29. *Photochemical Transformations. Part II.*[1] *The Constitution of Lumisantonin.*

By D. H. R. Barton, P. de Mayo, and Mohammed Shafiq.

Irradiation of santonin in ethanolic solution affords an isomer, lumisantonin, which has been shown to have the constitution (III). Lumisantonin affords photosantonic acid on irradiation in cold aqueous acetic acid. It is rearranged thermally by hot aqueous acetic acid, to 10-hydroxy-3-oxoguai-4-en-6 : 12-olide (II).

In Part I of this series [1] the light-induced conversion of santonin (I) into 10-hydroxy-3-oxoguai-4-en-6 : 12-olide (*iso*photosantonic lactone) (II) in aqueous acetic acid was reported. In further experiments on the photochemistry of santonin, directed towards the elucidation of the structure of " photosantonin," [2] we have discovered a new light-produced isomer. This compound has also been obtained by Professor Büchi (M.I.T.), Professor Jeger (E.T.H., Zürich), and by Professor Cocker (Trinity College, Dublin), whom we thank for their kind personal communications to this effect; they have suggested that it be called lumisantonin, and we are happy to agree. The present paper describes our own work on this compound. It affords the lactone (II) when refluxed with aqueous acetic acid *in the dark* and is an important intermediate in the light-induced reactions of santonin. A preliminary communication proposing the constitution (III) has already appeared.[3]

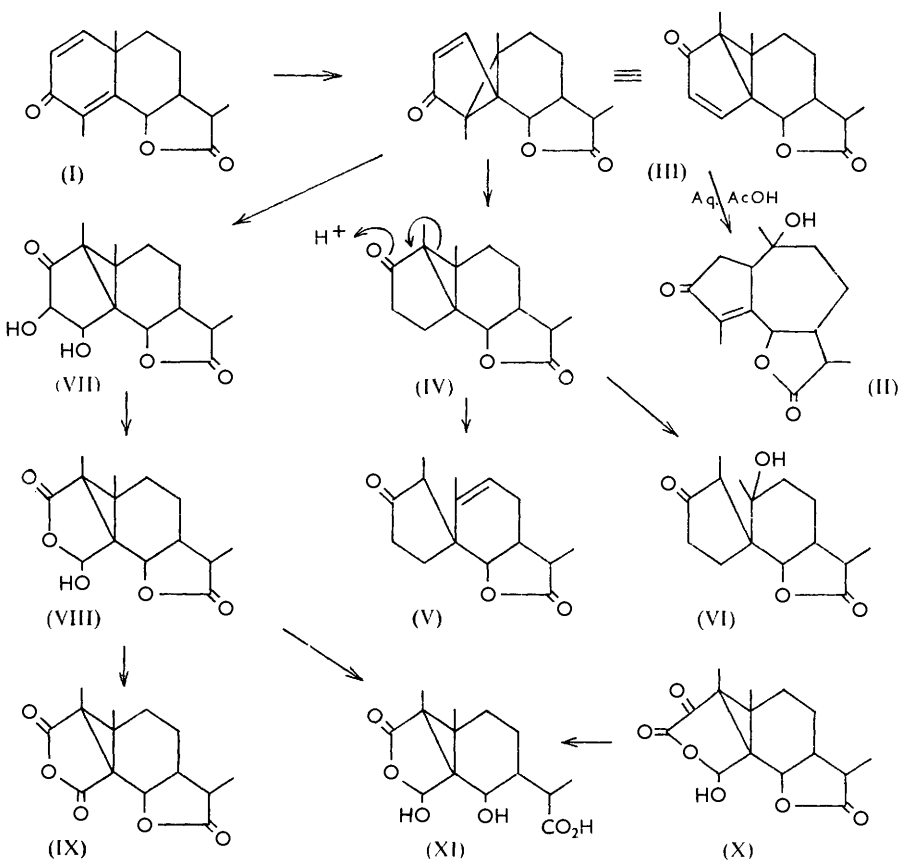
Lumisantonin, obtained along with photosantonin by irradiation of santonin in ethanol solution, is assigned this constitution [3] on the basis of the following evidence. Its infrared spectrum showed bands in Nujol at 1765 (γ-lactone) and 1703 and 1663 cm.$^{-1}$ ($\alpha\beta$-unsaturated *cyclo*pentenone) and in CCl_4 at 1785 (γ-lactone) and 1703 and 1670 cm.$^{-1}$ ($\alpha\beta$-unsaturated *cyclo*pentenone). Its ultraviolet absorption spectrum showed a broad band at 239 mμ (ε 5800) indicative of an $\alpha\beta$-unsaturated ketone. It contained three *C*-Me groups as determined both chemically and by quantitative infrared measurements.

