetate (XXI; R = Ac) (6·0 g.) in aqueous 45% acetic acid (150 ml.) was irradiated under reflux in a nitrogen atmosphere until the rotation was −20°. The neutral product was chromatographed over

[13] Ishikawa, *J. Pharm. Soc. Japan*, 1956, **76**, 504, 507.

alumina (grade III; 60 g.). Elution with benzene–acetone (9 : 1) afforded *isophotoartemisic lactone acetate* (XXII; R = Ac) (5%). Crystallised from ethyl acetate this formed plates, m. p. 230—233°, $[\alpha]_D$ +120° (*c* 1·45), $\lambda_{max.}$ 239 mμ (ε 13,900), $\nu_{max.}$ 3540 and 3436 (OH), 1787 (γ-lactone), 1712 (cyclopentenone), and 1649 (conjugated C:C) cm.$^{-1}$ (Found: C, 63·55; H, 7·05. $C_{17}H_{22}O_6$ requires C, 63·35; H, 6·9%). The derived 2,4-*dinitrophenylhydrazone* crystallised from ethyl acetate as orange-red leaflets, m. p. 278—282°, $\lambda_{max.}$ 383 mμ (ε 32,600 in $CHCl_3$) (Found: N, 10·9. $C_{23}H_{26}N_4O_9$ requires N, 11·15%).

Dihydroisophotoartemisic Lactone Acetate (XXIII; R = Ac).—Isophotoartemisic lactone acetate (645 mg.) in ethanol (100 ml.) was hydrogenated over 10% palladised charcoal (190 mg.). Crystallisation of the product from ethyl acetate gave *dihydroisophotoartemisic lactone acetate* (XXIII; R = Ac) as needles (446 mg.), m. p. 180—183°, $[\alpha]_D$ −7° (*c* 1·79), $\nu_{max.}$ 3577 (OH), 1767 (γ-lactone), 1734 (cyclopentanone and acetate) cm.$^{-1}$ (Found: C, 63·2; H, 7·5. $C_{17}H_{24}O_6$ requires C, 62·95; H, 7·45%).

This compound (132 mg.) in 60% perchloric acid–acetic acid (1 : 4; 10 ml.) was kept at room temperature for six days (ultraviolet control). The neutral product was chromatographed over alumina (grade III; 1·5 g.). Elution with benzene–ether, sublimation *in vacuo*, and crystallisation from chloroform–light petroleum gave *anhydrodihydroisophotoartemisic lactone acetate* (XXIV; R = Ac) as needles, m. p. 208—213°, $[\alpha]_D$ +47° (*c* 0·75), $\lambda_{max.}$ 226 mμ (ε 16,800), $\nu_{max.}$ 1776 (γ-lactone), 1742 (OAc), 1711 (cyclopentenone), and 1613 (conjugated C:C) cm.$^{-1}$ (Found: C, 66·5; H, 7·25. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%).

Reduction of Isophotoartemisic Lactone Acetate (XXII; R = Ac) *with Chromous Chloride*.—The lactone acetate (583 mg.) in acetic acid (15 ml.) and acetone (15 ml.) was treated under nitrogen with M-chromous chloride[14] (10 ml.) at room temperature for 2½ days. Separation of the product into acidic and neutral fractions showed that the latter was negligible. Crystallisation of the acidic fraction from ethyl acetate afforded the *keto-acid* (XXV) (498 mg.) as prisms, m. p. 209—213°, $[\alpha]_D$ +118° (*c* 0·95), $\lambda_{max.}$ 242 mμ (ε 14,900), $\nu_{max.}$ 3500—2900 (OH and CO_2H), 1732 (OAc), 1692 (cyclopentenone), and 1630 (conjugated C:C) cm.$^{-1}$ (Found: C, 63·25; H, 7·3. $C_{17}H_{24}O_6$ requires C, 62·95; H, 7·4%).

6-*Epiartemisin* (XXVI; R = H) *and its Derivatives*.—This compound was prepared according to Sumi's directions [11] and found to crystallise (30%) from ethyl acetate–ether in two forms, m. p. 156—157° (plates) and 165—166° (prisms). Both showed the same $[\alpha]_D$ [−213° (*c* 1·26)] and the same infrared spectra in chloroform, but gave different spectra in Nujol.

