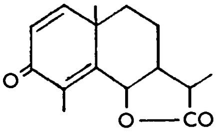
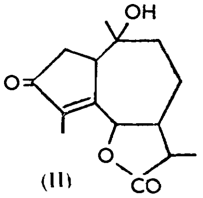
674. *Photochemical Transformations. Part V.* The Constitutions of Photosantonic Acid and Derivatives.*

By D. H. R. BARTON, P. DE MAYO, and M. SHAFIQ.

Experiments are described [1] which, when coupled with those of other workers, lead to the structure (XI; R = H) for photosantonic acid. The place of this acid in the pattern of the light-induced transformations of santonin is discussed, together with the nature of possible unstable intermediates.

IN previous Parts of this series [2,3] the constitutions of two of the irradiation products of santonin (I), namely, *iso*photosantonic lactone (II) and lumisantonin [4] (III), have been established. Photosantonic acid, the photochemical transformation product of santonin which received the most attention from the earlier workers,[5] can be prepared by irradiation of santonin in aqueous acetic acid or in aqueous solution containing one equivalent of potassium hydroxide. The corresponding ester, photosantonin, was produced [5] by irradiation in ethanolic solution. It was believed to be a dibasic acid, but it has been shown [2] that the supposed dibasic acid is the solvated acid lactone: crystallisation from non-aqueous solvents gives the non-solvated form.


(I)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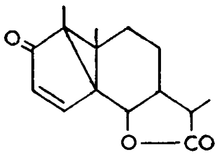
(III)

Photosantonin, $C_{17}H_{24}O_4$, contains an ethylenic linkage since, on titration with monoperphthalic acid, it consumes one atom of oxygen with formation of an epoxide. The environment of this double bond, in both photosantonin and in the derived hydroxy-acid ester, was shown by ozonolysis: acetone, characterised as its 2 : 4-dinitrophenylhydrazone, was obtained. The relation of this ethylenic linkage, now proved to be part of an *iso*propylidene grouping, to the carboxyl function in photosantonic acid was shown by a similar monoperphthalic acid oxidation. In place of the corresponding oxide a hydroxy-dilactone was obtained, derived by attack of the carboxyl group on the incipient epoxide. Since this substance exhibited bands in the infrared spectrum at 1755 (original γ-lactone) and 1735 (new lactone) cm.$^{-1}$, it must be a δ-lactone, whence two possibilities, A and B, for the partial structure of this hydroxy-dilactone follow. In a similar way bromination of photosantonic acid gave a bromo-lactone, also, since it had an infrared band at 1730 cm.$^{-1}$, to be formulated as a δ-lactone. This was reduced

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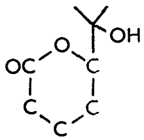

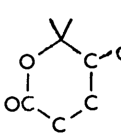
(B)

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* Part IV, *J.*, 1958, 688.

[1] For a preliminary communication, see Barton, de Mayo, and Shafiq, *Proc. Chem. Soc.*, 1957, 345.

[2] *Idem, J.*, 1957, 929.

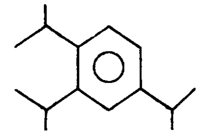
[3] *Idem, J.*, 1958, 140.

[4] See also Arigoni, Bosshard, Bruderer, Büchi, and Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732; Cocker, Crowley, Edward, McMurry, and Stuart, *J.*, 1957, 3416.

[5] For summary see Simonsen and Barton, " The Terpenes," Vol. III, p. 292, Cambridge Univ. Press, 1952.

back to photosantonic acid with zinc and acetic acid, which regeneration precludes the possibility of rearrangement during the bromination.

The earlier Italian workers[5] found that passage of hydrogen chloride through an ethanolic solution of photosantonic acid and subsequent base-hydrolysis gave a mixture of optically active and racemic aromatic dicarboxylic acids which they formulated as (IV). By distillation from barium hydroxide, the racemic acid was converted into the hydrocarbon (V), the structure of which was convincingly established. However, the alternative structure (VI) for the dicarboxylic acid is in accord with its further degradation products, and in addition explains why, when photosantonic acid is heated with hydriodic acid to give pyrophotosantonic acid,[5] only one carboxyl group is lost [the pyro-acid would be (VII)].



