STUDIES IN SESQUITERPENOID CHEMISTRY

A Thesis submitted by

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in fulfilment of the requirements for the degree of Doctor of Philosophy in the University of London.

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ABSTRACT

After a brief conspectus of the naturally occurring cyclic sesquiterpenoids the chemistry of three sesquiterpenoid lactones, α-santonin, artemisin and geigerin, is reviewed, their stereochemistry, in particular, being examined. The constitution and stereochemistry of lumisantonin and isophotosantonic lactone, two of the photolytic transformation products of santonin, are then reviewed. The final chapter in the Introduction is concerned with the immediate background to the work described in this thesis. The project had as its object the demonstration of the value of isophotosantonic lactone in the study of sesquiterpenoid chemistry. The progress made by previous workers is summarised.

In the Discussion, further chemistry of isophotosantonic lactone is described, in particular the preparation of a derivative suitable for X-ray crystallographic analysis, and the stereochemical identity of this derivative and isophotosantonic lactone at the five common asymmetric centres is demonstrated. Independent chemical evidence supporting the most significant conclusion of the X-ray analysis - the reversal of the

previously accepted configuration at C_{11} - is presented. The synthesis of deoxygeigerin and the stereochemical changes occurring in that synthesis are described, and certain conclusions drawn. The arguments previously used in support of the wrong stereochemistry of santonin and certain recent reports on the subject are discussed.

Several unsuccessful approaches to the synthesis of geigerin are described, and a successful synthetic route is presented, the final product being detected by the use of radio-isotope dilution techniques.

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PART I

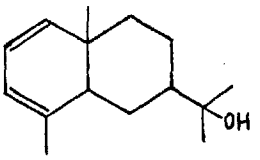
INTRODUCTION

CHAPTER 1

THE CYCLIC SESQUITERPENOIDS

It goes without saying that the investigation of the structures, reactions and synthesis of the naturally occurring terpenes and steroids has been one of the most fruitful sources of growth in our knowledge of organic chemistry in recent years. While sesquiterpenoid chemistry has not been as intensively investigated as has that of the higher terpenes and the steroids, yet there is to be found in it a wealth of fascinating chemistry, and a remarkable variety of structures. Sorm[1], in a recent review, lists twenty-seven carbon skeletons found among sesquiterpenoid natural products, and of these eighteen have been detected within the last sixteen years; in fact, even this list is not complete. A brief selection will illustrate the variety that is to be found, both in carbon skeleton and in the number, nature and disposition of the functional groups.

In the eudesmane group, for example, we find such compounds as occidentalol(1)[2], junenol (2)[3], eremophilone (3) and furanoeremophilone (4)[5].



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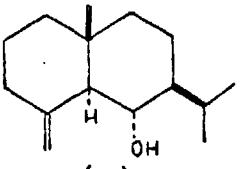

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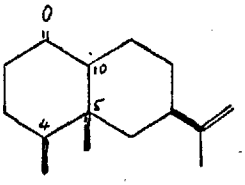

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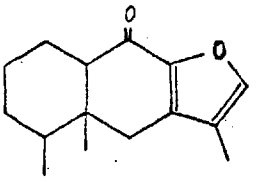
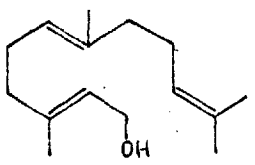


(4)

These last two (3 and 4) have undergone a methyl shift during biogenesis from their hypothetical precursor, farnesol (5), from C_{10} to C_5, and thus do not strictly belong in the eudesmane group. A number of important lactones are to be found in this group, including ψ-santonin (6)[6], alantolactone (7)[7], α-santonin (8) and its C_{11}-epimer, β-santonin, and artemisin (9). Some of these will be discussed in greater detail in another chapter. The cadinane group, less important, includes such compounds as cadinol (10)[8] and cubeb camphor (11)[9], and in recent years there has appeared another group, compounds whose biogenesis appears to follow the pattern of rings A and B of the higher terpenes: drimenol (12)[10], drimenin (13) and confertifolin (14)[11]. A most important group is that of the perhydroazulenic sesquiterpenes, especially those with the carbon skeleton of guaiane (15). This group, like that of the eudesmanes, is too large to mention



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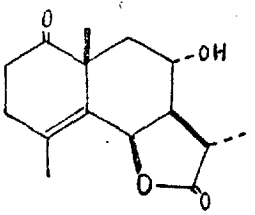

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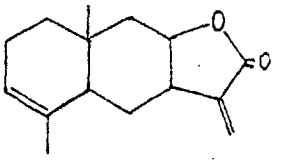

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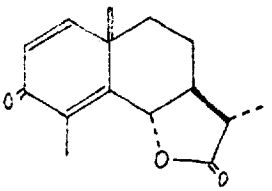

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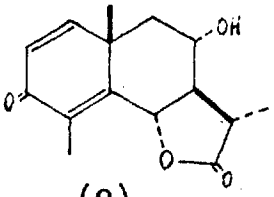

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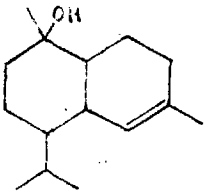

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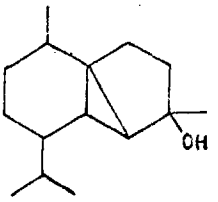

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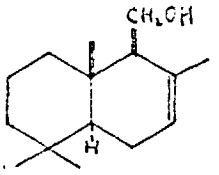

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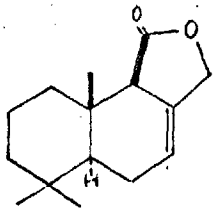

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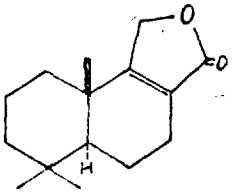

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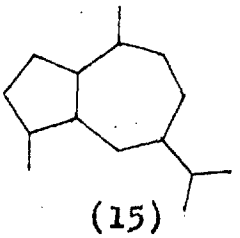

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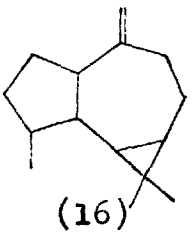
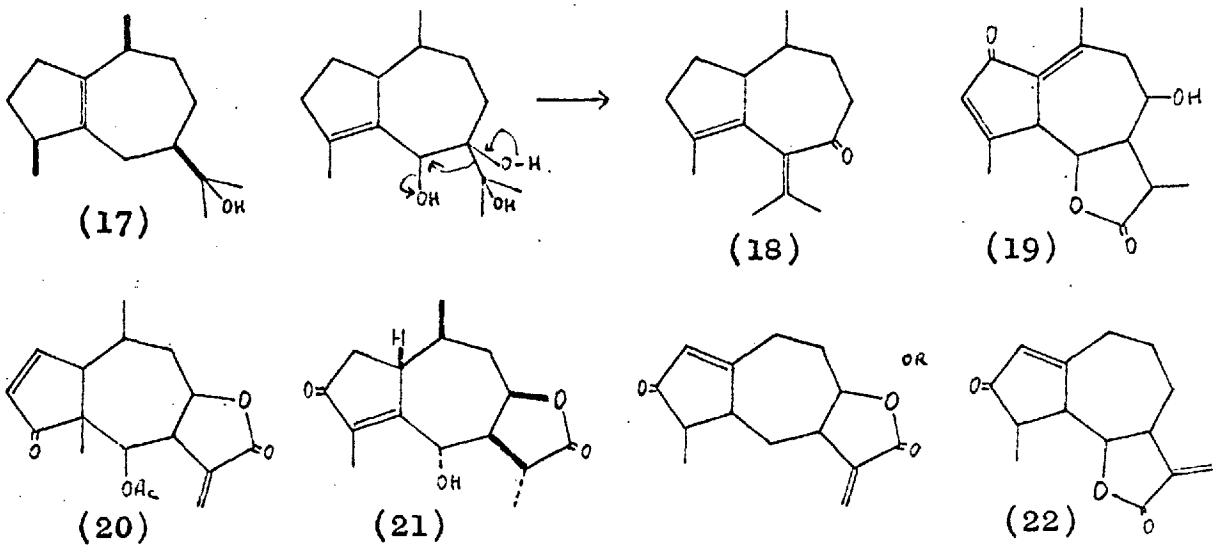


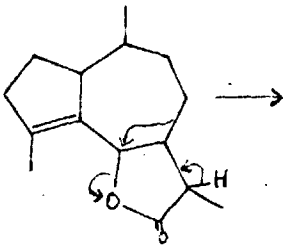
(16)

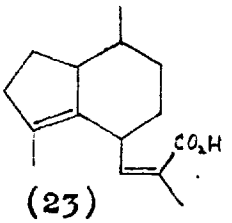
more than a representative few. There is the hydrocarbon aromadendrene (16)[12], the alcohol guaiol (17)[13], the ketone zierone (18)[14], whose skeleton it is suggested may be formed from a guaiane skeleton by some simple shift such as the one shown, and a variety of lactones, such as matricarcin (19)[15], balduilin (20)[16], geigerin (21)[17-19], and the interesting norsesquiterpenoid mexicanin E (22)[20].



(17) (18) (19) (20) (21) (22)

In all probability valerinic acid (23)[21], possessing an unusual carbon skeleton, is derived from a guaianolide by a rearrangement such as that shown. A sesquiterpenoid of unusual structure is widdrol (24)[22], yet with obvious derivation from a farnesol-type precursor, and other unusual skeletons are found in e.g. cuparene (25)[23] (one of the few naturally occurring aromatic sesquiterpene hydrocarbons), saussurea lactone (26)[24], longifolene (27)[25], and cedrol (28(a))[26], which looks more familiar, and biogenetically suggestive, written as in (28(b)). A more recently reported[27] compound of similar skeleton is shellolic acid (29).





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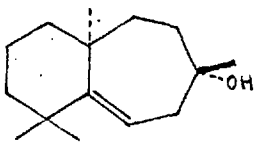

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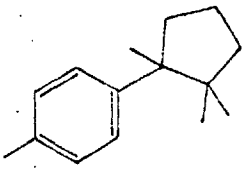

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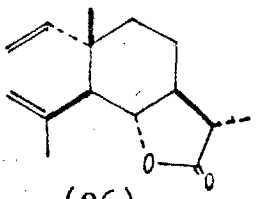

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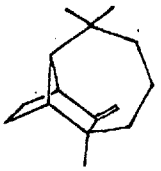

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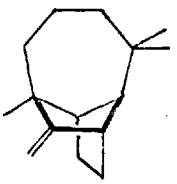

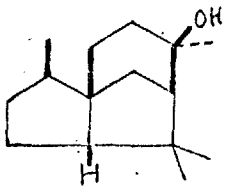

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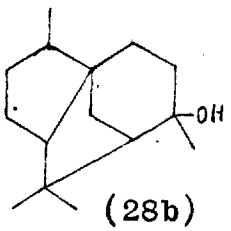

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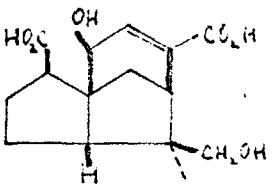
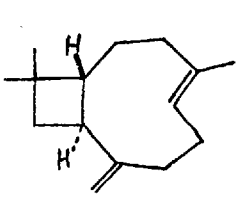


(29)

The most notable feature of sesquiterpenoid chemistry in recent years has been the discovery of a number of nine-, ten- and eleven-membered ring compounds. Several recent reviews[1,28] have dealt exclusively with these compounds. The most interesting aspect of their chemistry is the variety of transannular reactions which they undergo. The nine-membered ring compound caryophyllene (30)[29], for example, on treatment with acid affords, among other products, caryolan-1-ol (31) and clovene (32), while under

more vigorous conditions ψ-clovene (33) and isoclovene (34)[30] are obtained.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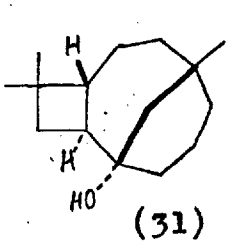
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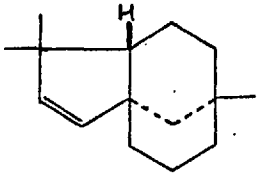
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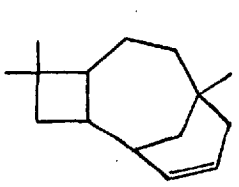
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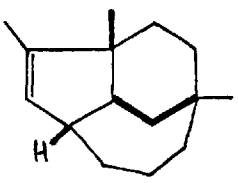
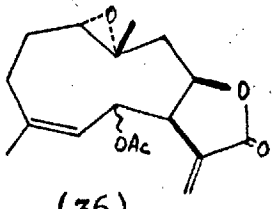

(34)

Several examples of eleven-membered rings are known, e.g. humulene (35)[31], but it is the rapidly growing class of ten-membered ring compounds which has attracted most interest. Since the elucidation of the structure of pyrethrosin (36)[32] numbers of such compounds have been reported, most of them as a result of the work of Sorm and his collaborators[1]. One, germacrone (37), is an αβ-unsaturated ketone, but all the other ten-membered ring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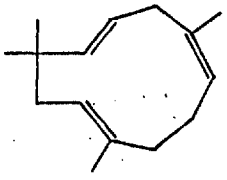
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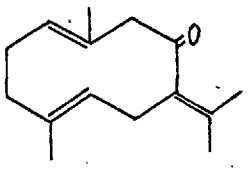
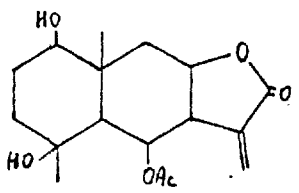

(37)

sesquiterpenoids reported so far are lactones. Here, too, there are found some interesting transannular cyclisation reactions, cyclisations to a decalin skeleton being the most common. Pyrethrosin, for example, affords (38), (39) and (40), on treatment with boron trifluoride, acetic anhydride

and p-toluenesulphonic acid, and sodium dichromate in aqueous acetic acid, respectively. In the chemistry of germacrone and of costunolide (41) another cyclisation is found: reduction of germacrone to germacrol, followed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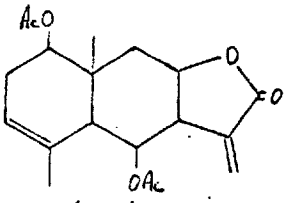
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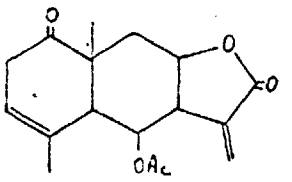
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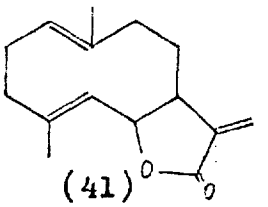
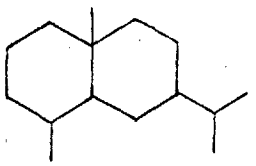

(41)

by hydrogenation in acidic medium gave selinane (42), while dehydration of germacrol followed by hydrogenation afforded elemane (43). Similarly, pyrolysis of dihydrocostunolide afforded saussurea lactone (26), and it has been suggested[24] that this compound, isolated by distillation from the same source as dihydrocostunolide, is an artefact.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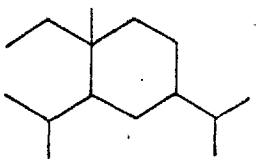
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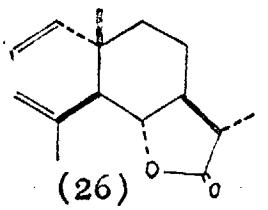

(26)

Great advances have been made in recent years in the determination of absolute conformation in the sesquiterpenoids. Those methods which have been applied in other fields have proved of value here, too: degradation to compounds of known stereochemistry and optical rotatory

dispersion measurements have been applied and conformational analysis and X-ray crystallography have been of use where the absolute configuration of one or more centres is already known by other means. Certain empirical rules governing molecular rotation contributions have also been applied. Some of these methods have at times been misleading, and need to be applied with care, but there can be no doubt that through their use our knowledge of the stereochemistry of this family of organic compounds has advanced a great deal. There yet remains a great deal to be done, both in determination of configuration and in determination and analysis of conformational effects, especially in the compounds with seven-membered or larger rings.

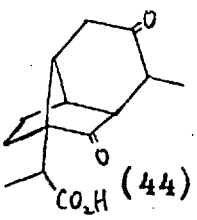
CHAPTER 2

THE SESQUITERPENOID LACTONES

A large number of the naturally occurring sesquiterpenoids are γ-lactones, and not unnaturally their study has made a major contribution to sesquiterpene chemistry. It will be necessary here to discuss only three of these in any detail, α-santonin (8), artemisin (9), and geigerin (21).

2.1 α-Santonin

The chemistry of santonin has been investigated for over a century. Its comparatively simple structure has displayed a variety of extraordinary and fascinating reactions. The correct constitution was published[33] in 1929, and its total synthesis appeared[34] in 1954. Among the more unusual of its reactions is its transformation by vigorous base treatment into santonic acid (44)[35], which in turn can be converted into isosantonide (45), and a most important transformation is that which santonin undergoes on mild acid treatment, affording by means of a dienone-phenol rearrangement one of the desmotroposantonins (46)[36]. Six stereoisomers of this constitution are known, and their interconversions have played an important part in the discussions that have taken place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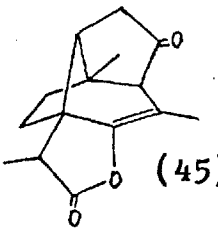
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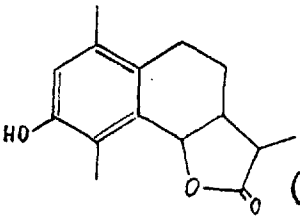
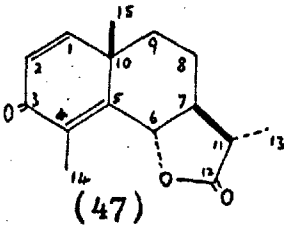

(46)

on the stereochemistry of santonin.

The stereochemistry of the eudesmane sesquiterpenoids has recently been lucidly reviewed[37] by Cocker and McMurray. The configuration of α-santonin at C_6, C_7 and C_{10} (47) has not been the subject of any significant dispute and the evidence for the configuration shown can be briefly summarised.