Lumisantonin was readily hydrogenated to a dihydro-derivative (IV) which showed infrared bands at 1770 (γ-lactone) and 1703 cm.$^{-1}$. The identical ketone frequencies in (III) and (IV) are not unexpected, since there is the same relation between the carbonyl frequencies of umbellulone and β-dihydroumbellulone [4] where a comparable structural

[1] Part I, Barton, de Mayo, and Shafiq, *J.*, 1957, 929.
[2] See Simonsen and Barton, " The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 292.
[3] Barton, de Mayo, and Shafiq, *Proc. Chem. Soc.*, 1957, 205.
[4] Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115.

change is postulated. The frequency at 1703 cm.$^{-1}$ is, therefore, indicative of a *bicyclo*-[3 : 1]hexan-2-one system. Dihydrolumisantonin gave no colour with tetranitromethane and was stable to ozone, but it showed an ultraviolet absorption maximum at 214 mμ (ε 4600) characteristic [4] of conjugated ketone and *cyclo*propane groups.

When dihydrolumisantonin was refluxed with aqueous acetic acid it furnished an isomer (V) and the corresponding tertiary alcohol (VI). The isomer (V) had three CMe groups and showed infrared bands at 1765 (γ-lactone) and 1735 cm.$^{-1}$ (normal *cyclo*pentanone). It gave a colour with tetranitromethane and showed only an isolated ethylenic linkage in its ultraviolet absorption spectrum. The production of an additional ethylenic linkage under such mild conditions, when coupled with the spectroscopic data, constitutes a proof of the presence of a conjugated ketone group and *cyclo*propane ring in lumisantonin. The constitution (VI) follows from its genesis, the failure to show absorption in the far ultraviolet region, and infrared bands at 3430 (hydroxyl), 1750 (γ-lactone), and 1726 cm.$^{-1}$ (*cyclo*pentanone).

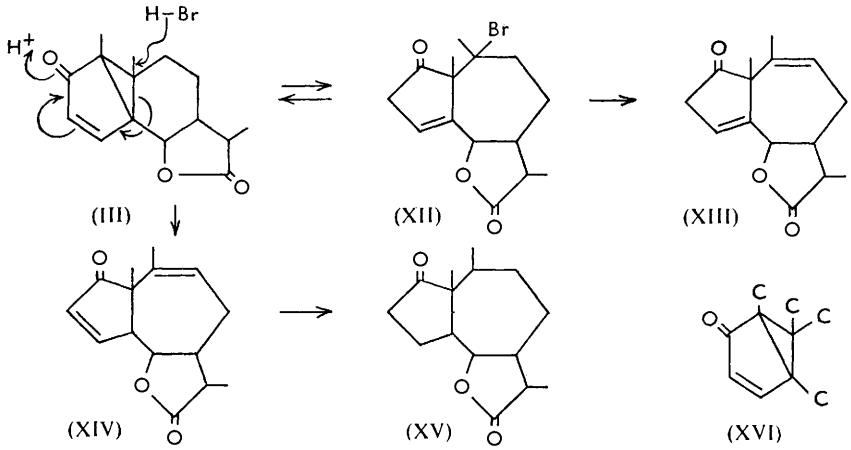


Treatment of lumisantonin (III) with osmium tetroxide furnished a crystalline glycol VII). This gave infrared bands at 3360 (hydroxyl), 1770 (γ-lactone), and 1726 cm.$^{-1}$ (*cyclo*pentanone), had the same ultraviolet absorption as dihydrolumisantonin (IV), and consumed two mols. of periodic acid to afford a C_{14} aldehydo-acid. This acid is regarded as existing in the lactol form (VIII) since it exhibited no ultraviolet or infrared aldehyde absorption. It gave a positive Fehling's test (lumisantonin and its dihydro-derivative

did not, under the same conditions) and consumed one atom of oxygen on titration with chromic acid. The product of oxidation was characterised as an anhydride (IX) by its infrared spectrum which showed bands at 1830 (anhydride) and 1770 cm.$^{-1}$ (superimposed anhydride and γ-lactone bands). The position of the anhydride band at 1830 cm.$^{-1}$ is what might be expected [5] for a succinic anhydride attached to a *cyclo*propane ring.

