# PHOTOCHEMICAL TRANSFORMATIONS OF SANTONIN

Thesis submitted

by

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of

Doctor of Philosophy

of the

University of Glasgow

Chemistry Department

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CONTENTS

## SESQUITERPENOIDS

The chemistry of terpenoids has long been an active centre of investigations for organic chemists. This has not only been because of their intrinsic interest, but because they have lent themselves to theoretical and mechanistic as well as synthetic studies. As a result, the field has been actively explored for over a century.

A terpenoid can best be defined as a compound whose carbon skeleton is either (a) theoretically constructed from isoprenoid (1) units or (b) has at some stage in its biogenesis had a carbon skeleton so constructed[1]. Hence a sesquiterpenoid can be defined as a compound, built up of three isoprene units. The great majority of these compounds can be regarded as made up of these three isoprene units joined together in head to tail fashion. It was this so called 'isoprene rule' which led chemists to the elucidation of the 'biogenesis' of the terpenoids.

### The isoprene rule and the biogenesis of sesquiterpenoids

During the investigations by Ruzicka and co-workers[2] on cadinene and eudesmol, it was realised that their carbon skeletons could, formally, be formed from farnesol (2). This facilitated the elucidation of their structures to a great

extent. It was also noticed that farnesol, and the sesquiterpenoids derived from it, contained three isoprene units in regular head to tail arrangement. This, therefore, represents the common structural feature which interlinks the various sesquiterpenoids.

This isoprene rule has found extensive application in the field of sesquiterpenoid chemistry. It is found that each group of sesquiterpenoids has its own special variation of the rule, as is illustrated in table I. Even the somewhat peculiar-looking carbon skeletons of such compounds as $\alpha$-santalene, patchouli alcohol, cedrene[3] and caryophyllene[4] etc.etc. are derivable from that of farnesol. This very close structural relationship of farnesol with other sequiterpenoids led to the formulation of the 'farnesol rule' which postulates that the carbon skeletons of most of the sesquiterpenoids can be derived, formally, from that of farnesol. This is a special case of the 'isoprene rule'.

It was later found that only carotol[5], from the sesquiterpenoid family defied the farnesol rule, although it was built up of three irregular isoprene units. Laserpitin has recently been shown to have the same skeleton as carotol. Eremophilone[7] was found to be the only exception to the isoprene rule. Sir Robert Robinson[8] has suggested that even the carbon skeleton of eremophilone (4) can be derived from

an eudesmol type precursor (5) by the migration of a methyl group.

The preceding discussion of the isoprene rule as well as of the farnesol rule suggests that farnesol, or its equivalent, may possibly be the biogenetic precursor of the sesquiterpenoids. Indeed, the acid-catalysed cyclisation of farnesol or nerolidol was experimentally accomplished in Zurich[9]. Amongst the products formed were bisabolene and a mixture of hexahydrocadalenes (Table I).

The process of biogenetic conversion of farnesol to the various sesquiterpenoids has, therefore, been interpreted as occuring through the formation of cation intermediates[10]. This theory predicts satisfactorily the products of cyclisations of these reactions.

In the laboratory only a few of the possible cyclisations have been carried out. The course of such cyclisation is not only dependent on reaction mechanism, but to a considerable degree, also on the conformation of the precursor as well as the intermediate. In nature, enzymes bring about the required conformation and then cause the reaction to follow specific routes. The recent discovery by Tavolmina that mevalonic acid is a very efficient biogenetic precursor for squalene and hence for cholesterol etc., is of

great significance.[11,12] It may well be that mevalonic acid, containing two isoprene units, is also the biogenetic precursor for farnesol and hence for all the sesquiterpenoids formally derivable from it.

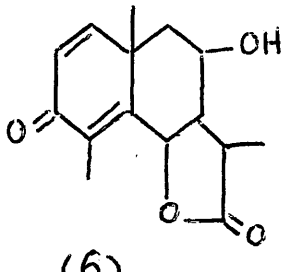
It shall not therefore be out of place to mention here some of the sesquiterpenoids relevant to the present study and their interesting reactions.

Sesquiterpenoid lactones

Possibly the most interesting sub-group in the sesquiterpenoids is that of the lactones, many of which are bitter principles. Amongst these sesquiterpenoid lactones based on the decalin system, santonin (38), to be described later, is the most important. Others include artemisin[3,14] (6) and ψ-santonin[3,90] (7); although ψ-santonin is not a cyclohexadienone it still undergoes the acid-catalysed aromatisation to desmotropo ψ-santonin (8). (See page 11 ).

Pyrethrosin, another interesting sesquiterpenoid lactone, first isolated in 1891, has recently been shown by Barton and de Mayo to represent a new type of monocarbocyclic sesquiterpenoid[15]. Pyrethrosin (9) contains two ethylenic linkages, (one of which is conjugated with the lactone), an acetoxyl group and a cyclic ethereal oxygen atom. On heating

with acetic anhydride and toluene-p-sulphonic acid, pyrethrosin is converted into the cyclic derivative (10). This cyclisation suggests that the ring structure of pyrethrosin may be of some biogenetic significance, because, if one writes a ten-membered ring as in (11), then it is possible to construct, by establishing different bonds across the ring, the carbon skeletons of most of the bicyclic sesquiterpenoids.

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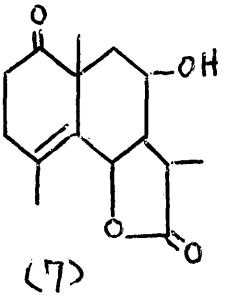


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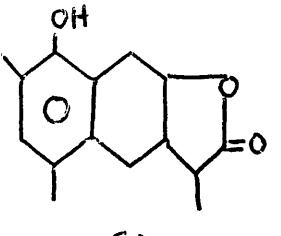


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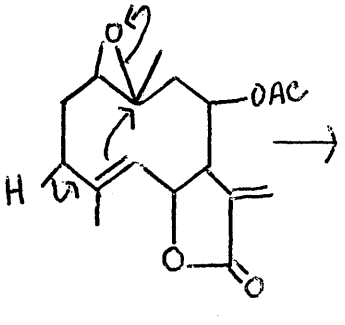


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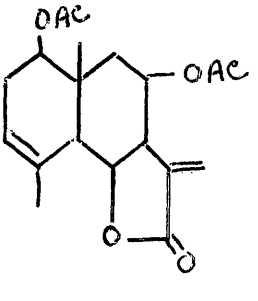


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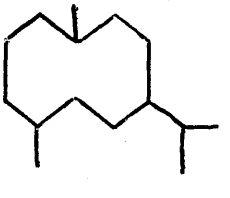
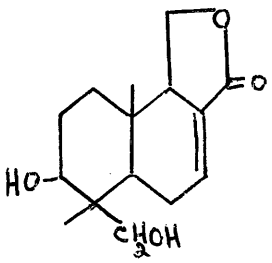


(11)

The dicyclofarnesol skeleton, usually found in di and triterpenoids, has recently been discovered in the sesquiterpenoid lactone iresin[16] (12). Drimenol[17] is now the second sesquiterpenoid compound shown by Brooks and Overton to possess the same skeleton (13).

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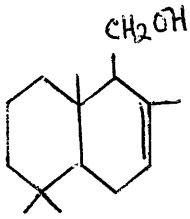


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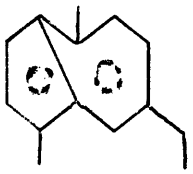

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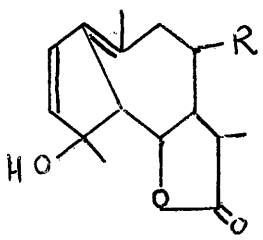


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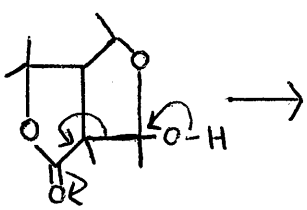

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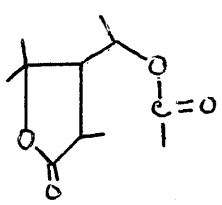

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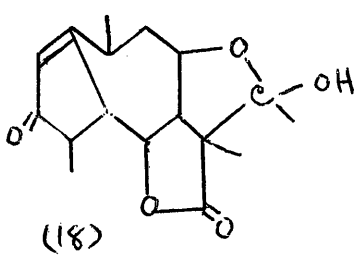


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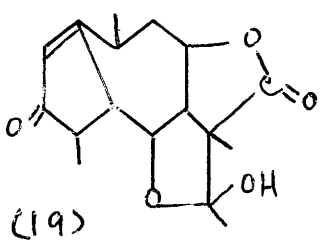


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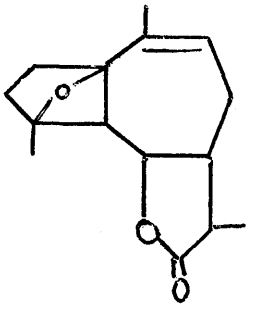
The chemistry of azulenic sesquiterpenoids has recently received serious attention. One may mention the 'chamazulene precursors' which afford chamazulene (14) with great facility[18,19]. Intensive investigation of the oil of wormwood has revealed the presence of an interesting yellow dihydro chamazulene, known as chamazulenogen, which is converted into chamazulene on mere exposure to air. Artabsin[20] (15 R = H) is the original chamazulenogen precursor in wormwood oil, while matricin[21] (15, R = OAC) has been shown to be the chamazulene precursor of oil of chamomile.

Tenulin and helenalin are the two bitter principles of various 'Helenium species'. The early work[22] on tenulin has recently been extended by Barton & de Mayo[23]. Tenulin,(18), a $\gamma$-lactone, contains an $\alpha\beta$- unsaturated cyclopentenone system and a hydroxyl group. Under very mild conditions tenulin is isomerised to <u>iso</u> tenulin which does not contain any hydroxyl grouping but instead has a true acetate residue. This masking of the acetate group was elegantly explained on the basis of this and other evidence as shown in formulae (16) and (17). Herz and co-workers[24] have favoured an alternative structure for tenulin, differing in the position of the carbonyl group. More recently the support has been withdrawn in favour of (18) on the basis of molecular rotation studies and nuclear magnetic resonance spectra[25]. It may however be mentioned that the

alternative structure (19) for tenulin is still being considered by Herz.[25]

Arborescin[26], isolated from '*Artemisia arborescenes*' is an isomer of artabsin, for which the constitution[26] (20) has been proposed. The structure contains the unusual feature of a trimethylene oxide ring. The constitution (20) however, is not entirely certain and the formulae (21) and (22) still



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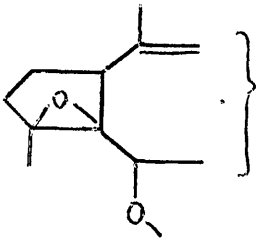

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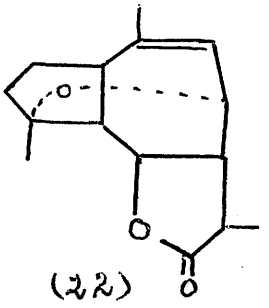

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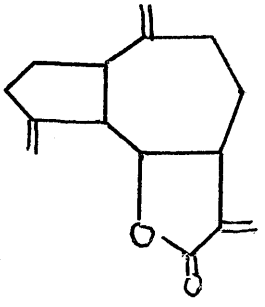

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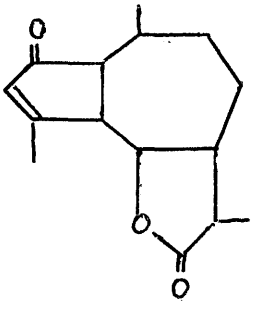

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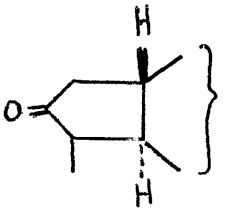


(25)

'costus oil' and [illegible] (24) from '*Carpesium abrotanoides*'.

alternative structure (19) for tenulin is still being considered by Herz.[25]

Arborescin[26], isolated from 'Artemisia arborescenes' is an isomer of artabsin, for which the constitution[26] (20) has been proposed. The structure contains the unusual feature of a trimethylene oxide ring. The constitution (20) however, is not entirely certain and the formulae (21) and (22) still remain to be excluded.

Other sesquiterpenoid lactones for which structures have been proposed are, dehydrocostus lactone[27] (23) from 'costus oil' and carpesia lactone[28,29] (24) from 'Carpesium abrotanoides'.

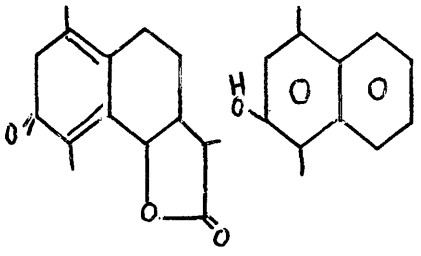
The stereochemical aspects of sesquiterpenoid compounds have not been investigated so intensively as in di and triterpenoids. The methods are, however, the same and one can mention degradation to a compound of known orientation, ring formation, conformational analysis[30] and stereospecific synthesis. The first method, however, also provides information on absolute configuration. Where degradation is not convenient, molecular rotation technique is resorted[31] to. Even then, the relative or absolute stereochemistry of a great number of sesquiterpenoid compounds is known. In this context one may mention the names of zingiberene[32], ~~e~~desmol[33], α-cyperone[34] and santonin[35] etc.etc.

Information about the stereochemistry of the perhydroazulenic sesquiterpenoids is scarce. However, mention may be made of a recent paper by Djerassi and Herz on the absolute configurations of dihydro-tenulin and dihydro-helenalin, their derivatives and iso photosantonic lactone[25]. They have shown by rotatory dispersion measurements that all these compounds have the absolute configuration (28) about the ring junction.

Of the sesquiterpenoid lactones the most important compound is santonin which has been the subject of investigations[3] for over a century, and even now it presents

many interesting problems. The main reactions which led to the elucidation of the structure of santonin are summarised in the following section.

Constitution of santonin



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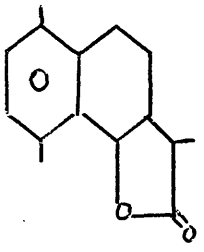

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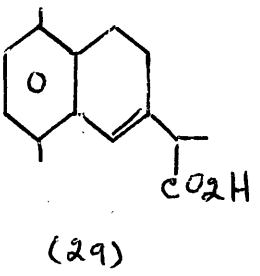

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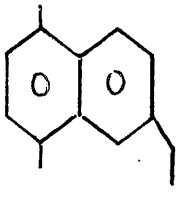

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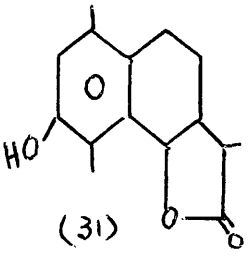

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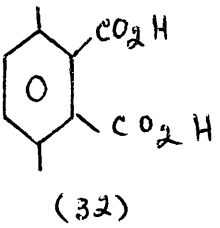

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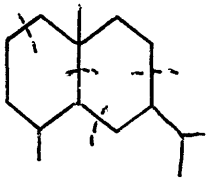

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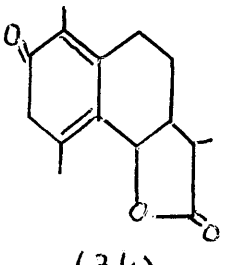

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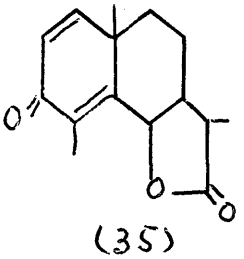


(35)

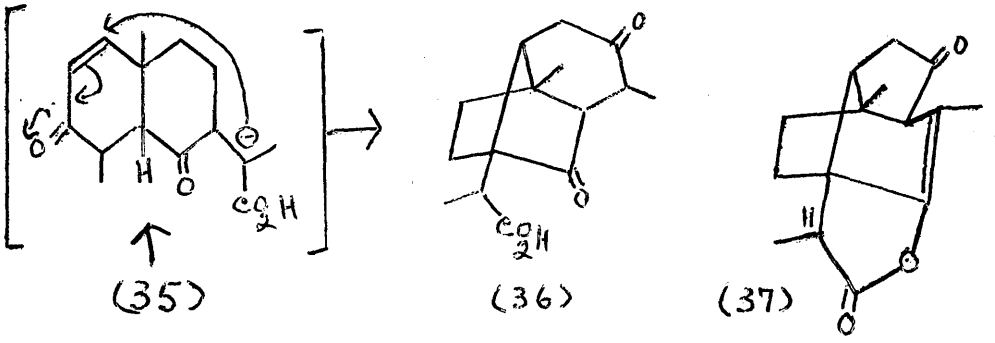
Santonin has the molecular formula $C_{15}H_{18}O_3$. On hydrogenation[3] it afforded two tetrahydro-derivatives, namely $\alpha$-tetrahydrosantonin and $\beta$-tetrahydrosantonin, showing the presence of two double bonds. Zinc dust distillation afforded 1:4-dimethylnaphth-2-ol (27) in small yields[36]. On the reduction of santonin $\beta$-oxime, its acetate, or of santonin phenyl hydrazone with sodium amalgam, followed by treatment with nitrous acid, hyposantonin (28) and its stereoisomer isohyposantonin were obtained[37]. The corresponding hydroxy acid of hyposantonin on dehydration with alcoholic hydrochloric acid afforded the compound (29). This on decarboxylation and dehydrogenation furnished 1:4-dimethyl-7-ethyl naphthalene[3] (30).

Hyposantonin, or its isomer, on potassium permanganate oxidation produces 3:6-dimethyl phthalic acid[3] (32) showing that the lactone grouping cannot be in the same ring as the two methyl groups and, therefore, as that containing the ketonic oxygen atom. Finally, santonin on treatment with fuming hydrochloric acid in the cold undergoes aromatisation to give the desmotroposantonin[3] (31). This suggests that the two double bonds of santonin are probably situated in the same carbon ring as the ketonic oxygen atom. These experimental evidences led Andreocci to suggest formula(26)for santonin. However, formula (34) equally well explains the reactions outlined above and was therefore proposed by Cannizzaro and

Grucci. It may however be noticed that these formulae are the ketonic forms of the corresponding phenols.

The first and powerful criticism of the various formulae proposed for santonin came from Clemo, Haworth and Walton[38], who pointed out that none of the formulae could be regarded as being built up from three isoprene residues. They therefore in a classical paper suggested that such a head to tail joining of the three isoprene units would give rise to the eudesmol type carbon skeleton (34) suggested as the constitution of santonin. They also suggested that the formation of desmotroposantonin from santonin must involve a migration of the quaternary methyl group, a reaction which already had an analogy[39]. They also proved by the synthesis of racemic desmotroposantonin that this substance was correctly represented by formula (31), and assigned the correct structure (35) to santonin which was later supported by the degradational evidence. The structure (35) for santonin has recently been confirmed by synthesis[40,13,49].

Santonin undergoes many reactions of theoretical interest. Its aromatisation to give the corresponding phenol, desmotroposantonin, under the influence of acid, has already been mentioned. Amongst others is its conversion into santonic acid (36) on prolonged treatment with alkali, by an internal Michael reaction[40] as indicated.