Configuration at C_{10}: The C_{10} methyl group of eudesmol (48) has been correlated[38] with the C_{10} methyl group in the steroids by degradation to the enantiomer (49) of the acid (50)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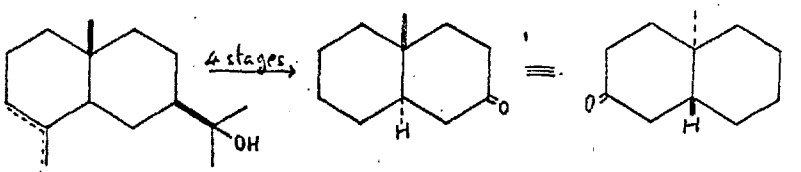
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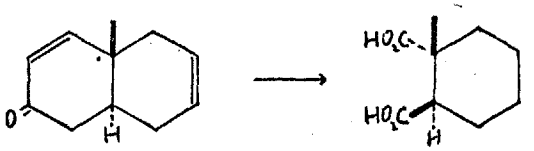
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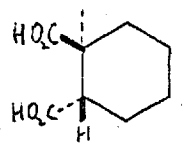
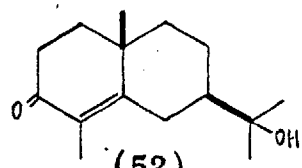

(49)

obtained from the steroid intermediate (51). Carissone (52) has been related[39] to eudesmol, the cyperones (α,53; β,54) have been related[40] to carissone, and santonin has in turn been related[41] to β-cyperone (54). Optical rotatory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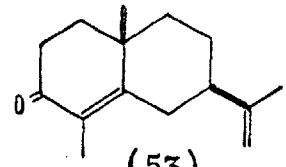
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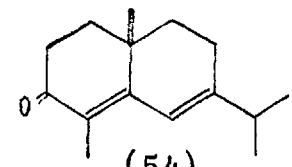
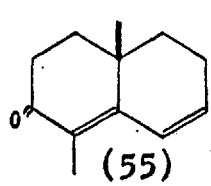

(54)

dispersion evidence,[42] too, points to the β-methyl configuration at C_{10}.

Configuration at C_7: Santonin itself has not been related to any compound whose configuration at C_7 is known. All naturally occurring sesquiterpenoids whose configuration at this centre was known, however, had the side chain in the β-configuration. The most direct evidence in the case of santonin was in the reaction employed[34] in the synthesis of santonin for the introduction of the propionic acid side chain: the addition of methylmalonic ester to the dienone (55). In the closely analogous addition[43] of malonic ester to the steroid dienone (56) the addend was known to take up the β-configuration (equatorial). In (55), too, addition was considered[34,44] likely to afford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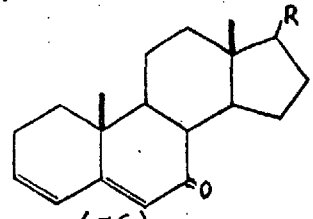
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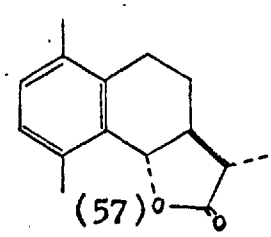
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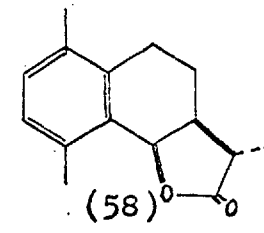

(58)

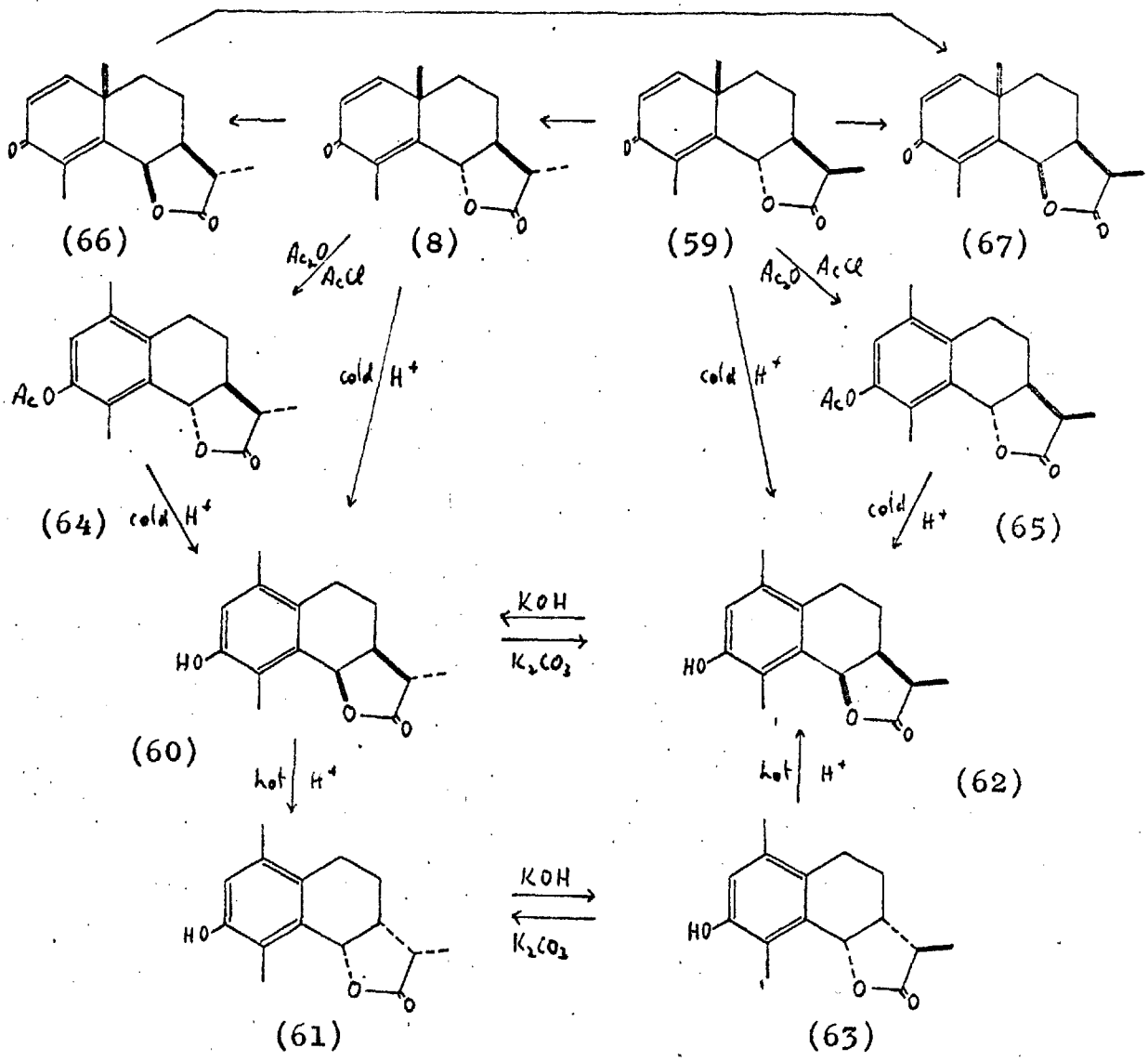
the compound with a β (equatorial) side chain.

Configuration at C_6: Santonin may be converted under very mild conditions to hyposantonin (57), which on mild treatment with alkali followed by acidification affords isohyposantonin (58). This can most reasonably be interpreted as a transformation from a trans to a cis lactone. This was confirmed by the properties of the desmotroposantonins (46). Of the six known epimers four are cis lactones[36], and the other two, more recently prepared[45] under very mild conditions from α-santonin and β-santonin (59), could readily be transformed into two of the previously known compounds. This, too, suggests that α- and β-santonin, epimeric at C_{11}, are both trans lactones, thus both having the lactonic oxygen at C_6 in the α-configuration.

The remaining asymmetrical centre in santonin, C_{11}, has been the subject of much discussion, and both configurations have been supported.[44-48] The most cogent arguments[44] for the β-configuration of the C_{11}-methyl group in α-santonin were derived from the chemistry of the desmotroposantonins.[36,45] Treatment of α-santonin (8) with cold dilute sulphuric acid affords (-)α-desmotroposantonin (60), which on treatment with hot acid is converted to an epimer, (+)β-desmotroposantonin (61). Treatment of

β-santonin (59) with cold dilute acid affords (-)β-desmotroposantonin (62). On fusion with potassium hydroxide the epimer (62) yields (60), and, under similar conditions, from epimer (61) a fourth epimer, (+)α-desmotroposantonin (63) is obtained, which affords (62) on heating with dilute acid. The changes effected by alkali fusion are reversed[49] by heating with anhydrous potassium carbonate in xylene. Finally, as was mentioned previously, α-santonin and β-santonin afford the acetates of the two trans lactones, (64) and (65) respectively, on treatment with acetic anhydride and acetyl chloride, and these epimerise in cold dilute acid to the acetates of (60) and (62) respectively. Together with the transformation of β-santonin into α-santonin with potassium carbonate in xylene[45], and of 6-epi-α-santonin (66) into 6-epi-β-santonin (67) with potassium tert. butoxide;[50] this may be summarised as follows:

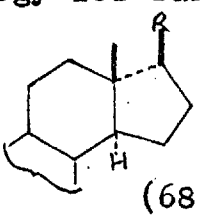
(See Page 20)



Throughout this thesis the correct configuration of santonin is used in the figures; thus, tentatively, in the above diagram the C_{11} configurations are opposite to those previously assigned.

It was considered that the reversal by treatment with potassium carbonate of the changes produced by alkali

fusion indicates that alkali fusion, conditions sufficiently drastic to remove a proton from a carbon adjacent to a carboxylate anion, must lead to the most stable carboxylate anion, whereas potassium carbonate will lead to the most stable configuration in the closed lactone form.[44] Thus it appeared that the enantiomorphs (61) and (62) must be more stable than their C_{11} epimers, (63) and (60) respectively; it was considered obvious[44] that the 6α, 7α-lactone would be more stable with a β-methyl at C_{11}, and this implies a C_{11} β-methyl in α-santonin. This line of reasoning appeared most cogent, and for lack of more concrete evidence gained almost universal acceptance, the opposite view being held, on grounds which appeared weaker than those outlined above, by only a few.[47,48] Miki[48], for example, argued from the preferred 17β configuration in the steroids, taking rings C and D (68) of the steroids as an analogy for santonin (69; enantiomer).



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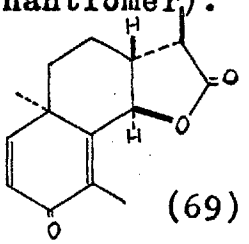
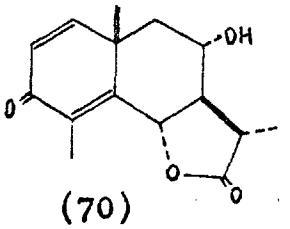


(69)

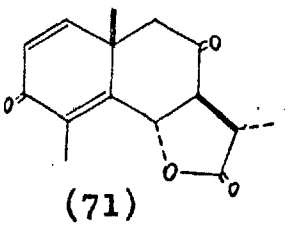
2.2 Artemisin

Artemisin, long considered[51] to be 7-hydroxysantonin, was later[52] shown to be 8-hydroxysantonin (70). Its reaction with reagents to which tertiary alcohols are

inert and its oxidation with chromium trioxide to a dehydro compound (71) demonstrated the secondary nature of the hydroxyl group. The position of the additional oxygen function, and the direction of closure of the lactone ring, are shown by the transformation of the diketone (71) on treatment with decinormal sodium hydroxide solution into the conjugated diketo acid (72). The isomer (73) would give rise to the diketo-acid (74) on



(70)



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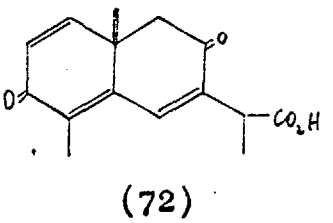

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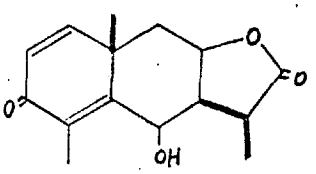

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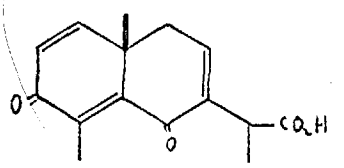


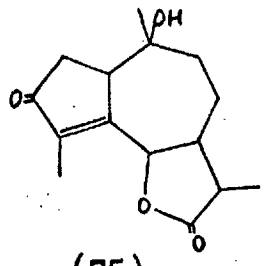
(74)

similar treatment, which would be clearly distinguishable, spectroscopically, from (72). Artemisin was shown to have the same stereochemistry as α-santonin at the four asymmetric centres in common by conversion into the latter by two stages which could not have affected any of these four centres. The alcohol was first converted into the iodide by means of triphenylphosphite methiodide, and this was reduced with de-activated Raney nickel to afford α-santonin. The hydroxyl at the remaining asymmetric

centre, C_8, was assigned the α-configuration on the basis of its molecular rotational contribution (positive) in accordance with the generalisation of Klyne and Stokes.[53] This assignment is supported by the ease of esterification of artemisin; it is firmly established by evidence to be described in this thesis.

2.3 Geigerin

Geigerin, a constituent of Geigeria aspera, a toxic South African plant, was shown by Perold[54] to be a perhydroazulenic sesquiterpenoid lactone (guaianolide). The constitution (75) was proposed, but as this was the constitution assigned to isophoto-α-santonic lactone[55], Barton and Levisalles[17] further examined its chemistry, and showed it to have the constitution (76; R=OH). Contrary to previous reports geigerin was readily acetylated, and could be oxidised to dehydrogeigerin (77). Reduction of geigerin with zinc and acetic acid afforded deoxy-geigerin (76; R=H), which suggested an α-ketol or its vinylogue.



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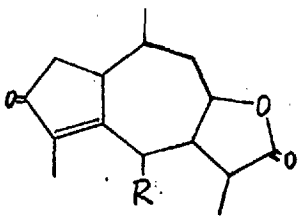

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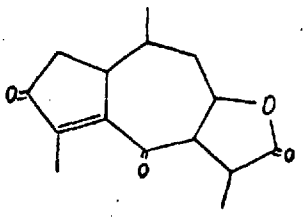
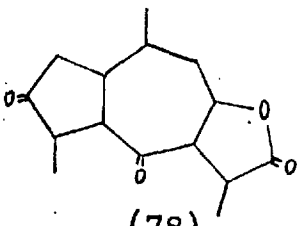


(77)

The ready reduction of dehydrogeigerin (77) with zinc and acetic acid to the diketone (78) excluded the first possibility, and the location of the free hydroxyl group at C_6 (and thus the lactonic oxygen at C_8) was confirmed by alternative preparations of deoxygeigerin: (i) treatment of geigerin methanesulphonate (76; R=OSO_2CH_3) with sodium iodide and reduction of the product with zinc; (ii) treatment of dihydrogeigerin methanesulphonate (79) with refluxing collidine.



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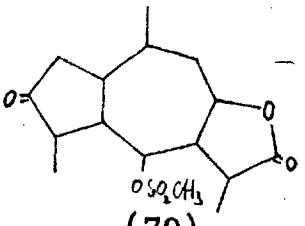

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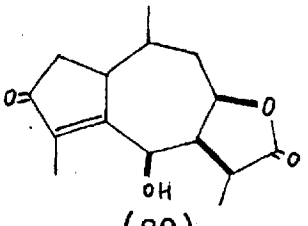

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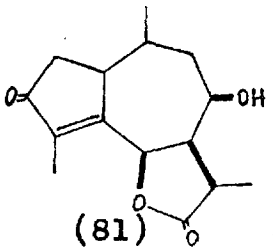
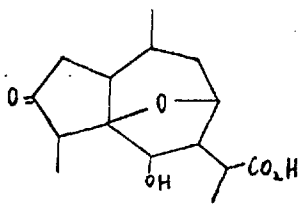


(81)

This led to the constitution (76; R=OH), which found confirmation in the formation of a mixture of two isomeric γ-lactones, 6-epigeigerin (80) and 6-epiallogeigerin (81), on treatment of geigerin methanesulphonate with dilute aqueous sodium hydroxide. Allogeigeric acid, the product obtained on mild alkaline treatment of geigerin and which was shown to revert to geigerin on treatment with acid, was assigned the constitution (82), which satisfactorily explains all the known properties of this compound.

Stereochemistry was assigned at C_1, C_6, C_7 and C_8 as follows: allogeigeric acid failed to lactonise, even on sublimation at 200°C: therefore, the propionic acid side chain and the C_6-hydroxyl group must be trans. On acidification allogeigeric acid reverts to geigerin, with none of the isomeric C_6-lactone being formed, and it was reasoned that this suggested that the side chain and the C_8-hydroxyl group are cis. At least one compound is now known (see p.75) where of two possible lactones, one cis, the other trans, the trans lactone is formed exclusively, but in fact the conclusion reached in the case of geigerin was later proved correct. Assuming the usual β-configuration of the C_7 side chain led to α and β configurations for the oxygen functions at C_6 and C_8 respectively. C_1 was assigned[56] the β-hydrogen configuration on the evidence of optical rotatory dispersion studies, but the model used for comparison was cholest-14-en-3β-ol-16-one benzoate (83), the 5- and 6-membered C and D rings being taken as an analogy for the fused 5- and 7-membered rings of the guaianolides. There is no warrant for this analogy, and in at least one case (isophoto-α-santonic lactone; see later) the wrong configuration was assigned. No evidence was available as to the configuration at C_{10}



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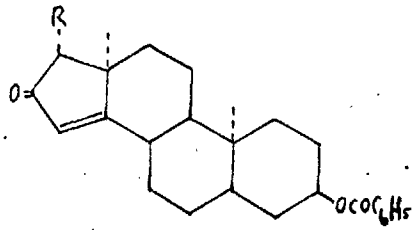

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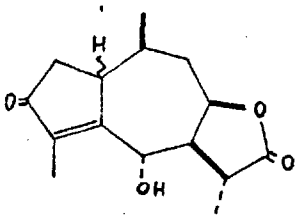


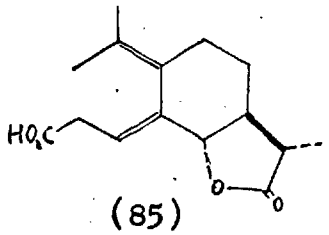
(84)

or C_{11}, but a recent X-ray crystallographic analysis[19] revealed the stereochemistry at C_{10} and C_{11} (84; see p.35), and confirmed the earlier assignments at C_6, C_7 and C_8.

2.4 Lumisantonin and Isophoto-α-santonic Lactone

One of the most interesting and important of the properties of santonin has been its sensitivity to light, and it will be appropriate to include in this section a discussion of the constitution and stereochemistry of two of the lactones formed by irradiation of santonin. It had been observed many years ago[57] that santonin was sensitive to light, and attempts had been made to determine the nature of the irradiation products, but it was not until recently that the constitutions of the three main products were established. Photosantonic acid, produced together with lumisantonin by irradiation of α-santonin in ethanol, has been shown[58] to possess the constitution (85), remarkable in view of its derivation from santonin. In the present

discussion, however, the more important products are lumisantonin (86) and isophoto-α-santonic lactone (87), formed by irradiation in ethanol or dioxan, and aqueous acetic acid, respectively.