This evidence conclusively proves the presence of the grouping (CO·CH:CH) in lumisantonin. Ozonolysis studies confirm this. Treatment of lumisantonin with ozone gave formic acid (0·4 mol.) and a small amount of crystalline compound formulated as (X) (or equivalent open formula). This showed infrared bands at 3440 (hydroxyl) and 1755 cm.$^{-1}$ (broad band). With alkaline hydrogen peroxide the compound (X) was cleaved to a carboxylic acid (XI), the constitution of which followed when it was obtained also by opening the lactone ring of the lactol (VIII) with alkali.

Brief treatment of lumisantonin with hydrogen bromide in acetic acid afforded a non-conjugated *cyclo*pentenone (XII). This gave infrared bands (in CCl_4) at 1792 (γ-lactone), 1752 (βγ-unsaturated *cyclo*pentenone), and (in Nujol) at 1627, 802, 752, and 722 cm.$^{-1}$ (triply substituted ethylenic linkage). On treatment with boiling pyridine this product (XII) furnished a new non-conjugated dienone (XIII) [showing three CMe groups and infrared bands (in CCl_4) at 1792 (γ-lactone) and 1752 (βγ-unsaturated *cyclo*pentenone) and (in Nujol) at 1643, 815, 741, and 727 cm.$^{-1}$ (triply substituted double bond)] as well as



re-formed lumisantonin. The reversibility of the opening of the *cyclo*propane ring is thus demonstrated.

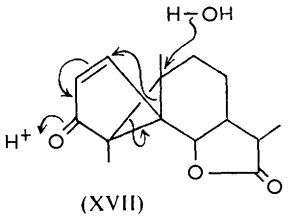
The bromo-ketone (XII) was unstable at room temperature: it liquefied and then resolidified to give a new conjugated dienone (XIV). The latter contained three *C*-Me groups and showed infrared bands at 1760 (γ-lactone), 1697 and 1660 (conjugated *cyclo*pentenone), and at 1630 and 722 cm.$^{-1}$ (triply substituted ethylenic linkage). The ultraviolet absorption spectrum disclosed an αβ-unsaturated ketone band at 220 mμ indicative [6] of the monosubstituted *cyclo*pentenone chromophore as shown in (XIV). On catalytic hydrogenation the ketone (XIV) readily consumed two mols. of hydrogen to give a saturated tetrahydro-ketone (XV).

The results described above show that lumisantonin must contain the partial expression (XVI). The full formula (III) may be deduced if one considers also the following readily occurring rearrangements of lumisantonin. Treatment with acetic acid containing a trace of perchloric acid afforded the 10-acetoxy-compound (cf. II). As mentioned above,

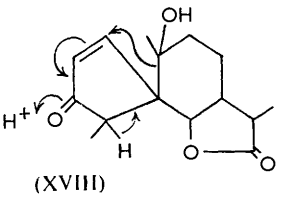
[5] Jones and Sandorfy in Weissberger's " Technique of Organic Chemistry," Vol. IX, Interscience Publ. Inc., New York, p. 456.

[6] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; Gillam and West, *J.*, 1942, 486.

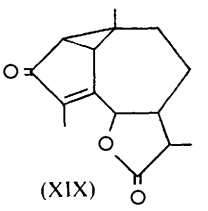
heating lumisantonin with aqueous acetic acid gave the 10-hydroxy-compound (II) itself. These rearrangements can be interpreted as in (XVII) * or as involving an intermediate (XVIII) which undergoes further rearrangement as indicated. The mild acid conditions required make the latter possibility somewhat improbable. It is of interest that opening of the *cyclo*propane ring by hydrogen bromide (see above), although leading to a different carbon skeleton, involves the same $C_{(5)} : C_{(10)}$ electron pair. With hydrogen bromide this electron pair becomes part of a π-bond system whereas with aqueous acetic acid it moves to establish a new carbon–carbon bond.