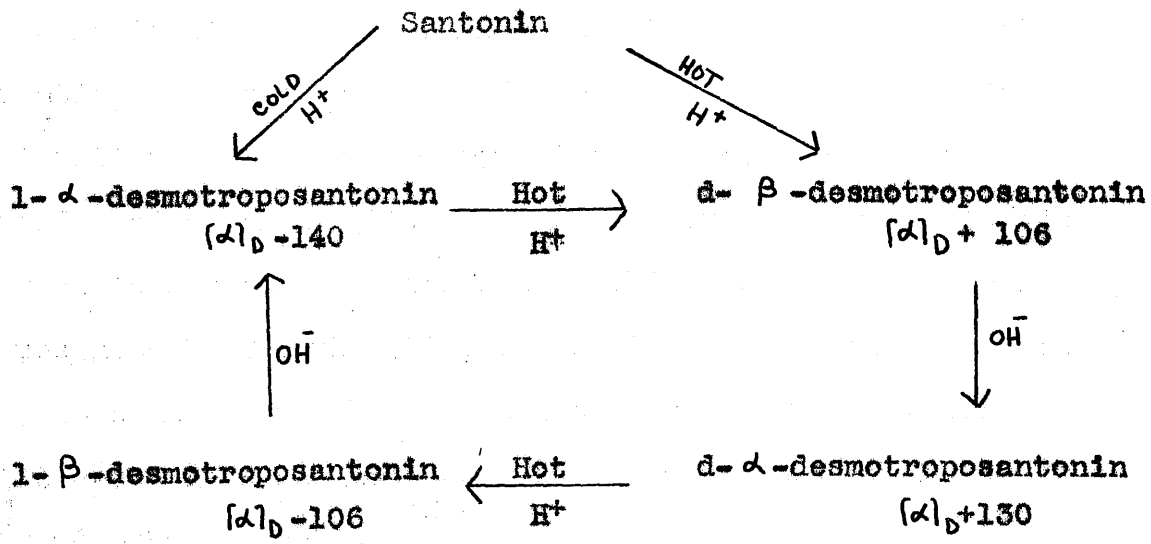
(35) (36) (37)

Other interesting derivatives of santonin are santonide and parasantonide[40,41] (37), two isomeric compounds, produced when santonic acid (36) is treated with acetic acid followed by heating at 260-300°C. These compounds have been shown to differ in their configuration at $C_{11}$. Woodward has postulated the participation of (quasi) three membered ring intermediates for this reaction.

Stereochemistry of santonin

The elucidation of the stereochemistry of santonin originated with a study of its molecular rotation data, and the configurational inter-relationship of various

desmotroposantonins. It has already been mentioned that santonin on treatment with acid is converted into d- desmotroposantonin (32). The elucidation of this stereochemical problem was greatly facilitated by the isolation of two new desmotroposantonins. Huang Minlon[45] showed that all the active isomeric desmotroposantonins were inter-convertable by the action of either an acid or a base. This has been illustrated in the following chart.

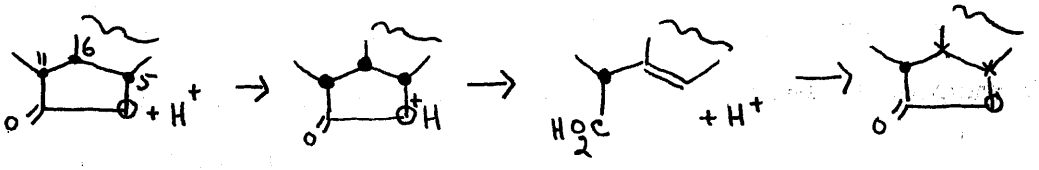



where α and β denote low and high melting compounds respectively.

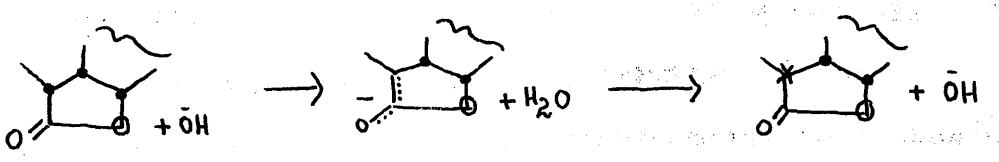
It is also apparent from the chart that l- β -desmotroposantonin is an optical enantiomorph of d- β -desmotroposantonin. Similarly d- α -desmotroposantonin and l- α -desmotroposantonin are both optically enantiomorphic.

A plausible mechanism for these interconversions of various desmotroposantonins was also suggested by Huang Minlon[46]. He showed that treatment of an $\alpha$-desmotroposantonin (scheme a) with acidic reagents led to inversion at the asymmetric centres 5 and 6. Likewise fusion with potassium hydroxide of a $\beta$-desmotroposantonin caused inversion at $C_{11}$ as illustrated in scheme B.

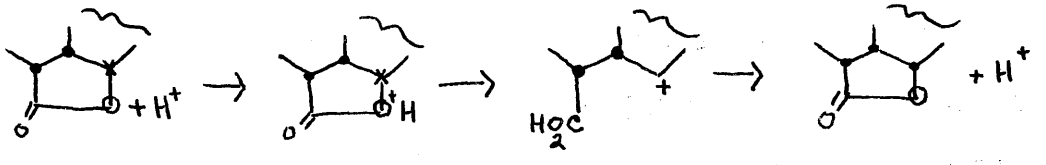
Scheme a



Scheme B



Scheme C



All desmotroposantonins can be recovered from their corresponding hydroxy-acids on ring closure with an acid. It therefore seems satisfactorily established that they have the lactone ring fused in the more stable position at $C_5$ and $C_6$. Clemo[47] has shown this to be the cis-position from a consideration of molecular models. Hyposantonin (31), on the other hand must have the lactone ring trans-fused since its corresponding hydroxy-acid lactonises back to an isomer of hyposantonin on treatment with dil.acid. Barton[48] has suggested that in the cases where trans-lactones are encountered, such a mechanism as outlined in scheme C might be operative.

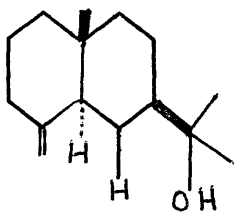
Desmotroposantonins on reduction with zinc dust and acetic acid afford the corresponding deoxy hydroxy-acids (43) known as santonous and desmotroposantonous acids, which differ in their configuration at $C_6$ and $C_{11}$. By a consideration of the molecular rotation of the desmotroposantonins and the corresponding santonous and desmotroposantonous acids Hwang Minlon tentatively proposed, according to the principle of optical superposition, signs for the contributions of the various asymmetric centres.[46] The additivity of the molecular rotations is not very satisfactory and the stereochemistry has preferably been discussed in the following way. Let the configurations at

$C_5$, $C_6$ and $C_{11}$ in l-$\alpha$-desmotroposantonin be denoted by X, Y and Z, and let the alternative configurations at these centres be $X'$, $Y'$ and $Z'$.

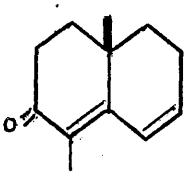
The formation of hyposantonin from santonin has already been mentioned (page ll ). This conversion which is brought about under very mild conditions implies that santonin too, like hyposantonin, contains the <u>trans</u>-fused lactone. On the basis of the above discussion one can assign the following configurations to d-$\beta$-desmotroposantonin and santonin, relative to l-$\alpha$-desmotroposantoin,

| Substance | Configurations relative to l- -desmotroposantonin. | | |
|---|---|---|---|
| | $C_5$ | $C_6$ | $C_{11}$ |
| l-$\alpha$-desmotroposantonin | X | Y | Z |
| d-$\beta$-desmotroposantonin | $X'$ | $Y'$ | Z |
| Santonin | $X'$ | Y | Z |
| | X | or, $Y'$ | Z |

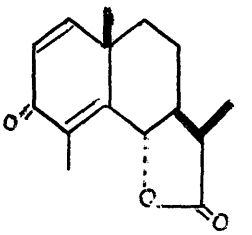
as indicated in the above chart. Since santonin may be transformed into d-$\beta$-desmotroposantonin (<u>cis</u>-lactone fusion) via the l-$\alpha$-desmotroposantonin (again <u>cis</u>-lactone fusion) santonin must be $C_5(X')$, $C_6(Y)$ and $C_{11}(Z)$, and there must be therefore a mechanism (scheme C) for the inversion of $C_5$ without altering $C_6$.



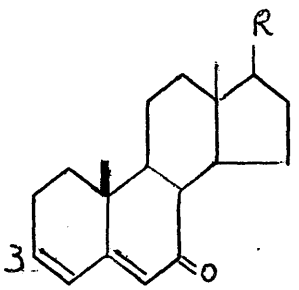

(38)



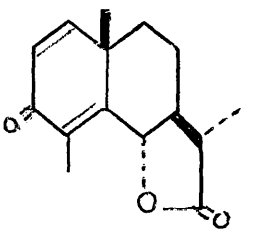

(39)



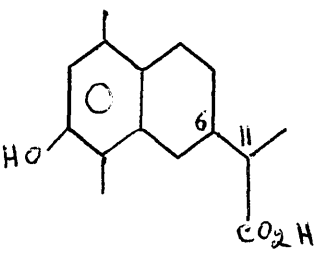

(41)




(40)




(42)




(43)

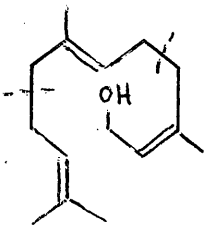
That the $C_9$ methyl group is axial and the $\alpha$-propionic acid side-chain equatorial in santonin, is likely in view of the similar configurations in the sesquiterpenoid α-desmol[33] (38). Confirmation of the equatorial configuration at $C_6$ has recently been provided by Japanese workers through the synthesis[49] of santonin, by the reaction sequence involving the addition of methyl malonic ester to (39) which finds a parallel in a closely analogous addition of malonic ester to choles 7$\alpha$-3:5-dien-7-one (40). In the latter it has been shown that

the addend takes up the β-position at $C_3$, cis to the angular methyl group.[50] This, in turn, also supports the cis placements of the angular methyl group and the side chain at $C_6$ in santonin.[51] Now, since santonin has the trans lactone fusion this implies that it must have the configuration shown in (41). The configuration at $C_{11}$ in santonin has appeared more difficult to assign. Corey, Woodward[51,41,52,53] and others are of the view that the methyl group at $C_{11}$ has the β-orientation. Their view is not universally accepted since Miki and others[41] regard the α-orientation at $C_{11}$ as the correct configuration.

The stereochemistry of β-santonin can be deduced from that of α-santonin. β-santonin on treatment with acidic reagents affords 1-β-desmotroposantonin. Hence β-santonin should have the isomeric configuration at $C_{11}$ with regard to santonin, and is assigned the formula (42).

# TABLE NO: 1

(1)

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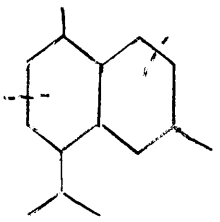

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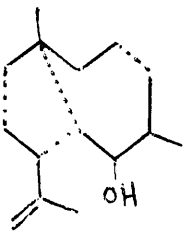


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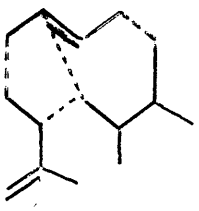

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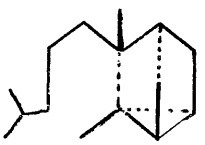
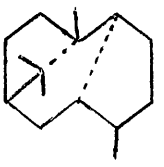
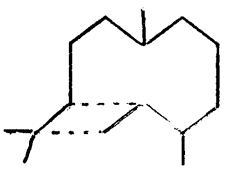


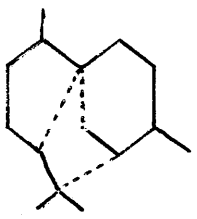
α-SANTALENE



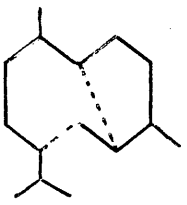
PATCHOULI ALCOHOL



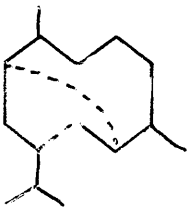
CARYOPHYLLENE



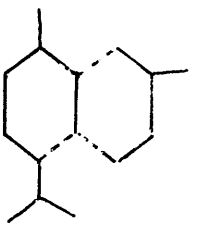
CEDRENE



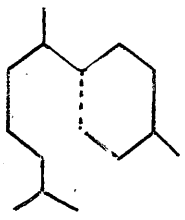
GUAIOL



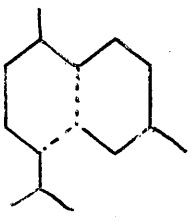
VETIVONE



CAROTOL



BISABOLENE



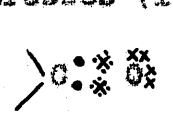
HEXAHYDROCADALENE

[only skeletons are shown]

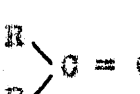
PHOTOACTIVATION OF CARBONYL COMPOUNDS

In absorption spectroscopy, molecules absorb light undergoing rotational, vibrational and electronic changes dependent upon the wave-length of the light absorbed.[54] From the view-point of photochemical change, only the electronic spectra are important. These arise from transitions between electronic states, and involve relatively large energy differences. These therefore, occur usually at short wave-lengths.

In the carbonyl group[54] one of the orbitals of both the carbon and the oxygen are involved in the sigma (σ) component and another pair forms the pi ( π ) component of the double bond. The electrons of the sigma orbital are depicted by dots while those of the pi orbital are denoted by asterisks. The lone pairs of the oxygen are represented by crosses (1).



(1)



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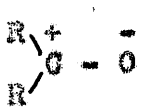

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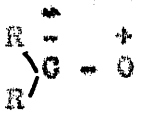

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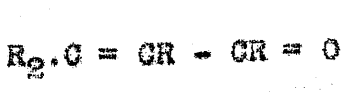

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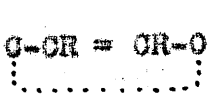

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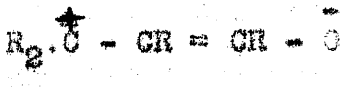

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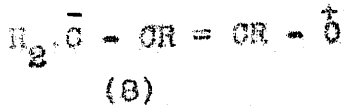

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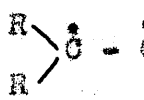


(8a)

where the dotted line represents the 'formal bond' i.e. the spins of the electrons at the C and oxygen are opposed.

In the region between about 1500A and the visible, saturated aldehydes and ketones show three absorption bands. These occur at 2900A, 1900A and 1500A and are said to be due to transitions between the normal or ground state of the molecule and the three different electronically excited states. The absorption band at 1500A may be expected to arise from the electronically excited states corresponding to those of the system $R_2C = CR_2$. It is, indeed, observed that this band is found in the same general region and with the same intensity as those which occur in the ultraviolet spectra of the corresponding olefines. The relevant excited state for a saturated aldehyde or ketone can be described as a hybrid of (principally) the three structures (2);(3) and (4). The ground state too is a hybrid of (principally) these structures; the various canonical forms differing in weight. Similarly the corresponding excited states for an $\alpha\beta$ unsaturated carbonyl compound may be represented as a hybrid of numerous structures of which (5), (6),(7) and (8) are the more important.

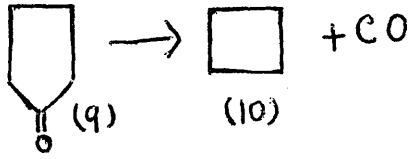
The other two absorption bands, i.e. at 2900A and 1900A arise from corresponding excited states involving the non-bonding electrons of the oxygen atom. That at 2900A arises from an excitation of an electron, belonging to one of the unshared pairs on the oxygen atom to an antibonding $\pi$ orbital. This excited state which must be clearly

distinguished from a diradical (triplet state) (8a) may be converted photochemically (or otherwise) into this form. In certain of these reactions it seems very probable that it is the diradical that reacts, but perhaps in intramolecular reactions this may not necessarily be so. At the present moment intimate details of the processes are not known.

Photochemical reactions of carbonyl compounds

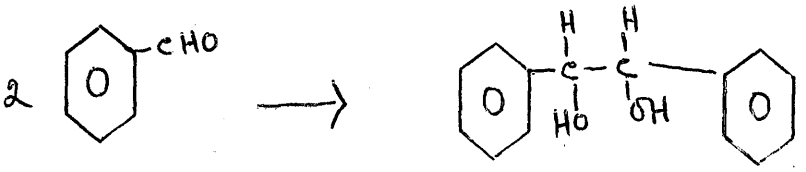
A molecule on the absorption of light energy becomes excited and is therefore no longer in the thermodynamic equilibrium with its surroundings. It must therefore, lose energy in one of the three following ways: (1) as fluorescence or phosphorescence, (2) as thermal energy and (3) as chemical energy by transformation into new compounds, or species. One must therefore distinguish between a vapour phase reaction and the reaction in solution. In the former case the excited molecule can only lose part or all of its energy by following either process (1) or (3). Hence vapour phase reactions are usually attended by extensive decompositions. One may cite the example of acetone[55] which on vapour phase irradiation is disrupted into acetyl and methyl radicals which produce ethane, carbon monoxide and biacetyl by subsequent reactions etc. The yield of biacetyl is quite dependent on temperature.

With rise in temperature, methane becomes the important product and the yield of biacetyl and ethane are considerably reduced. Similarly the high temperature photolysis of cyclopentanone (9) results in the formation of cyclobutane (10) and carbon monoxide.[56]

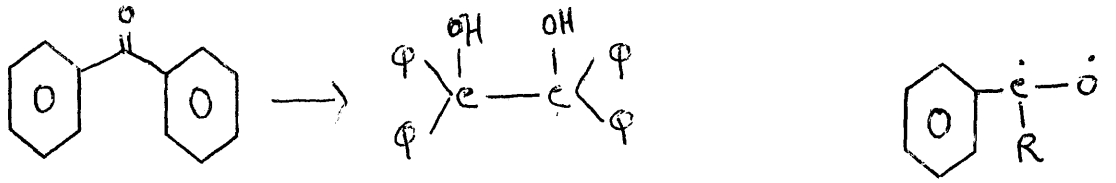



On the other hand, photochemical reactions in solution behave "moderately", since they can get rid of part or whole of their energy by collision with other molecules (of solvent etc.). These reactions therefore, call into play the "radical intermediates" which give rise to the interesting photo-products. This is illustrated in the sequel by various examples.

Aromatic ketones and aldehydes are transformed into their corresponding pinacols, when their alcoholic solutions are exposed to sunlight, e.g. benzaldehyde[57] (11) furnishes the hydrobenzoin (12) while compound (14) results when benzophenone (13) is irradiated in isopropyl alcohol.[58,59] The reaction can be interpreted as occurring through the participation of the radical intermediate (15) which after coupling abstracts hydrogen from the solvent to produce the required product.



(11) (12)



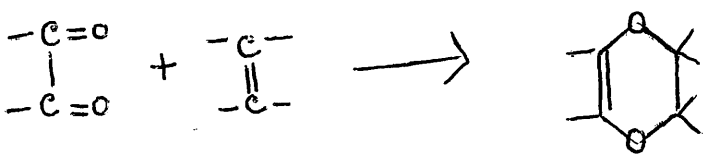
(13) (14) (15)

The formation of pinacols is probably not a general reaction because fluorenone[60] and xanthone[61] have been found to be stable to isopropyl alcohol in sunlight. Steric reasons are probably operative, because the pinacol (16) on reaction with acetone in sunlight furnishes the corresponding ketone (17) and isopropyl alcohol.

Similarly benzoyl-diphenyl methane (18) in benzene solution is transformed photolytically into 1,1,2,2, tetraphenyl ethane (21) and benzaldehyde.[62] The reaction has been explained on the formation of the usual radical intermediates (19) and (20). The latter dimerises to furnish compound (21) while the former stabilises itself in the form of benzaldehyde. The attack of the radical (20) on (18) to yield the compound (21) and a benzoyl radical is not excluded.