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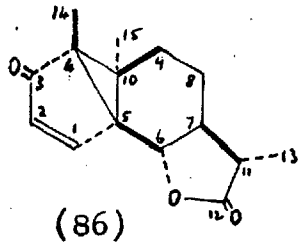
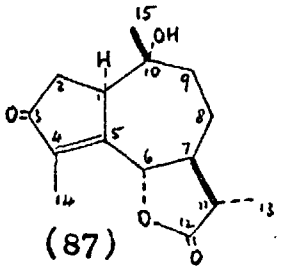


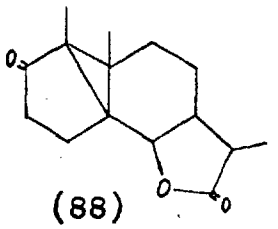
(86)



(87)

Lumisantonin: Lumisantonin was assigned[59] the constitution shown (86) chiefly on evidence which can be summarised as follows: The ultraviolet absorption (λ_{max} 239 mμ (ε, 5,800)), indicated an αβ-unsaturated ketone, and thus the infrared spectrum defined the three oxygen atoms in the molecule as one cyclopentenone (1703 cm^{-1}.) and one γ-lactone (1765 cm^{-1}.). A comparison of the infrared spectrum of dihydrolumisantonin (88) (ν_{max}, 1770, 1703 cm^{-1}.) with that of lumisantonin suggested some residual conjugation with the carbonyl group in the dihydro compound, and this was borne out by its ultraviolet spectrum, which showed a maximum at 214 mμ (ε, 4,600), often associated with a cyclopropane ring conjugated with a ketone. The presence of a cyclopropane ring is supported by the facile rearrangement of dihydrolumisantonin to an unsaturated

isomer, formulated as (89). A series of oxidative degradative steps (90 - 91) proved the presence of the



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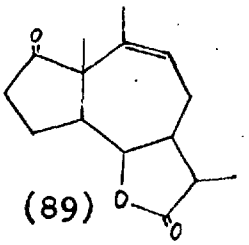

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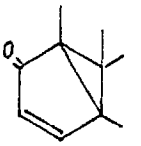

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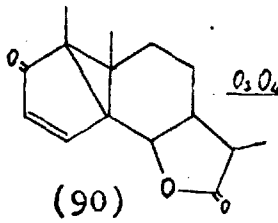

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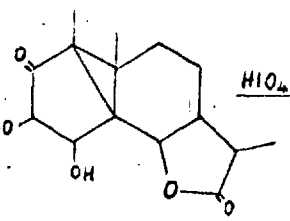
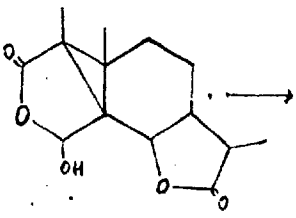
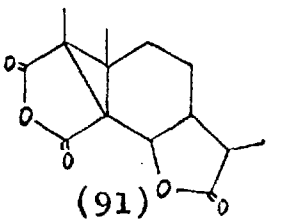


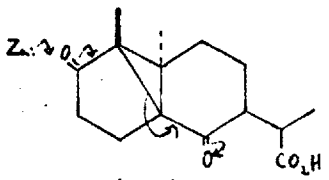




(91)

grouping -CO-CH=CH- , and this led to the partial expression (92). In the light of its genesis from santonin, and its conversion to isophoto-α-santonic lactone (87) by refluxing aqueous acetic acid in the dark, lumisantonin was assigned the constitution (90).

The stereochemistry shown in (86) was derived[60] as follows: Dihydrolumisantoninic acid on oxidation with chromic acid afforded the diketo acid (93) which on reduction with zinc and acetic acid followed by potassium borohydride reduction and chromic acid oxidation gave the keto-lactone (94). The optical rotatory dispersion curve of this compound was similar to that of friedelin (95); this suggests the β-methyl configuration at C_{10}. On treatment with hydrogen bromide lumisantonin affords the



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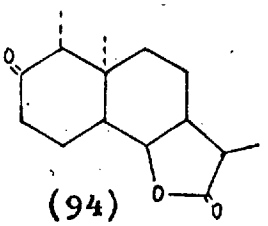

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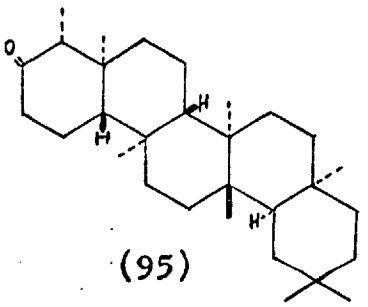
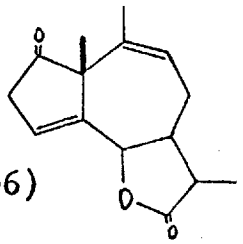


(95)

doubly unsaturated compound (96), whose optical rotatory dispersion curve shows a Cotton effect opposite to that shown by the steroid (97). As C_4 cannot have been affected in this transformation it was assigned the β-methyl configuration. As was commented in the discussion



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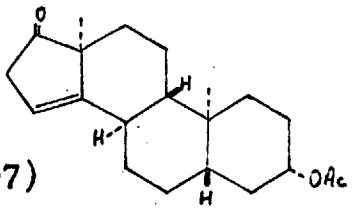
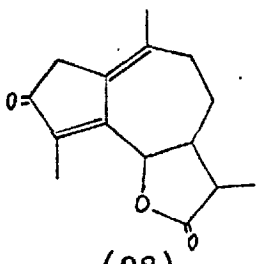


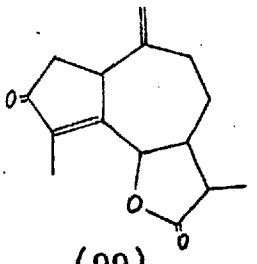
(97)

of geigerin it must be borne in mind that the fused 5- and 6-membered steroidal C/D rings are not adequate for comparison with fused 5- and 7-membered rings; the configuration at C_4 and C_5 should follow from that at C_{10}, however, as both the 5- and the 6-membered rings must be cis-fused to the cyclopropane ring. The stereochemistry at C_6, C_7 and C_{11} is the same as that in α-santonin, and thus the complete stereochemistry is as depicted in (86).

Isophoto-α-santonic Lactone (87): This, the product of irradiation of α-santonin in aqueous acetic acid, was assigned[55] the constitution shown largely on the basis of oxidative degradation. The compound analysed for the addition of one molecule of water to santonin, and the infrared spectrum revealed a γ-laotone, a hydroxyl group, and a second carbonyl group, a cyclopentenone since its absorption maximum shifted from 1710cm^{-1}. to 1740 cm^{-1}. in the dihydro compound. The position of the maximum in the ultraviolet (238 mμ) suggested that the double bond was fully substituted. The compound could be dehydrated with perchloric acid and acetic acid to a conjugated dienone (98), while dehydration with thionyl chloride and pyridine afforded the 10(15)-anhydro compound (99), which showed a band at 890 cm^{-1}. in the infrared, afforded formaldehyde on ozonolysis, and analysed for one fewer C-methyl than its precursor on Kuhn-Roth oxidation. Ozonolysis of the isophoto compound itself afforded acetic acid and a keto-di-γ-lactone with no hydroxyl function (100), and acid-catalysed hydrogenation followed by dehydrogenation gave



(98)



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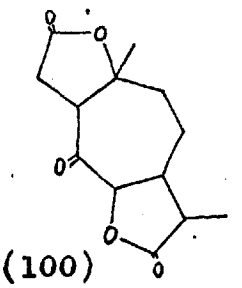
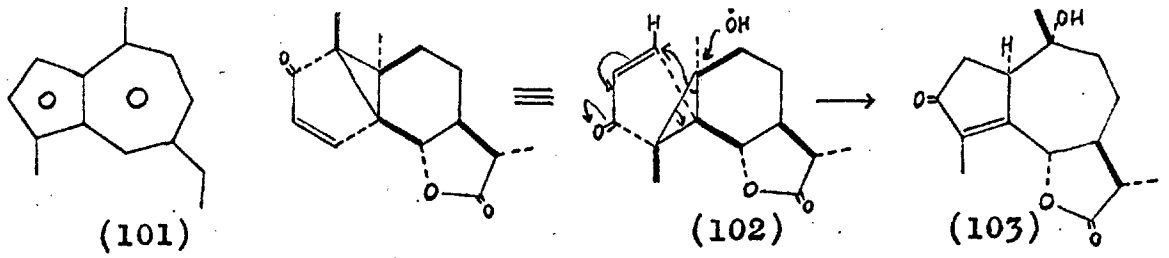


(100)

chamazulene (101). On this evidence, and bearing in mind the constitution of its precursor, santonin, the constitution (87) could be assigned, and this was supported by much other chemical evidence.

The asymmetric centres at C_6, C_7 and C_{11} in santonin cannot be affected in the transformation into the isophoto compound, and this is borne out[50] by the production of one stereoisomer of isophoto-α-santonic lactone in each case on irradiation of 6-epi-α-santonin (66), β-santonin (59), and 6-epi-β-santonin (67). The two remaining centres in isophoto-α-santonic lactone, C_1 and C_{10}, were more difficult to define, and conflicting views are found in the literature. On the basis of optical rotatory dispersion measurements Djerassi[56] proposed the β-hydrogen configuration at C_1, but it must be noted, as pointed out above (p.25), that the model used for comparison, cholest-14-en-3β-ol-16-one benzoate (83), is not a satisfactory one. A more convincing argument[50] is based on the conversion of lumisantonin to isophoto-α-santonic lactone by boiling aqueous acetic acid in the dark. If this change involves inversion at every stage, and can be represented as in (102), then the



(101) (102) (103)

stereochemistry of the isophoto compound would be as shown (103). This view is supported by the fact that dehydration of isophoto-santonic lactone with thionyl chloride and pyridine affords in good yield the 10(15)-anhydro compound (99), and none of the conjugated isomer.

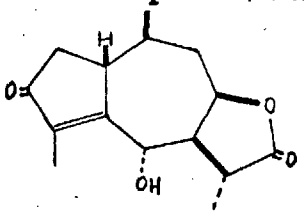
CHAPTER 3

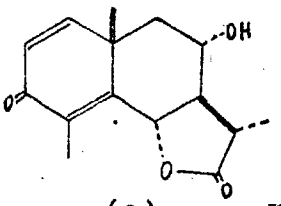
THE BACKGROUND TO THE PRESENT WORK

In a review in 1957[29] Barton and de Mayo predicted that the photochemical transformation of santonin to isophotosantonic lactone must ultimately prove useful in further investigation of the guaianolides, and particularly of their stereochemistry. The work to be described in this thesis formed part of the investigation which had as its object the complete elucidation of the stereochemistry of isophotosantonic lactone, and the substantiation of this prediction by effecting a correlation between santonin and a naturally occurring guaianolide, and ultimately a synthesis of the latter. The earlier work in this investigation (Barton and Pinhey) must now be briefly reviewed.

The constitution of geigerin (21), the most suitable naturally occurring guaianolide for this project, indicated artemisin (9) as starting point. The acetate of artemisin had already been shown[61] to give a normal isophoto compound, isophoto-artemisic lactone acetate (104), on irradiation in aqueous acetic acid; this needed to be extended to the C_6 and C_8 epimers. 6-Epiartemisin (105) had already been

prepared[52] by treatment of artemisin with dry hydrogen chloride in dimethyl formamide. 8-Epiartemisin (106) was prepared by treatment of artemisin methanesulphonate with cold decinormal aqueous alkali, 8-epialloartemisin (107) being obtained in addition. 6-Epi-8-epiartemisin (108) was similarly prepared from 6-epiartemisin methanesulphonate.


(21)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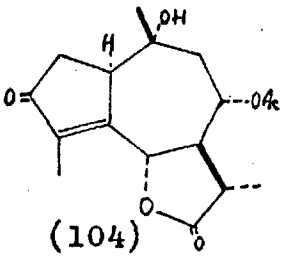
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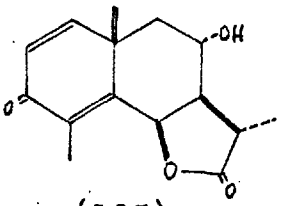
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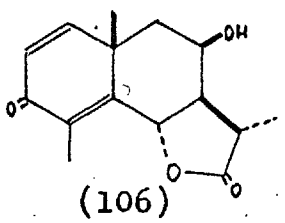
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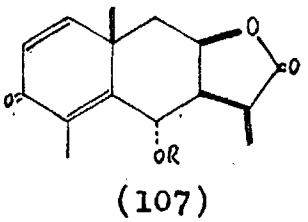
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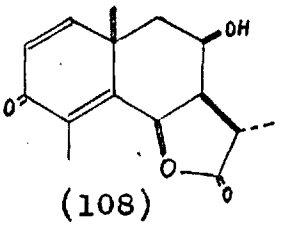
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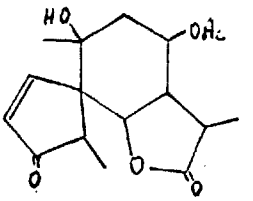
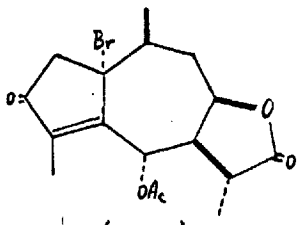

(109)

The acetates of 8-epiartemisin and 6-epi-8-epiartemisin afforded the expected isophoto compounds; 8-epialloartemisin acetate (107; R=Ac) unfortunately afforded an anomalous product, probably (109).

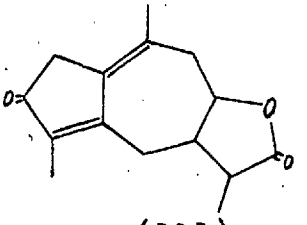
An obvious need was that of further knowledge of the stereochemistry of geigerin, and in the absence of appropriate chemical methods a derivative containing a 'heavy' atom was prepared and submitted to X-ray crystallographic analysis: geigerin acetate was brominated with

N-bromosuccinimide to afford bromogeigerin acetate, whose relative stereochemistry was shown[19] to be (110). The entry of the bromine atom at C_1 obscures the configuration of geigerin at that centre, but the earlier allocation of relative stereochemistry at C_6, C_7 and C_8[17] was confirmed.

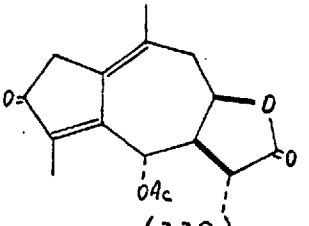
Another important preliminary to a synthetic approach to geigerin was to attempt a correlation of artemisin and geigerin, by means of a compound such as (111), where three asymmetric centres (including those at C_1 and C_{10}, both of uncertain stereochemistry in isophotosantonic lactone) have been eliminated. This correlation was



(110)

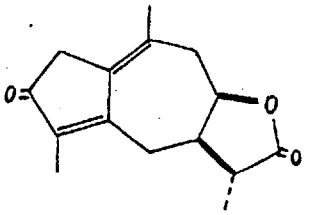


(111)

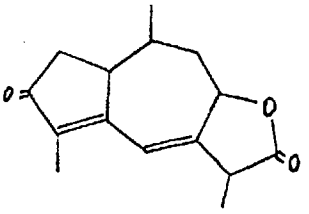


(112)

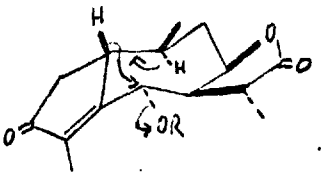
accomplished as follows: bromogeigerin acetate (110) on refluxing with dimethylformamide afforded the dienone (112) which on reduction with chromous chloride yielded anhydrogeigerin (113), previously[17] formulated as (114); n.m.r. spectroscopy confirmed the revised constitution. Anhydrogeigerin (which can also be obtained from geigerin methanesulphonate and collidine) is possibly formed via a 1,3-hydride shift, as in (115).



(113)



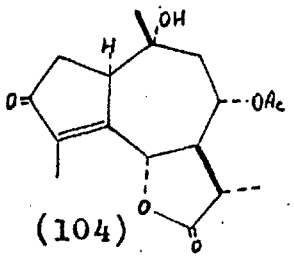
(114)



(115)

Chromous chloride reduction of isophotoartemisic lactone acetate (104) afforded the acid (116) which on treatment with perchloric and acetic acid at 70° was dehydrated to a dienone lactone epimeric with anhydrogeigerin, into which it was readily transformed by brief treatment at room temperature with 1% ethanolic potassium hydroxide. This correlation established the absolute configuration of geigerin at C_7, and thus that of bromogeigerin acetate as shown in (110); the configuration at C_{11} is thus the same as that previously accepted for C_{11} in α-santonin. It also demonstrated that the configuration of geigerin was attainable at C_6, C_7 and C_{11} in the synthetic series. In view of the prevalent opinion on the stereochemistry of α-santonin at the time it was suggested[18] that the final (epimerisation) stage of the synthesis of anhydrogeigerin involved C_8, C_{11} remaining intact throughout. It is now apparent that in fact C_{11} must be affected at some stage. It was subsequently

shown that the same 'epianhydrogeigerin' could be obtained from dehydration, with perchloric and acetic acid, of 8-epiisophotoartemisic acid acetate (117), which demonstrates the possibility of inversion at C_8 in the acid dehydration stage, but the stereochemistry of 'epianhydrogeigerin' is not yet certain.