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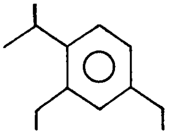
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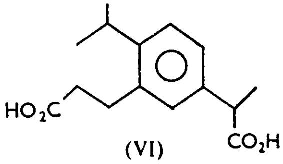
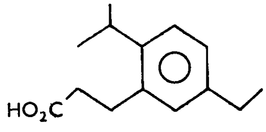


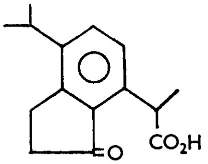
(VI)



(VII)

Repetition of the preparation of the aromatic dicarboxylic acids followed by cyclisation in concentrated sulphuric acid gave an indanone (VIII), characterised as the methyl ester 2 : 4-dinitrophenylhydrazone. This demonstrates the correctness of formulæ (VI) and (VII).

With this evidence the partial structure (IX) can be written for photosantonic acid, one



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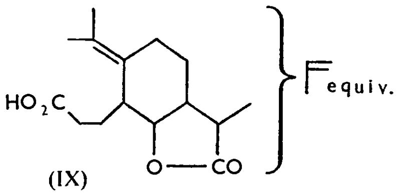

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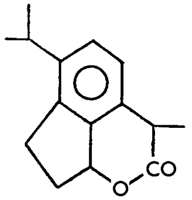
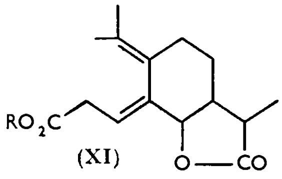
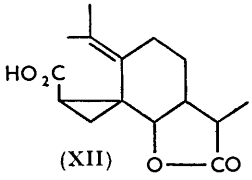


(X)

double-bond or ring remaining to be incorporated. In the latter case the proviso must be made that on treatment with hydrogen chloride the ring is cleaved with generation of a double-bond.



(XI)



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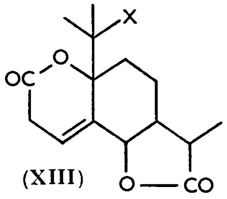

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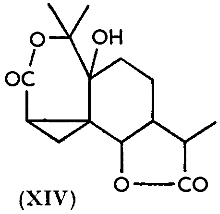

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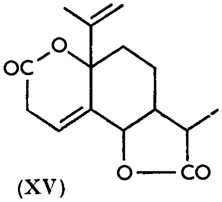

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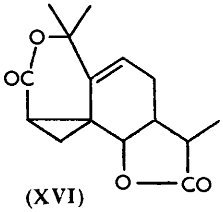
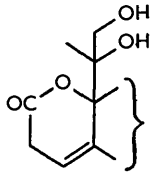


(XVI)

Support for (IX) was adduced as follows. First, the carboxyl group in (VIII) was shown to be δ to the ketonic function by reduction to the alcohol with potassium borohydride and cyclisation to the δ-lactone (X). Secondly, photosantonin and photosantonic acid contain one methyl group less than santonin (Kuhn–Roth determination). Finally, oxidation with acidic permanganate solution gave succinic acid, in agreement with the presence of the grouping $\cdot C\cdot CH_2\cdot CH_2\cdot C\cdot$.

From this evidence, and from the fact that photosantonic acid is not an αβ-unsaturated acid, two structures (XI; R = H) or (XII), can be deduced. Correspondingly, (XIII; X = OH) or (XIV) will be then the hydroxy-lactone. By dehydration of the hydroxy-lactone with thionyl chloride and pyridine an anhydro-compound was obtained now to be formulated as (XV) or (XVI). Since the anhydro-compound did not show the intense band ($\varepsilon \sim 150$) near 890 cm.$^{-1}$ expected of an *iso*propenyl group as in (XV), because it did not give formaldehyde easily on ozonolysis, and because the bromo-lactone mentioned above is rather stable to ozone, the structure (XII) for photosantonic acid was initially favoured.[1] This formula adequately accounted for the ultraviolet spectrum of photosantonin (see Experimental section) and for the fact that this spectrum was unchanged on reduction of the compound with lithium aluminium hydride to give the corresponding triol, characterised as its triacetate.