Trans- $\pi$ -oxocamphor (22) furnishes another example by transforming itself photolytically into 1-methyl-4-acetyl cyclohex-2-one (28), in the presence of oxygen[63]. The reaction is stated to proceed probably through the intermediates (23 to 25). The radical intermediate (25) abstracts a hydrogen atom from (22) to produce (26) which is then said to react with it further to produce the desired compound (28) through the intermediate (27). (For formulae see Table 2).

Certain o-quinones and 1,2 diketones on photolytic reaction with substituted olefines afford the 1,4 dioxins. This general reaction is illustrated in 'scheme a' below.



Scheme a

Such photoreactions have been shown to occur with benzil, dianisil and phenanthroquinone[71,72] etc. This reaction may be compared with the addition of aldehydes and ketones to olefines. For example, Buchi[73] has shown that benzaldehyde (29) reacts with 2-methyl-2-butene (30) when compound (31) results. Structure (32) for the photo-product (31) was ruled out on the basis of acid-catalysed cleavage when no acetone could be isolated. Compound (33) under similar acid treatment did afford acetone.

Kharash[72] has explained the addition of aldehydes to terminal olefines on the basis of the radical intermediate (34), which then attacks the olefine. This mechanism may be true in certain cases. However, Buchi has pointed out that in his case, this reaction mechanism does not hold good, because it should preferentially produce compound (32) rather than (31). Secondly, such a mechanism cannot be applied to ketones. Buchi has instead, postulated that the excited state of an aldehyde group would give rise to the diradical (35) which in turn would react with the olefine to give the diradical (36), and this on saturation would afford the desired product (31).

On the other hand substituted acetylenes react with aldehydes photolytically to produce $\alpha\beta$ - unsaturated ketones containing the system[74] (37). Benzaldehyde, for instance, reacts with 5-decyne to give the adduct (38). For this reaction a reasonable intermediate postulated by Buchi is the oxetene

(39) which would be expected to re-arrange to the desired compound (38). Acetophenone behaves similarly and likewise furnishes (38 $R_{1,2} = CH_3$). (For formulae see Table (3) ).

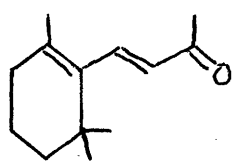
Jeger[75] has very recently provided another interesting example of the light induced dienone-phenol re-arrangement. Thus prolonged irradiation of 1,dehydro-o-acetyl testosterone (40) in dioxane results in the formation of the corresponding phenols (41) and (42).

Unsaturated conjugated ketones mechanistically behave similarly in most of the instances. For example, the ketone (43) on excitation shall give rise to the diradical (44) which can either dimerise or react with (43) to give the diradical (45). This intermediate diradical is equivalent to (46) which then stabilises itself with the formation of a cyclobutane derivative. One therefore finds that 3,5-dimethyl-cyclohexenone (47) yields the photo-dimer (48) or (49), in alcoholic solution, and on exposure to sunlight.[76]

It may however be anticipated that the diradical intermediate (44) may saturate itself internally if so permitted. And one finds that a solution of bicyclo(2,2,1) heptadiene-2,3-dicarboxylic acid (50) in absolute ether, on irradiation furnishes the isomer[77] (51). (For formulae see Table 4).

Buchi has recently provided another interesting example where under the influence of light, rearrangement of

a carbonyl compound occurs to give a cyclopropane derivative.[78] A solution of trans- β-ionone (52) on irradiation in ethanol yields two new isomeric compounds (53) and (54), the latter



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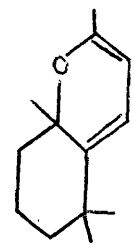

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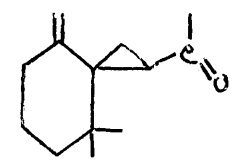

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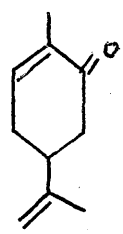

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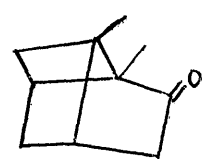


(56)

(54) would be desirable.

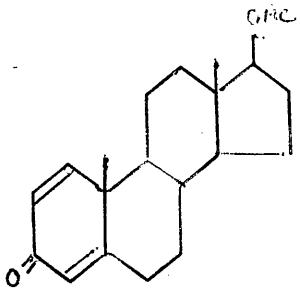
Finally, the cyclisation of carvone (55) to carvone camphor[79,80] may be mentioned which takes place under the influence of light. The mechanism of this cyclisation follows the general pattern and its analogy has already been cited (see formula 61).

a carbonyl compound occurs to give a cyclopropane derivative.[78] A solution of trans- β -ionone (52) on irradiation in ethanol yields two new isomeric compounds (53) and (54), the latter only in small yield.[78]

It may be mentioned that more evidence in favour of structure (54) would be desirable.

Finally, the cyclisation of carvone (55) to carvone camphor[79,80] may be mentioned which takes place under the influence of light. The mechanism of this cyclisation follows the general pattern and its analogy has already been cited (see formula 61).

TABLE NO : IV

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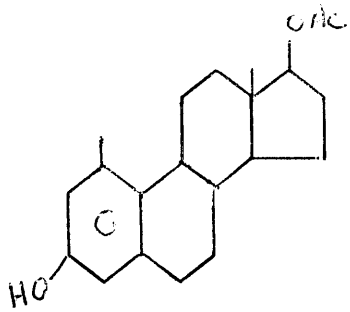


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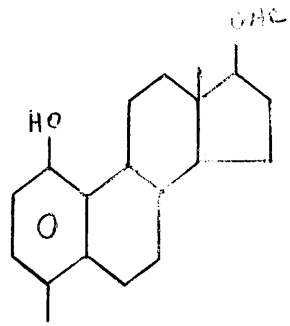


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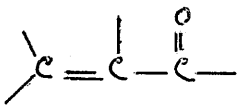

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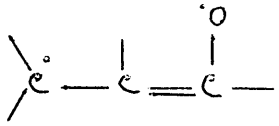

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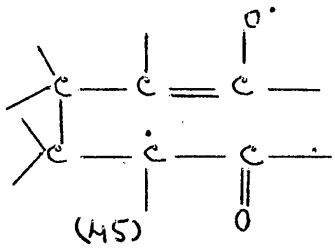

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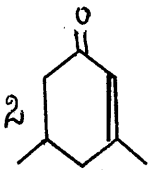

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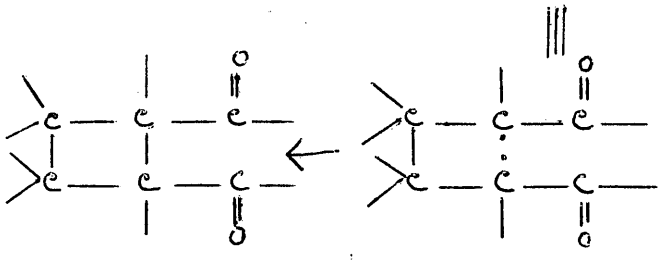

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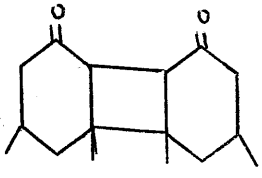

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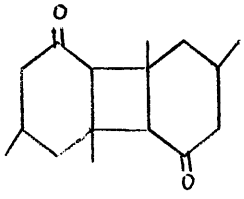

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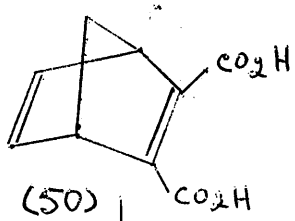


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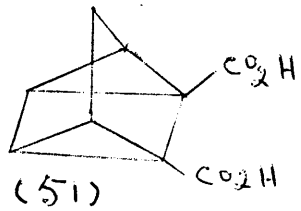


(51)

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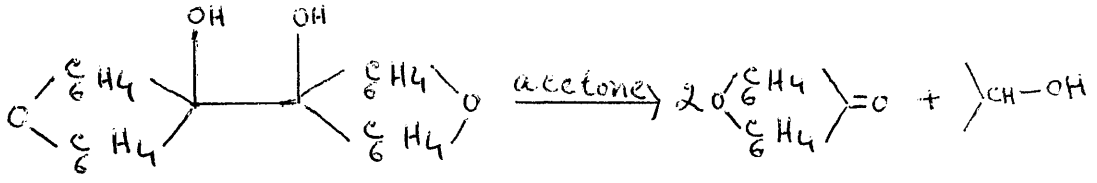


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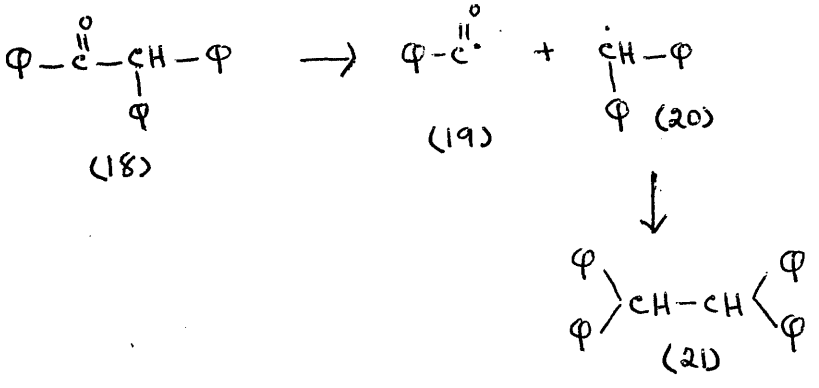

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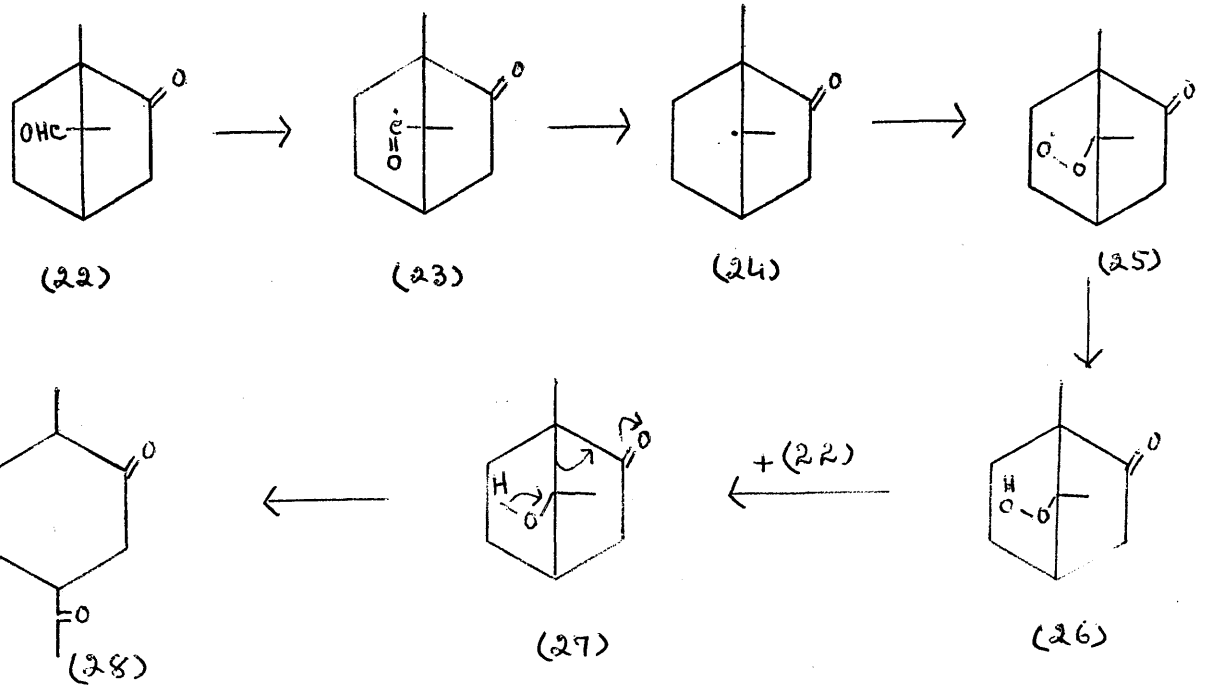
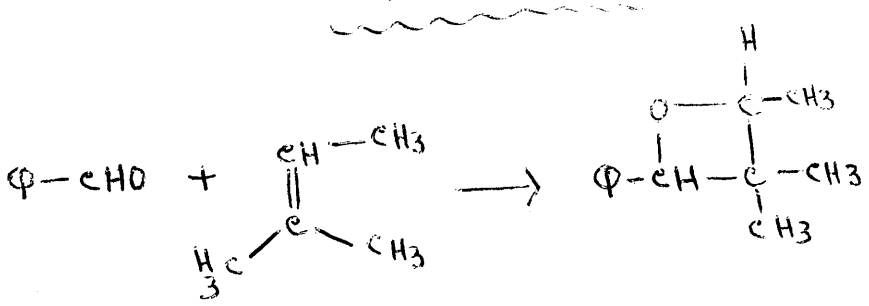



(22) (23) (24) (25) (26) (27) (28)

TABLE NO: 3



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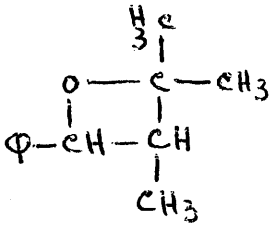

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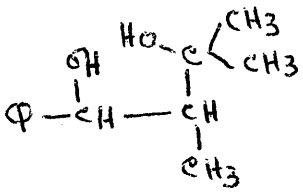

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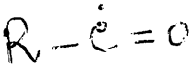

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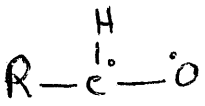

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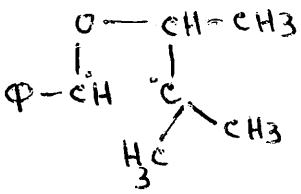

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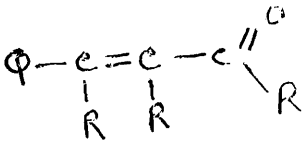

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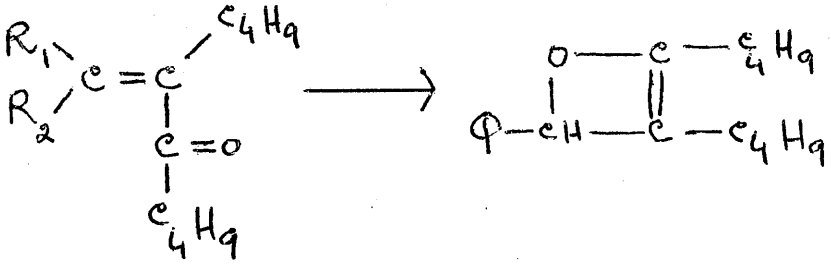


(38) $R_1 = \Phi$
$R_2 = H$

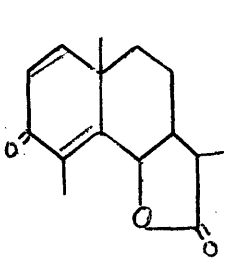
(39)

## STRUCTURE OF ISOPHOTOSANTONIC LACTONE

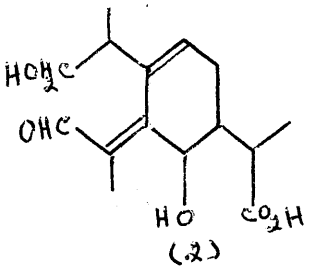
(For rest of the formulae see Table 5)

Santonin (1), like other cyclic di-enones, is sensitive to light and gives rise to very interesting transformations. Francesconi and Sestini[81] found that by irradiation in sunlight of a solution of santonin in one equivalent of potassium hydroxide photosantonic acid $C_{15}H_{22}O_5$ was formed. Villavecchia[82] showed that in a similar manner, santonin in alcoholic solution on exposure to sunlight was transformed into the ethyl ester of photosanton-lactonic acid, also known as photosantonin, together with photosantonic acid and a substance, $C_{17}H_{24}O_4$ mp.154-155°, $[\alpha]_D$ +76.8 in ethanol.

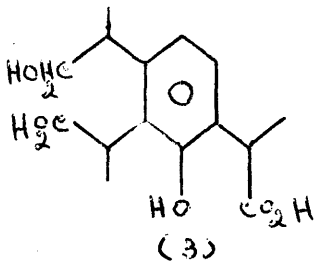
In a similar irradiation of santonin in acetic acid, Cannizzaro and others[82-85] isolated photosantonic acid, an isomeric substance known as isophotosantonic acid $C_{15}H_{22}O_5$ and a compound



(1)



(2)



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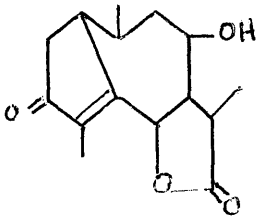


(4)

STRUCTURE OF ISOPHOTOSANTONIC LACTONE

(For rest of the formulae see Table 5)

Santonin (1), like other cyclic di-enones, is sensitive to light and gives rise to very interesting transformations. Francesconi and Sestini[81] found that by irradiation in sunlight of a solution of santonin in one equivalent of potassium hydroxide photosantonic acid $C_{15}H_{22}O_5$ was formed. Villavecchia[82] showed that in a similar manner, santonin in alcoholic solution on exposure to sunlight was transformed into the ethyl ester of photosanton-lactonic acid, also known as photosantonin, together with photosantonic acid and a substance, $C_{17}H_{24}O_4$ mp.154-155°, $[\alpha]_D$ +76.8 in ethanol.

In a similar irradiation of santonin in acetic acid, Cannizzaro and others[82-85] isolated photosantonic acid, an isomeric substance known as isophotosantonic acid $C_{15}H_{22}O_5$ and a compound $C_{30}H_{38}O_7$ mp.300° of unknown constitution.

By irradiation in aqueous acetic acid solutions of santonin, a variety of photochemical products including photosantonic acid, isophotosantonic acid, isophotosantonic acid diacetate and the acetate of isophotosantonic acid lactone have been obtained.[81] Another substance, known as photosantoninic acid, $C_{30}H_{42}O_9$, results when santonin is irradiated in three equivalents of aqueous potassium hydroxide.[81]

Cannizzaro, Francesconi and Venditi showed that isophotosantonic acid, to which they eventually assigned the structure (2), gave an oxime, a monoacetate, a diacetate and a phenyl-hydrazone. These reactions therefore, indicated the presence of a hydroxyl group and a carbonyl function (though not necessarily an aldehyde) in isophotosantonic acid lactone. On oxidation with acid potassium permanganate, of isophotosantonic acid, the so called bis-hydroxy isophotosantonic acid resulted, said to possess the formula (3). In addition it will be recalled that these deductions were necessarily based on the (incorrect) structure proposed for santonin at that time.

The evidence cited to support the structure of isophotosantonic acid is very insufficient. It is, for instance, remarkable that a primary alcoholic group in (3) would survive acid-permanganate oxidation. It seemed, therefore desirable to reinvestigate the problem.

We found that the main photochemical transformation product of santonin in aqueous acetic acid solution was the so-called "isophotosantonic acid", obtainable in 30% yield or more. For irradiation purposes a bare mercury arc (125 W) lamp was used as an approximation to the conditions observed by earlier workers who employed solar energy. Earlier literature gives no indication as to the yield of isophotosantonic acid nor of that of the other photo-products. The so-called photosantonic acid was also isolated, though in lesser amounts, as a second photo-product.

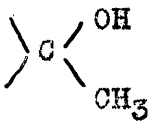
isoPhotosanic acid was originally assigned the composition $C_{15}H_{22}O_5$ and was shown to be converted into isophotosantonic acid lactone either by warming at 100°C or on treatment with acetyl chloride. We found that both isophotosantonic acid and isophotosantonic acid lactone are neutral substances, showing a band in the infrared spectrum at 1776 $cm^{-1}$ (γ-lactone; Nujol) which showed that the so-called acid is merely the hydrated form of the corresponding lactone. This was found to be the case, because 'isophotosantonic lactone' on crystallisation from aqueous alcohol furnished the hydrated form, while crystallisation from non-aqueous solvents afforded the non-hydrated form. Hence isophotosantonic acid will be described as isophotosantonic lactone in the sequel.