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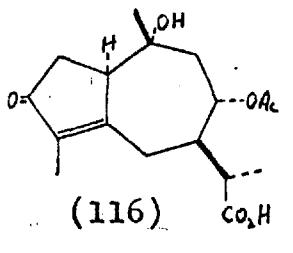

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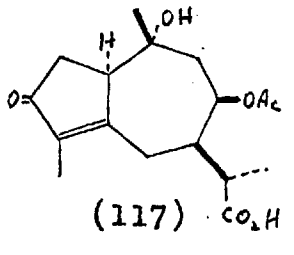
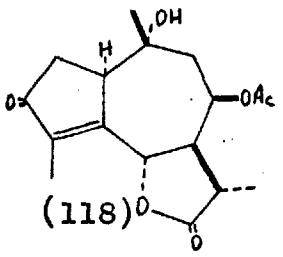


(117)

The next stage was to investigate methods of removal of the C_{10} hydroxyl group and of obtaining the correct stereochemistry at C_1 and C_{10}. Work on the chemistry of isophotosantonic lactone had shown[55] that dehydration with perchloric and acetic acid afforded the conjugated dienone (98), whereas treatment of the isophoto compound with thionyl chloride and pyridine produced the 10(15)-anhydro compound (99). Hydrogenation of the conjugated isomer afforded a crystalline dihydro derivative which it was shown (see Discussion) could not be epimerised at C_1 under either acidic or basic conditions. Anhydrogeigerin, too, gave a dihydro derivative (not deoxygeigerin), also unchanged by acid or base. Accordingly, the approach

using thionyl chloride and pyridine was investigated. 8-Epiisophotoartemisic lactone acetate (118) on dehydration under these conditions afforded the nonconjugated anhydro compound (119). This on hydrogenation over palladised strontium carbonate afforded in high yield the dihydro compound (120; R=Ac) which could be hydrolysed with aqueous sodium bicarbonate at 90°C to the alcohol, shown to be (120; R=H) by its reacetylation to its precursor. Deoxygeigerin (121) had recently been synthesized from



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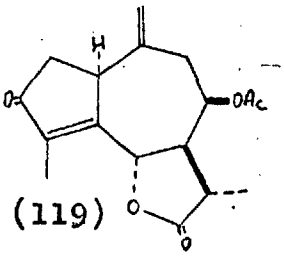

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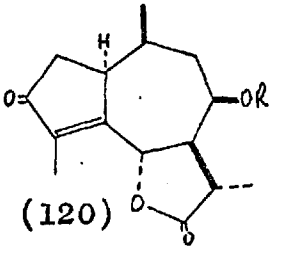

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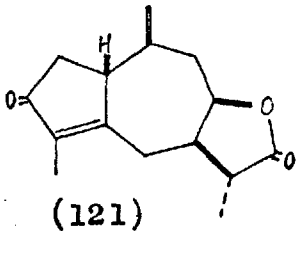
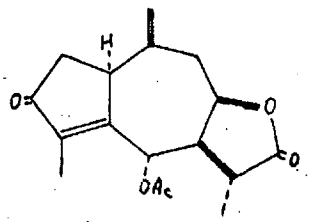


(121)

artemisin (see Discussion) through the acetate (120; R=Ac) as an intermediate; this established that hydrogenation of the 10(15) double bond proceeded from the α-face of the molecule, leading to the desired configuration at C_{10}. Dihydroanhydro-8-epiisophotoartemisic lactone (120; R=H), then, was thought to be epimeric with geigerin only at C_1, as it was of course still assumed that the configuration at C_{11} in the two series was the same. Bromogeigerin acetate (110), however, on hydrogenolysis over palladised calcium carbonate afforded 1-epigeigerin acetate (122)

which on bicarbonate hydrolysis yielded a compound different from the lactone (120; R=H). The apparent conclusion, at that time scarcely acceptable, was that in fact the configuration at C_{11} in α-santonin should be reversed. However, the initial synthesis of deoxygeigerin involved acid treatment of the uncharacterisable acid (123), and this could not safely be assumed to have



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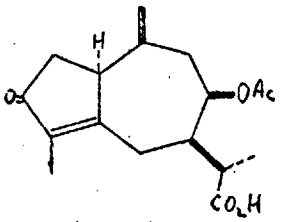

(123)

effected no stereochemical change.

PART II

DISCUSSION

CHAPTER 4

FURTHER CHEMISTRY OF ISOPHOTOSANTONIC LACTONE

Two aspects of the chemistry of the isophoto compounds were of especial relevance to this work. The first was the need for more precise knowledge of their stereochemistry, especially at C_1, C_{10} and C_{11}. The second was the need for further knowledge of the methods whereby the C_{10} hydroxyl group could be removed, and for methods of obtaining different configurations at C_1 and C_{10}.

4.1 The Stereochemistry of the Isophoto Compounds

It had been argued[50] that in the conversion of lumisantonin (1)[*] to isophotosantonic lactone (2) (see p.31) the introduced hydroxyl group would approach from the α-face of the lumisantonin molecule, leading to a $C_{10}\alpha$ hydroxyl group, and to a $C_1\alpha$ hydrogen. This conclusion was supported by the thionyl chloride-pyridine dehydration

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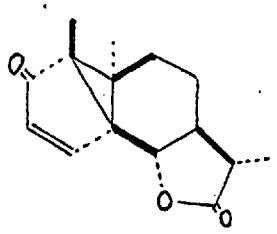
[*]Numeration of formulae in Part II is independent of that in Part I.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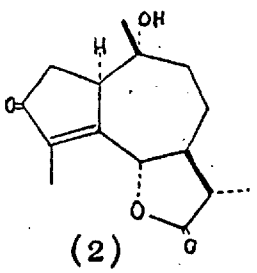
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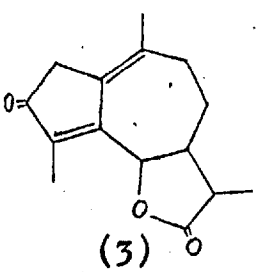
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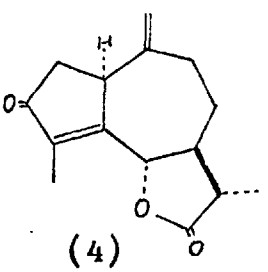
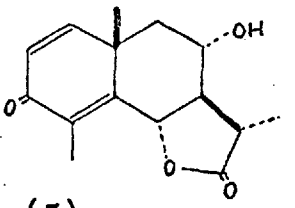

(4)

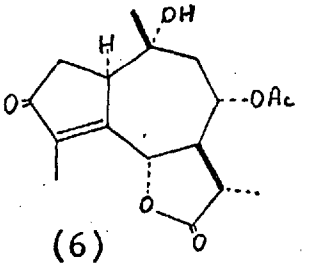
of isophotosantonic lactone to afford, not the conjugated unsaturated compound (3), but the unconjugated 10(15)-anhydro compound (4), suggesting that the C_{10} hydroxyl group is <u>cis</u> to the C_1 hydrogen. But more certain evidence was thought desirable.

An approach that suggested itself was the utilisation of the 8-hydroxyl group of artemisin (5), which had been assigned the α-configuration by Sumi[52], on the basis of the rule of Klyne and Stokes[53] relating to molecular rotational contributions. If a cyclic carbonate, for example, could be formed between the C_8 and C_{10} hydroxyl groups of an isophotoartemisic lactone their <u>cis</u> relationship would be established, and their α-configuration receive further support.

Unfortunately, artemisin itself affords no characterisable irradiation product, but its acetate affords[61] a normal isophoto compound (6) in low yield. Before the acetate could be removed hydrogenation of the double bond



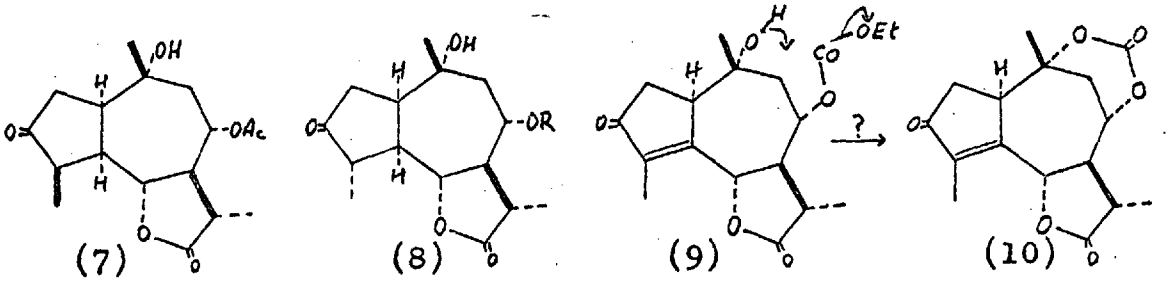
(5)



(6)

was necessary to prevent vinylogous β-elimination of the C_{10} hydroxyl group. Dihydroisophotoartemisic lactone acetate had been prepared[50], and was reported to have a specific rotation of -7^{o}. Repetition of this reduction was found to afford a product whose specific rotation varied from experiment to experiment, varying from -18^{o} when the uptake of hydrogen took more than 15-20 minutes to -26^{o} in an experiment when uptake was complete within ten minutes. Treatment of this compound at room temperature with hydrogen chloride in chloroform produced a compound with specific rotation $+10^{o}$. This behaviour is analogous to that of the dihydroisophoto-α-santonic lactones[50], being due to epimerisation at C_4. In this case, however, the initial product (7) is more unstable than the santonin analogue, being epimerised readily on prolonged contact with the catalyst to the stable epimer (8; R=Ac). The previously reported product is thus a mixture of epimers. Attempted hydrolysis of the acetate with alkaline hydroxide yielded no characterisable product,

but treatment with aqueous sodium bicarbonate afforded a crude product from which the pure deacetyl compound (8; R=H) could be isolated only in low yield. Before sufficient of this compound could be obtained for the next stage it was conceived that the same final result might more easily be attained via isophotoartemisic lactone carbethoxylate ('cathylate') (9), if that could be prepared. Elimination of ethanol might then be possible between the C_{10} hydroxyl group and the C_8 cathylate, leading to the desired cyclic carbonate (10), in view of

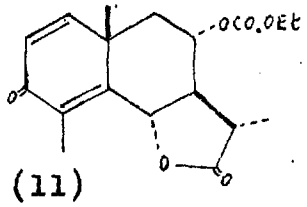


the fact that cathylation of 1,2- and 1,3-diols, for example, frequently proceeds direct to the cyclic carbonate[62]. It is true that in general this does not apply to tertiary hydroxyl groups, but the value of the desired result was felt to compensate for the slim chances of success. Artemisin cathylate (11), prepared as described by Sumi[52], was transformed by irradiation in aqueous acetic acid into the isophoto compound (9), surprisingly in yield slightly superior to that obtained in the preparation of isophotoartemisic lactone acetate.

Catalytic hydrogenation furnished the dihydro compound, presumably with the stable configuration at C_4 (8; R=CO_2Et), as the product was induced to crystallise only after passage through an alumina column.

Several methods were used in attempts to induce cyclisation of the isophoto compound or its dihydro derivative: pyrolysis, treatment with pyridine, and treatment with sodium hydride all proved unsuccessful, and no further attempts were made to establish the configuration at C_1 and C_{10} by chemical means. The alternative approach, of course, was by X-ray crystallography.

The p-bromophenylhydrazone of dihydroisophoto-α-santonic lactone had been prepared[50], but had been found to form twinned crystals and to be unsuitable for X-ray analysis. However, dihydroisophoto-α-santonic lactone acetate (12; R=H)[50], on treatment with bromine in acetic



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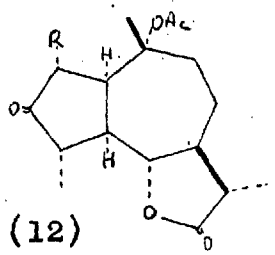


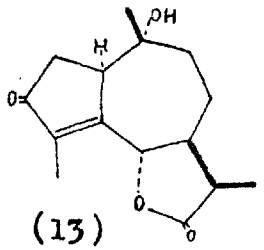
(12)

acid at room temperature, furnished a crystalline bromo-compound which was submitted for X-ray crystallographic

analysis. On completion about a year later this analysis revealed[63] the relative stereochemistry shown (12; R=Br). By the time this result was known independent chemical evidence had been obtained supporting what is the most significant fact disclosed by this analysis: the 11β(H) configuration at C_{11}, opposite to that previously accepted. The chemical evidence will be presented in Chapter 5.

Before it could be assumed, however, that the configuration at C_{11} in this bromo-derivative was the same as that of α-santonin itself it was necessary to establish that there existed no possibility of inversion during any of the stages between santonin and this compound. This was done as follows: isophoto-β-santonic lactone (13) was hydrogenated, the product converted to the stable C_4 epimer (14; R=H) by treatment with dilute aqueous alkali, and this stable dihydro compound converted to the acetate (14; R=Ac), the same conditions being used for each stage as were used in the α-series. At each stage a compound different from its counterpart in the α-series was obtained. Moreover, the molecular rotational differences accompanying each stage were closely comparable in both series. Thus the possibility of any change at C_{11} is eliminated from all but the last stage. The last

stage was eliminated by reduction with chromous chloride of the bromo-derivative to its precursor, thus demonstrating that no change at C_{11} could have accompanied the bromination. Thus the configuration at C_1, C_{10} and C_{11} is the same in both the isophoto compound and the bromo derivative. The revised configuration at C_{11} has subsequently been confirmed, by degradation of α-santonin to (+)-benzoylalanine[64], and by X-ray crystallographic analysis of 2-bromosantonin (15)[65]. Some of the



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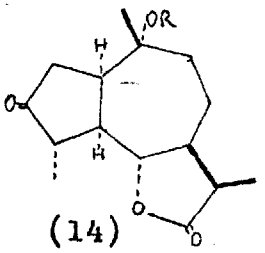

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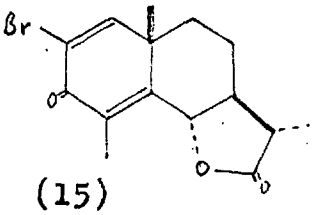


(15)

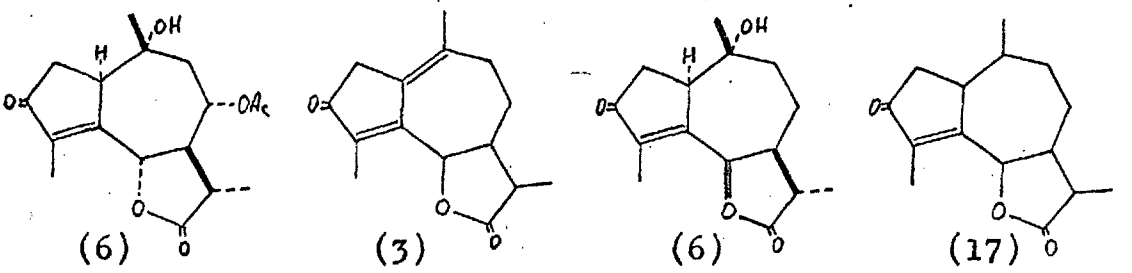
implications of the revision of the configuration of α-santonin at C_{11} will be discussed later. The result at C_1 and C_{10} in the isophoto compound vindicates the mechanistic argument reviewed in Chapter 2.

4.2 The Chemistry of C_1 and C_{10} in Isophotosantonic Lactone

In a synthesis of geigerin from artemisin the C_{10} hydroxyl group in isophotoartemisic lactone acetate (6) would at some stage have to be removed, and the correct configuration at that centre and at C_1 obtained.

Isophotosantonic lactone was obviously a good model for a study of the chemistry of these centres.

Acid-catalysed dehydration of isophotosantonic lactone was known[55] to give the conjugated dienone (3). The potential usefulness of the conjugated anhydro compound as an intermediate was complicated by the fact that 6-epiisophotosantonic lactone (16) gave the same anhydro compound on dehydration under the same conditions[50], showing that at least one of the asymmetric centres of



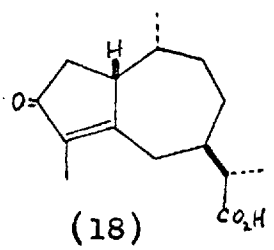
the lactone ring is affected under these conditions. Nevertheless it was obviously desirable to investigate the hydrogenation of this product. Hydrogenation over palladised charcoal (interrupted after absorption of one mole-equivalent of hydrogen) furnished dihydroanhydro-isophoto-α-santonic lactone (17) as a crystalline solid. It was expected that the hydrogen atoms at C_1 and C_{10} would be cis (probably both in the α-configuration) and that treatment with acid or base would readily isomerise the dihydroanhydro compound at C_1 to a more

stable 1β(H), 10α(H) configuration. In fact this compound was found to resist even vigorous treatment under either acidic or basic conditions.

It is now known (see p.50) that hydrogenation of dihydroanhydroisophoto-α-santonic lactone takes place from the β-face of the molecule. In the event, the synthetic approach to geigerin was made via the 10(15)-anhydro compounds obtained from thionyl chloride-pyridine dehydration (see p.30), without further investigation of the isophotosantonic lactone model. The unexpected resistance to epimerisation at C_1 will be referred to again in Chapter 5.

Reference has been made above to the formation of a single anhydro compound from both isophoto-α-santonic lactone and its C_6 epimer, on acid-catalysed dehydration. This compound is probably the <u>cis</u> lactone, the strongly acidic conditions causing epimerisation at C_6 by protonation of the C_3 oxygen atom. It was hoped that this point could be clarified by further hydrogenation of the dihydroanhydro compound. It had been found[50] to be general among the isophoto compounds that on hydrogenation those compounds with <u>cis</u> lactones (6α(H)) suffered hydrogenolysis of the C_6-O bond, whereas those compounds

having <u>trans</u> lactones underwent normal hydrogenation of the double bond. Thus it was expected that further hydrogenation of the dihydroanhydro compound would furnish the acid (18). In fact, a neutral, noncrystalline material was obtained, presumably the saturated compound (19). This is probably to be explained by the stereochemistry at C_1. The isophoto compounds which undergo hydrogenolysis of the C_6-O bond have the α(H) configuration at C_1; hydrogenation of the 1(10) double bond, however, affords the β-configuration at C_1, as shown by the work of Büchi and Loewenthal[66] in the synthesis of epicyclocolorenone (20) from isophoto-α-santonic lactone. These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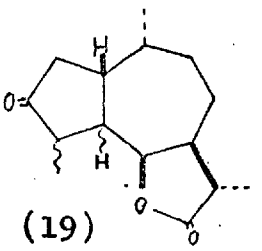
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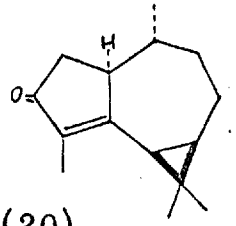
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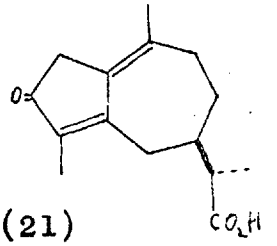
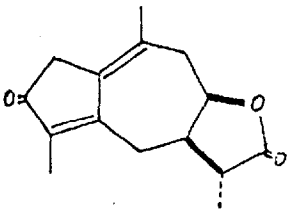

(21)

workers found that hydrogenation of the acid (21) derived from isophotosantonic lactone afforded a mixture of 1β(H), 10β(H) and 1α(H), 10α(H) compounds, with the former preponderating. This is supported by the hydrogenation of anhydrogeigerin (22) (see p.65). In dihydroanhydro-isophoto-α-santonic lactone (17), then, the inverted configuration at C_1 probably so alters the conformation

at C_6 from that of 6-epiisophoto-α-santonic lactone (16), for example, that hydrogenolysis cannot take place.