No band was observed at 3050 cm.$^{-1}$ in the infrared spectrum of photosantonin or in the derived triol although this was to be expected[6] from the presence of a CH_2 in a *cyclo*propane ring. However, this was largely discounted by the discovery that dimethyl *trans*-*cyclo*propane-1 : 2-dicarboxylate also did not show this band. Additional indications of the unreliability of this characteristic have appeared.[7]



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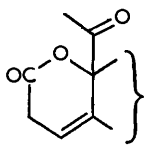

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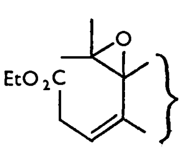

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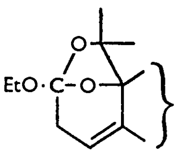
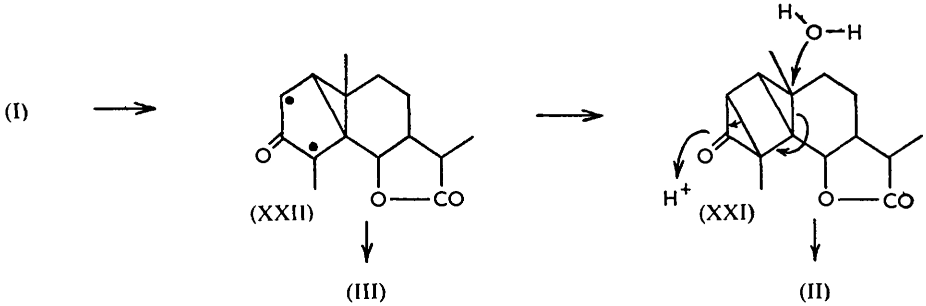


(XX)

Very recently van Tamelen and his collaborators[8] have provided further evidence in favour of the part structure (IX) and, in addition, on the basis of nuclear magnetic resonance measurements, have demonstrated the presence of a vinylic hydrogen in photosantonin. This strongly supports structure (XI). We have now found that the intensity of the 890 cm.$^{-1}$ band, characteristic of the *iso*propenyl group, is profoundly modified by the presence of an α-substituent. Thus 1 : 2-dimethylallyl benzoate has a band at 890 cm.$^{-1}$ (ε *ca.* 25) comparable with that of the anhydro-compound (about 27).*



The correctness of structure (XI), first proposed by van Tamelen,[8] has been confirmed as follows. Treatment of the anhydro-compound with osmium tetroxide gives a separable mixture of two diols (XVII). Both of these with periodic acid take up one atom of

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* We are grateful to Dr. E. S. Waight for his unpublished results.

[6] Cole, *J.*, 1954, 3807.

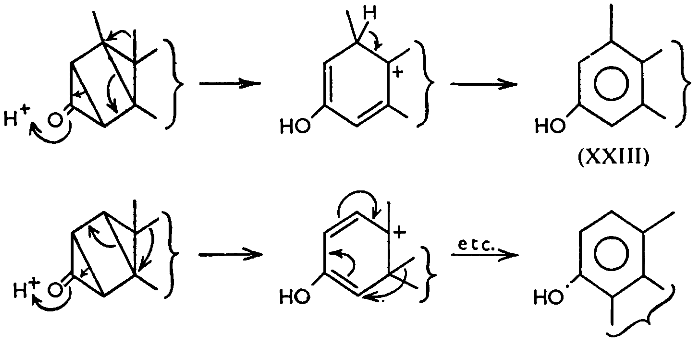
[7] Allen, Davis, Humphlett, and Stewart, *J. Org. Chem.*, 1957, **22**, 1291.

[8] van Tamelen, Levin, Brenner, Wolinsky, and Aldrich, *J. Amer. Chem. Soc.*, 1958, **80**, 501.

oxygen to give the same nor-ketone (XVIII). The alternative structure (XVI) would, of course, give a diketone without the loss of a carbon atom. The only evidence remaining against formula (XI; R = H) for photosantonic acid is its abnormal ultraviolet absorption spectrum. van Tamelen [8] has already commented on this and there is some analogy with 1 : 2-dimethylene*cyclo*hexane [9] to suggest that the spectrum of a compound like (XI; R = H) might be highly abnormal.

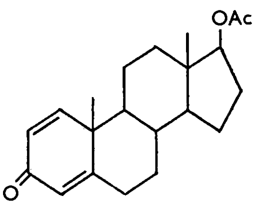
An interesting transformation product of photosantonin epoxide (XIX) was obtained on treatment with the boron–trifluoride ether complex. The product [10] showed no carbonyl band in the infrared spectrum other than that at 1778 cm.$^{-1}$ due to the γ-lactone, and is accordingly formulated as the orthoester (XX). In agreement with this, dissolution in aqueous ethanol containing hydrochloric acid rapidly converted it into the same hydroxy-dilactone (XIII; X = OH) obtained by the direct action of monoperphthalic acid on photosantonic acid (IX; R = H).