As already mentioned, isophotosantonic lactone was said to contain a hydroxyl group and a carbonyl group, provisionally regarded as an aldehyde. isoPhotosantonic lactone was now found to be stable to chromic acid at room temperature. Hence the hydroxyl group must be tertiary and the carbonyl function ketonic in nature. In accord with this, isophotosantonic lactone was not found to give any of the tests (Angeli-Remini etc.) characteristic of aldehydes.

The nature of the functional groups in isophotosantonic lactone was also supported by the infrared spectrum which showed bands at 3470 (hydroxyl); 1776 ($\gamma$-lactone) 1693 and 1660 $cm^{-1}$ ( $\alpha\beta$-unsaturated cyclopentenone). Its ultraviolet absorption spectrum had a strong band at 239 m$\mu$ ( $\varepsilon$ ,13000) indicative of the presence of a fully substituted cyclopentenone[86] (c.f. desacetyl neotenulin[87] (4) which has $\lambda$ max 240 m$\mu$ ( $\varepsilon$ ,16000) ).

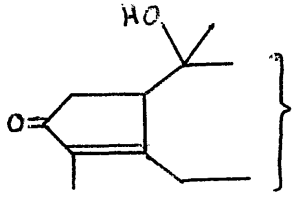
On hydrogenation with 5% palladised charcoal, isophotosantonic lactone afforded the corresponding dihydro derivative $C_{15}H_{22}O_4$ which exhibited a band in the infrared spectrum at 1728 $cm^{-1}$ indicative of the cyclopentanone grouping. Since the dihydro derivative was saturated towards tetranitromethane, isophotosantonic lactone must have two carbocyclic rings.

Thionyl chloride-pyridine dehydration of isophotosantonic lactone produced an anhydro-compound, $C_{15}H_{18}O_3$, which

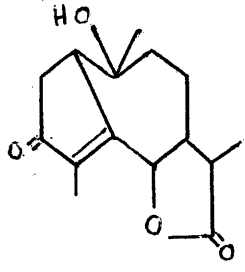
had
infrared bands at 1770 (γ-lactone) 1690 and 1643 $cm.^{-1}$ (indicative of cyclopentenone) and a band at 906 $cm.^{-1}$ in chloroform. This indicated the formation of an exocyclic methylene grouping, $\rangle C = CH_2$, on dehydration. This was supported by the Kuhn-Roth C-methyl determinations when the andydro-derivative had only two C-methyls, as compared with the parent compound which was shown to contain three C-methyls. Ozonolysis of the anhydro-compound, in confirmation, yielded formaldehyde. It is to be concluded that the original lactone, therefore, contains the grouping  Since the anhydro compound showed a maximum in the ultraviolet at 236 mμ (ε 12600), essentially identical with that of the parent lactone, the exocyclic double bond is not in conjugation with the enone system. In contrast, dehydration of the parent lactone under acidic conditions afforded an oily conjugated dienone ( λ max 305 mμ: ε ,11,000) characterised as its crystalline 2:4-dinitrophenylhydrazone.

Ozonolysis of the parent lactone followed by steam distillation afforded acetic acid and a neutral compound, $C_{13}H_{16}O_5$. This exhibited bands in the infrared at 1770 and 1760 $cm.^{-1}$ indicative of the presence of two γ-lactones. The other carbonyl function which was responsible for the formation of an oxime, showed a band in the infrared at 1720 $cm.^{-1}$ and had

a maximum in the ultraviolet at 294 mμ ( ε 50). The dilactone gave a positive Fehling test suggestive of a potential α-ketol system. The absence of the original hydroxyl group and the formation of a new γ-lactone implies that the carboxyl group generated from the original carbonyl group on ozonolysis had lactonised with the hydroxyl group to form the new γ-lactone. Hence, on the above evidence partial expression (5) can be written for isophotosantonic lactone. Now, if one has regard to the constitution of its precursor santonin (1), one can write the interesting structure (6) for isophotosantonic lactone, when the dilactone $C_{13}H_{16}O_5$ can be satisfactorily formulated as (7).




(5)

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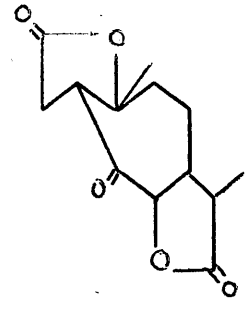
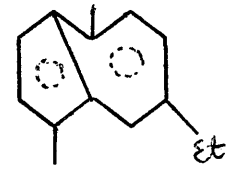



(7)




(8)

The structure (6), 10-hydroxy-3-oxo-guai-4-en -6:12-olide*, was confirmed in a simple manner. On acid-catalysed hydrogenation, it afforded a mixture of saturated alcohols (no cyclopentanone band in the infrared) which furnished chamazulene[88] (8), on dehydrogenation over palladised charcoal. One can, therefore, formulate the non-conjugated anhydro compound as (41) when the isomeric conjugated dienone will be (10). Similarly dihydroisophotosantonic lactone can be assigned the formula (11).

The acetate of isophotosantonic lactone was prepared by the method of Cannizzaro and Faberis[83]. This was shown to be the normal tertiary acetate as distinct from the possible enol-acetate, by its ultraviolet absorption spectrum which had a maximum at 239 mμ ($\varepsilon$ 13000). In accordance with this, the infrared showed no hydroxyl band.

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* We adopt here the proposal by Sorm[87] that such lactones should be named in terms of guianolide. The numbering that is employed here is convenient in that it shows the relationship of the guiane skeleton to the santonic acid or eudesmane skeletons. It also corresponds to steroid and polyterpenoid numbering and may have implications in terms of absolute configuration.

The experiments outlined below support the constitution ( 6) assigned to isophotosantonic lactone. A more detailed study of the ozonolysis of the photo-product (6) revealed that if the ozonide were decomposed hydrolytically, but without subsequent steam distillation, an isomeric neutral dilactone $C_{13}H_{16}O_5$ $[\alpha]_D^{\circ}+70^{\circ}$ (pyridine) resulted. The infrared showed the presence of two γ-lactones (bands at 1777 and 1750 $cm.^{-1}$) and a carbonyl band at 1720 $cm^{-1}$ (Nujol). Its relationship to the already described neutral dilactone (8) was proven, when on standing in pyridine for 18 hours it mutarotated to $-31^{\circ}$, and the first mentioned stable dilactone was isolated in quantitative yield, characterised by m.p., mixed m.p. and infrared spectrum. It is therefore obvious that the two compounds are isomeric at one or both of the asymmetric centres, $\alpha$ to the carbonyl function, and that steam distillation is a sufficiently vigorous process to induce isomerisation.

When, however, the ozonide of the parent lactone was decomposed by hydrogenation then the triketone (12) $C_{15}H_{20}O_6$, resulted. This exhibited a maximum in the ultraviolet at 290 mμ ($\varepsilon$ 71) and showed a band in the infrared at 1715 $cm^{-1}$, indicative of the presence of an acyclic or cyclohexanone ketone. Its formation is not unexpected on mechanistic grounds, because if the ozonide is represented by partial

formula[88] (13), it would furnish the triketone (12) under the conditions employed. That compound (12) is an α-diketone was shown by its treatment with alkaline hydrogen peroxide, when one mole of acetic acid was obtained.

On reduction with sodium borohydride, isophotosantonic lactone furnished the saturated alcohol (18) and the corresponding unsaturated alcohol (14,R=H). The latter on ozonolysis was converted into the diketone (16, R=H) $C_{15}H_{22}O_6$. Acetylation of the unsaturated alcohol (14,R=H) resulted in the formation of an oily acetate (14,R=AC) which was characterised by its conversion into the crystalline acetoxy diketone (16,R=AC) which gave a positive Fehling test.

Treatment of the oily acetate (14,R=AC) with osmium tetroxide produced the corresponding crystalline diol (17) which consumed one mole of periodic acid after 18 hours. On similar treatment with osmium tetroxide, the parent lactone (6) afforded the triol (18) which consumed one mole of periodic acid very rapidly, the reaction being complete within 15 minutes. The product formed was a neutral bis-lactone having the composition $C_{15}H_{20}O_6$. The above results suggest that in the triol (18) cleavage occurs between $C_3$ and $C_4$,

The bis-lactone $C_{15}H_{20}O_6$ was found to be identical in every respect with the so-called "bis-hydroxy isophotosantonic

acid" obtainable by the acid permenganate oxidation of the isophotosantonic lactone (6). In the infrared spectrum this substance showed bands at 3430 (hydroxyl) 1760 (strength indicative of two γ-lactones) and 1710 $cm^{-1}$ (aliphalic ketone or equivalent). In accord with this, it had a maximum in the ultraviolet at 295 mμ (ε 40). The oxidation product was stable to chromic acid, showing that the hydroxyl group is tertiary in nature and a positive iodoform test confirmed the presence of a methyl ketone. On the above evidence the compound can be formulated as (19) or (20), arising from the intermediate (21; partial structure).

Structure (19) for the oxidation product was favoured on two reasons. Firstly, there is analogy in compound (7) for the lactone system of (19). Secondly, the compound (19) could not be dehydrated, starting material being recovered, under conditions which readily effect the dehydration of the parent lactone (6). However, the resistence of (19) to further oxidation by periodic acid or lead tetra-acetate would favour (20), but for the fact that steroidal 17 α-hydroxy-20-ketones of the partial structure (22) are notoriously resistant to these reagents.[89]

The acidic potassium permanganate oxidation of the parent lactone (6) can possibly be interpreted as occurring through the formation of the triol (18) which is then oxidised further to the required product (19) in a manner similar to that of periodate cleavage.

## Experimental

All melting points reported throughout the experimental portion were taken on the Köfler block, unless specified to the contrary. All rotations were determined in chloroform solution unless stated otherwise.

The phrase "in the usual way" implies in general, dilution with water, extraction with chloroform, washing successively with dil. aqueous hydrochloric acid and dilute sodium bicarbonate solution ~~and~~ (as required), followed by water. The chloroform layer was dried over anhydrous sodium sulphate and evaporated in vacuo.

isoPhotosantonic Lactone (10-Hydroxy-3-oxoguai-4-en-6:12-olide) (6). - Santonin (4.0 g.) in 45:55-acetic acid: water (110 ml.) was irradiated in a quartz flask under reflux with a bare mercury arc (125 W) lamp until the rotation fell to approx. 2° (about seven hours). Removal of the solvent under reduced pressure afforded a gum which was separated by means of sodium hydrogen carbonate into acidic and neutral fractions. The neutral fraction (3.2 g.) was chromatographed over silica gel (110 g.) collecting 20 fractions. Elution with ether-acetone (1:2) (four fractions) afforded 'isophotosantonic lactone' (1.2 g.), m.p. (from ethyl acetate - light petroleum) 165-167°, $[\alpha]_D$ + 129° (c, 1.34), $\lambda$ max. 239 m$\mu$ ($\varepsilon$, 13,000)

(Found: C, 68.2; H, 7.35; C-Me, 17.5. Calc. for $C_{15}H_{20}O_4$ C, 68.15; H, 7.65; 3C-Me, 17.0%). Crystallisation from aqueous ethanol afforded material of the same m.p. (Found: C, 64.05; H, 7.6. Calc. for $C_{15}H_{20}O_4.H_2O$ C 63.8; H, 7.85%). The compound gave negative Schiff, Angeli-Rimini and Fehling tests.

The acidic fraction (760 mg.) was chromatographed over silica gel (27g.) (20 fractions). Elution with benzene-ether (5:1) (4 fractions) gave photosantonic acid (160 mg.), m.p. (from chloroform-light petroleum) 154-155°, $\lambda$ max.210 mμ ( $\varepsilon$ 6700), $[\alpha]_D$ - 129° (c, 1.3) (Found: C, 68.4; H, 7.6. Calc. for $C_{15}H_{20}O_4$ C, 68.15; H, 7.65). Further elution with ether-acetone (2:1) (3 fractions) afforded some 'isophotosantonic lactone' (144 mg.).

The acetate of 'isophotosantonic acid lactone' was prepared by the method of Cannizzaro and Fabris.[6] 'Isophotosantonic lactone' (150 mg) was refluxed with acetic anhydride (5.5 ml) in the presence of anhydrous sodium acetate (10 mg) for 3 hours, usual working up and recrystallisation from ethyl acetate-light petroleum this had m.p. 175-177° (capillary), $[\alpha]_D$ + 58° (c, 0.53 in ethanol), $\lambda$max. 239 mμ ( $\varepsilon$ ,13,000). Cannizzaro and Fabris recorded m.p. 183°, $[\alpha]_D$ + 59° (in ethanol) for this compound. In the infra-red the acetate showed bands

at 1770 (γ-lactone), 1730 and 1260 (acetate), 1703 and 1635 cm.$^{-1}$ (cyclopentenone).

3-oxoguai-4:10(15)-dien-6:12-olide (9β). - 10-Hydroxy-3-oxoguai-4-en-6:12-olide (6) (56 mg.) in pyridine (3 ml.) was treated with thionyl chloride (240 mg.) at 0° for 10 minutes. Isolation of the product and chromatography over silica gel (2 g.) (six fractions) gave, on elution with benzene (two fractions), 3-oxoguai-4:10(15)-dien-6:12-olide (9β) (20 mg.), m.p. (from ethyl acetate-ether-light petroleum) 113-115°, λmax. 236 mμ (ε, 12,600), $[\alpha]_D$ + 378° (c, 1.21) (Found: C, 73.15; H, 7.1; C-Me, 14.9. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.35; 2 C-Me, 12.2%). Ozonolysis of the anhydro compound (73 mg.) in methylene dichloride (50 ml.) at -30° for 30 minutes (disappearance of u.v. max. at 236 mμ) followed by steam distillation into aqueous dimedone (removal of methylene dichloride in vacuo) gave the formaldehyde-dimedone compound (17.8 mg.; 20%), identified by m.p. and mixed m.p. A similar ozonolysis of the anhydro compound (65 mg.) followed by conversion of the acidic portion of the steam distillate to the p-bromophenacyl ester gave, after chromatography over alumina (2 g., Brockmann Grade 5), p-bromophenacyl acetate (29 mg.; 50%) identified by m.p. and mixed m.p. Compound (9β) (30 mg.) in ethyl acetate (5 ml.) was hydrogenated with 5%

palladised charcoal. Uptake of 1 mole of hydrogen in 5 minutes. Usual working up of the product furnished the oily dihydro derivative $\lambda_{max.}$ 236 mμ ($\varepsilon$, 12400). Infra red spectrum showed that band at 906 $cm^{-1}$ due to the grouping $\rangle C = CH_2$ has disappeared. On ozonolysis the dihydro-derivative furnished 0.8 mole of acetic acid.

Acid Catalysed Dehydration of 10-Hydroxy-3-oxoguai-4-en-6:12-olide (6). - The hydroxy-lactone (300 mg.) in acetic acid (10 ml.) was treated on the steam bath for 45 minutes with a 7% solution of perchloric acid in acetic acid (30 ml.). Chromatography of the product over silica (9 g.) gave, on elution with benzene and with benzene-ether (2:1) a gum showing $\lambda_{max.}$ 305 mμ ($\varepsilon$, 11,300). This was converted into the 2:4-dinitrophenylhydrazone in the usual way by dissolving the gum in absolute alcohol (5 ml.), adding the reagent (400 mg) dissolved in conc. sulphuric acid (2 ml) and warming on the steam bath for 10 minutes. Usual working up and chromatography over bentonite-celite and elution with chloroform gave 3-oxoguai-4:1(10)-dien-6:12-olide (10) 2:4-dinitrophenyl hydrazone, m.p. (from chloroform-ethanol) 232-238° (decomp.), $\lambda_{max.}$ 405 mμ ($\varepsilon$, 26,600 in $CHCl_3$) (Found: N, 13.4. $C_{21}H_{22}O_6N_4$ requires N, 13.15%). In the infra-red the compound showed a band at 1765 $cm^{-1}$ ($\gamma$-lactone).

Ozonolysis of 10-Hydroxy-3-oxoguai-4-en-6:12-olide (6). - (a) The keto-lactone (100 mg.) in chloroform (40 ml.) was ozonised at -10° for 25 minutes (disappearance of band at 239 mμ). Steam distillation and conversion of the volatile acidic portion to the p-bromophenacyl ester (removal of $CHCl_3$ in vacuo) gave, on chromatography over alumina (2.5 g.; Brockmann Grade 5), eluting with benzene-light petroleum (b.p. 60-80°) (1:20), p-bromophenacyl acetate (20 mg.; 20%), identified by m.p. and mixed m.p. The residue from the steam distillation afforded the stable 2:5-dihydroxy-5-methyl-3-oxocycloheptane-4-acetic-1-α-propionic dilactone (7), m.p. (from ethyl acetate) 198-212° (decomp.), $[\alpha]_D$ - 31° (c, 0.80 in pyridine). $\lambda_{max.}$ 294 mμ( ε ,50) (Found: C, 61.8; H, 6.65; C-Me, 12.25; equiv. 126.1, 126.4. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4; 2 C-Me, 11.9%; equiv. 126.1). This compound gave a positive Fehling's test, but was stable to chromic acid in acetic acid at room temperature during 1½ hours. The derived oxime, prepared with pyridine-hydroxylamine hydrochloride in the usual way, had m.p. (from methanol-ether-light petroleum) 214-224° (decomp.), $[\alpha]_D$ + 90° (c, 0.66) (Found: C, 58.25; H, 6.1; N, 5.75. $C_{13}H_{17}O_5N$ requires C, 58.4; H, 6.4; N. 5.25%).

(b) A similar ozonolysis, but with decomposition of the ozonide with cold water furnished the labile dilactone (7) m.p. (from ethyl acetate) 198-212° (decomp.), $[\alpha]_D$ + 70° (c, 0.69 in

pyridine) (Found: C, 61.7; H, 6.65 %). After 18 hours in pyridine the rotation had changed to -31° characteristic of the stable dilactone (see above). Isolation gave the stable dilactone itself identified by m.p., rotation and infra-red spectrum.

(c) 10-Hydroxy-3-oxoguai-4-en-6:12-olide (70 mg.) in ethyl acetate (5 ml.) was ozonised at -60° for about 30 minutes (disappearance of u.v. max. at 239 mμ). Palladised charcoal catalyst was added and the solution hydrogenated as it warmed to room temperature. Crystallisation from ethanol-light petroleum gave the triketone {α-[4-(2:3-dioxobutyl)-2:5 dihydroxy-5-methyl-3-oxocycloheptyl] propionic 2-lactone} (13), m.p. 154-156°, $[\alpha]_D$ + 20° (c, 0.66 in ethanol), $\lambda$ max. 290 mμ (ε, 71) (Found: C, 61.05; H, 6.5. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%). The compound gave a positive Fehling's test but was not cleaved by lead tetra-acetate in acetic acid solution at room temperature. Treatment of the triketone (54 mg.) in ethanol (5 ml.) containing aqueous N-sodium hydroxide (1 ml.;) with 30% hydrogen peroxide (3 ml.;) for 15 minutes (excess of peroxide destroyed with platinum black) gave, on acidification with diluted sulphuric acid and steam distillation acetic acid (0.9 mol. by titration), characterised as the p-bromophenacyl ester (m.p. and mixed m.p.), as sole volatile product.