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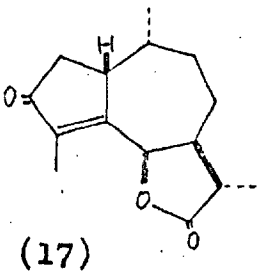

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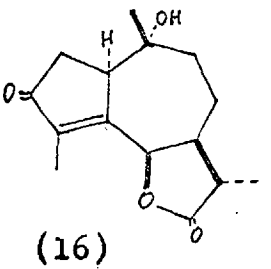

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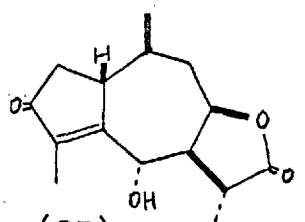
CHAPTER 5

THE SYNTHESIS OF DEOXYGEIGERIN

The main purpose of the present study, as was explained in Chapter 3, has been the demonstration of the value of isophotosantonic lactone and its analogues, as synthetic guaianolides, in the study of the chemistry of the natural guaianolides. As an example, the natural product geigerin (23) was chosen, for correlation with the isophoto compounds and ultimately for synthesis from an isophoto compound.

The first correlation was achieved (see Chapter 3) with the synthesis[18] of anhydrogeigerin (22). The next



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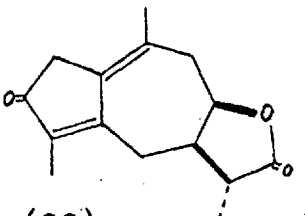

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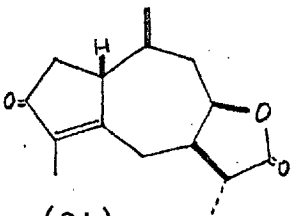

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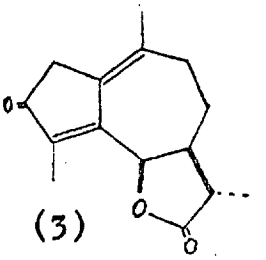
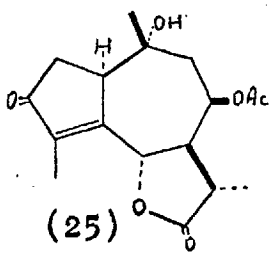


(3)

logical step was the synthesis of deoxygeigerin (24), a compound having two more asymmetric centres than anhydrogeigerin.

In view of the discouraging results of the work on conjugated anhydroisophotosantonic lactone (3) and its

dihydro derivative a route was sought via the thionyl chloride-pyridine dehydration product. Dehydration of 8-epiisophotoartemisic lactone acetate (25) under these conditions gave a fair yield (up to 75%) of the nonconjugated anhydro compound (26), and this on selective hydrogenation over palladised strontium carbonate furnished dihydroanhydro-8-epiisophotoartemisic lactone acetate (27; R=Ac) in high yield. Reduction of this compound



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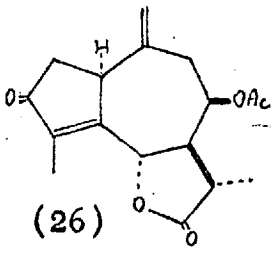

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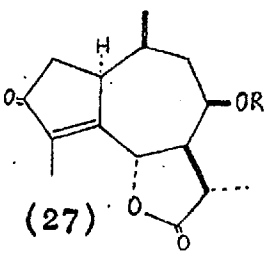
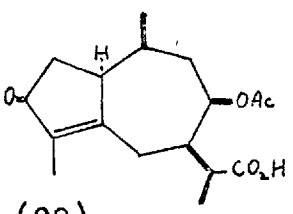
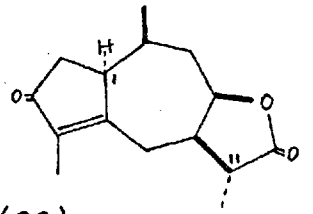


(27)



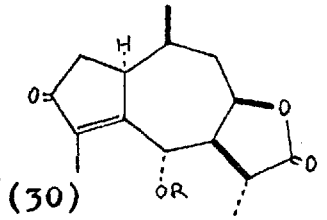
(28)

with chromous chloride afforded the acid acetate (28) as a colourless gum which could not be induced to crystallise but possessed the expected spectral properties. Hydrolysis with potassium hydroxide failed to afford any characterisable neutral product, but treatment with 5% sulphuric acid for several hours at 90° yielded a crystalline neutral compound ($[\alpha]_D$, -59°) whose analysis and spectral properties were consistent with the constitution (29). This compound, on brief treatment with ethanolic potassium hydroxide, was transformed into deoxygeigerin (24), identical in all respects with material



(29)

obtained from geigerin. At the time that this work was done santonin (and thus artemisin) was still assumed to have the same configuration at C_{11} as that of geigerin; the epimer of deoxygeigerin described here was thus originally assigned the configuration shown in (29), the final base-epimerisation being considered to affect C_1. Shortly after this, however, dihydroanhydro-8-epiisophotoartemisic lactone (27; R=H) was obtained by bicarbonate hydrolysis of the acetate, and found to be distinct from both geigerin and 1-epigeigerin (30; R=H) (See Chapter 3). This cast great doubt on the traditional view of the stereochemistry of α-santonin, and indicated that further work was needed, on the synthesis of deoxygeigerin in particular. Two questions presented themselves: Did the acid cyclisation of the acid acetate (28) also effect some stereochemical change? Could it be established which of the two possible centres (C_1 and C_{11}) was in fact affected by alkaline treatment of the epimer of deoxygeigerin?



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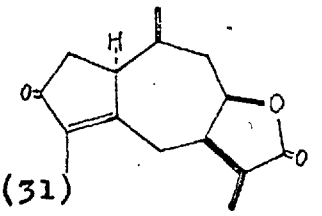
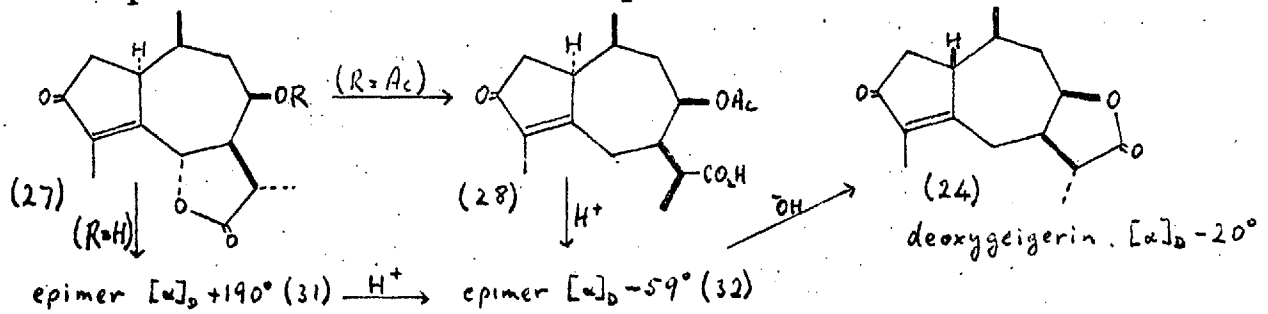


(31)

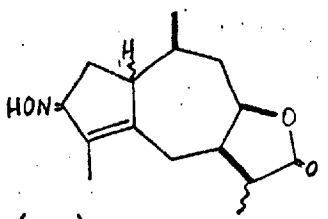
In an attempt to avoid the noncrystalline stage in the synthesis of deoxygeigerin the now available dihydroanhydro-8-epiisophotoartemisic lactone (~~26~~ 27; R=H) was reduced with chromous chloride to furnish, not the expected previously known epimer ($[\alpha]_D$, -59°) of deoxygeigerin, but a new epimer (31) ($[\alpha]_D$, $+190^\circ$). In view of the mildness of the conditions used this compound must have the same configuration at C_1 and C_{11} as isophotosantonic lactone. This epimer, on treatment on the steam bath with 5% sulphuric acid, was transformed into the previously known epimer ($[\alpha]_D$, -59°). The position so far can be represented as follows:



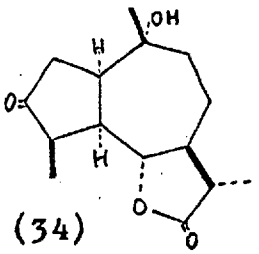
The evidence up to this stage shows the epimer (31) ($[\alpha]_D$, $+190^\circ$), with the same configuration at C_1 as the

isophoto compounds (presumably 1α(H)), to undergo change at <u>two</u> centres (C_1 and C_{11}) during its transformation into deoxygeigerin, since three epimers are involved. This alone is not sufficient evidence, however, for the reversal of the traditional stereochemistry of α-santonin at C_{11}: C_{11} might conceivable be inverted in each of the epimerisation stages. This could be clarified in two ways: (a) The possibility of inversion at C_1 could be eliminated by oximination (33). If, for example, the oxime of the epimer ($[\alpha]_D$, -59°) was transformed into the oxime of deoxygeigerin on treatment with alkali, C_{11} alone could have been involved. If no change was observed, C_1 alone must be the centre affected in the epimerisation of the parent ketone. (b) C_1 could be similarly 'immobilised' by hydrogenation of the 4(5) double bond. This method could be applied to both the acid- and the alkali-induced changes.

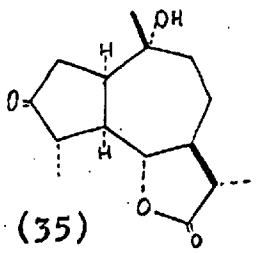
The oxime method was first attempted. Although on paper it seemed plain that oximination would eliminate any possibility of epimerisation at C_1 it was necessary to establish this by application to model compounds. The



(33)



(34)



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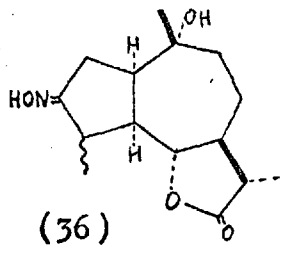
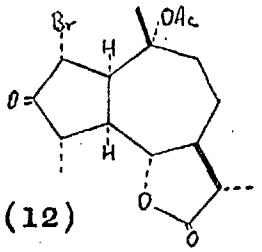


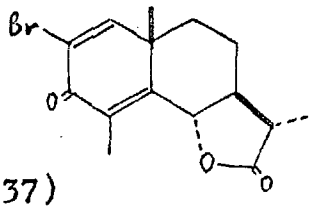
(36)

epimers of dihydroisophotosantonic lactone (34 and 35), known[50] to differ at C_4, appeared satisfactory for this purpose. Accordingly, the oximes (36) of the two dihydroisophotosantonic lactones were prepared, and the oxime of the unstable epimer (34) was found to be unaffected by base, even under conditions more vigorous than those adequate for the epimerisation of the ketone. With this encouragement the oximes of deoxygeigerin and its epimer ($[\alpha]_D$, -59°) were prepared; here, too, the oxime of the unstable epimer was found to be stable in alkaline solution, once again using conditions more vigorous than those used for the epimerisation of the ketone. Subsequent events showed these results to be misleading, but at the time it was argued that the base epimerisation of the epimer ($[\alpha]_D$, -59°) must take place at C_1, the centre 'immobilised' by oximination, and at this centre alone. Thus C_{11} can be affected in the acid epimerisation alone. Hence it was argued that α-santonin and artemisin must have the opposite configuration to geigerin, at C_{11}, contrary to common belief.

This conclusion was reached[67] simultaneously with the completion of the X-ray crystallographic analysis[63] of bromodihydroisophoto-α-santonic lactone acetate (12), this, too, reversing the traditional α-santonin configuration



(12)



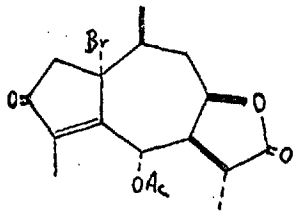
(37)

at C_{11}. The corrected configuration was subsequently supported, first by degradation[64] of α-santonin to (+)-benzoylalanine, and later by X-ray crystallographic analysis[65] of 2-bromosantonin (37).

It was realised at this stage that a defect existed in the arguments underlying the conclusions drawn from the oxime experiments. Epimerisation had been prevented by a change introduced into the molecule; it had been assumed that this change could have affected no centre other than the one it was designed to affect. The possibility (however unlikely it might initially appear) that oximination prevents inversion at C_{11} had not been eliminated. More positive evidence would be afforded if a change introduced into the molecule did not affect the course of the reaction - for example, if the dihydro derivative of the epimer ($[\alpha]_D$, +190°) afforded the dihydro derivative of the epimer ($[\alpha]_D$, -59°) on treatment with acid.

Further knowledge of these epimers of deoxygeigerin

and their relationship was therefore desirable, and the first aim was to confirm the conclusion drawn from the oxime experiment. Bromogeigerin acetate (38) had been prepared[18] by bromination of geigerin acetate with N-bromosuccinimide, and had been hydrogenolysed to 1-epigeigerin acetate (30; R=Ac). It is safe to assume that this compound can differ from geigerin acetate only in its configuration at C_1. 1-Epigeigerin acetate had been deacetylated by treatment with bicarbonate, and this compound was now shown to be (30; R=H) (i.e. with unchanged stereochemistry and unchanged direction of closure of the lactone ring) by reacetylation to its precursor.



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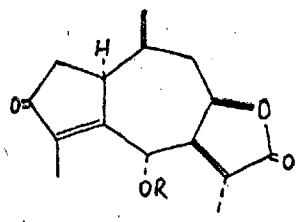
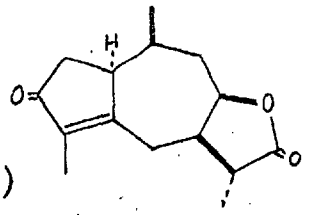


(30)

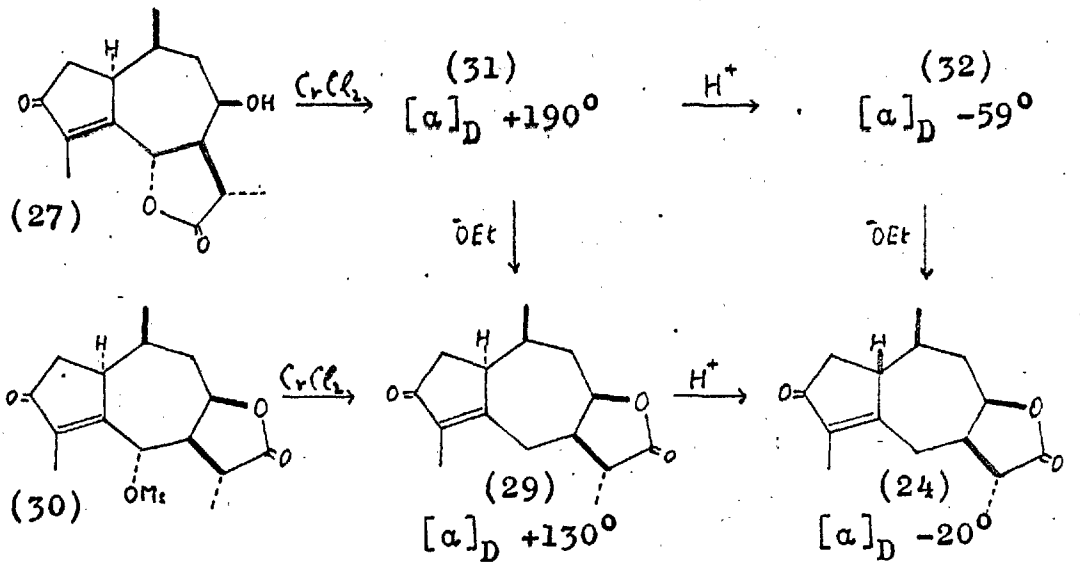
1-Epigeigerin methanesulphonate (30; R=SO_2CH_3) was now prepared, and this was smoothly and rapidly reduced by chromous chloride. The product was not the expected epimer ($[\alpha]_D$, -59°), which had been regarded as 1-epideoxygeigerin, but a fourth epimer, with $[\alpha]_D$ $+130^\circ$. By virtue of its genesis this epimer can only be 1-epideoxygeigerin (29). It was now found that the new epimer could be obtained by treatment of the epimer ($[\alpha]_D$, $+190^\circ$) with ethanolic potassium

hydroxide, and could in turn be converted into deoxygeigerin by treatment with dilute sulphuric acid on the steam-bath.



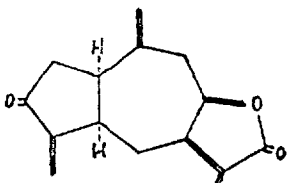
(29)

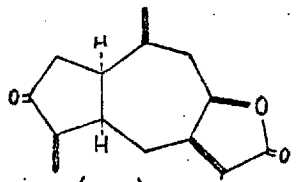
We can now represent the relationship of the epimers as follows:



The acid-induced transformation of l-epideoxygeigerin into deoxygeigerin can affect only C_1; it seems likely, therefore, that both acid epimerisations affect C_1 alone, and both alkaline epimerisations affect C_{11} alone, but this needed to be established rigidly before the chemical evidence for the configuration of santonin could be considered adequate.

The epimer ($[\alpha]_D$, +190°) on hydrogenation over palladised charcoal furnished a crystalline dihydro derivative (39) which on treatment with ethanolic potassium hydroxide afforded a product, recrystallisable with difficulty and with considerable loss, of which insufficient could be obtained for complete characterisation. This product had a melting point of 115-125°C, which was not improved by further purification. Similar hydrogenation of 1-epideoxygeigerin afforded a crystalline dihydro derivative (40) which on treatment with ethanolic potassium hydroxide afforded a product, purifiable only in low yield to a melting point of 115-125°C, which on admixture with the compound obtained from the epimer ($[\alpha]_D$, +190°) melted over the same range. Apparently hydrogenation of the 4(5) double bond so alters the molecular geometry that one configuration at C_{11} is no longer so strongly favoured as in the case of the unsaturated compounds, and a mixture is obtained.

(31) ⟶  (39)

(29) ⟶  (40)

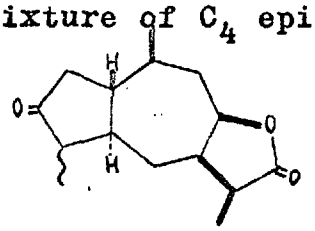
⟶ mixture mp.115-125°

In view of the unsatisfactory melting points of the stable dihydro compounds the series was repeated with the second pair of epimers.