6-Epiartemisin (440 mg.) in pyridine (3 ml.) was kept at 0° for 14 hr. with redistilled methanesulphonyl chloride (1·0 ml.). Crystallisation of the product from ethyl acetate–ether gave 6-*epiartemisin methanesulphonate* (XXVI; R = Me·SO_2) (95%) as prisms, m. p. 135—136°, $[\alpha]_D$ −140° (*c* 1·10), $\lambda_{max.}$ 243 mμ (ε 13,000), $\nu_{max.}$ 1783 (γ-lactone), 1668 (cyclohexadienone), and 1638 (conjugated C:C) cm.$^{-1}$ (Found: C, 56·2; H, 5·7. $C_{16}H_{20}O_6S$ requires C, 56·45; H, 5·9%).

This methanesulphonate (3·3 g.) was dissolved with agitation in aqueous 0·1N-sodium hydroxide (300 ml.) and kept at room temperature for 14 hr. Acidification with aqueous 2N-sulphuric acid, saturation with salt, and thorough extraction with methylene dichloride (10 × 30 ml.) gave, after crystallisation from ethanol, 6-*epi*-8-*epiartemisin* (XXVII; R = H) as prisms, m. p. 170—175°, $[\alpha]_D$ −271° (*c* 1·10), $\lambda_{max.}$ 247 mμ (ε 12,300), $\nu_{max.}$ 3400 (OH), 1780 (γ-lactone), 1663 (cyclohexadienone), and 1633 (conjugated C:C) cm.$^{-1}$ (Found: C, 68·55; H, 6·6. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). The corresponding *acetate* (XXVII); R = Ac), prepared by treatment with pyridine–acetic anhydride overnight at room temperature, crystallised from ethyl acetate–ether as prisms, m. p. 148—150°, $[\alpha]_D$ −261° (*c* 1·11), $\lambda_{max.}$ 245 mμ (ε 13,000), $\nu_{max.}$ 1778 (γ-lactone), 1740 (OAc), 1665 (cyclohexadienone), and 1634 (conjugated C:C) cm.$^{-1}$ (Found: C, 67·15; H, 6·6. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

6-Epi-8-epiartemisin (155 mg.) in " AnalaR " acetic acid (10 ml.) was treated with chromium trioxide (105 mg.) at room temperature for 2 hr. Working-up in the usual way and crystallisation from methanol gave 6-*epi*-8-*dehydroartemisin* (XXVIII) as prisms, m. p. 135—145° (depends on rate of heating), $[\alpha]_D$ −418° (*c* 0·75), $\lambda_{max.}$ 244 mμ (ε 12,000), (in 1% ethanolic KOH) 255 and 321 mμ (ε 7900 and 16,200, respectively), $\nu_{max.}$ 1783 (γ-lactone), 1720 (cyclohexanone), 1665 (cyclohexadienone), and 1638 (conjugated C:C) cm.$^{-1}$ (Found: C, 68·85; H, 6·15. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

6-*Epi*-8-*epi*-*isophotoartemisic Lactone Acetate* (XXX; R = Ac).—6-Epi-8-epiartemisin acetate (XXVII; R = Ac) in aqueous 45% acetic acid (520 ml.) was irradiated under reflux in a

[14] Cole and Julian, *J. Org. Chem.*, 1954, **19**, 131.

nitrogen atmosphere until the rotation was −85°. The neutral fraction, crystallised from ethyl acetate–ether, gave 6-*epi*-8-*epi-isophotoartemisic lactone acetate* (XXX; R = Ac) (1·15 g.) as prisms, m. p. 171—174°, $[\alpha]_D$ −71° (*c* 1·12), $\lambda_{max.}$ 242 mμ (ε 11,600), $\nu_{max.}$ 3460 (OH), 1776 (γ-lactone), 1740 (OAc), 1704 (cyclopentenone), and 1644 (conjugated C:C) cm.$^{-1}$ (Found: C, 63·55; H, 7·75. $C_{17}H_{22}O_6$ requires C, 63·35; H, 7·9%). Chromatography of the mother-liquors over alumina (grade III) and elution with benzene–acetone (9 : 1) gave further material (total yield, 31%).