10-Hydroxy-3-oxoguaian-6:12-olide. - 10-Hydroxy-3-oxoguai-4-en-6:12-olide (1.0 g.) in ethanol (100 ml.) was hydrogenated over 5% palladised charcoal (500 mg.; for 3 hours (uptake of 1 mol. of hydrogen). Chromatography of the product over silica gel (35 g.) (17 fractions) afforded, on elution with ether (6 fractions), 10-hydroxy-3-oxoguaian-6:12-olide (1), m.p. (from ethyl acetate-benzene-light petroleum) 135-138°, $[\alpha]_D$ - 46° (c, 1.16) (Found: C, 67.45; H, 8.1. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%).

Oxidation of 10-Hydroxy-3-oxoguai-4-en-6:12-olide with Potassium Permanganate.- The hydroxy-lactone was oxidised with potassium permanganate as described by Francesconi and Venditti[80] to furnish the dilactone (19) isophotosantonic lactone (250 mg.) was dissolved in water (12.5 cc) and to it was added conc. sulphuric acid (3 cc) followed by dropwise addition of 2.5% $KMnO_4$ in water (4.16 ml). Left overnight in the refrigerator. Usual working up afforded the desired compound. On recrystallisation from ethyl acetate this had m.p. 286-288°, $[\alpha]_D$ + 34° (c, 1.0), $[\alpha]_D$ + 112° (c, 0.67 in pyridine), $\lambda_{max.}$ 295 mμ($\varepsilon$,40) (Found: C-Me, 16.1. $C_{15}H_{20}O_6$ requires for 3 C-Me, 15.2%). The compound gave a positive iodoform test and was stable to chromic acid for 2 hours at 60° in acetic acid solution. It was not dehydrated by thionyl chloride-pyridine at 0° or at room temperature (recovered unchanged).

This dilactone was also obtained in the following way. 10-Hydroxy-3-oxoguai-4-en-6:12-olide (50 mg.) in dry dioxan (0.5 ml.) was treated with osmium tetraoxide (63 mg.) for four days at room temperature. Cleavage of the osmate with hydrogen sulphide and crystallisation of the product from methanol ethyl acetate-light petroleum afforded 4:5:10-trihydroxy-3-oxoguaian-6:12-olide (18), m.p. 193-198° (decomp.), $[\alpha]_D$ - 17° (c, 1.02), infra-red bands at 3400 (hydroxyl), 1760 (γ-lactone) and 1740 $cm.^{-1}$ (cyclopentanone) (Found: C, 59.95; H, 7.65. $C_{15}H_{22}O_6$ requires C, 60.4; H, 7.45%). This triol consumed 0.96 mol. of periodic acid in 15 minutes after which there was no further uptake of oxidant. Consumption of lead tetra-acetate in acetic acid was the same. The triol (90 mg.) in water (45 ml.) was treated with 0.05 N periodic acid (27 ml.;) until one mol. of oxidant had been consumed (15 minutes. Dilution with water, extraction with chloroform followed by washing with water and crystallisation of the product from ethyl acetate gave the dilactone (19) (see above), identified by m.p., mixed mp., rotation ( $[\alpha]_D$ + 113° (c, 0.62 in pyridine) ) and infra-red spectrum (Found: C, 60.55; H, 6.85. Calc. for $C_{15}H_{20}O_6$ C, 60.8, H, 6.8 %).

Reduction of 10-Hydroxy-3-oxoguai-4-en-6:12-olide with Sodium Borohydride.- The hydroxy-lactone (300 mg.) in ethanol (2 ml.) was treated with sodium borohydride (400 mg.) in the

same solvent (3 ml.) for 90 minutes. The complex was decomposed with dil.acetic acid. Extraction with chloroform and crystallisation of the product from ethyl acetate-light petroleum furnished 3:10-dihydroxyguai-4-en-6:12-olide (14; R = H), m.p. 205-208°, $[\alpha]_D$ + 87° (c, 0.86), no high intensity u.v. absorption (Found: C, 67.6; H, 8.45. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35 %). Acetylation (pyridine-acetic anhydride at room temperature overnight) gave an oily mono-acetate to which further reference is made below.

Fractional crystallisation of the mother liquors from the sodium borohydride reduction from methanol-ethyl acetate-light petroleum gave the saturated 3:10-dihydroxyguaian-6:12-olide (15) m.p. 95-97°, $[\alpha]_D$ + 16° (c, 0.82) (Found: C, 63.0; H, 9.0. $C_{15}H_{24}O_4.H_2O$ requires C, 62.9; H, 9.15 %).

Ozonolysis of 3:10-dihydroxyguai-4-en-6:12-olide (100 mg.) in chloroform (100 ml.) at -25° for 30 minutes, decomposition of the ozonide with water and crystallisation of the product from ethyl acetate-light petroleum afforded the dihydroxydiketone {α-[2:5-dihydroxy-4-(2-hydroxy-3-oxobutyl)-5-methyl-3-oxocycloheptyl] propionic 2-lactone} (16; R = H), m.p. 196-208° (decomp.), $[\alpha]_D$ - 8° (c, 0.58 in pyridine) (Found: C, 60.75; H, 7.45. $C_{15}H_{22}O_6$ requires C, 60.4; H,7.45%). Similar ozonolysis of the oily acetate gave the corresponding

acetate (16; R = Ac), m.p. (from ethyl acetate-light petroleum) 178-181°, $[\alpha]_D$ + 104° (c, 1.04) (Found: C, 57.15; H, 7.45. $C_{17}H_{24}O_7.H_2O$ requires C, 56.95, H, 7.3 %). The compound gave a positive Fehling's test.

Treatment of the oily acetate (47 mg.) in dioxan (6 ml.) with osmium tetroxide (56 mg.) for 14 days at room temperature and cleavage of the derived osmate with hydrogen sulphide gave 3-acetoxy-4:5:10-trihydroxyguaian-6:12-olide (17), m.p. (from methanol-ethyl acetate-light petroleum) 192-194°, $[\alpha]_D$ + 19° (c, 0.95) (Found: C, 58.25; H, 7.45. $C_{17}H_{26}O_7.\frac{1}{2}H_2O$ requires C, 58.15; H, 7.75% ). This compound consumed 1.1 mol. of periodic acid during 18 hours at room temperature after which there was no further uptake.

Dehydrogenation.- 10-Hydroxy-3-oxoguai-4-en-6:12-olide (1.0 g.) in 'AnalaR' acetic acid (80 ml.) containing 72% perchloric acid (5 drops) was hydrogenated using a platinum catalyst. The gummy product (no ketonic band in the infra-red spectrum) was dehydrogenated in portions (200 mg.) by heating with 10% palladised charcoal (200 mg.) for 15 minutes under nitrogen at 320° (Wood's metal bath). The combined product was extracted with light petroleum (b.p. 60-80°) and the blue solution filtered through alumina (5 g.; Brockmann Grade 5),

the column being further developed with benzene-light petroleum (b.p. 60-80°) (1:2). The combined eluates were extracted with 80% phosphoric acid to concentrate the azulenic material. Isolation from the phosphoric acid solution in the usual way, by diluting it with water and extracting with petrol ether, gave on treatment with trinitrobenzene, the chamazulene-trinitrobenzene adduct (equivalent to 6.2 mg. of chamazulene), identified by m.p., mixed m.p. and ultra-violet and visible absorption spectra.

## STRUCTURE OF LUMISANTONIN

(For rest of the formulae see tables 6,7,8 and 9)

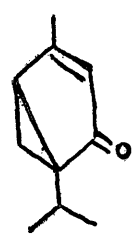
On irradiation of santonin in alcoholic solution, the ethyl ester of photosantonic acid, also known as photosantonin, is produced (see page 29 ). In addition, we have also discovered a new light-produced isomer of santonin. Prof.Buchi (M.I.T), Prof.Jeger (E.T.H. Zurich) and Prof.Cocker (Trinity College,Dublin) have also obtained this compound. They, through personal communications, suggested that it be given the name "Lumisantonin" which we have accepted.

Lumisantonin has the composition $C_{15}H_{18}O_3$, and exhibits bands in the infrared spectrum at 1765 ($\gamma$-lactone), 1703 and 1663 $cm.^{-1}$ ($\alpha\beta$-unsaturated cyclopentenone). In accord with this, it had a broad peak in the ultraviolet at 239 m$\mu$ ($\varepsilon$ ,5800). Lumisantonin contained three C-methyl groups as determined both chemically (Kuhn-Roth oxidation) and by quantitative infrared measurements. Lumisantonin on treatment with aqueous potassium carbonate afforded the corresponding hydroxy-acid (36) which had bands in the infrared at 3455 (hydroxyl) and a broad band at 1690 $cm.^{-1}$ (superimposed cyclopentenone and carboxyl groups).

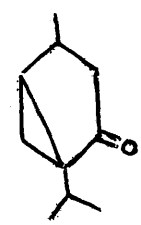
Lumisantonin, on hydrogenation with 5% palladised charcoal, in ethyl acetate afforded a crystalline dihydro-derivative, $C_{15}H_{20}O_3$, which was found to be stable to ozone

and did not give a colour in the tetranitromethane test. Lumisantonin, therefore, must contain three carbocyclic rings.

Dihydrolumisantonin showed bands in the infrared at 1770 ($\gamma$-lactone) and 1703 $cm.^{-1}$ The identical carbonyl frequencies in lumisantonin and its dihydro-derivative suggest that the carbonyl group in dihydrolumisantonin is still conjugated with some sort of 'unsaturation'. That this was a cyclopropane ring was suggested by a comparison of the spectra with those of umbellulone (1) and $\beta$-dihydroumbellulone[91] (2). The former showed the carbonyl frequency in the infrared at 1716 $cm.^{-1}$, almost identical with that of its dihydro-derivative (2) which exhibited the carbonyl frequency at 1719 $cm.^{-1}$.



(1)



(2)

In addition, the ultraviolet spectrum of dihydrolumisantonin, $\lambda$max. 214 m$\mu$ ($\varepsilon$, 4600) was almost identical with that of $\beta$-dihydroumbellulone[91], $\lambda$ max 210 m$\mu$ ($\varepsilon$, 2470).

Dihydrolumisantonin, when refluxed with aqueous acetic acid furnished an isomer and a substance with the empirical

formula, $C_{15}H_{22}O_4$. The isomer had three C-methyls in the Kuhn-Roth determination, and showed bands in the infrared at 1765 ($\gamma$-lactone) and 1735 $cm.^{-1}$ (normal cyclopentanone). It exhibited a positive tetranitromethane test and showed only an isolated ethylenic linkage in its ultraviolet absorption spectrum, $\lambda$ max 208 m$\mu$ ($\varepsilon$, 1900). 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 cyclopropane ring conjugated with the carbonyl group. This was further confirmed in a simple manner.

Treatment of lumisantonin with osmium tetroxide furnished a crystalline glycol $C_{15}H_{20}O_5$. This gave infrared bands at 3360 (hydroxyl), 1770 ($\gamma$-lactone) and 1726 $cm.^{-1}$ (cyclopentanone). This had the same ultraviolet spectrum as dihydrolumisantonin and consumed two mols of periodic acid to afford an aldehydo-acid $C_{14}H_{18}O_5$. This 'acid' on oxidation with sodium dichromate at room temperature consumed one atom of oxygen and afforded a compound $C_{14}H_{16}O_5$, characterised as an anhydride by its infrared spectrum, which showed bands at 1830 (anhydride) and 1770 $cm.^{-1}$ (superimposed anhydride and $\gamma$-lactone). The position of the anhydride band at 1830 $cm.^{-1}$ is suggestive[92] of a succinic anhydride attached to a cyclopropane ring. This evidence also conclusively proves the disecondary nature of the double bond present in lumisantonin. On the basis of all this

evidence lumisantonin must possess the partial structure shown in the expression (3).

Lumisantonin, on refluxing in aqueous acetic acid in the dark furnished isophotosantonic lactone (4,R = H). Similarly, treatment with acetic acid containing a trace of perchloric acid afforded the 10-acetoxy compound (4, R = $\overset{\ominus}{A}\overset{\oplus}{c}$). Therefore, one can write the complete structure (5) for lumisantonin, when its dihydro-derivative would be represented by formula (6). (For the mechanism of the acid catalysed conversion of (5) to (4) see page 55 ). Similarly, formula (7) can be assigned to lumisantonin-diol when its periodate-cleavage product would have the formula (8). However, this acid is regarded as existing in the lactol form (9) on the basis of infrared and ultraviolet absorption spectra. (No carbonyl absorption). It gave a positive Fehling test (lumisantonin and its dihydro-derivative did not under the same conditions), and exhibited infrared bands at 3292 (hydroxyl) and 1755 $cm.^{-1}$ ( $\gamma$-lactone superimposed on $\gamma$ -lactol). The corresponding anhydride can, therefore, be assigned the constitution (10).

The isomer of dihydrolumisantonin, formed by refluxing the latter with aqueous acetic acid, in a manner indicated in (6) would then find expression in formula (11),

when the constitution (12), for the corresponding tertiary alcohol, would follow from its genesis, the failure to show absorption in the far ultraviolet region, and from infrared bands at 3360 (hydroxyl), 1770 ( $\gamma$-lactone) and 1726 $cm.^{-1}$ (cyclopentanone).

Additional evidence to support structure (5) for lumisantonin is described in the sequel. Treatment of lumisantonin with ozone gave formic acid (0.4 mol characterised as its sodium salt in the infrared) and a small amount of a crystalline compound, $C_{15}H_{18}O_6$, formulated as (13) (or equivalent open formula). This showed infrared bands at 3440 (hydroxyl) and 1755 $cm.^{-1}$ ( $\gamma$-lactone superimposed on $\delta$-lactol or equivalent). With alkaline hydrogen peroxide the compound (13) was cleaved to a carboxylic acid, $C_{14}H_{20}O_6$, (14), the constitution of which followed when it was obtained also by opening the lactone ring of the lactol (9) with alkali.

Brief treatment of lumisantonin with hydrogen bromide in acetic acid afforded a non-conjugated cyclopentenone (15). This gave infrared bands (in $CCl_4$) at 1792 ( $\gamma$-lactone) 1752 ($\beta\gamma$-unsaturated cyclopentenone) and (in Nujol) at 1627, 802, 752 and 722 $cm.^{-1}$ (triply substituted ethylenic linkage). On treatment with boiling pyridine, compound (15) furnished a new non-conjugated dienone (16) along with re-formed lumisantonin.

This (16) had three C-methyls in the Kuhn-Roth determination and exhibited infrared bands (in $CCl_4$ at 1792( $\gamma$-lactone) and 1752 ($\beta\gamma$-unsaturated cyclopentenone) and (in Nujol) at 1643, 815, 741, and 727 $cm^{-1}$ (triply substituted double bond). The re-formation of lumisantonin demonstrates the reversibility of the opening of the cyclopropane ring.

The bromo-ketone (15) was unstable at room temperature: it liquified and then resolidified to furnish a new conjugated-dienone (17). This had three C-methyl groups (Kuhn-Roth determination) and showed infrared bands at 1760 ($\gamma$-lactone) 1697 and 1660 $cm^{-1}$ ($\alpha\beta$-unsaturated cyclopentenone) and at 1630 and 722 $cm^{-1}$ (triply substituted double bond). In accord with the assigned structure (17) it had a maximum in the ultraviolet at 220 m$\mu$ ($\varepsilon$,10,800). On catalylic hydrogenation the ketone (17) consumed two mols of hydrogen to give a saturated tetrahydro-ketone (18).

Finally, the conversion of lumisantonin into isophotosantonic lactone may be briefly discussed. The rearrangement can be interpreted as in (19)*. However, the participation of the intermediate (20) cannot be entirely ruled out, although the mild acid conditions required for this rearrangement make the latter possibility somewhat improbable. It may be noted

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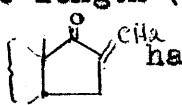
* We are grateful to Prof. Woodward (Harvard) for pointing out that the rearrangement could be regarded equally as proceeding through a cyclobarbatonium ion[94].

with interest that the opening of the cyclopropane ring by hydrogen bromide (see above), although leading to a different carbon skeleton, involves the same $C_5:C_{10}$ electrons pair. With hydrogen bromide, this electrons pair becomes part of a $\pi$-bond system, whereas with aqueous acetic acid it moves to establish a new carbon-carbon bond.

In a recent paper Cocker and co-workers[95] have reported the isolation of lumisantoninic acid from the irradiation of santonin in one equivalent of potassium hydroxide. This acid is stated to lactonise very easily to give what is known as lumisantonin, to which constitution (21) has been assigned by them. It should be noted that the constants for both lumisantonin and the related acid are in good agreement with those recorded by us and it must therefore be assumed that these compounds are identical.

As has been conclusively proven, lumisantonin contains the grouping - CO.CH:CH -, which function is not contained in formula (21). Similarly, many other results that have been described in the previous pages are incompatible with the constitution (21) for lumisantonin. For example, lumisantonin under acidic conditions yields isophotosantonic lactone. It would then be anticipated that dihydrolumisantonin under similar conditions would furnish the corresponding dihydro isophotosantonic lactone. But it has already been

shown that this does not happen, (see formula 12). The correct structure assigned to lumisantonin (5) therefore, finds additional support, because even their results based on (21) can be explained better on the structure (5), as is briefly discussed in the following pages.

It is stated that lumisantonin on treatment with boron trifluoride in acetic acid furnishes the isophotosantonic lactone acetate (4, R = Ac) and an unsaturated compound (22). This showed bands in the infrared at 1775 ($\gamma$ -lactone) 1716 and 1647 $cm^{-1}$ ($\alpha\beta$-unsaturated cyclopentenone) and at 832 $cm^{-1}$ ($\rangle C = CH_2$), and had a maximum in the ultraviolet at 219.5 m$\mu$. It is apparent that structure (22) should exhibit an ultraviolet maximum at much higher wave length[96] (c.f. steroids containing the partial expression  have $\lambda$ max 228 m$\mu$ (~~~13,000) and its genesis is mechanistically difficult of interpretation). In fact this compound is identical with the conjugated dienone obtained by us and can therefore be correctly represented by formula (17), which also explains the data cited above satisfactorily.

It is also stated that lumisantonin, on treatment with hydrochloric acid gas affords (23), which is rapidly hydrogenated to the dihydro-compound. The compound (23) is stated to be convertible to (24) on dehydrochlorination. Apart from the fact that the formation of the chloro-derivative (23)

cannot be explained in a satisfactory manner, on the basis of (21), it is surprising that a tetrasubstituted double bond is stated to be hydrogenated rapidly.

This compound (23) is, in fact, correctly represented by the constitution (25) analogous to (15), which on dehydrochlorination, would afford the re-formed lumisantonin analogously (see formula (15) ). Therefore the dehydrochlorinated compound (24) should in fact be re-formed lumisantonin; the reported data are identical, except for the rotation, which must be assumed to be an experimental error. (Reported rotation for compound (24) is -136).

Similarly, dihydrolumisantonin under similar acidic conditions, is stated to furnish compound (26). (mp.210-212, $[\alpha]_D$ + 48 ). This compound is identical with the double bond isomer of dihydrolumisantonin (mp. 192-202 D Kofler; $[\alpha]_D$ + 52). and should be correctly represented by formula (11).

It is also stated that dihydrolumisantonin on reduction with potassium borohydride in aqueous methanol afforded (27) in small yield, presumed to be formed via the intermediate (28). It has also been suggested that such dehydrations are unusual, but may result from release of strain in the molecule. However the compound (27) would appear more strained than (28), and although this reaction

seems to be unusual, it is probable that (29) is the intermediate. This loses water by opening of the cyclopropane ring during the working up of the reaction which probably involves the use of an acid, to give compound (30), which already has an analogy (see formula 6).