(XVII)



(XVIII)



(XIX)

By the irradiation of santonin in various solvents under different conditions the products obtained may be varied. The following facts are significant. Irradiation in hot aqueous acetic acid [1] gives the lactone (II). Irradiation in cold (0°) aqueous acetic acid affords equal amounts of this and of photosantonic acid. Lumisantonin (III) affords the lactone (II) with hot aqueous acetic acid, but is stable in the cold solvent. This suggests that there is a direct route from santonin to the lactone (II) not *via* lumisantonin, as well as a probable thermal route [3] through lumisantonin. In agreement, irradiation of lumisantonin in the cold gives photosantonic acid but no lactone (II).

It is possible, therefore, that irradiation of santonin gives an " activated state " which may collapse to lumisantonin or to the lactone (II) depending on the conditions of the experiment (temperature, acidity, etc.). The lumisantonin may then be transformed photochemically into photosantonic acid (or photosantonin) or thermally to the lactone (II). At present we visualise only the one route for the formation of photosantonic acid.

Professors Büchi and Jeger have been kind enough to send us a copy of their interesting paper on lumisantonin.[8] This provides independent evidence of the correctness of the constitution (III) and is so interpreted. Professor Cocker has also kindly sent us the proofs of his paper [9] on the same subject. The latter provides valuable experimental facts which we consider, when correctly viewed, to provide support for formula (III). The constitution (XIX) proposed by Cocker and his collaborators [9] does not comply with the evidence reported in the present paper. In particular it does not contain the system CO·CH:CH.

Experimental

$[\alpha]_D$ are in $CHCl_3$ unless stated otherwise; ultraviolet absorption spectra refer to EtOH solution. Infrared spectra were kindly determined by Dr. G. Eglinton and his colleagues, for Nujol mulls unless specified to the contrary. The silica for chromatography was supplied by B.D.H.; the term light petroleum refers to the fraction of b. p. 40—60°.

Lumisantonin.—Santonin (14 g.) in absolute ethanol (600 ml.) was irradiated in a Pyrex flask under reflux with a 125 w Crompton bare-arc mercury lamp. The progress of the

* We are grateful to Professor R. B. Woodward (Harvard) for pointing out that the rearrangement could be regarded equally as proceeding through a *cyclo*butonium ion.[7]

[7] See Roberts and Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 3542; Woodward and Kovach, *ibid.*, 1950, **72**, 1009.

[8] Arigoni, Bosshard, Bruderer, Büchi, Jeger, and Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732.

[9] Cocker, Crowley, Edward, McMurry, and Stuart, *J.*, 1957, 3416.

reaction was followed by the growth of an infrared peak at 1707 cm.$^{-1}$. Previous studies had shown that the best yield was obtained if the reaction was interrupted when this peak was, with the exception of the lactone carbonyl band, the strongest present in the carbonyl region of the spectrum. Isolation of the product and chromatography over silica gel (500 g.) gave, after elution with benzene–light petroleum (1 : 1) and crystallisation from the same solvents, *lumisantonin* (III) (1·8 g.), m. p. 153—155°, $[\alpha]_D$ −169° (*c* 1·2), $\lambda_{max.}$ 239 mμ (ε 5800) (Found: C, 73·3; H, 7·1; *C*-Me, 14·9. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35; 3*C*-Me, 18·3%). Elution of the column with benzene–light petroleum (1 : 4) then afforded, after crystallisation (from carbon tetrachloride–light petroleum), photosantonin (2·0 g.), m. p. 67—68·5°, $[\alpha]_D$ −121° (*c* 1·3 in EtOH).

Dihydrolumisantonin.—Lumisantonin (50 mg.) in ethyl acetate (5 ml.) was hydrogenated in the presence of 5% palladised charcoal (50 mg.), 1 mol. of hydrogen being absorbed. Crystallisation from ethyl acetate–light petroleum gave *dihydrolumisantonin* (IV), m. p. 160—162°, $[\alpha]_D$ −59° (*c* 0·9), $\lambda_{max.}$ 214 mμ (ε4600) (Found: C, 72·95; H, 7·75. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). The compound was recovered unchanged under the ozonolytic conditions used for the degradation of lumisantonin.