This photo-compound (58 mg.) in ethanol (5 ml.) was hydrogenated (1 mol.) over 10% palladised barium sulphate (50 mg.). The acidic fraction (55 mg.), crystallised from ethyl acetate, gave the *carboxylic acid* (XXXI; R = Ac) as prisms, m. p. 105—120° (solvated), $[\alpha]_D$ +37° (*c* 0·83), $\lambda_{max.}$ 242 mμ (ε 14,000), $\nu_{max.}$ 2900—3400 (OH and CO_2H), 1733 (OAc and CO_2H), 1690 (cyclopentenone), and 1631 (conjugated C:C) cm.$^{-1}$ (Found: C, 61·3; H, 7·4. $C_{17}H_{24}O_6$,EtOAc requires C, 61·15; H, 7·8%).

The same acid (XXXI; R = Ac) (56 mg.) was obtained (m. p., mixed m. p., and infrared spectrum) when 8-epi-isophotoartemisic lactone acetate (XXXV; R = Ac) (see below) (105 mg.) in acetone (5 ml.) was treated with M-chromous chloride (3 ml.) at room temperature under nitrogen for 2 days.

8-*Epiartemisin* (XXXIV; R = H) *and its Derivatives*.—Artemisin (1·0 g.) in pyridine (10 ml.) and redistilled methanesulphonyl chloride (1 ml.) was kept overnight at 0°. Crystallisation of the product from acetone afforded *artemisin methanesulphonate* (XXI; R = Me·SO_2) (90%) as prisms, m. p. 179—181°, $[\alpha]_D$ −56° (*c* 1·36), $\lambda_{max.}$ 237 mμ (ε 10,800), $\nu_{max.}$ 1790 (γ-lactone), 1670 (cyclohexadienone), and 1645 and 1622 (conjugated C:C) cm.$^{-1}$ (Found: C, 56·75; H, 6·1. $C_{16}H_{20}O_6S$ requires C, 56·5; H, 5·9%).

The powdered methanesulphonate (10·0 g.) was dissolved with agitation in aqueous 0·1N-sodium hydroxide (1 l.) and kept overnight at room temperature. The solution was acidified with 2N-sulphuric acid, saturated with salt, and extracted thoroughly with chloroform (6 × 250 ml.). Crystallisation from ethanol gave a product (4·5 g.) as prisms, m. p. 215—225°. For purification this was acetylated with pyridine–acetic anhydride overnight at room temperature, to give 8-epiartemisin acetate (XXXIV; R = Ac). Easily purified by crystallisation from ethanol, this formed prisms, m. p. 141—142°, $[\alpha]_D$ −201° (*c* 0·82), $\lambda_{max.}$ 240 mμ (ε 11,800), $\nu_{max.}$ 1785 (γ-lactone), 1740 (OAc), 1667 (cyclohexadienone), and 1640 and 1617 (conjugated C:C) cm.$^{-1}$ (Found: C, 67·1; H, 6·5. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%). The mother-liquors remaining after removal of the fraction, m. p. 215—225° (see above), was allowed to evaporate slowly. It deposited a second crop of crystals, m. p. 160—180°, which crystallised from ethyl acetate for furnish the *isomer* (XXIX) of 8-epiartemisin (1·1 g.) as needles, m. p. 177—178°, $[\alpha]_D$ −140° (*c* 0·92), $\lambda_{max.}$ 240 mμ (ε 9700), $\nu_{max.}$ 3420 (OH), 1770 (γ-lactone), 1665 (cyclohexadienone), and 1630 (conjugated C:C) cm.$^{-1}$ (Found: C, 68·85; H, 7·1. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Treatment with pyridine–acetic anhydride overnight at room temperature gave the corresponding *acetate*. This crystallised from ether–methanol as prisms, m. p. 119—120°, $[\alpha]_D$ −120° (*c* 0·99), $\lambda_{max.}$ 241 mμ (ε 11,900), $\nu_{max.}$ 1780 (γ-lactone), 1748 (OAc), 1668 (cyclohexadienone), and 1636 (conjugated C:C) cm.$^{-1}$ (Found: C, 67·3; H, 6·75. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