For all these reasons, the structure (21) for lumisantonin is to be rejected. In addition, the proposed ionic mechanism involving the intermediate (35) for the formation of lumisantonin is untenable, because such excited states arise from N-B and N-V transitions.[54] These occur by the absorption of light of wavelength below 200 mμ, whilst we have prepared these photo-compounds using glass vessels which cut off all the light having wavelength roughly below 290 mμ. (For data see also the chart below).

| Our Compounds | Cocker's Compounds |
|---|---|
| Compound (17)<br>m.p. 128-130°; $[\alpha]_D$ -168° (c,1.62)<br>λ max 220 mμ(ε 10800). | Compound (22)<br>m.p. 129-130°; $[\alpha]_D$ -171°(c, .4)<br>λ max 219.5 (ε 13,800). |
| Lumisantonin<br>m.p. 153-155° $[\alpha]_D$ -169° (c 1.2)<br>λ max 239 mμ(ε 5800) | Compound (24)<br>m.p. 150-151° $[\alpha]_D$ -137°<br>(c, 0.26) λ max 237.5 mμ<br>(ε 6,310). |
| Compound (11)<br>m.p. 192-202° $[\alpha]_D$ + 53° (c 0.93) | Compound (26)<br>m.p. 210-211°; $[\alpha]_D$ + 48°<br>(c, 1.03). |

Recently, another paper, by Jeger, Buchi and co-workers[97], which also deals with the constitution of lumisantonin, has appeared. Although they have 'reluctantly' proposed the constitution (5) for lumisantonin, they have not interpreted most of their results in terms of structural formulae. Therefore an effort will be made, in the following pages, to discuss some of the key compounds. The structures of the rest of the compounds can then be deduced in a simple manner.

Lumisantonin is stated to furnish an isomer called pyrolumisantonin, on heating at 200°C. This should be correctly represented by formula (17) with which it is identical. Pyrolumisantonin probably arises through the formation of the non-conjugated dienone (16) which isomerises thermally to (17).

The aldehydo-acid (9) has also been obtained by Professors Buchi, Jeger and their colleagues through the same reaction sequence, and has been stated to be stable towards chromic acid at room temperature. On the basis of this evidence they have dismissed the presence of an aldehyde group. This experiment is of great significance since we found that the aldehydo-acid (9) could be smoothly oxidised to the corresponding anhydride (10); a result which had a strong bearing on the structure of lumisantonin. The corresponding

hydroxy-acid (14) on reduction with sodium borohydride is said to give a dihydroxy-diacid mono-lactone $C_{14}H_{20}O_5$ which should probably be represented by formula (31), since on elimination of one molecule of water it affords the dilactone (32), also obtainable by sodium borohydride reduction of (9).

Similarly dihydrolumisantonin affords a hydroxy-methylene derivative which is stated to furnish a triacid-monolactone $C_{15}H_{20}O_6$, on treatment with alkaline hydrogen peroxide. The hydroxy methylene derivative can be correctly represented by formula (33), when the triacid mono-lactone would possess structure (34).

Finally we would like to point out that all but one of the photo-products of santonin can now possibly be formulated. Santonin on irradiation in alcoholic solution furnishes a compound $C_{17}H_{24}O_4$, m.p. 154-155 $[\alpha]_D$ + 76.8 (in alcohol), apart from photosantonin[82]. This compound has also been isolated by Prof. Jeger and co-workers[97] who have suggested that it is probably ( ⅃ , R = $C_2H_5$).

On the other hand santonin on irradiation in three equivalents of potassium hydroxide affords photosantoninic acid[81] $C_{30}H_{42}O_9$. This compound has also been obtained[95,97] by the treatment of lumisantonin with alkali. Therefore its

formation can possibly be explained by the addition of one molecule of water to lumisantonin to give (37) which adds to another molecule of lumisantonin (Michael addition) to give (38). Of course, alkali treatment also implies that the two lactone rings in photosantoninic acid are open. In accord with its possible formulation (38) photosantonic acid gives a diethyl ester, and a dilactone monoacetate[81]. Photosantoninic acid on hydrogenation with platinum oxide affords a compound $C_{30}H_{42}O_8$[95]. This indication that the hydroxyl group is situated in an environment that facilitates its elimination under these mild conditions, to produce a double bond, which is finally hydrogenated, also lends support to the formulation (38). Therefore dihydrophotosantoninic acid may possibly be represented as (39).

## Experimental

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 reaction was followed by the growth of a peak at 1707 $cm.^{-1}$ in the infra-red. Previous studies had shown that the optimum 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 (5) (1.8 g.), m.p. 153-155°, $[\alpha]_D$ - 169° (c 1.2), $\lambda_{max.}$ 239 mμ ($\varepsilon$ 5800) (Found: C, 73.3; H, 7.1; C-$CH_3$, 14.9. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.35; C-$CH_3$ (for 3 groups) 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).

Lumisantoninic Acid.-(36) Lumisantonin (150 mg.) was treated with potassium carbonate (300 mg.) in 6 ml. of 1:2 water-alcohol mixture for 24 hours. Separation into acidic and neutral fractions and crystallisation of the acidic fraction from ethyl acetate-petrol afforded luminsantoninic acid

m.p. 85-90° (mostly melted) with resolidification and finally melting at 135°C. $\lambda_{max.}$ 242 (ε 5160) $[\alpha]_D$ = - 80 ( 0.875) (found: C, 65.85; H, 7.65; $C_{15}H_{20}O_4 \cdot \frac{1}{2} H_2O$ requires: C, 66.0; H, 7.75).

Dihydroluminsantonin.- 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 (6), m.p. 160-162°, $[\alpha]_D$ - 59° (c 0.9), $\lambda_{max.}$ 214 mμ (ε 4600) (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 (60 ml.) was ozonised at -25° for 25 min. (until disappearance of the max. in the ultraviolet at 239 mμ). Steam distillation afforded 0.4 mol. formic acid (identified by the infrared spectrum of its sodium salt KCl disc ) and no acetic acid. Isolation of the residue from the steam distillation and crystallisation from water gave the lactol (13), 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).

The Action of Hydrogen Peroxide on the Lactol (13).- The lactol (53 mg.) in ethanol (10 ml.) containing 4N sodium hydroxide (2 ml.) was treated with 30% hydrogen peroxide (3 ml.) and allowed to stand for 20 min. Excess $H_2O_2$ was decomposed, by acidification with dil. HCl followed by extraction with chloroform, and crystallisation from acetone-petroleum ether gave the carboxylic acid (14), 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 (5) with Osmium Tetroxide.- Lumisantonin (400 mg.) in dry dioxane (5 ml.) was treated with osmium tetroxide (540 mg.) and the mixture allowed to stand for 5 days. Decomposition of the complex with hydrogen sulphide and crystallisation of the product from methanol-chloroform-light petroleum gave the diol (7), 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(7).- The diol (150 mg.) in ethanol (25 ml.) was treated with 0.05 N aqueous periodic acid (80 ml.) and allowed to stand 2 hr. (consumption of 2.2 atoms of oxygen). Isolation of the product by extraction with chloroform followed by washing of the chloroform layer with water and crystallisation from

chloroform-light petroleum afforded the cleavage product (9) m.p. 127-129° with solidification and remelting at 172-3°, $[\alpha]_D$ - 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 cleavage product (9), (46 mg.) in ethanol (2.5 ml.) containing sodium hydroxide (1 ml.; 4N) was allowed to stand at room temperature for 30 min. Isolation of the product in the usual way and crystallisation from chloroform-light petroleum afforded the acid (14) identified by m.p., mixed m.p. and infrared spectrum.

Oxidation of the Cleavage Product (9).- The substance (47 mg.) in acetic acid (10 ml.) was treated with sodium dichromate (67 mg.) and the mixture allowed to stand for 22 hr. (uptake of 1 atom of oxygen). Isolation of the product in the usual way gave the anhydride (10) as a glass which was purified by sublimation at 150°/$10^{-4}$ mm., m.range 66-69°, $[\alpha]_D$ - 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).

The Formation of 10-Hydroxy-3-oxoguai-4-en-6:12-olide (4, R=H). Lumisantonin (50 mg.) in 45% aqueous acetic acid (3 ml.) was refluxed in the dark for 3 hr. (no further change in $[\alpha]_D$). Evaporation and crystallisation of the

product from ethyl acetate-light petroleum gave the guaiholide (4, R=H) (20 mg.), m.p. and mixed m.p. 165-167°, having the same infrared spectrum as an authentic specimen.

The Formation of 10-Acetoxy-3-oxoguai-4-en-6:12-olide

Lumisantonin (102 mg.) in acetic acid (5 ml.) was treated with perchloric acid (70%; 0.05 ml.) and the mixture allowed to stand for 18 min. Isolation of the product was affected by extraction with chloroform followed by washing of the chloroform layer with sodium bicarbonate and then water, and chromatography over silica gel(4 g.) gave, on elution with benzene and crystallisation from ethyl acetate-light petroleum, the required acetate, m.p. 175-177° identical in every respect with an authentic sample prepared according to the method of Cannizzaro and Fabris.[10]

The Reaction of Dihydrolumisantonin with Acetic Acid

Dihydrolumisantonin (6) (200 mg.) in 45% aqueous acetic acid solution (17 ml) was refluxed for 6 hr. (no further change in rotation). Isolation of the product and chromatography over silica gel (7 g.) gave, on elution with benzene and crystallisation from chloroform-light petroleum, the ketone (11), 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-$CH_3$, 17.03. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1; C-$CH_3$ (for 3 C-$CH_3$) 18.15%).

Elution of the column with benzene-ether (4:1) and crystallisation from chloroform-light petroleum gave the hydroxy-ketone (12), 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%).

The Reaction of Lumisantonin with Hydrogen Bromide.- Lumisantonin (100 mg.) in benzene (2 ml.) was treated with hydrogen bromide in acetic acid (5 drops; 50% w/v.) and the mixture allowed to stand for 5 min. After isolation by extraction with chloroform and washing the chloroform layer with bi-carbonate followed by water, the product was crystallised from ethyl acetate-light petroleum to give the bromo-ketone (15), m.p. 111-114°, $[\alpha]_D$ - 130° (c 1.45) (Found: C, 55.6; H, 6.25; Br, 24.2. $C_{15}H_{19}O_3$ Br requires C, 55.55; H, 5.85; Br, 24.4%).

Spontaneous Decomposition of the Bromo-Ketone (15).- The bromo-ketone (150 mg.) was allowed to stand at room temperature. It liquefied after 2 days and on further keeping (ca. 1 week) crystallised. It was dissolved in chloroform, washed with sodium bicarbonate, then with water, and chromatographed over silica gel (6 g.). Elution with benzene-light petroleum (3:1) gave, after crystallisation from carbon tetrachloride-light petroleum, the dienone (17) m.p. 128-130°, $[\alpha]_D$ - 168° (c 1.62), $\lambda$max. 220 m$\mu$ ($\varepsilon$ 10850) (Found: C, 72.95;

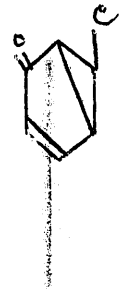
H, 7.35; C-Me, 16.8. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.35; C-Me (for 3 C-Me), 18.3%).

The dienone (17) (46.7 mg.) in ethyl acetate (5 ml.) was hydrogenated over palladised charcoal (5%; 32 mg.) when 2 mol. hydrogen was absorbed. Isolation of the product and crystallisation from light petroleum gave the ketone (18) 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 (15) with Pyridine.- The bromo-ketone (300 mg.) in pyridine (15 ml.) was refluxed for 6 hr. Isolation of the product by extraction with chloroform, washing the chloroform layer with dil. hydrochloric acid followed by sodium bicarbonate and then water and chromatography over silica gel (12 g.) gave, after elution with benzene-light petroleum (1:1) and crystallisation from ethyl acetate-light petroleum, the dienone (16), m.p. 181-183°, $[\alpha]_D$ - 200° (c 0.74) (Found: C, 73.0; H, 6.8; C-$CH_3$, 14.6. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.35; C-$CH_3$ (for 3 C-$CH_3$), 18.3%).

Further elution of the column with benzene gave lumisantonin (5) identified by m.p., mixed m.p., rotation $[\alpha]_D$ + 165° (c 0.87) ) and infrared spectrum.

TABLE NO 6



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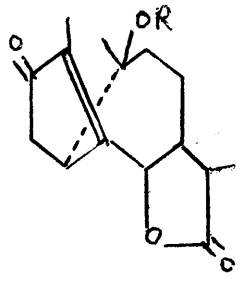

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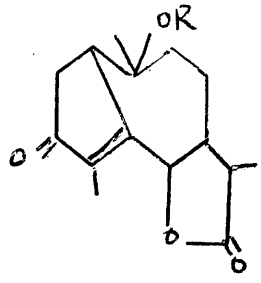

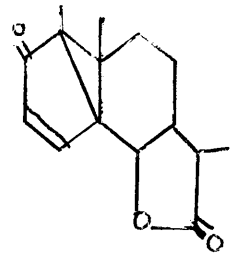

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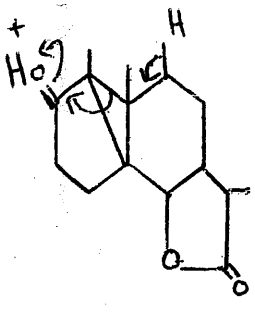

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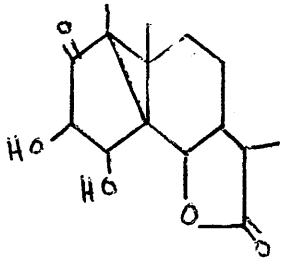

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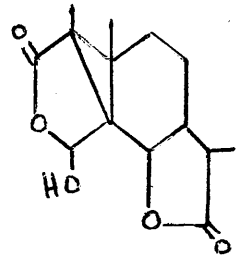

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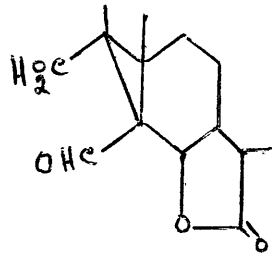

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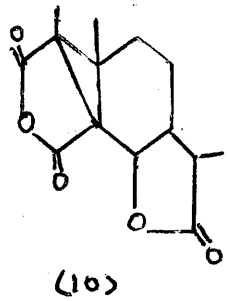

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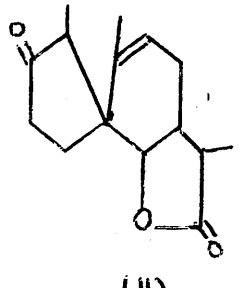

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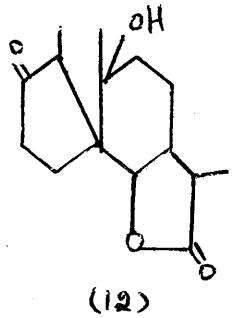

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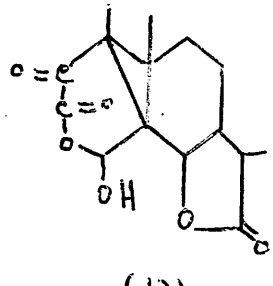

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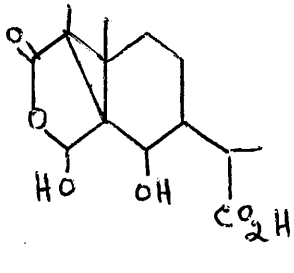

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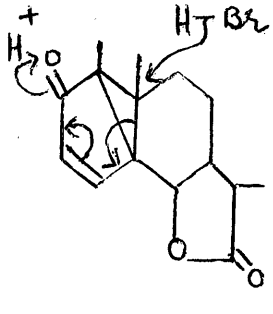

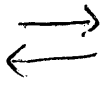

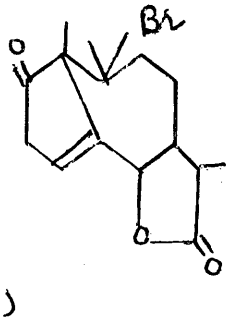

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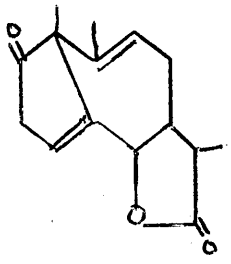

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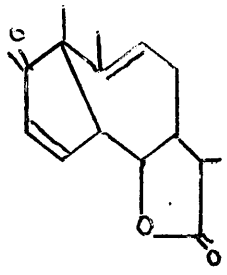

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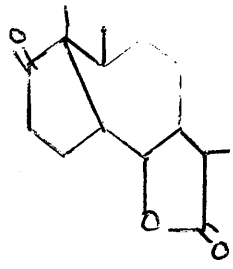

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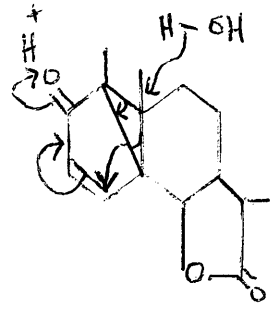


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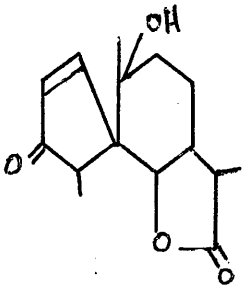


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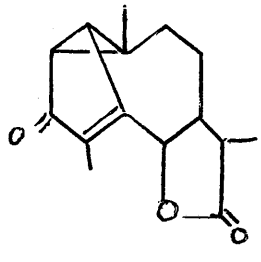

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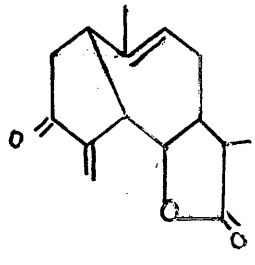

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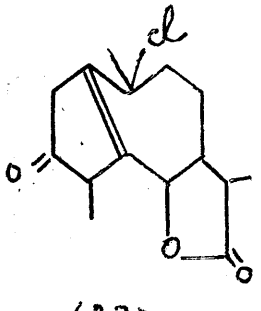


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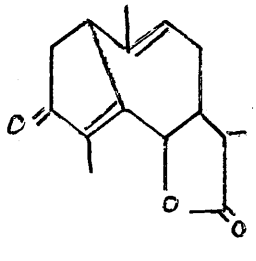

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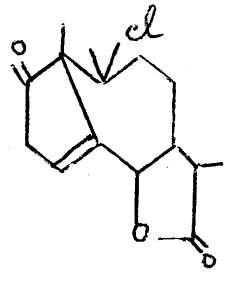


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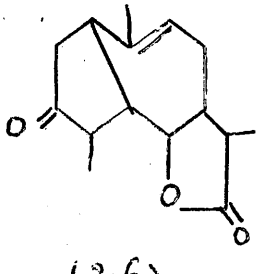

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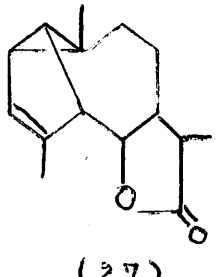

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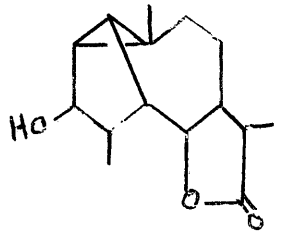


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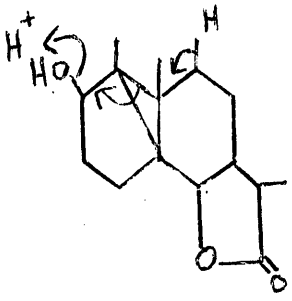

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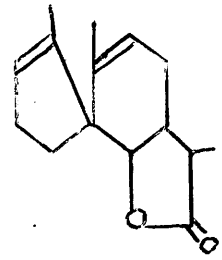