Ozonolysis of Lumisantonin.—Lumisantonin (200 mg.) in chloroform (600 ml.) was ozonised at −25° for 25 min. (until disappearance of the max. at 239 mμ). Steam-distillation afforded 0·4 mol. of formic acid [identified by the infrared spectrum of its sodium salt (KCl disc)] but no acetic acid. Isolation of the residue from the steam-distillation, and crystallisation from water, gave the *lactol* (X), m. p. 86—89°, $[\alpha]_D$ −20° (*c* 1·2) [Found: C, 60·85; H, 6·35%; equiv. (by titration), 147. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·15%; equiv. (for 2 acidic functions), 147].

Action of Hydrogen Peroxide on the Lactol (X).—The lactol (53 mg.) in ethanol (10 ml.) containing 4N-aqueous sodium hydroxide (2 ml.) was treated with 30% hydrogen peroxide (3 ml.) and set aside for 20 min. Working up in the usual way and crystallisation from acetone–light petroleum gave the *carboxylic acid* (XI), m. p. 195—200° (decomp.), $[\alpha]_D$ +59° (*c* 0·87 in EtOH) (Found: C, 58·9; H, 6·8. $C_{14}H_{20}O_6$ requires C, 59·15; H, 7·1%).

Reaction of Lumisantonin (III) *with Osmium Tetroxide.*—Lumisantonin (400 mg.) and osmium tetroxide (540 mg.) in dry dioxan (5 ml.) were set aside for 5 days. Decomposition of the complex with hydrogen sulphide and crystallisation of the product from methanol–chloroform–light petroleum gave the *diol* (VII), m. p. 178—183° (decomp.), $[\alpha]_D$ +35° (*c* 1·11), $\lambda_{max.}$ 214 mμ (ε 4200) (Found: C, 64·25; H, 7·1. $C_{15}H_{20}O_5$ requires C, 64·25; H, 7·2%).

Periodic Acid Cleavage and Hydrolysis of the Diol (VII).—The diol (150 mg.) in ethanol (25 ml.) was treated with 0·05N-aqueous periodic acid (80 ml.) and kept for 2 hr. (consumption of 2·2 atoms of oxygen). Isolation of the product and crystallisation from chloroform–light petroleum afforded the cleavage *product* (VIII), m. p. 127—129° with solidification and remelting at 172—173°, $[\alpha]_D$ −25° (*c* 0·85) (Found: C, 63·15; H, 6·6. $C_{14}H_{18}O_5$ requires C, 63·15; H, 6·8%). The substance gave a positive Fehling's test.

The product (VIII) (46 mg.) in ethanol (2·5 ml.) containing 4N-aqueous sodium hydroxide (1 ml.) was kept at room temperature for 30 min. Isolation of the product in the usual way and crystallisation from chloroform–light petroleum afforded the acid (XI), identified by m. p., mixed m. p., and infrared spectrum.

Oxidation of the Cleavage Product (VIII).—The substance (47 mg.) in acetic acid (10 ml.) was treated with sodium dichromate (67 mg.) and set aside for 22 hr. (uptake of 1 atom of oxygen). Isolation of the product in the usual way gave the *anhydride* (IX) as a glass which was purified by sublimation at 150°/10^{-4} mm.; it then melted over the range 66—69° and had $[\alpha]_D$ −105° (*c* 1·13) [Found: C, 63·35; H, 6·3%; equiv., 96·5. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%; equiv. (as tribasic acid), 84·8].

Formation of 10-*Hydroxy*-3-*oxoguai*-4-*en*-6 : 12-*olide* (II).—Lumisantonin (50 mg.) in 45% acetic acid (3 ml.) was refluxed in the dark for 3 hr. (no further change in $[\alpha]_D$). Crystallisation of the product from ethyl acetate–light petroleum gave the guaianólide (II) (20 mg.), m. p. and mixed m. p. 165—167°, having the same infrared spectrum as an authentic specimen.

Formation of 10-*Acetoxy*-3-*oxoguai*-4-*en*-6 : 12-*olide*.—Lumisantonin (102 mg.) in acetic acid (5 ml.) was treated with 70% perchloric acid (0·05 ml.). After 18 min. isolation of the product, chromatography over silica gel (4 g.), elution with benzene, and crystallisation from ethyl acetate–light petroleum gave the required acetate, m. p. 175—177° identical with an authentic sample prepared by the method of Cannizzaro and Fabris.[10]

[10] Cannizzaro and Fabris, *Ber.*, 1886, **19**, 2261.