The existence of two routes for the photochemical conversion of santonin (I) into the lactone (II) has already been discussed.[3] There is a direct route, certainly operative for temperatures at or below room temperature, and an indirect route *via* lumisantonin (III) which may be of some significance in refluxing aqueous acetic acid, although this is not obligatory. It is possible that there may be an unstable intermediate such as (XXI),[11] formed through (XXII), in the direct process. This, by the action of aqueous solvent, could be readily transformed, as indicated, into *iso*photosantonic lactone (II). Lumisantonin (III) might be derived from (XXII) by a simple redistribution of electrons.



(XXIII)

(XXIV)



(XXV)

It is of some interest that the intermediate (XXI) would account for the formation of phenols of both the *meta*- (as XXIII) and *para*-type (as XXIV) observed by Jeger and his collaborators [12] in the irradiation of the steroid (XXV).

EXPERIMENTAL

Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$ solutions; ultraviolet absorption spectra were determined, for EtOH solutions, on the Unicam S.P. 500 Spectrophotometer; infrared spectra refer to Nujol mulls unless otherwise indicated. Unless stated to the contrary, the light petroleum used was of b. p. 40—60°. M. p.s were determined on the Kofler block.

Photosantonin (XI; R = Et).—Santonin (12 g.) in ethanol (600 ml.) was irradiated in a Pyrex flask by means of a bare mercury arc (125 w), the process being followed by infrared spectroscopy. When the new peak in the carbonyl region (at 1736 cm.$^{-1}$) was stronger than all others in that region except that due to the γ-lactone the reaction was interrupted. Evaporation, chromatography on silica (450 g.), and elution with benzene–light petroleum (1 : 4), gave photosantonin (IX; R = Et) (4·8 g.), m. p. 67—68·5° (from carbon tetrachloride–light petroleum), $[\alpha]_D$ −121° (*c* 1·3 in EtOH), ε 8500 at 204 mμ (Found: *C*-Me, 14·6. Calc. for $C_{17}H_{24}O_4$: 3*C*-Me, 15·6%).

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[9] Blomquist and Longone, *J. Amer. Chem. Soc.*, 1957, **79**, 3916.

[10] This compound has also been prepared by Professor G. Büchi (M.I.T.) (personal communication).

[11] Barton, *Proc. Chem. Soc.*, 1958, 61.

[12] Dutler, Bosshard, and Jeger, *Helv. Chim. Acta*, 1957, **40**, 494.

The ester (95 mg.) in ethanol (3 ml.) was shaken with 10% aqueous potassium carbonate (2 ml.) at room temperature for 24 hr. Isolation of the acidic fraction and crystallisation from ethanol–light petroleum gave the *hydroxy-dicarboxylic acid monoethyl ester*, m. p. 138—140°, $[\alpha]_D$ −24° (*c* 1·12) (Found: C, 65·6; H, 8·25; OEt, 15·05. $C_{17}H_{26}O_5$ requires C, 65·8; H, 8·45; 1OEt, 14·5%). Attempted acetylation of the hydroxy-acid re-formed photosantonin, identified by m. p., mixed m. p., and infrared spectrum.

Photosantonic Acid (XI; R = H).—A Kuhn–Roth determination gave *C*-Me 9·8% (Calc. for $C_{15}H_{20}O_4$: 2*C*-Me, 11·4%). Esterification of the acid (41·3 mg.) with ethereal diazomethane gave, after evaporation and crystallisation of the product from ether–light petroleum, the *methyl ester* (XI; R = Me), m. p. 54·5—55°, $[\alpha]_D$ −119° (*c* 0·85) (Found: C, 69·15; H, 8·05. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·95%).

Ozonolysis of Photosantonin.—The ester (70 mg.) in methylene dichloride (40 ml.) was ozonised at −60° for 20 min., after which there was no ultraviolet absorption in the 210 mμ region. Steam-distillation of the product into a solution of 2 : 4-dinitrophenylhydrazine in dilute sulphuric acid followed by isolation of the derivative and chromatography on bentonite–kieselguhr gave acetone 2 : 4-dinitrophenylhydrazone (14 mg., 23%), identified by m. p. and mixed m. p. (Found: C, 45·6; H, 4·4; N, 23·65. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·25; N, 23·5%). Under similar conditions the corresponding hydroxy-acid (see above) (72 mg.) also gave acetone 2 : 4-dinitrophenylhydrazone (13·5 mg., 24%).