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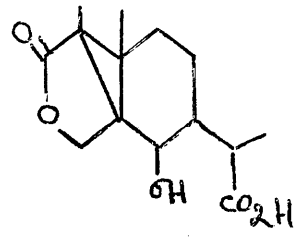

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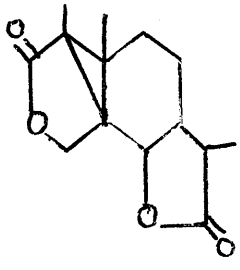

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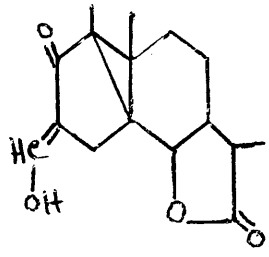

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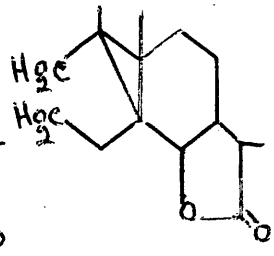

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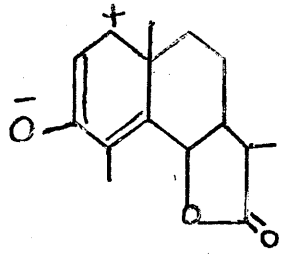

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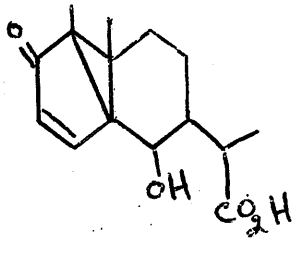

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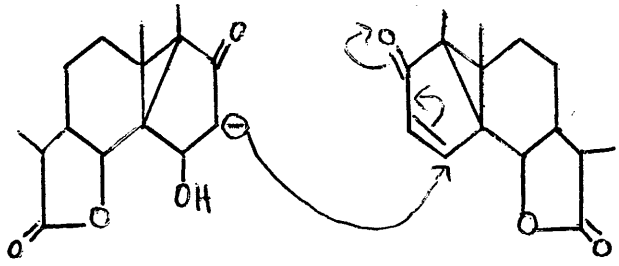

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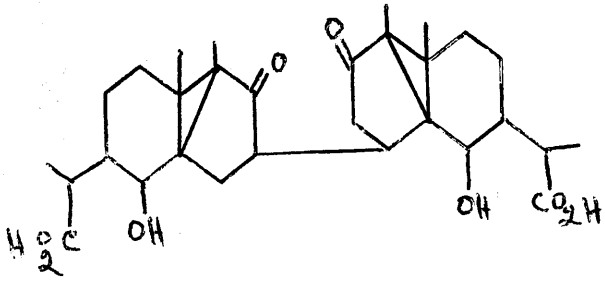

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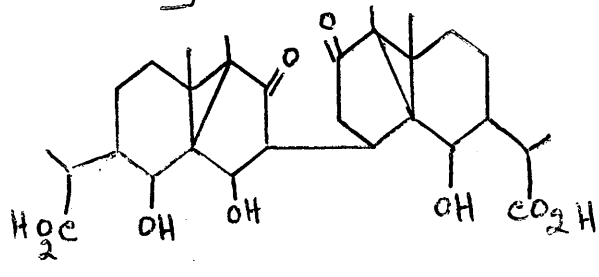


(38)

## CONSTITUTION OF PHOTOSANTONIC ACID

(For rest of the formulae see Tables 10 & 11)

As has already been mentioned, Francesconi[81], Sestini[81] and others[82-85], isolated photosantonic acid as an irradiation product of santonin. To this substance was assigned the structure (1) on the following evidence. Treatment with alcoholic hydrochloric acid was stated to give a mixture of two stereoisomeric 'dehydrophotosantonic acids' $C_{15}H_{20}O_4$, represented as (2). Both these acids were said to be converted into a third isomer, on heating above the melting point. All these 'dehydro-acids' were reported to afford the dimethyl-phthalide (3) on oxidation with chromic acid, while distillation with barium hydroxide resulted in the formation of 2:4 diethylisopropyl benzene (4) which likewise afforded (3), on chromic acid oxidation. On distillation with soda lime (3) afforded acetone and isophthalic acid (5), whilst 2:4:6 trinitro-1:3 diethyl-benzene (6) resulted from the nitration of (4). The latter was also prepared by the nitration of 1:3 diethyl-benzene (7). Photosantonic acid (1) on heating with hydroiodic acid or in an inert atmosphere furnished pyrophotosantonic acid $C_{14}H_{20}O_2$, stated to possess structure (8) which likewise afforded (4) on distillation with barium hydroxide. By warming at 100°C, photosantonic acid is stated to give the corresponding lactone (9).

It will be recalled that these deductions were necessarily based on the (incorrect) structure proposed for santonin at that time. In addition, the formation of the pyro-compound (8) is somewhat peculiar in that it involves the decarboxylation of only one of the two carboxyl groups, though both have the same environment. Moreover, the evidence cited above is insufficient to furnish a conclusive proof for the formula (1) proposed for photosantonic acid. It seemed, therefore, desirable to reinvestigate the problem.

We have found that the ethyl ester of "photosantonic acid lactone" can, if so desired, be isolated as the main photochemical transformation product of santonin in ethanol solution, in about 40% yield.

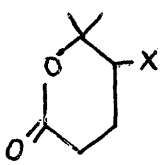
Photosantonic acid, as stated before, was originally assigned the composition $C_{15}H_{22}O_5$ and was shown to be converted to the corresponding lactone, on heating at 100°C. We found that <u>both</u> photosantonic acid and its corresponding lactone are lactonic substances exhibiting bands in the infrared spectrum at 1760 and 1777 $cm.^{-1}$ ($\gamma$-lactones) respectively. This implies that the so-called photosantonic acid is merely the hydrated form of the corresponding lactone. This was found to be the case because "photosantonic acid lactone" on crystallisation from aqueous ethanol afforded the hydrated form whilst, on

crystallisation from non-aqueous solvents, the non-hydrated form resulted. That the hydroxy acid probably does not lose water to give the corresponding lactone by warming at 100° was subsequently supported by the observation that the corresponding hydroxy acid of photosantonin melted at 138-140°C, while the lactone itself melted at 67-69°C.

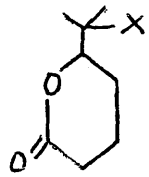
Photosantonic acid contains a carboxyl group, since it is known to afford the corresponding methyl and ethyl esters, the latter also known as photosantonin. In accord with this the acid showed infrared bands at 1720 (carboxyl C = O) and 1650 $cm^{-1}$ (double bond). The presence of a double bond in photosantonic acid was also supported by its ultraviolet absorption spectrum which had a maximum at 210 mμ ($\epsilon$,6700). Photosantonic acid had two C-methyl group in Kuhn-Roth determination, whilst photosantonin contained three C-methyl groups.

Photosantonin, on treatment with potassium carbonate, affords the corresponding hydroxy-acid $C_{17}H_{26}O_5$ which showed bands in the infrared at 3240 (hydroxyl) 1730 (ester carbonyl) and 1690 $cm^{-1}$ (carboxyl carbonyl). On attempted acetylation, photosantonin was regenerated. Ozonolysis of both photosantonin and its corresponding hydroxy-acid, afforded acetone, which implies that the double bond in photosantonic acid is present in an <u>iso</u>propylidene grouping.

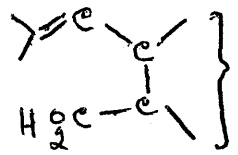
Photosantonic acid, on bromination consumed one mol. of bromine, and afforded the corresponding bromo-lactone $C_{15}H_{19}O_4$ Br which exhibited bands in the infrared at 1777 ( $\gamma$ -lactone) and 1730 $cm.^{-1}$ ( $\delta$ -lactone). This establishes the relative positions of the carboxyl group and the isopropylidene group in photosantonic acid. The bromo-lactone was stable to ozone, but was reduced by zinc dust and acetic acid back to the starting acid. Photosantonic acid, therefore, contains only one double bond and hence two carbocyclic rings. Therefore partial expression (10) or (11) can be written for the bromo-lactone.



(10) X = Br
(12) X = OH



(11) X = Br
(13) X = OH

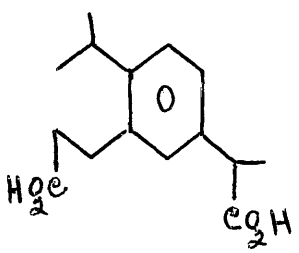


(14)

On treatment with monoperphthalic acid, photosantonic acid afforded the corresponding hydroxy-dilactone $C_{15}H_{20}O_5$, with consumption of one atom of oxygen. This showed bands in the infrared spectrum at 3430 (tertiary hydroxyl: on attempted acetylation gave back starting material), 1755 ($\gamma$-lactone), and 1735 $cm.^{-1}$ ($\delta$-lactone). Hence the partial expression (12) or (13) can be assigned to the hydroxy-dilactone. On dehydration with thionyl chloride and pyridine the latter was converted into the corresponding anhydro-dilactone $C_{15}H_{18}O_4$. This had infrared bands at 1770 ($\gamma$-lactone), 1726 ($\delta$-lactone), and 1643 $cm.^{-1}$ (double bond), and did not give formaldehyde on ozonolysis. Hence the bromo- and the hydroxy-dilactones are correctly represented by partial formulae (10) and (12) respectively, when photosantonic acid itself would possess the partial expression (14).

Now it has already been stated that the Italian workers obtained the hydrocarbon (4) from photosantonic acid, the structure of which was well established. This hydrocarbon resulted by the stepwise decarboxylation of the 'dehydrophotosantonic acids' formulated by them as (2). However, stepwise decarboxylation implies some difference in the environment of the two carboxyl groups, a fact better explained by the alternative structure (15) for the 'dehydro-acids'. The

correctness of the latter has been shown by the acid catalysed cyclisation of the 'dehydro-acids' to the corresponding hydrindanone (16) which exhibited a broad band in the infrared at 1695 $cm^{-1}$ (superimposed 5-membered aromatic ketone and carboxyl group). In accord with this formulation it had a maximum in the ultraviolet at 254 mμ ($\varepsilon$,8700) and furnished the corresponding methyl ester 2:4-dinitrophenylhydrazone. The relationship of the carbonyl group to the remaining carboxyl group in (16) was shown by its reduction with sodium borohydride, to the corresponding crystalline alcohol $C_{15}H_{20}O_3$ (17), which had bands in the infrared at 3226 (hydroxyl) and 1718 $cm^{-1}$ (carboxyl group). This on heating afforded the corresponding oily δ-lactone, $C_{15}H_{18}O_2$, (18), which showed infrared bands at

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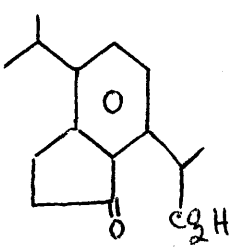


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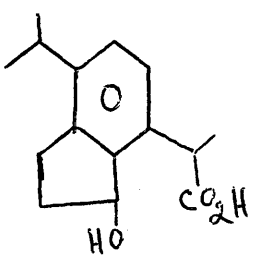


(17)

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and (22) respectively, when the corresponding hydroxy-acid of photosantonin would have the formula (23).

correctness of the latter has been shown by the acid catalysed cyclisation of the 'dehydro-acids' to the corresponding hydrindanone (16) which exhibited a broad band in the infrared at 1695 $cm^{-1}$ (superimposed 5-membered aromatic ketone and carboxyl group). In accord with this formulation it had a maximum in the ultraviolet at 254 mμ ($\varepsilon$,8700) and furnished the corresponding methyl ester 2:4-dinitrophenylhydrazone. The relationship of the carbonyl group to the remaining carboxyl group in (16) was shown by its reduction with sodium borohydride, to the corresponding crystalline alcohol $C_{15}H_{20}O_3$ (17), which had bands in the infrared at 3226 (hydroxyl) and 1718 $cm^{-1}$ (carboxyl group). This on heating afforded the corresponding oily $\delta$-lactone, $C_{15}H_{18}O_2$, (18), which showed infrared bands at 3058, 1626, 1597 (aromatic), 1736 ($\delta$-lactone), 1147 and 1101 $cm^{-1}$ (1:2:4-trisubstituted aromatic).

The above results require that the carboxyl group of photosantonic acid be both $\beta$ and $\gamma$ to the cyclo-hexane ring. This requirement and that of incorporating the second carbocyclic ring is met by the expression (19) for photosantonic acid. Hence the corresponding bromo-lactone, hydroxy-dilactone and anhydro-dilactone can be represented by formulae (20),(21) and (22) respectively, when the corresponding hydroxy-acid of photosantonin would have the formula (23).

Structure (19) for photosantonic acid was supported by the following experiments. Oxidation of photosantonin with acid permanganate afforded succinic acid, also characterised as its p-bromophenacyl ester, whilst reaction with monoperphthalic acid furnished the corresponding mono-epoxide $C_{17}H_{24}O_5$ (24), which had bands in the infrared (in $CCl_4$) at 1790 (γ-lactone) and 1737 $cm.^{-1}$ (ester-carbonyl). On treatment with boron trifluoride etherate, the epoxide was converted into the corresponding ortho-ester (25) (no ester carbonyl band in the infrared) which in accord with its formulation afforded the hydroxy-dilactone (21) on treatment with dilute acid. Reduction of photosantonin with lithium aluminium hydride gave the corresponding crystalline triol $C_{15}H_{26}O_3$ (26), which furnished the oily triacetate $C_{21}H_{32}O_6$ (27), showing acetate bands in the infrared at 1724 and 1242 $cm.^{-1}$ (broad band).

It should be mentioned that neither photosantonin, nor the derived triol (26), and its triacetate (27), showed the band in the 3050 $cm^{-1}$ region expected[98] of a $CH_2$ cyclopropane stretching frequency. The importance of this was largely discounted when it was found that trans-cyclopropane-dicarboxylic acid di-methyl ester also did not show this band; Recently further indication of the unreliability of this characteristic has appeared.[99]

## Experimental

Photosantonin.- Santonin (12 gm.) in ethanol (600 ml.) was irradiated in a pyrex flask by means of a bare mercury arc (125 W) lamp, the process being followed by infrared spectroscopy. When the peak at 1736 $cm^{-1}$ in the carbonyl region was stronger than all others in that region, except that due to the γ-lactone, the reaction was interrupted. Evaporation and chromatography on silica (450 gm.) gave, by elution with benzene-light petroleum (1:4), photosantonin (4-8 g.), m.p. 67-68.5°, (from carbon tetrachloride-light petroleum) $[\alpha]_D$ -121° (c 1.3 in ethanol) (found C-Me, 14.6; calc.for $C_{17}H_{24}O_4$, (3C - methyls) 15.6%).

The ester (95 mg.) in ethanol (3 ml.) was added to an aqueous potassium carbonate solution (10%, 2 ml.) and the mixture shaken at room temperature for 24 hours. Isolation of the acidic fraction, and crystallisation from ethanol-light petroleum gave the hydroxy dicarboxylic acid, monoethyl ester (23), m.p. 138-140°, $[\alpha]_D$ -24 (c 1.12) (found C, 65.6; H, 8.25; Ethoxyl, 15.05, $C_{17}H_{26}O_5$ requires C, 65.8; H, 8.45; Ethoxyl (1-O Et) 14.5%). Attempted acetylation of the hydroxy-acid led to the formation of photosantonin, identified by m.p., mixed m.p. and infrared spectrum.

Photosantonic acid.- A Kuhn-Roth determination gave C-Me, 9.81 calculated for $C_{15}H_{20}O_4$ (2C -Me), 11.36%. Crystallisation of photosantonic acid from aqueous ethanol gave the hydrated form (found C, 64.2; H, 7.1, calculated for $C_{15}H_{20}O_4.H_2O$ C, 63.8; H, 7.85%). Esterification of the acid (41.3 mg.) with an ethereal solution of diazomethane, after evaporation and crystallisation of the product from ether-light petroleum afforded the methyl ester m.p. 54.5-55°C. $[\alpha]_D$-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 minutes, after which time there was no absorption in the ultraviolet 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 in the usual way, and chromatography on bentonite-Kieselguhr gave acetone 2:4-dinitrophenyl-hydrazone (14 mg; 23%) identified by m.p. and mixed m.p. (Found C, 45.6; H,4.4; N, 23.65; Calculated for $C_9H_{10}O_4N_4$; C, 45.4; H, 4.25; N, 23.5%). Under similar conditions corresponding hydroxy-acid (23) (72 mg.) also gave acetone 2:4-dinitrophenyl-hydrazone (13.5 mg; 24%).

Photosantonin Epoxide.- The ester (100 mg.) in ether (50 ml.) was treated with an excess (5 ml., 0.3N) of an ethereal solution of monoperphthalic acid and the mixture allowed to stand overnight. Titration indicated an uptake of 0.97 atom of oxygen. Isolation of the product in the usual way and crystallisation from carbon tetrachloride-light petroleum gave the epoxide (24), m.p. 87-90°; $[\alpha]_D$ +10 (C 1.27) $\varepsilon$204 mμ 4900 (Found C, 66.45; H, 7.65; $C_{17}H_{24}O_5$ requires C, 66.2; H, 7.85%).

Photosantonin orthoester.- The epoxide (100 mg.) in ether (50 ml.) was treated with the boron trifluoride-ether complex (2 ml.) and the mixture allowed to stand for 4 minutes, at room temperature. It was then added to sodium bicarbonate (aqueous, 50 ml.) being shaken vigorously. The ethereal layer was then washed with water. Usual working up and crystallisation from chloroform-light petroleum afforded the orthoester (25) m.p. 167-169° $[\alpha]_D$ +98 (C 1.03), $\varepsilon$204 mμ 3100, (Found C,66.0; H,7.6; Ethoxyl 14.5 $C_{17}H_{24}O_5$ requires C, 66.2; H, 7.85; Ethoxyl (1-O Et) 14.6%).

The ortho-ester (100 mg.) in alcohol (50 ml.) was treated with concentrated hydrochloric acid (5 ml.) followed by dilution with water (50 ml.). After 30 minutes the mixture was further diluted and the product isolated in the usual way.

Crystallisation from ethyl acetate-light petroleum then afforded the hydroxy dilactone (21), m.p. 172-175°, $[\alpha]_D$ +41 (C 1.53), $\varepsilon$ 204 m$\mu$ 2300 (found C, 64.25; H, 7.05; $C_{15}H_{20}O_5$ requires C 64.25; H, 7.2%). The same substance was also prepared in the following way. Photosantonic acid (128 mg.) in chloroform (50 ml.) was treated with an ethereal solution of monoperphthalic acid (2 ml; 1.5 N) and the mixture allowed to stand at room temperature overnight. Titration then indicated the consumption of 1.06 atoms of oxygen. Isolation of the product in the usual way afforded the hydroxy-dilactone (21) identified by m.p., mixed m.p. $[\alpha]_D$ +41 (C 1.5), and infrared spectrum. The compound was recovered unchanged after attempted acetylation (acetic anhydride-pyridine).

The unsaturated dilactone (22).- The hydroxy dilactone (50 ml.) in pyridine (3 ml.) was treated with thionyl chloride (400 mg.) and the mixture allowed to stand at 0° for 15 minutes. Decomposition of the excess acid-chloride with water and isolation of the product in the usual way afforded the anhydro-compound (22) m.p. 137-139°, $[\alpha]_D$ +88 (C 1.02) $\varepsilon$ 204 m$\mu$ 3800 (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 any formaldehyde dimedone.