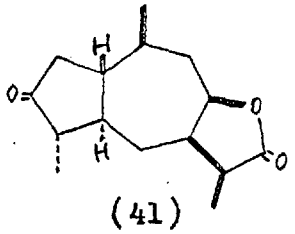
Hydrogenation of the epimer ($[\alpha]_D$, -59°) gave a mixture, presumably of C_4 epimers (cf. the case of isophotoartemisic lactone acetate, where the unstable epimer produced on hydrogenation readily epimerises in contact with the catalyst - see p.43). This mixture could not be separated but on treatment with ethanolic potassium hydroxide it afforded a mixture of readily separable epimers, the minor constituent (41; obtained only in very small amount) melting at 139-144°, and the major constituent (42) melting at 220-222° ($[\alpha]_D$, +140°). Hydrogenation of deoxygeigerin furnished a compound (42) identical with the major constituent of the above mixture of alkali-epimerised dihydro compounds. This dihydrodeoxygeigerin on alkaline

treatment afforded the same mixture of epimers: minor constituent, m.p. 139-144°; major constituent, m.p. 219-222° ($[\alpha]_D$, +137°). These observations are most reasonably interpreted as follows:

(32) $[\alpha]_D$ -59° ⟶ mixture of C_4 epimers $\xrightarrow{\bar{O}Et}$ mixture of C_{11} epimers

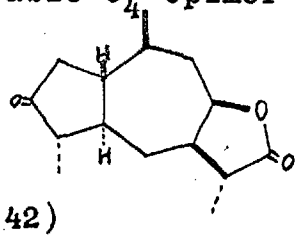


unstable m.p.140°



(41)

(24) ⟶ stable C_4 epimer $\xrightarrow{\bar{O}Et}$ stable m.p.220°

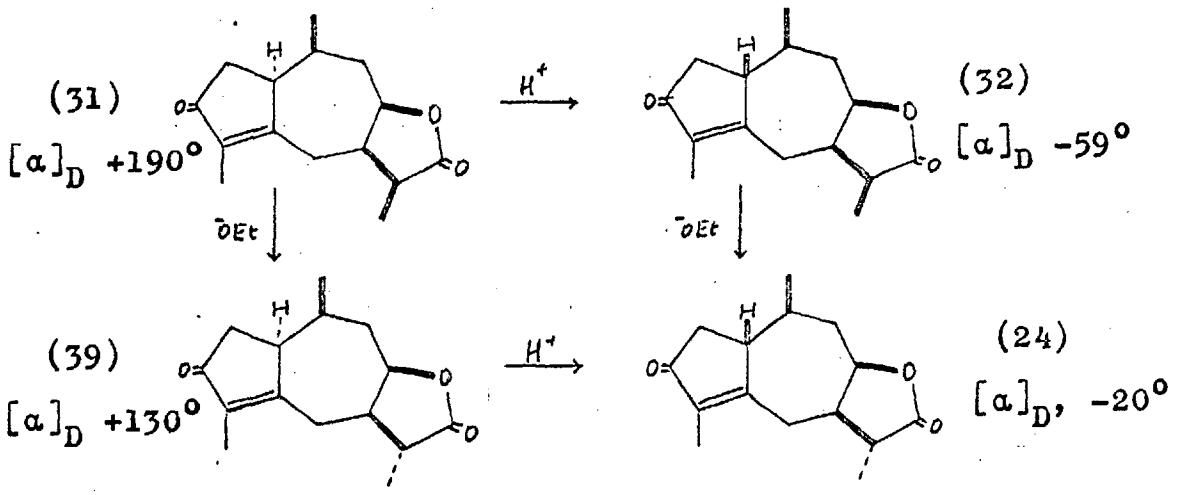


(42)

(42)

Once again we find that hydrogenation of the double bond - with the bridge-head C_5 becoming tetrahedral instead of trigonal - so alters the geometry of the molecule that a mixture of C_{11} epimers is obtained. At all events the series establishes that C_{11} is the centre affected by alkaline conditions, and C_1 by acid, and the revised stereochemistry of α-santonin is chemically confirmed. The final pattern of relationships is represented below; the epimers ($[\alpha]_D$, +190°) and ($[\alpha]_D$, -59°) must of course

be 1-epi-11-epideoxygeigerin and 11-epideoxygeigerin respectively:



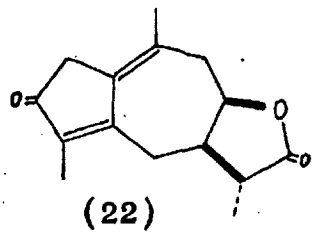
Other facts emerge from these results. It is apparent that isophotosantonic lactone and geigerin are of opposite configuration not only at C_{11} but also at C_1. In the isophoto compound this centre is known from the X-ray analysis to have the α(H) configuration: hence in geigerin we have a β hydrogen at this centre, the centre unresolved by the X-ray analysis of bromogeigerin acetate (see p.35). The β-configuration had been assigned[56] to this hydrogen on the basis of optical rotatory dispersion evidence, but in this series interpretations based on this method in the past have been almost as often wrong as right. The chemical evidence now establishes this configuration and completes the stereochemistry of geigerin.

The configuration of artemisin at C_8, too, is now

firmly established. The α-configuration was originally assigned by Sumi[52] on the basis of the sign of the molecular rotation difference between artemisin and santonin, applying a generalisation of Klyne and Stokes[53]. Such generalisations and empirical rules have proved of great value, but their limitations need to be borne in mind. Here, however, Sumi's allocation is established on direct chemical evidence: the oxygen at C_8 in geigerin has the β-configuration, as shown by X-ray analysis, and thus 1-epigeigerin and 1-epideoxygeigerin, too, have the β-configuration at this centre. It is safe to assume that this centre cannot have been affected by the mild alkaline conditions of the transformation of 1-epi-11-epideoxygeigerin into 1-epideoxygeigerin, and the former was derived by a series of mild reactions from 8-epiisophotoartemisic lactone acetate. Artemisin, therefore, must have the opposite configuration at C_8, i.e. an α hydroxyl group.

Another minor point clarified by the study of the four deoxygeigerin epimers is the mode of hydrogenation of the 1(10) double bond in conjugated dienones such as anhydrogeigerin (22) and anhydroisophotosantonic lactone (3). Anhydrogeigerin, on hydrogenation over palladised charcoal, affords a well-defined dihydro compound (43)

($[\alpha]_D$, +20°), distinct from deoxygeigerin and its epimers. Hydrogenation must take place from the β-face, therefore, contrary to earlier expectations and in agreement with the findings of Büchi and Loewenthal[66] on the hydrogenation of the acid (21) derived from isophotosantonic lactone (see p. 50).



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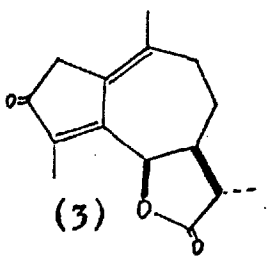

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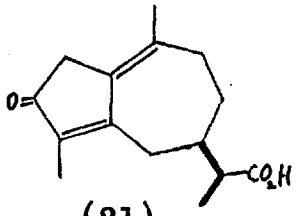

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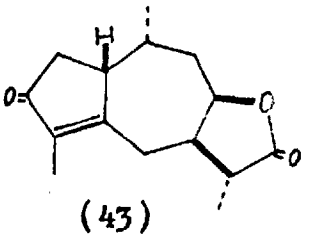
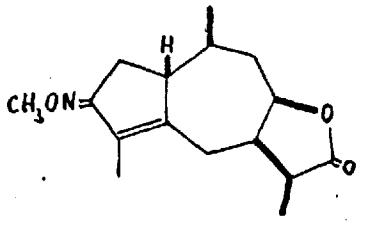
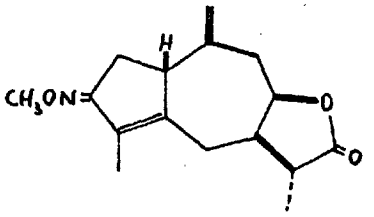


(43)

It is now necessary to return to the weaknesses of the oxime experiments. The conclusions drawn from this series have been overthrown by subsequent findings, and it is now evident that oximination of the C_3 carbonyl group prevents epimerisation at C_{11}. The explanation that suggests itself is that electrostatic repulsion by the oxime anion in alkaline solution prevents the approach of a second anion to another part of the molecule under such mildly alkaline conditions. This could be tested by the use of the O-methyloximes. The O-methyloximes of 11-epideoxygeigerin and deoxygeigerin (44 and 45 respectively) were obtained in high yield as nicely crystalline compounds by the action of methoxy-amine on the ketones. Treatment of 11-epideoxygeigerin O-methyloxime (44) with ethanolic



(44)



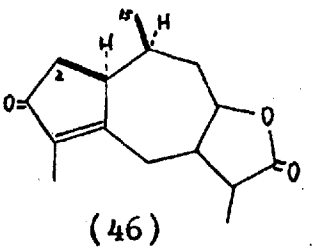
(45)

potassium hydroxide furnished a mixture of compounds, separable to afford the starting material and deoxygeigerin O-methyloxime (45). This result confirms the conclusions reached from the study of the dihydro derivatives of deoxygeigerin and its epimers and supports the explanation offered above for the failure of the oxime of 11-epideoxygeigerin to be inverted at C_{11} in alkaline solution.

Before the inadequacy of the oxime experiment had been realised a similar reaction was carried out with epianhydrogeigerin. The final stage in the synthesis of anhydrogeigerin (22) had been the treatment of an epimer with dilute potassium hydroxide solution (see p.36). In this case, too, there are two centres capable of inversion under these conditions: C_{11} (being α to the lactone carbonyl group) and C_8 (by vinylogous β-elimination of the lactone to a trienone acid followed by readdition). The oximes of epianhydrogeigerin and anhydrogeigerin were prepared, and here, too, it was found that the oxime of the unstable epimer was stable in alkaline solution. It

is now apparent, of course, that this result is of no significance: the configuration of epianhydrogeigerin is still obscure.

An aspect of the stereochemistry of the deoxygeigerin epimers that merits brief discussion is the reasons for the favoured configurations. The changes at C_1 are not difficult to rationalise. It is to be expected that the configuration shown in (46), with the bulky C_{15} methyl and C_2 methylene groups *cis* in relation to the seven-membered



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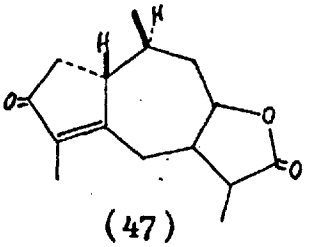


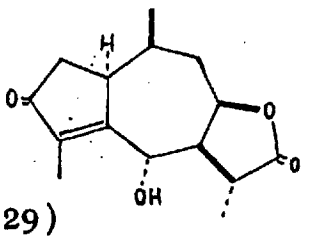
(47)

ring, would be less stable than (47) with C_2 and C_{15} *trans*. And, as has been shown, this is supported by experiment. The stereochemistry at C_{11} is more complex. The sesquiterpenoids with the lactone fused to a six-membered ring have been extensively studied, and much is known of their stereochemical behaviour at C_{11}, but even here the 'lactone rule' of Cocker *et al.*[68] and Dauben *et al.*[69] (which states that in compounds with a *trans*-fused lactone ring the stable configuration at C_{11} is that with the C_{11} methyl group *trans* to the C_7 hydrogen, and with *cis*-lactones the

configuration with the C_{11} methyl group cis to the C_7 hydrogen) was based very largely on the assumption of the wrong configuration of α-santonin at C_{11} and on arguments which had been used in support of the wrong configuration. This rule will obviously require re-examination, and time will tell whether any valid rule can be evolved. In the case of compounds with the lactone ring fused to a seven-membered ring the problem is complex and it is doubtful whether any generally applicable empirical rule will ever be formulated. Molecular models suggest that even in the guaianolides, where the seven-membered ring is fused to two five-membered rings, a remarkable degree of flexibility is possible, and transitions between conformations of widely differing appearance and with utterly contrasting stereochemical implications probably require very little energy and take place with great ease. At present conformational analysis of systems such as these is very difficult because of the limited data available. The work described here, however, provides for the first time a series of guaianolides whose absolute configuration and some of whose stereochemical behaviour are known.

It was stated above that the behaviour of the asymmetric centre at C_1 can be rationalised. There is one important and interesting qualification that must be

added, however. If the β-methyl group at C_{10} implies a stable 1β(H) configuration, then 1-epigeigerin (30) should be unstable. An early attempt to convert 1-epigeigerin into geigerin by alkaline treatment had no effect. We now know, of course, that this centre is inverted by acid



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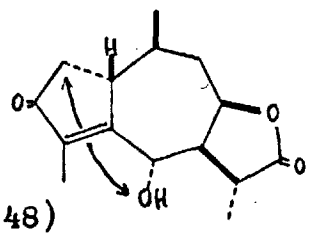
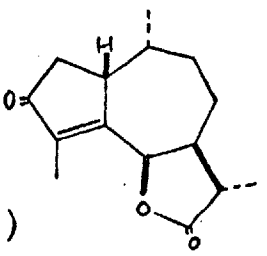


(48)

treatment in the deoxygeigerin epimers; 1-epigeigerin is unchanged by this treatment, however. This stability could be rationalised as being due to an opposing 1,3-interaction (48) which would favour the 1α(H) configuration. From molecular models such interaction appears highly unlikely, but if it were possible geigerin might be unstable at C_1, and inverted by acid treatment. This, too, was tried, with no success. As under no conditions is a mixture of 1-epigeigerin and geigerin obtained, or one transformed into the other, it would appear that there is some factor in these molecules, assooiated with the presence of the hydroxyl group at C_6, which prevents enolisation toward C_1. It is of interest to recall that dihydro-anhydroisophotosantonic lactone (49) is similarly stable



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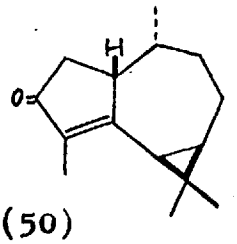
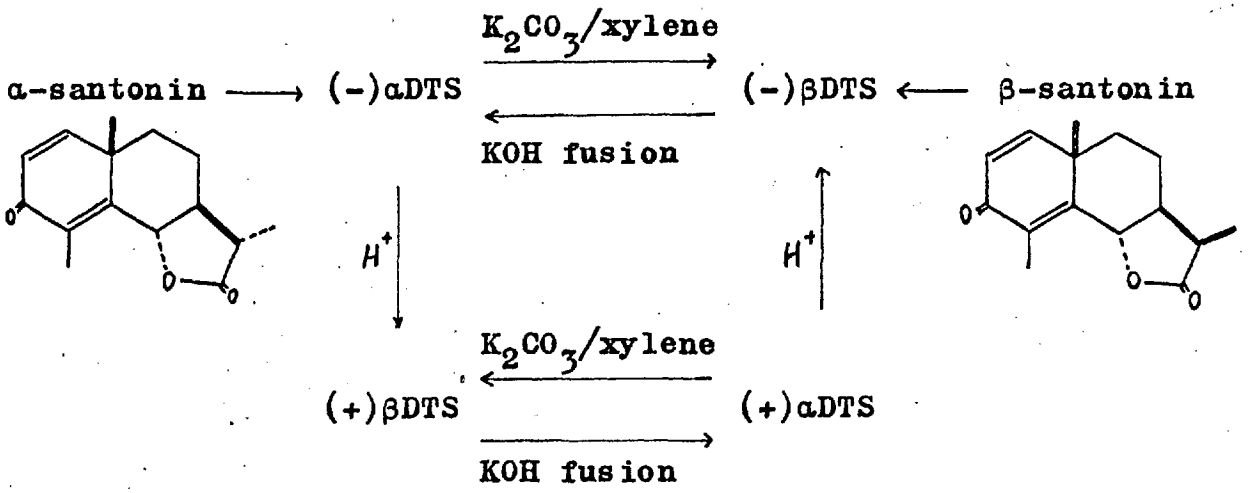


(50)

to both acid and base (see page 49), and to observe that cyclocolorenone (50) is epimerised at C_1 by methoxide ion[66]. No explanation can be offered for this behaviour.

The establishment of the configuration of α-santonin at C_{11} not only necessitates the re-examination of compounds which have been assigned stereochemistry either on the basis of direct correlations with santonin or on the basis of empirical rules which rested heavily on the wrong configuration of santonin for support: it also requires that some further consideration be given to the arguments on which the wrong stereochemistry was assigned to α-santonin, in particular to the chemistry of the desmotropo-santonins. The transformations of these compounds have been set out in Chapter 2, and may here be represented simply as follows:

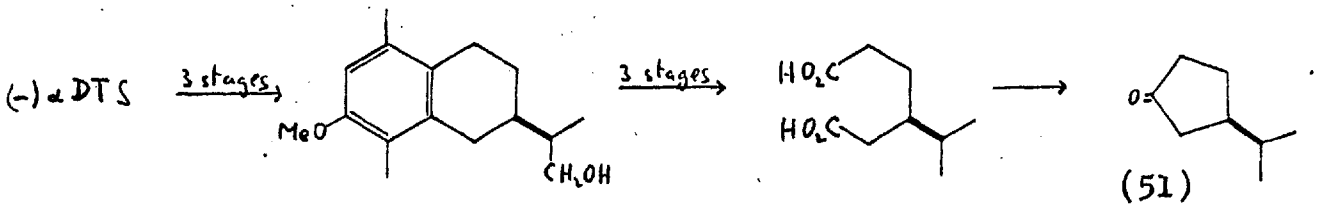


'DTS' = 'desmotroposantonin'

All four of these compounds are cis-lactones, and it was argued[44] that the base-induced changes affect C_{11} and the acid-induced changes affect C_6 and C_7. Of epimeric pairs at C_{11}, the compound stable to potassium carbonate in xylene - conditions which should not open the lactone ring - was assumed to be the compound with the most stable configuration at C_{11}, i.e. (-)β DTS must have the most stable configuration at C_{11} on the basis of the above diagram. Examination of molecular models clearly suggests that with a β-orientated cis-lactone the stable configuration would be that with the α methyl group at C_{11}. Accordingly β-santonin was assigned the C_{11}-α-methyl configuration, and α-santonin the opposite.