Photosantonin Epoxide (XIX).—The ester (100 mg.) in ether (50 ml.) was treated with an excess (5 ml.) of ethereal 0·3N-monoperphthalic acid and kept overnight. Titration indicated an uptake of 0·97 atom-equiv. of oxygen. Isolation of the product and crystallisation from carbon tetrachloride–light petroleum gave the *epoxide* (XIX), m. p. 87—90°, $[\alpha]_D$ +10° (*c* 1·27), ε 4900 at 204 mμ (Found: C, 66·45; H, 7·65. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

Photosantonin Ethyl Orthoester (XX).—The epoxide (100 mg.) in ether (50 ml.) was treated with the boron trifluoride–ether complex (3 ml.) and kept for 4 min. at room temperature. Isolation of the product in the usual way and crystallisation from chloroform–light petroleum afforded the *orthoester* (XX), m. p. 167—169°, $[\alpha]_D$ +98° (*c* 1·03), ε 3100 at 204 mμ (Found: C, 66·0; H, 7·6; OEt, 14·5. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85; 1OEt, 14·6%).

The orthoester (100 mg.) in alcohol (50 ml.) was treated with concentrated hydrochloric acid (5 ml.), and the mixture diluted with water (50 ml.). After 30 min. the mixture was further diluted and the product isolated in the usual way. Crystallisation from ethyl acetate–light petroleum then afforded the *hydroxy-dilactone* (XIII; X = OH), m. p. 172—175°, $[\alpha]_D$ +41° (*c* 1·53), ε 2300 at 204 mμ (Found: C, 64·25; H, 7·05. $C_{15}H_{20}O_5$ requires C, 64·25; H, 7·2%). The same substance was prepared in the following way. Photosantonic acid (128 mg.) in chloroform (50 ml.) was treated with ethereal 1·5N-monoperphthalic acid (2 ml.) and kept at room temperature overnight. Titration indicated the consumption of 1·06 atom-equivs. of oxygen. Isolation of the product in the usual way afforded the hydroxy-dilactone, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +41° (*c* 1·5)}, and infrared spectrum. The compound was recovered after attempted acetylation (acetic anhydride–pyridine) at room temperature overnight.

The Unsaturated Dilactone (XV).—The hydroxy-dilactone (XIII; X = OH) (50 mg.) in pyridine (3 ml.)w as treated with thionyl chloride (400 mg.) and kept at 0° for 15 min. Decomposition of the excess of acid chloride with water and isolation of the product in the usual way afforded the *anhydro-compound* (XV), m. p. 137—139°, $[\alpha]_D$ +88° (*c* 1·02), ε 3800 at 204 mμ (Found: C, 68·45; H, 6·95. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Ozonolysis, as described for photosantonin, and steam-distillation into a solution of dimedone did not afford formaldehyde dimethone.

Photosantonic Acid Bromo-lactone (XIII; X = Br).—Photosantonic acid (108 mg.) in chloroform (30 ml.) containing bromine (1·7 mol.) was kept for 2 min., titration then indicating the uptake of 1·1 mol. of bromine. Isolation of the product and crystallisation from chloroform–light petroleum afforded the *bromo-lactone* (XIII; X = Br) (81 mg.), m. p. 173—177° $[\alpha]_D$ +30° (*c* 1·46), ε 2400 at 204 mμ (Found: C, 52·55; H, 5·8; Br, 23·4. $C_{15}H_{19}O_4Br$ requires C, 52·5; H, 5·6; Br, 23·3%).

The bromo-lactone (21·7 mg.) in acetic acid (2 ml.) containing zinc dust (40 mg.) was refluxed for 4 hr. Isolation in the usual way afforded regenerated photosantonic acid, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ −129° (*c* 1·0)}, and infrared spectrum.

Oxidation of Photosantonin.—Photosantonin (500 mg.), suspended in water (10 ml.), was treated dropwise with 5% aqueous potassium permanganate (135 ml.) on the steam-bath. At the same time 8% sulphuric acid was added so that the solution remained faintly acidic during the oxidation. After removal of manganese salts and manganese dioxide the volume was reduced to 10 ml. and the residue continuously extracted with ether. Conversion of the material removed by the ether into the *p*-bromophenacyl derivative gave this ester of succinic acid, identified by m. p. (210—212°), mixed m. p., and analysis (Found: C, 46·9; H, 3·7; Br, 30·9. Calc. for $C_{20}H_{16}O_6Br_2$: C, 46·9; H, 3·15; Br, 31·2%). The acid itself was also isolated from the ether extract by crystallisation from ether–light petroleum and identified by m. p., mixed m. p., and infrared spectrum (KCl disc).