Photosantonic acid bromo-lactone (20).- The acid (108 mg.) in chloroform (30 ml.) containing bromine (1.7 mol) was allowed to stand for 2 minutes, titration indicating the uptake of 1.1 mol. of bromine. Usual working up by adding it to water followed by extraction with chloroform and washing of the chloroform layer with water afforded the desired compound (81 mg.) m.p. (from chloroform-light petroleum) 173-177° (decomp) $[\alpha]_D$ +30 (C 1.46), $\varepsilon$ 204 mμ 2400 (found C,52.55; H, 5.8; Br, 23.4; $C_{15}H_{19}O_4$ Br requires C, 52.50; H,5.6; Br, 23.3%). On attempted ozonolysis under the conditions described for photosantonin, the compound was recovered unchanged.

The bromo-lactone (21.7 mg.) in acetic acid (2 ml.) containing zinc dust (40 mg.) was refluxed for 4 hours. Isolation in the usual manner afforded regenerated photosantonic acid identified by m.p., mixed m.p. $[\alpha]_D$ -129 (C 1.0) and by infrared spectrum.

Oxidation of photosantonin.- Photosantonin (500 mg.) suspended in water (10 ml.) was oxidised with aqueous potassium permanganate (5%, 135 ml.) on the steam bath, the oxidant being added dropwise. At the same time 8% sulphuric acid was added so that the medium remained faintly acidic during the course of the oxidation. After removal of the manganese salts and manganese dioxide, the volume was reduced to 10 ml. and continuously extracted with ether. Conversion of the residue,

after evaporation of the ether, to the p-bromophenacyl derivative gave the 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; calculated for $C_{18}H_{16}O_6Br_2$%, C, 46.9; H,3.15; Br, 31.2%). The acid itself was also isolated from the ether extract, by crystallisation from ether and light petroleum and identified by m.p., mixed m.p. and infrared spectrum (KCl disc).

Cyclisation of the 'dehydrophotosantonic acids'

Photosantonin (1 gm.) in ethanol (20 ml.) was subjected to a stream of dry hydrogen chloride gas for 6 hours at room temperature, the mixture then being left overnight. Isolation of the product followed by alkaline hydrolysis in aqueous ethanolic solution then gave acidic material. Chromatography of this on silica gave, on elution with benzene-ether (25:1), a mixture of active and racemic 'dehydrophotosantonic acids' m.p. 133-135° $[\alpha]_D$ +18 (C 3.1 in ethanol). The acid mixture (140 mg.) in conc.sulphuric acid (3 ml.) was heated on the steam bath for 5 minutes. Isolation of the product in the usual way, followed by chromatography over silica (5 gm.) gave on elution with benzene the hydrindanone (16) m.p. 111-112° (from ethyl acetate-light petroleum) $[\alpha]_D \pm 0$ (C 1.2 in Ethanol) $\lambda_{max}$ 254 mμ ($\varepsilon$ 8700)(found C, 73.55; H, 7.7 $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.35%). The hydrindanone (60 mg.) was methylated

with an ethereal solution of diazomethane, and the product treated with Brady's reagent to give the 2:4-dinitrophenylhydrazone m.p. 104-107° (from ethyl acetate-light petroleum) $\lambda$max 390 m$\mu$ ($\epsilon$ 35,000) (found C, 59.85; H, 5.55; N, 12.5: $C_{22}H_{23}N_4O_6$ requires C, 60.2; H, 5.3; N, 12.65%).

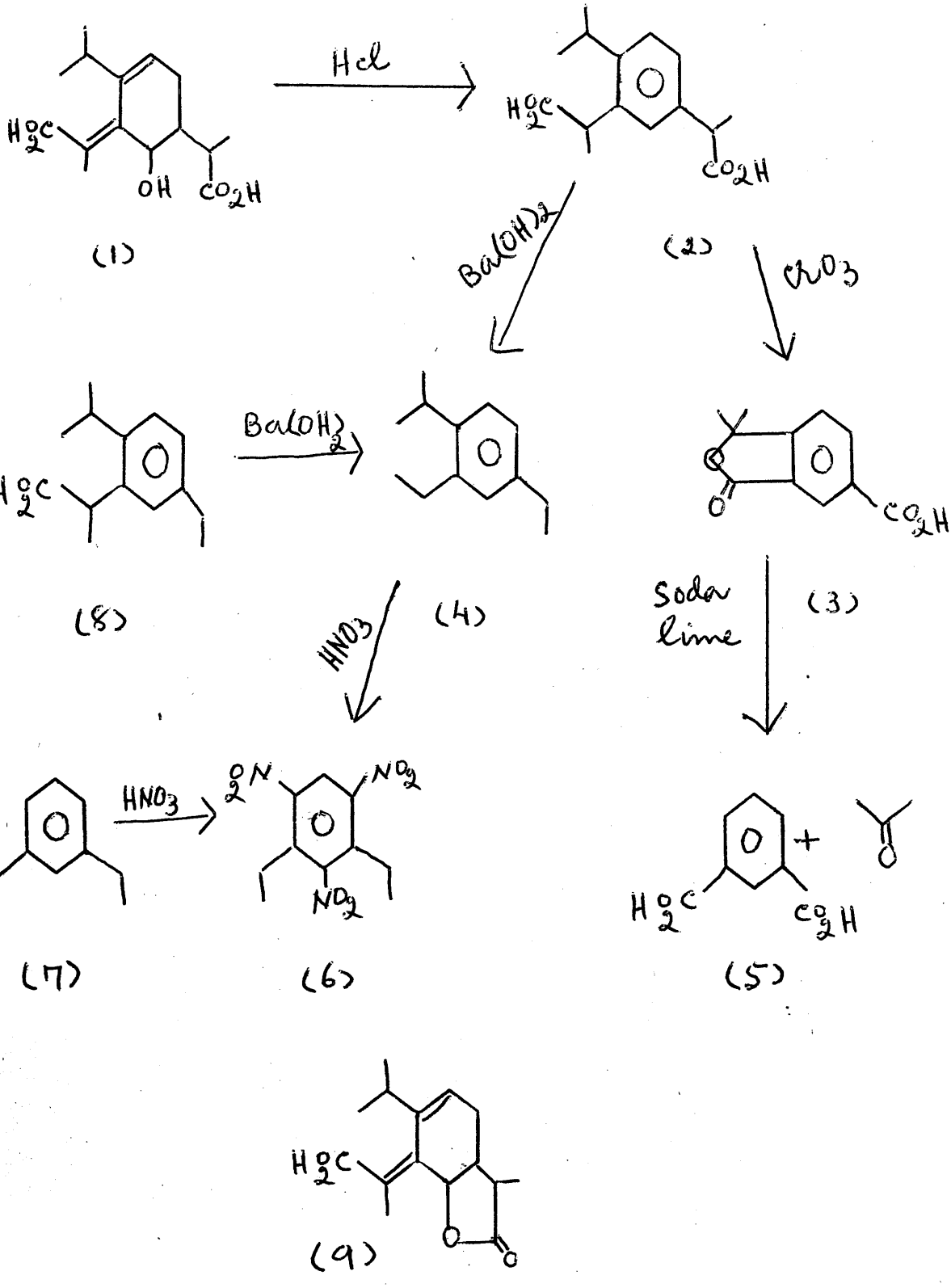
Reduction of the hydrindanone (16).- The hydrindanone (90 mg.) was allowed to stand in ethanolic solution (3 ml.) containing potassium borohydride (200 mg.) for 10 minutes. Isolation of the product and crystallisation from a mixture of chloroform, ether and light petroleum then afforded the hydrindanol (17) 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%).

Lactonisation of the hydrindanol.- Hydrindanol (50 mg.) was heated at 130°C for 1 hour. After separation into acidic and neutral parts, the neutral oil was subjected to sublimation at 150°/.001 mm. to give the oily lactone (18) (found C, 78.0; H, 8.0 $C_{15}H_{18}O_2$ requires C, 78.25; H, 7.9%).

Lithium aluminium hydride reduction of photosantonin.- Photosantonin (500 mg.) in ether (100 ml.) was treated with a solution of lithium aluminium hydride (1.5 gm.) in ether (100 ml.). After 17 hours the excess reagent was decomposed by ethyl acetate. Acidification with dilute acetic acid followed by usual working up and isolation afforded the triol (86; 300 mg.) m.p. 127.5 - 129.5° (from chloroform-light petroleum) $(\alpha)_D$ -69 (C 2.1) (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 acetylated overnight with acetic anhydride (3 ml.). Usual working up afforded the oily triacetate (27) which was purified by sublimation at 150°/ .001mm. (found C, 66.6; H, 8.75: $C_{21}H_{32}O_6$ requires C, 66.3; H, 8.5).

# TABLE NO 9



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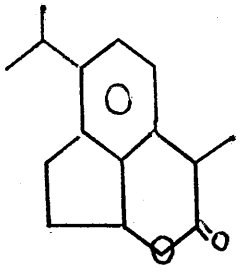

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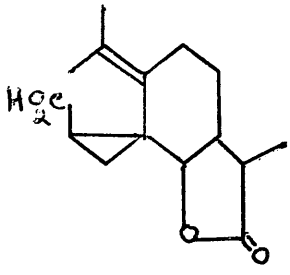

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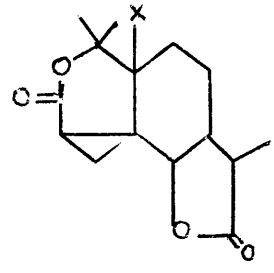
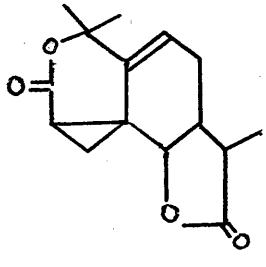


(20) X = Br

(21) X = OH



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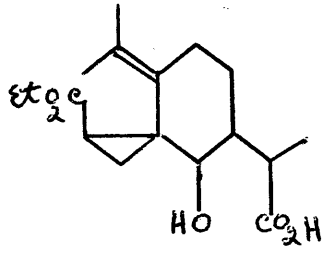

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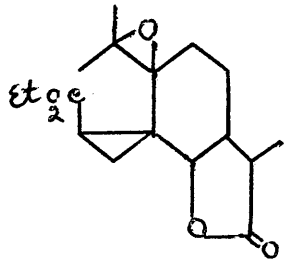

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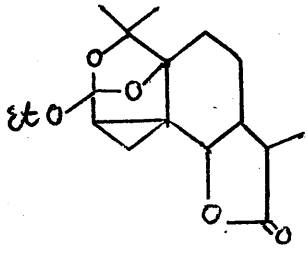

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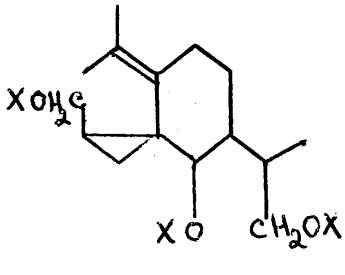
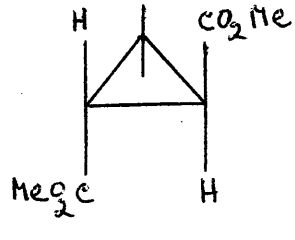


(26) X = H

(27) X = Ac



## POSSIBLE MECHANISM FOR THE FORMATION OF PHOTO-PRODUCTS FROM SANTONIN

(For formulae see table 11)

Santonin (1) on irradiation both in hot as well as in cold aqueous acetic acid solution, furnishes equal amounts of photosantonic acid (4) and isophotosantonic lactone (3). Lumisantonin (5) on the other hand, on irradiation in cold aqueous acetic acid affords only photosantonic acid and no isophotosantonic lactone. Now if it be assumed that lumisantonin is the only source for photosantonic acid, then the photochemical transformation of santonin into photosantonic acid implies the participation of lumisantonin as an intermediate.

Since lumisantonin (5) is also converted into isophotosantonic lactone (3) in the dark under the influence of hot acid, it might imply that isophotosantonic lactone may in part be formed fromthe former, when santonin is irradiated in aqueous acetic acid under reflux. That this, at least in large part, is not true is indicated by the fact that the rate of photochemical conversion of lumisantonin to photosantonic acid is much faster than the rate of its acid-catalysed transformation into isophotosantonic lactone. This is also supported by the fact as mentioned above that both hot and cold irradiations of santonin yield equal amounts of photosantonic

acid and isophotosantonic lactone. Besides, the photochemical conversion of (5) to (4) appears to be independent of temperature since the former on irradiation in aqueous dimethyl formamide under reflux furnishes only photosantonic acid.

It seems, therefore, probable that santonin on excitation gives rise to the intermediate (6) through the excited state $(1)^*$ and possibly the diradical (2). This process has some analogy in, for instance, the well known transformation of carvone to the cyclobutane derivative, carvone camphor, and the formation of the cyclobutane photo-isomer of bicyclo 2,2,1 heptadiene-2:3 dicarboxylic acid, (see page 27 ). Such an intermediate (6) could readily be transformed, by the action of solvent into isophotosantonic lactone. Lumisantonin would then arise from alternative stabilisation of the diradical (2) attended by rearrangement. Excitation of lumisantonin (5) could then produce a second intermediate (7) via the excited state $(5)^*$. This, because of the considerable strain in the molecule would then undergo transformation into photosantonic acid (or its derivatives) under the influence of an extremely weak acid, e.g. ethanol or water.

## Experimental

Cold irradiation of Santonin:- Santonin (500 mg.) in aqueous acetic acid (25 ml; 45:55-acetic acid: water V/V) was irradiated between -5° to +5° for 2 hours. The product was separated into acidic and neutral fractions. Both were chromatographed over silica to give photosantonic acid (50 mg; 10%), isophotosantonic lactone (45 mg; 9%) and starting material (70 mg; 14%).

Hot irradiation of Santonin.- Santonin (500 mg.) in aqueous acetic acid(25 ml; 45:55-acetic acid: water V/V) was irradiated under reflux using exactly the same conditions as under cold irradiation. In fact both irradiations were performed at the same time using the same lamp. Usual working up as above gave photosantonic acid (58 mg; 11.6%), isophotosantonic lactone (40 mg; 8%) and santonin (15 mg; 3%).

A mixture of santonin (120 mg.), isophotosantonic lactone (101 mg.) and photosantonic acid (100 mg.) on separation into acidic and neutral fractions followed by chromatography of both the fractions gave back photosantonic acid (70 mg;70%), isophotosantonic lactone (50 mg; 50%) and santonin (120 mg; 75%).

Irradiation of santonin in aqueous acetic acid containing a stronger acid.-

a) Santonin (1 gm.) in aqueous acetic acid (37 ml; 45:55-acetic acid: water V/V) was irradiated under reflux for 1 hour. Usual working up afforded photosantonic acid (11 mg.); isophotosantonic lactone (15 mg.) and santonin (605 mg.).

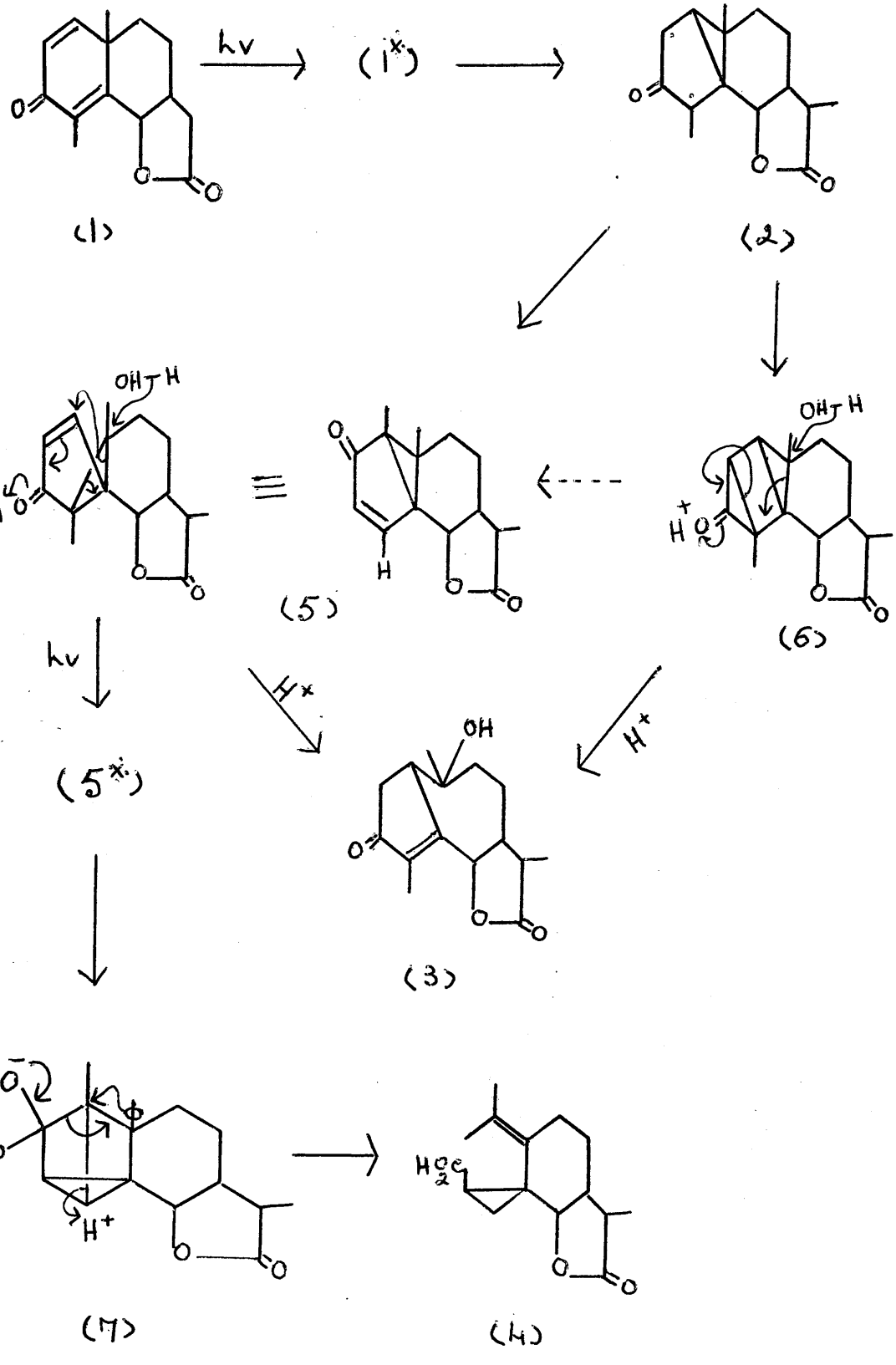
b) Santonin (1 gm.) was irradiated under exactly the same conditions as in (a) in 37 cc. of aqueous acetic acid containing monochloroacetic acid (370 mg.). Usual working up yielded photosantonic acid (8.6 mg.), isophotosantonic lactone (24 mg.) and santonin (599 mg.).

Cold irradiation of Lumisantonin.- Lumisantonin (500 mg.) was dissolved in acetic acid (12 ml.) and the mixture then diluted with water (14 ml.). Irradiation of the mixture at $-5^{\circ}$ $+5^{\circ}$ followed by isolation of the acidic portion in the usual way gave after crystallisation from chloroform-light petroleum, photosantonic acid (350 mg.) identified by m.p. mixed m.p. No isophotosantonic lactone could be isolated by chromatography.

Irradiation of Lumisantonin in dimethyl formamide.- Lumisantonin (286 mg.) in dimethyl formamide (11 cc.ml.) and water (8 ml.) was irradiated under reflux for 45 minutes.

Separation into acidic and neutral portions followed by chromatography of both the fractions yielded photosantonic acid (114 mg.) identified by m.p. and mixed m.p. and lumisantonin (64 mg.) identified by m.p. and mixed m.p. No isophotosantonic lactone could be isolated by chromatography.

TABLE NO: 11



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