The first stage in the re-examination of the evidence was the confirmation[69] of the accepted view of the configuration

at C_7, by degradation of (-)αDTS to 3-isopropyl cyclopentenone (51), by the route shown below. (+)βDTS was similarly degraded to the enantiomer of (51). More recently, however, there has appeared[70] a report that



repetition of the potassium carbonate-xylene reactions reveals that the preponderating product is insoluble in the reaction mixture; it is stated that the use of potassium t-butoxide in t-butanol produces an equilibrium favouring the other product. This would harmonise the interpretation of the desmotroposantonins with the known configuration of the santonins. The author suggests that in the case of the acid epimerisations, too, the products obtained were not the more stable but the less soluble. This suggestion is necessary in order to avoid a thermodynamically impossible cycle of transformations. If this latest evidence can be confirmed, especially by a repetition of the acid inversions under satisfactory conditions, the problem would be satisfactorily resolved, but it is possible that these transformations may yet prove more complex than hitherto suspected

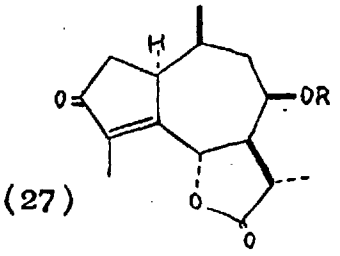
CHAPTER 6

THE SYNTHESIS OF GEIGERIN

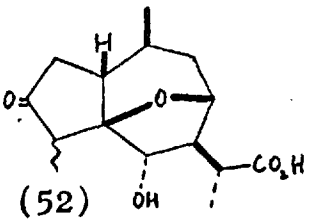
The first attempt at the synthesis of geigerin, mentioned in Chapter 3, led only to dihydro-anhydro-8-epiartemisic lactone (27; R=H), originally thought to be epimeric with geigerin only at C_1 since it was assumed at that stage that geigerin and artemisin had similar configurations at C_{11}. When 1-epigeigerin was subsequently prepared, however, and found to be different from the synthetic compound, it became clear that at least one other centre was involved.

At that stage it seemed not unreasonable to hope that, as the syntheses of both anhydrogeigerin and deoxygeigerin had had as their final stage a base-induced epimerisation, treatment of dihydroanhydro-8-epiisophotoartemisic lactone under similar conditions might transform it into the required epimer, geigerin.

Since geigerin exists in alkaline solution largely as allogeigeric acid (52)[17], and in geigerin chemistry was the only compound known to behave in this way, the alkaline treatment of the synthetic compound (27; R=H) was followed



(27)

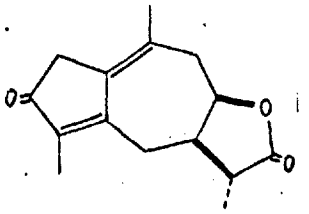


(52)

in the ultraviolet; if geigerin was produced it would immediately be transformed into allogeigeric acid, and a decrease in absorption at 240 mμ, it was expected, would indicate the formation of geigerin. Encouragingly, the absorption at 240 mμ due to the cyclopentenone system fell to about 10% of its initial value. Only unchanged starting material, however, was recovered from the reaction. It is noteworthy that this compound, too, apparently exists in alkaline solution in an allogeigeric acid - like form, as evidenced by the ultraviolet absorption of the alkaline solution and the very slow reversion to the neutral lactone form on re-acidification. (Although this lactone does not engage the hydroxyl which participates in the ether bridge formation it is impossible for a <u>trans</u> lactone to close towards C_6 while the ether bridge exists[17]). Alkaline treatment of l-epigeigerin, originally done in an attempt to convert l-epigeigerin to geigerin, showed, on similar evidence, that it behaves similarly. These are the only compounds known to behave in this way; neither

6-epigeigerin nor deoxygeigerin forms a compound of this type[17], and the requirements would seem to be a 6α- and an 8β-hydroxyl group. It is remarkable that this unusual reaction appears to be unaffected by the configuration at C_{11} or even at the bridge-head, C_1.

Anhydrogeigerin (22) and deoxygeigerin (24) had both



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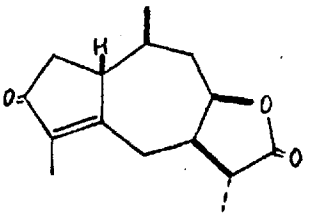
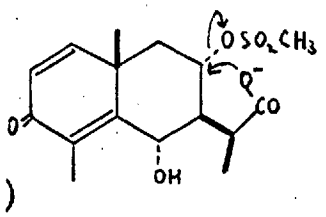


(24)

been synthesized by final inversion of a synthetic epimer; dihydroanhydro-8-epiisophotoartemisic lactone (~~26~~[27]; R=H) had failed to undergo a similar inversion. Two structural features are common to the two former compounds and differentiate them from the hypothetical geigerin precursor: the first is the absence of a C_6 oxygen function; the seoond is the direction of closure of the lactone ring. It was reasoned that irrespective of which centre was involved in the final epimerisation - and at that stage this was unknown - one or both of these factors must be responsible for the difference in behaviour between the anhydrogeigerin and deoxygeigerin epimers on the one hand and dihydroanhydro-8-epiisophotoartemisic lactone on the

other. If the reason lay in the presence or absence of the C_6 oxygen function this could be overcome only by removing it, synthesizing deoxygeigerin and re-oxidising to geigerin, an approach which did not appeal. It was hoped, therefore, that the explanation lay in the direction of closure of the lactone ring, and that this obstacle might be overcome as follows: In the preparation of 8-epiartemisin, artemisin methanesulphonate is dissolved slowly in decinormal aqueous alkali, and inversion is effected by intramolecular displacement of the methanesulphonate by carboxylate anion (53). This implies that



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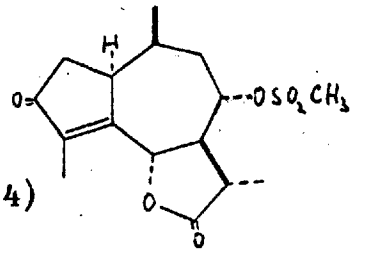
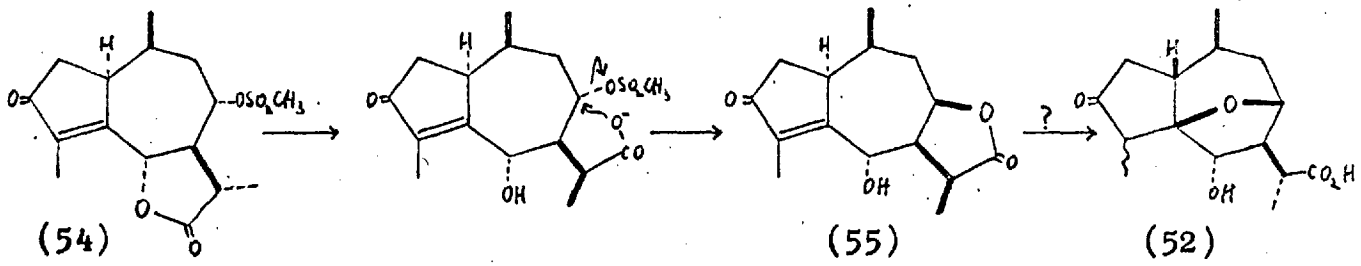
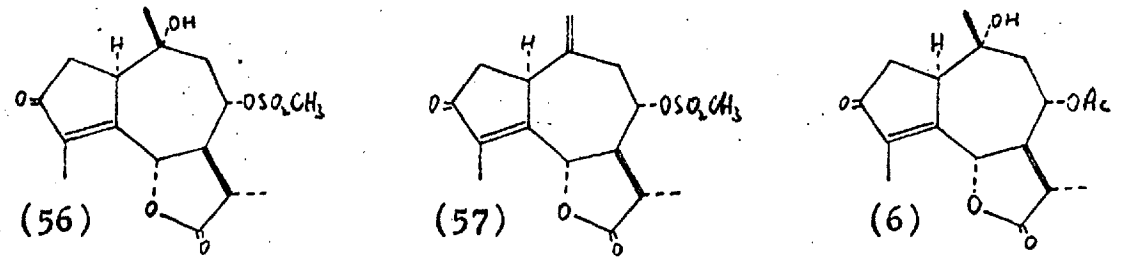


(54)

at least momentarily there exists an intermediate with the lactone closed towards C_8. If the epimerisation at C_8 could be delayed to the final stage of the synthetic series, i.e. if the compound (54) could be obtained, treatment with alkali, proceeding via the intermediate (55), might be hoped to afford at least some geigerin, by epimerisation of the intermediate before its lactone re-opens in the alkaline solution.



To this end, artemisin methanesulphonate was irradiated in refluxing aqueous acetic acid, and a normal isophoto compound (56) was obtained. Dehydration with thionyl



chloride and pyridine proceeded smoothly, the anhydro compound (57) being obtainedin over 60% yield. Hydrogenation of this compound, however, although proceeding with absorption of the calculated volume of hydrogen, afforded a colourless gum having the expected spectral properties, which could not be induced to crystallise. The product is probably a mixture of C_{10} epimers, the bulky 8α substituent preventing hydrogenation taking place exclusively from the α face as in the case of the 8β-acetate. Similarly, isophotoartemisic lactone acetate (6) was dehydrated in the usual manner to furnish a crystalline anhydro-compound

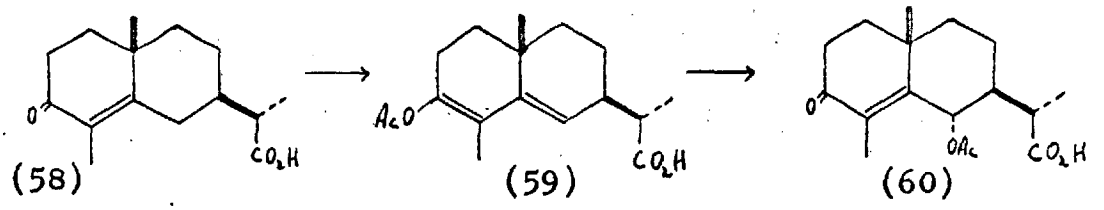
which, on hydrogenation, afforded a colourless non-crystalline material; thus the 8α acetoxyl group, too, appears to hinder to some extent hydrogenation from the α face of the molecule.

The noncrystalline dihydroanhydroisophotoartemisic lactone methanesulphonate mixture was then treated with cold decinormal aqueous alkali. Both acid and neutral fractions of the product were intractable gums, but the acidic fraction, on prolonged treatment with cold dilute mineral acid, afforded a small amount of dihydroanhydro-8-epiisophotoartemisic lactone (27; R=H).

This attempt had failed. Later evidence - the evidence presented in Chapter 5 - showed that two inversions were involved in the synthesis of deoxygeigerin. In the light of this the above approach could never have succeeded. It showed, however, that the crucial structural factor enabling 11-epideoxygeigerin to be transformed into deoxygeigerin under basic conditions was probably not the direction of the lactone ring but the absence of the C_6 oxygen function. The way to geigerin without removal of this function appeared closed. The only route open was the re-oxidation of deoxygeigerin.

The first approach attempted was the method originally used by the Japanese workers[34] in the synthesis of santonin:

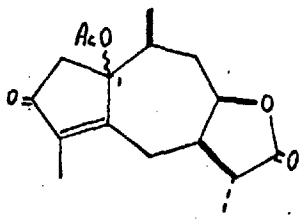
the enone acid (58) had been converted into its enol acetate (59) and this on oxidation with peracetic acid had furnished the acetate (60). This approach was attempted by Dr. T. Miki,



(58) (59) (60)

one of the Japanese team responsible for the santonin synthesis, during a period spent at Imperial College. However, several attempts at preparing the enol acetate of deoxygeigerin met with no success, and this approach was abandoned.

Deoxygeigerin was now found to be oxidised by lead tetra-acetate in glacial acetic acid solution at room temperature, in the presence of boron trifluoride[71]. The product was a highly crystalline compound, isolatable in good yield, which was neither geigerin acetate nor 6-epigeigerin acetate, although it analysed for a monoacetoxydeoxygeigerin. It was presumably 1- or 2-acetoxydeoxygeigerin (61 or 62). The presence in the



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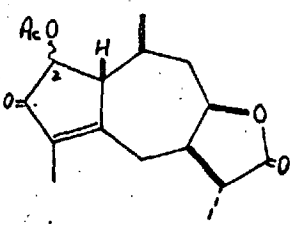

(62)

nuclear magnetic resonance spectrum of a doublet (τ, 4.34, 4.45) attributable to the proton at C_2 in (62) (coupling with the proton at C_1) indicated that the compound was 2-acetoxydeoxygeigerin (62). It is smoothly reduced to deoxygeigerin by chromous chloride, in contrast to geigerin acetate and 1-epigeigerin acetate, both of which resist attack by this reagent..

2-Acetoxydeoxygeigerin was obtained in such high yield and in such a state of purity in this reaction that there appeared little hope that an isolatable quantity of geigerin acetate might occur as a minor product. It was hoped, however, that the small amount of geigerin acetate that it was expected would be formed might be detected by radio-isotope dilution techniques. In a repetition of the acetoxylation experiment, therefore, sodium [1-^{14}C]-acetate was added to the solution of lead tetra-acetate in glacial acetic acid several hours before addition of deoxygeigerin and boron trifluoride. That adequate exchange of [1-^{14}C]-acetate had occurred was shown by the high activity of the 2-acetoxydeoxygeigerin isolated. The mother liquor from crystallisation of the major product was diluted with pure inactive geigerin acetate. The mixture was filtered through alumina and recrystallised to constant activity. Too little material remained, after

two constant values had been obtained, to recrystallise once more for a third constant value, as is desirable. The combined mother liquors were treated with 2,4-dinitrophenylhydrazine, and the derivative in turn was recrystallised to constant activity, three successive constant values being obtained, the activity corresponding to the final value obtained in the parent ketone.

The experiment was then repeated on a larger scale. On this occasion, however, after the three constant values had been obtained from recrystallisations of the geigerin acetate, only the final specimen was converted to the 2,4-dinitrophenylhydrazone. This was chromatographed and recrystallised and the activity measured. The activity corresponded to that of the parent ketone. The indicated yields were very low, being about 0.3% in the first experiment, and about 0.1% in the second, in which a shorter reaction time was used.

As the deoxygeigerin used in these experiments was derived from geigerin (by chromous chloride reduction of geigerin methanesulphonate) it was necessary to demonstrate that the activity retained after dilution was not in fact derived from natural geigerin persisting in the deoxygeigerin and being acetylated under the reaction conditions. A control experiment indicated the absence of any detectable

quantity of geigerin in the deoxygeigerin.

This is satisfactory evidence that geigerin acetate has indeed been formed, and this constitutes the first synthesis, although not a preparative one, of a naturally occurring guaianolide. This does not constitute a total synthesis, however, as artemisin, the starting material used here, has not yet been synthesized from α-santonin.

And so the final object of the work was achieved. In this final result, and in all the results arising from the study of the synthesis of deoxygeigerin, the value of the isophotosantonic and isophotoartemisic lactones in the study of the sesquiterpenoids is amply demonstrated.

EXPERIMENTAL

AND

REFERENCES

EXPERIMENTAL

Ultraviolet spectra were taken in ethanol, and rotations and infrared spectra in chloroform except where otherwise indicated. Irradiations were carried out with a bare 125 watt mercury arc lamp, using pyrex apparatus. 'Work-up' denotes extraction with the solvent indicated, the extracts being washed successively with 6N sulphuric acid (when pyridine was used), saturated aqueous sodium bicarbonate solution, and distilled water, and dried over sodium sulphate. 'Light petroleum' refers to the fraction, b.p. 60°-80°, unless otherwise indicated. Radio-activity measurements were done in a methane-flow proportional counter, measuring 'infinitely thin' films. The elemental analyses were by Miss J. Cuckney and staff (Imperial College).

Compounds first prepared by Dr. J. T. Pinhey and included here for the sake of completeness are indicated (J.T.P.).

Conjugated Anhydroisophoto-α-santonic lactone (3)[55]: Isophoto-α-santonic lactone (2 g.) was heated with 1:9 perchloric acid-acetic acid at 70°C, with control of the developing maximum at 305 mμ. When the optical density was almost constant (after four hours) the solution was worked up with methylene chloride. The neutral fraction was filtered in benzene through alumina (acid; grade III; 20 g.), affording on evaporation a light brown gum (820 mg.) which was hydrogenated directly without further purification.

Dihydroanhydroisophoto-α-santonic lactone (17)(J.T.P.): The gum (820 mg.) obtained from dehydration of isophoto-α-santonic lactone was hydrogenated in ethanol (50 ml.) over 5% palladium-charcoal (100 mg.) until one mole-equivalent of hydrogen had been absorbed. The filtrate and washings were evaporated, and worked up with methylene chloride. The product on recrystallisation from ethyl acetate-light petroleum, afforded dihydroanhydroisophoto-α-santonic lactone (170 mg.): m.p. 152-154°, $[\alpha]_D$, -104°; λ_{max}, 240 mμ (ε, 16,000); ν_{max}, 1783, 1706, 1653 cm^{-1}. ($CHCl_3$). (Found: C, 72.55; H, 8.2. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1%)

Attempted Epimerisation of Dihydroanhydroisophoto-α-santonic lactone: The compound was recovered unchanged from treatment with potassium t-butoxide at room temperature, and from treatment with 1:9 perchloric acid-acetic acid on the steam bath.

Hydrogenation of Dihydroanhydroisophoto-α-santonic lactone: The dihydro compound (50 mg.) in ethanol (5 ml.) was hydrogenated over 5% palladium-charcoal (25 mg.). (Hydrogen uptake, 1 mole-equivalent). The filtrate and washings were evaporated, and separated into neutral and acidic fractions by means of bicarbonate. The acidic fraction was negligible. The neutral fraction (47 mg.) could not be induced to crystallise.

Hydrogenation of Isophotoartemisic Lactone Acetate[5]: Isophotoartemisic lactone acetate (444 mg.) in ethanol (20 ml.) was hydrogenated over 10% palladium-charcoal until ca. 1.1 mole had been absorbed. Work-up in the usual way afforded a dihydroisophotoartemisin acetate (7) (285 mg.): m.p. 175-185°; $[\alpha]_D$, -18°. (Barton, Levisalles and Pinhey[50]: $[\alpha]_D$, -7°). This product (50 mg.) on treatment at room temperature with chloroform (10 ml.) containing 1.4% hydrogen chloride, afforded a new

dihydroisophotoartemisic lactone acetate (8; R=Ac), $[\alpha]_D$, $+10^\circ$.

Subsequent hydrogenations, using approximately equal amounts of catalyst and compound in order to get as rapid hydrogenation as possible, afforded products with $[\alpha]_D$, -20° (c, 1.08) and $[\alpha]_D$, -26° (c, 0.95).

Hydrolysis of Dihydroisophotoartemisic Lactone Acetate: The acetate (100 mg.) and sodium bicarbonate (100 mg.) in 50% ethanol (12 ml.) were heated on the steam bath for nine hours. Work-up in the usual way afforded a crystalline product (33 mg.), not properly characterised, with the expected infrared maxima. M.p. 180-188°.