The isomer (XXIX) (130 mg.) in " AnalaR " acetic acid (10 ml.) was treated with chromium trioxide (110 mg.) in the same solvent (50 ml.) at room temperature for 1¼ hr. Crystallisation of the product from methanol gave the *diketone* (XXXIII) (95 mg.) as prisms, m. p. 135—145° (depends on rate of heating), $\lambda_{max.}$ 251 mμ (ε 11,500), $\nu_{max.}$ (in Nujol) 1770, γ-lactone (cyclohexenone), 1660 (cyclohexadienone), and 1640 (conjugated C:C) cm.$^{-1}$ (Found: C, 69·15; H, 6·25. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%). The ultraviolet spectrum was essentially unchanged in ethanolic 1% potassium hydroxide, the absorption in the 300—320 mμ area being inspected especially carefully.

8-*Epi-isophotoartemisic Lactone Acetate* (XXXV) R = Ac).—8-Epiartemisin acetate (XXXIV; R = Ac) (2·5 g.) in aqueous 45% acetic acid (250 ml.) was irradiated under reflux in a nitrogen atmosphere until the rotation reached −73°. The product was separated into acid and neutral fractions in the usual way. Crystallisation of the neutral fraction from ethyl acetate–light petroleum gave 8-*epi-isophoroartemisic lactone acetate* (XXXV; R = Ac) (420 mg.) as prisms, m. p. 174—175°, $[\alpha]_D$ +72° (*c* 1·36), $\lambda_{max.}$ 239 mμ (ε 13,400), $\nu_{max.}$ 3400 (OH), 1785 (γ-lactone), 1747 (OAc), 1710 (cyclopentenone), and 1646 (conjugated C:C) cm.$^{-1}$ (Found: C, 63·35; H, 6·65. $C_{17}H_{22}O_6$ requires C, 63·35; H, 6·9%). Chromatography of the mother-liquors over alumina

(grade III; 20 g.) and elution with benzene–acetone (9 : 1) gave a further quantity (230 mg.) of this acetate.

The acid fraction crystallised easily from ethyl acetate–ether–light petroleum, to give an *analogue* of photosantonic acid as needles (200 mg.), m. p. 147—150°, $[\alpha]_D$ −192° (*c* 0·90), ε_{210} 8300, $\nu_{max.}$ 2700—3500 (CO_2H), 1773 (γ-lactone), 1730 (OAc), and 1705 (CO_2H) cm.$^{-1}$ (Found: C, 63·6; H, 7·05. $C_{17}H_{22}O_6$ requires C, 63·35; H, 6·9%).

Dihydro-8-epi-isophotoartemisic Lactone Acetate (XXXVI; R = Ac).—8-Epi-isophotoartemisic lactone acetate (83 mg.) in ethanol (5 ml.) was hydrogenated over 10% palladised barium sulphate (100 mg.) (uptake 1·2 mol.). Crystallisation of the neutral product from ethyl acetate–ether gave *dihydro-8-epi-isophoroartemisic lactone acetate* (XXXVI; R = Ac) (54 mg.) as prisms, m. p. 180—185°, $[\alpha]_D$ −115° (*c* 0·92), $\lambda_{max.}$ 288 mμ (ε 18), $\nu_{max.}$ 3420 (OH), 1766 (γ-lactone), and 1737 (OAc and cyclopentanone) cm.$^{-1}$ (Found: C, 63·1; H, 7·4. $C_{17}H_{24}O_6$ requires C, 62·95; H, 7·45%). The $[M]_D$ difference for this hydrogenation is the same as that between isophotosantonic lactone and its "unstable" dihydro-derivative. The artemisin analogue (XXXVI; R = Ac) is, therefore, assigned the unstable configuration at position 4.

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