Cyclisation of the "Dehydrophotosantonic Acid."—Photosantonin (1 g.) in ethanol (20 ml.) was subjected to a stream of hydrogen chloride for 6 hr. at room temperature, the mixture then being left overnight. Isolation of the product followed by alkaline hydrolysis in aqueous ethanol gave acidic material. Chromatography of this on silica and elution with benzene–ether (25 : 1) gave a mixture of active and racemic " dehydrophotosantonic acids," m. p. 133—135°, $[\alpha]_D$ +18° (*c* 3·1 in EtOH). The acid mixture (140 mg.) was heated in concentrated sulphuric acid (3 ml.) on the steam-bath for 5 min. Isolation and chromatography of the product on silica (5 g.), and elution with benzene, gave 7-1'-*carboxyethyl*-4-iso*propylindan*-1-*one* (VIII), m. p. 111—112° (from ethyl acetate–light petroleum), $[\alpha]_D$ ±0° (*c* 1·2 in EtOH), $\lambda_{max.}$ 254 mμ (ε 8700), showing a broad infrared maximum at 1695 cm.$^{-1}$ (Found: C, 73·55; H, 7·7. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The indanone (60 mg.) was methylated with ethereal diazomethane and the product treated with 2 : 4-dinitrophenylhydrazine, to give the 2 : 4-*dinitrophenylhydrazone*, m. p. 104—107° (from ethyl acetate–light petroleum), $\lambda_{max.}$ 390 mμ (ε 35,000) (Found: C, 59·85; H, 5·55; N, 12·5. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5; N 12·70%).

Reduction of the Indanone (VIII).—The indanone (90 mg.) was set aside in ethanolic solution (3 ml.) containing potassium borohydride (200 mg.) for 10 min. Isolation of the product and crystallisation from chloroform–ether–light petroleum afforded the *indanol*, m. p. 119—124° (rapid heating) (Found: C, 72·85; H, 8·15. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

This alcohol (50 mg.) was heated at 130° for 1 hr. After separation into acidic and neutral material the neutral oil was sublimed at 150°/0·001 mm., to give the oily *lactone* (X) (Found: C, 78·0; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·25; H, 7·9%).

Reduction of Photosantonin by Lithium Aluminium Hydride.—Photosantonin (500 mg.) in ether (100 ml.) was treated with a solution of lithium aluminium hydride (1·5 g.) in ether (100 ml.). After 17 hr. the excess of reagent was decomposed; isolation in the usual way afforded the *triol*, m. p. 127·5—129·5° (from chloroform–light petroleum), $[\alpha]_D$ −69° (*c* 2·1), ε 9400, 6800, and 1400 at 208, 220, and 240 mμ respectively (Found: C, 70·65; H, 10·3. $C_{15}H_{26}O_3$ requires C, 70·85; H, 10·3%). The triol (89 mg.) in pyridine (3 ml.) was treated overnight at room temperature with acetic anhydride (3 ml.). The oily *triacetate* thus formed was purified by sublimation at 150°/0·001 mm. (Found: C, 66·6; H, 8·75. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5%).

Preparation of the Nor-ketone (XVIII) (with O. C. Böckman).—The anhydro-compound (XV) (186 mg.) in dioxan (1·5 ml.) was added to a solution of osmium tetroxide (285 mg.) in dioxan (2 ml.) containing pyridine (3 drops). After 5 days the osmic ester was decomposed with hydrogen sulphide to give, after isolation in the usual way, by fractional crystallisation *diol-I*, m. p. 148—150° (from ethyl acetate–light petroleum), $[\alpha]_D$ +43° (*c* 0·77 in EtOH) (Found: C, 61·05; H, 7·0. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%), and *diol-II*, m. p. 220—225° (from ethyl acetate–ethanol), $[\alpha]_D$ +9° (*c* 0·74 in EtOH) (Found: C, 60·25; H, 6·9. $C_{15}H_{20}O_6,\frac{1}{2}C_2H_5OH$ requires C, 60·2; H, 7·25%).

In preliminary experiments both diols consumed one atom of oxygen on titration with periodic acid. The diol-I (25 mg.) in aqueous dioxan containing periodic acid (110 ml.; 0·035N) was allowed to stand 3 hr. Iisolation of the product gave the *nor-ketone* (XVIII), m. p. 97—98°, $[\alpha]_D$ +210° (*c* 1·1) (Found: C, 63·6; H, 6·15. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). The same compound was isolated by cleavage of diol-II.

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