Reaction of Dihydrolumisantonin with Acetic Acid.—Dihydrolumisantonin (IV) (200 mg.) in 45% acetic acid (17 ml.) was refluxed for 6 hr. (no further change in rotation). Isolation of the product, chromatography over silica gel (7 g.), elution with benzene, and crystallisation from chloroform–light petroleum gave the *ketone* (V), m. p. 192—202° (decomp.), $[\alpha]_D$ +53° (*c* 0·93), $\lambda_{max.}$ 208 mμ (ε 1900) (Found: C, 72·35; H, 8·15; *C*-Me, 17·03. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1; 3*C*-Me, 18·15%).

Elution of the column with benzene–ether (4 : 1) and crystallisation from chloroform–light petroleum gave the hydroxy-ketone (VI), m. p. 183—204° (decomp.), $[\alpha]_D$ +106° (*c* 1·00) (Found: C, 67·35; H, 8·5. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%).

Reaction of Lumisantonin with Hydrogen Bromide.—Lumisantonin (100 mg.) in benzene (2 ml.) was treated with 5 drops of a 50% w/v solution of hydrogen bromide in acetic acid, and the mixture kept for 5 min. After isolation in the usual way the product was crystallised from ethyl acetate–light petroleum, to give the *bromo-ketone* (XII), m. p. 111—114°, $[\alpha]_D$ −130° (*c* 1·45) (Found: C, 55·6; H, 6·25; Br, 24·2. $C_{15}H_{19}O_3Br$ requires C, 55·55; H, 5·85; Br, 24·4%).

Spontaneous Decomposition of the Bromo-Ketone (XII).—When kept at room temperature, the bromo-ketone (150 mg.) liquefied after 2 days and then gradually (*ca.* 1 week) crystallised. The product was chromatographed over silica gel (6 g.). Elution with benzene–light petroleum (3 : 1) gave, on crystallisation from carbon tetrachloride–light petroleum, the *dienone* (XIV), m. p. 128—130°, $[\alpha]_D$ −168° (*c* 1·62), $\lambda_{max.}$ 220 mμ (ε 10,850) (Found: C, 72·95; H, 7·35; *C*-Me, 16·8. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35; 3*C*-Me, 18·3%).

The dienone (XIV) (46·7 mg.) in ethyl acetate (5 ml.) was hydrogenated over 5% palladised charcoal (32 mg.), 2 mol. of hydrogen being absorbed. Isolation of the product and crystallisation from light petroleum gave the saturated *ketone* (XV), m. p. 62—65°, $[\alpha]_D$ −114° (*c* 1·16) (Found: C, 71·95; H, 8·56. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

Reaction of the Bromo-Ketone (XII) *with Pyridine.*—The bromo-ketone (300 mg.) in pyridine (15 ml.) was refluxed for 6 hr. Isolation of the product, chromatography over silica gel (12 g.), elution with benzene–light petroleum (1 : 1), and crystallisation from ethyl acetate–light petroleum, yielded the *dienone* (XIII), m. p. 181—183°, $[\alpha]_D$ −200° (*c* 0·74) (Found: C, 73·0; H, 6·8; *C*-Me, 14·6. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35; 3*C*-Me, 18·3%). Further elution of the column with benzene gave lumisantonin (III), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +165° (*c* 0·87)}, and infrared spectrum.

Cold Irradiation of Santonin.—Santonin (1·0 g.) in 45 : 55 (v/v) acetic acid–water (50 ml.) was irradiated between −5° to +5° for 1½ hr. The product was separated into acidic and neutral fractions. Both were chromatographed over silica, to give photosantonic acid (180 mg.) and 10-hydroxy-3-oxoguai-4-en-6 : 12-olide (II) (196 mg.), respectively.

Cold Irradiation of Lumisantonin (III).—Lumisantonin (500 mg.) was dissolved in acetic acid (12 ml.), and the mixture then diluted with water (14 ml.). Irradiation of the mixture at −5° to +5° for 1·5 hr., followed by isolation of the acidic portion in the usual way and crystallisation from chloroform–light petroleum, afforded photosantonic acid (350 mg.), identified by m. p. and mixed m. p. No *iso*photosantonic lactone could be isolated by chromatography.

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