Artemisin carbethoxylate (11)[52]: To a solution of artemisin (2.2 g.) in dry pyridine (20 ml.) was added dropwise, with cooling, ethyl chloroformate (redistilled; 3.5 ml.). The solution was left at room temperature overnight, then poured into water. The product crystallised on scratching , was filtered off, and recrystallised twice from aqueous ethanol: 2.2 g., m.p. 120-122°. $[\alpha]_D$, -31° (ethanol); -49° (chloroform); λ_{max}, 238 mμ (ε, 14,000); ν_{max}, 1782, 1740, 1668, 1640, 1620, 1275 cm^{-1}. (Sumi: m.p. 118-122°; $[\alpha]_D$, -30° (ethanol)).

Irradiation of Artemisin Carbethoxylate: The compound (2 g.) was irradiated in 45% aqueous acetic acid (200 ml.) at reflux temperature under nitrogen. In order to follow the reaction, 1 ml. aliquots were withdrawn, evaporated, worked up with methylene chloride, evaporated, the residue dissolved in chloroform (1 ml.), and the infrared absorption measured between 1650 and 1800 cm^{-1}. Irradiation was continued until the 1660-1680 cm^{-1}. doublet due to the cross-conjugated cyclohexadienone had virtually disappeared, and the developing band at 1710 cm^{-1}. was nearly as strong as the lactone band. The solution was then evaporated under reduced pressure, and worked up with methylene chloride. The product, after three recrystallisations from ethyl acetate - light petroleum, afforded pure isophotoartemisic lactone carbethoxylate (9) (170 mg.): m.p. 213-221°. Chromatography of the mother liquors over alumina (acid; grade III) afforded a further 50 mg.
$[\alpha]_D$, +111° (c, 1.04); λ_{max}, 238 mμ (ε, 14,500); ν_{max}, 3650, 1784, 1740, 1705, 1640 cm^{-1}. (Found: C, 61.06; H, 6.97. $C_{18}H_{24}O_7$ requires C, 61.35; H, 6.86%).

Dihydroisophotoartemisic Lactone Carbethoxylate (8; R=CO_2Et): Isophotoartemisic lactone carbethoxylate (103 mg.) was

hydrogenated in ethanol (8 ml.) over 10% palladium-charcoal (77 mg.). The reaction was stopped when 1.1 mole of hydrogen had been absorbed, and the filtrate and washings evaporated and worked up with methylene chloride. The product could not be induced to crystallise, but after chromatography in benzene on alumina (acid; grade III) the dihydroisophotoartemisic lactone carbethoxylate crystallised from ethyl acetate - light petroleum: 65 mg., m.p. 159-160°; $[\alpha]_D$, -5° (c, 0.71); γ_{max}, 3650, 1773, 1738, 1276 cm^{-1}. (Found: C, 60.98; H, 7.50. $C_{18}H_{26}O_7$ requires C, 61.00; H, 7.40%).

Both isophotoartemisic lactone cathylate and the dihydro derivative were unaffected by treatment with pyridine at room temperature, and attempts at cyclisation by pyrolysis were likewise unsuccessful, the only characterisable product in each casing being unchanged starting material. Treatment of isophotoartemisic lactone cathylate with sodium hydride in dry benzene was also without any effect.

Bromodihydroisophoto-α-santonic lactone acetate (12; R=Br): Dihydroisophoto-α-santonic lactone acetate[50] (200 mg.) in acetic acid (2 ml.) was treated with bromine (120 mg.) in acetic acid (0.85 ml.) with addition of hydrobromic acid - acetic acid (50%; 1 drop). After 3 minutes at room

temperature the solution had become colourless, and was diluted with water and worked up with methylene chloride in the usual way, special care being taken to evaporate the solvent at room temperature or below. Immediate recrystallisation was necessary to obtain a stable product. The 2-bromodihydroisophoto-α-santonic lactone acetate (70 mg.) was recrystallised from methylene chloride - light petroleum: m.p. 117-118° (decomp.); $[\alpha]_D$, -33° (c, 1.00); ν_{max}, 1776, 1745, 1735 (shoulder) cm^{-1}. (Found: C, 52.5; H, 6.4. $C_{17}H_{23}O_5Br$ requires C, 52.7; H, 6.0%)

Dihydroisophoto-β-santonic lactone (14; R=H)[50]: Isophoto-β-santonic lactone (13) (350 mg.) in ethanol (25 ml.) was hydrogenated over 10% palladium-charcoal (250 mg.). The product, crystallised from ethanol-ether, had $[\alpha]_D$, +43°. (Reported value: $[\alpha]_D$, +109°).

The compound ($[\alpha]_D$, +43°) (300 mg.) on treatment with ethanolic potassium hydroxide (12 ml.) at room temperature for two hours was converted into the stable epimer, m.p.223-225°; $[\alpha]_D$, +123° (c, 1.00).

Dihydroisophoto-β-santonic lactone acetate (14; R=Ac): Dihydroisophoto-β-santonic lactone (150 mg.) was refluxed in acetic anhydride (4 ml.) with anhydrous sodium acetate

(37 mg.) for three hours. Dilution and work-up with methylene chloride afforded, on recrystallisation from ethyl acetate - light petroleum, dihydroisophoto-β-santonic lactone acetate: m.p. 181-191°C; $[\alpha]_D$, +42° (c, 0.97); ν_{max}, 1765, 1737 (shoulder) 1730 cm^{-1}. (Nujol). (Found: C, 66.19; H, 7.83. $C_{17}H_{24}O_5$ requires C, 66.21; H, 7.85%).

Chromous Chloride Reduction of Bromodihydroisophoto-α-santonic lactone acetate: Bromodihydroisophoto-α-santonic lactone acetate (12; R=Br) (40 mg.) in acetone (2 ml.) was treated under nitrogen with chromous chloride solution (M/1 in N hydrochloric acid; 3 ml.) and the mixture left at room temperature overnight. Dilution with water and work-up with methylene chloride afforded dihydroisophoto-α-santonic lactone acetate (12; R=H), identified by m.p., mixed m.p. and rotation.

Acid-catalysed Dehydration of 6-Deoxyisophotoartemisic Acid Acetate (J.T.P.): The acid acetate (200 mg.), prepared[50] by chromous chloride reduction of isophotoartemisic lactone acetate, was heated in 1:9 perchloric acid - acetic acid (20 ml.) at 70° with control of the developing maximum at 300 mμ. Work-up with chloroform followed by filtration of the neutral product in benzene through alumina

(acid; grade III) afforded epianhydrogeigerin: m.p. 107-108°; $[\alpha]_D$, +18° (c, 0.99); λ_{max}, 299 mμ (ε, 15,500); ν_{max}, 1770, 1690, 1600 cm^{-1}. (Found: C, 73.05; H, 7.7. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.4%).

Dihydroanhydrogeigerin (43): Anhydrogeigerin (22) (100 mg.) in ethanol (5 ml.) was hydrogenated over 5% palladium-charcoal (50 mg.) (One mole-equivalent absorbed). The product crystallised from ether-light petroleum. Dihydroanhydrogeigerin: m.p. 139-141°; $[\alpha]_D$, +22° (c, 0.80); λ_{max}, 238 mμ (ε, 16,500); ν_{max}, 1760, 1694, 1645 cm^{-1}. (Found: C, 72.45; H, 8.4. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.15%).

8-Epiisophotoartemisic Lactone Acetate (25)[50]: Preparation of this compound by irradiation of 8-epiartemisin acetate afforded in many cases the compound reported. On one occasion, however, there was obtained a new crystalline form, m.p. 196-200°, whose infrared spectrum in Nujol varied from that of the older form; $[\alpha]_D$ and the infrared spectrum in chloroform were identical. In every subsequent preparation only this form was obtained.

Non-conjugated Anhydro-8-epiisophotoartemisic lactone acetate (26) (J.T.P.): 8-Epiisophotoartemisic lactone acetate (500 mg.) was dissolved in dry dioxan (1.5 ml.) and the solution cooled to -5°C. Thionyl chloride (2.5 ml.) was added to a mixture of dry pyridine (2.5 ml.) and dry dioxan (1 ml.) cooled in solid CO_2 and acetone. This mixture was warmed to -5°C, and added to the solution of the isophoto compound. The solution was warmed carefully (to ca. 10°C) to allow the dioxan to melt, then kept at -5°C for ten minutes, added cautiously to ice/water, and worked up with methylene chloride. The non-conjugated anhydro-8-epiisophotoartemisic lactone acetate was recrystallised from ethyl acetate - light petroleum: 360 mg., (76%): m.p. 131-132° (after 2-3 recrystallisations); $[\alpha]_D$, +192° (c, 1.09); λ_{max}, 236 mμ (ε, 13,200); ν_{max}, 1785, 1742, 1705, 1647 cm^{-1}. (Found: C, 66.9; H, 6.7. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%).

Dihydroanhydro-8-epiisophotoartemisic lactone acetate (27) (J.T.P.): The anhydro compound (650 mg.) in ethanol (100 ml.) was hydrogenated over 10% palladium on strontium carbonate (1.5 g.). The reaction was interrupted after 1.1 to 1.15 mole of hydrogen had been absorbed, and the product was recrystallised from ethyl acetate - light petroleum to afford dihydroanhydro-8-epiisophotoartemisic

lactone acetate: m.p. 161-164°; $[\alpha]_D$, +150° (c, 1.18); λ_{max}, 236 mμ (ε, 15,600); ν_{max}, 1785, 1742, 1703, 1645 cm^{-1}. (Found: C, 66.45; H, 7.2. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.25%).

Chromous Chloride Reduction of Dihydroanhydro-8-epiisophotoartemisic lactone acetate: To a solution of dihydroanhydro-8-epiartemisic lactone acetate (500 mg.) in acetone (30 ml.) was added chromous chloride solution (M/1 in N hydrochloric acid; 30 ml.) under nitrogen, and the mixture left tightly stoppered at room temperature for three days. The solution was diluted with water and extracted with chloroform. The acidic product was then extracted into sodium bicarbonate solution, and the bicarbonate solution was acidified, saturated with salt, and extracted with chloroform. The product (28), which failed to crystallise, was a colourless gum with the expected spectral properties.

Acid Hydrolysis of the Non-crystalline Acid Acetate: The compound (450 mg.) was heated with 5% sulphuric acid (48 ml.) on the steam bath for six hours. Work-up with methylene chloride gave a pale yellow gum which slowly crystallised. Purification by filtration in 2:1 benzene -

light petroleum through a short column of alumina (acid; grade III) and recrystallisation from ethyl acetate - light petroleum afforded 11-epideoxygeigerin (32): m.p. 127-128°; $[\alpha]_D$, -59° (c, 1.03); λ_{max}, 237 mμ (ε, 17,000); ν_{max}, 1770, 1696, 1643 cm^{-1}. (Found: C, 72.75; H, 8.35. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1%).

Conversion of 11-Epideoxygeigerin into Deoxygeigerin: 11-Epideoxygeigerin (20 mg.) dissolved in ethanol (0.5 ml.) was treated with 4% aqueous potassium hydroxide solution (0.5 ml.) at room temperature for two hours. The solution was then acidified and left for one hour. Work-up with methylene chloride gave, on recrystallisation from ethyl acetate - petroleum ether, deoxygeigerin (24), identical with authentic material derived from geigerin (m.p., mixed m.p., $[\alpha]_D$. The infrared spectra in Nujol were identical).

Hydrolysis of Dihydroanhydro-8-epiisophotoartemisic Lactone Acetate (J.T.P.): The acetate (660 mg.), water (40 ml.) and saturated sodium bicarbonate solution (20 ml.) were heated on the steam bath for 24 hours. The solution was acidified, left at room temperature overnight, saturated with salt and worked up with chloroform.

Recrystallisation from ethyl acetate - light petroleum afforded dihydroanhydro-8-epiisophotoartemisic lactone (27; R=H): m.p. 212-215°; $[\alpha]_D$, +184° (c, 0.86); λ_{max}, 238 mμ (ε, 14,000); ν_{max}, 3,400, 1777, 1700, 1645 cm^{-1}. (Found: C, 68.05; H, 7.6. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%).

The alcohol, on acetylation at room temperature overnight with acetic anhydride and pyridine, afforded its precursor (m.p. and mixed m.p.).

Treatment of Dihydroanhydro-8-epiisophotoartemisic Lactone with Base: The compound (3.7 mg.) was treated with 2% ethanolic potassium hydroxide solution (1 ml.) at room temperature for one hour (ε at 244 mμ had dropped to 1,400). The solution was acidified, left for several hours, and worked up with chloroform. The product was recrystallised to afford unchanged dihydroanhydro-8-epiisophotoartemisic lactone (m.p. and mixed m.p.).

Isophotoartemisic Lactone Methanesulphonate (56): Artemisin methanesulphonate (2 g.) in 45% aqueous acetic acid (200 ml.) was irradiated at reflux under nitrogen until the infrared absorption bands at 1660-1680 cm^{-1} had almost disappeared (see procedure for isophotoartemisic lactone

carbethoxylate). Removal of solvent and work-up with methylene chloride afforded a residue which crystallised readily. In order to free completely from starting material this material was chromatographed on ten times its own weight of alumina (acid; grade III), starting material being eluted with 20:1 benzene-acetone, and isophotoartemisic lactone methanesulphonate with 1:1 benzene-acetone, or with methylene chloride. Recrystallised from ethyl acetate: 140 mg.; m.p. 164-166° (decomp.); $[\alpha]_D$, +113° (c, 0.93; Acetone); λ_{max}, 238 mμ (ε, 15,200); ν_{max}, 3600, 1783, 1710, 1645, 1350, 1180 cm^{-1}. (Found: C, 53.84; H, 6.26; S, 9.10. $C_{16}H_{22}O_7S$ requires C, 53.65; H, 6.18; S, 8.95%).

Anhydroisophotoartemisic Lactone Methanesulphonate (57): Thionyl chloride (1 ml.) and dry pyridine (1 ml.), mixed at -60° and warmed to -5°, were added to a solution of isophotoartemisic lactone methanesulphonate (130 mg.) in dry pyridine (0.5 ml.) at -60°, and the mixture kept at -5° for ten minutes. The solution was then poured cautiously into ice/water, worked up with methylene chloride, and the product recrystallised from methylene chloride - ether to give non-conjugated anhydroisophotoartemisic lactone methanesulphonate (80 mg.; 64%): m.p. 130-131°; $[\alpha]_D$,

$+215^{o}$ (c, 0.61); λ_{max}, 234 mμ (ε, 12,000); ν_{max}, 1784, 1708, 1652 cm^{-1}.

Hydrogenation of Anhydroisophotoartemisic Lactone Methanesulphonate: The anhydro compound (20 mg.) in ethyl acetate (10 ml.) was hydrogenated over 10% palladium-calcium carbonate (100 mg.). (One mole-equivalent consumed). The product was a colourless gum with the expected spectral properties, but it could not be induced to crystallise.

Dehydration of Isophotoartemisic Lactone Acetate: On dehydration of isophotoartemisic lactone acetate (6) with thionyl chloride and pyridine under the conditions used in the preparation of anhydroisophotoartemisic lactone methanesulphonate a nicely crystalline anhydro compound was obtained, having the expected spectral properties.

Hydrogenation of this compound in ethanol over palladium - strontium carbonate proceeded smoothly, with the uptake of one mole-equivalent of hydrogen, but no crystalline product could be obtained.

Treatment of the Noncrystalline Dihydroanhydroisophotoartemisic Lactone Methanesulphonate with Base: The noncrystalline hydrogenation product (100 mg.) was dissolved with shaking in sodium hydroxide solution (0.1 N; 10 ml.)

and left at room temperature for 24 hours (ε at 234 mμ had dropped from 12,000 to 3,000). The solution was acidified, left for 1½ hours, extracted with chloroform and separated into neutral and acidic fractions by means of bicarbonate. The neutral fraction (19 mg.) failed to crystallise. The acid fraction (43 mg.) also failed to crystallise, but after treatment with 6N sulphuric acid (1 ml.) and 50% aqueous ethanol (10 ml.) for 3½ days at room temperature followed by work-up with chloroform it afforded a small amount of neutral material which crystallised from ethyl acetate - light petroleum to give dihydroanhydro-8-epiisophotoartemisic lactone (27; R=H) (9 mg.), identified by m.p., mixed m.p., and specific rotation.

1-Epigeigerin Acetate (30; R=Ac)(J.T.P.): Bromogeigerin acetate[50] (160 mg.) in ethyl acetate (8 ml.) was hydrogenated over 5% palladium-calcium carbonate (370 mg.) until hydrogen uptake had ceased (apparent uptake varied; usually 0.5-0.8 mole-equivalent). The product was filtered in methylene chloride through a short column of alumina (acid; grade III), to afford, on recrystallisation from ethyl acetate, 1-epigeigerin acetate (80 mg.): m.p. 166-168°; $[\alpha]_D$, +127° (c, 0.90); λ_{max}, 234 mμ (ε, 14,300); ν_{max}, 1778, 1747, 1707, 1646 cm^{-1}. (Found: C, 66.4; H, 7.3. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.25%).

1-Epigeigerin (30; R=H): (a) By bicarbonate hydrolysis (J.T.P.): 1-Epigeigerin acetate (crude; 230 mg.), distilled water (9 ml.) and saturated sodium bicarbonate solution (7 ml.) were heated on the steam bath for 20 hours. The solution was acidified, left at room temperature for 24 hours, and worked up with chloroform. Recrystallisation of the product from ethyl acetate - light petroleum afforded 1-epigeigerin (55 mg.): m.p. 203-204°; $[\alpha]_D$, +143° (c, 0.90); λ_{max}, 238 mμ (ε, 13,500); ν_{max}, 3350, 1770, 1702, 1640 cm^{-1}. (Found: C, 68.3; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%).

(b) By acid hydrolysis: 1-Epigeigerin acetate (160 mg.) was heated with 5% sulphuric acid (16 ml.) on the steam bath for six hours. Work-up with chloroform afforded 1-epigeigerin (82 mg.).

On treatment with acetic anhydride and pyridine at room temperature overnight 1-epigeigerin afforded 1-epigeigerin acetate (m.p. and mixed m.p.).

Treatment of 1-Epigeigerin with Base: 1-Epigeigerin (16 mg.) in ethanol (2.5 ml.) was treated with 2% aqueous potassium hydroxide solution (2.5 ml.) at room temperature. After 24 hours the extinction coefficient at 238 mμ had dropped to 1,500. After a further 2 days the solutionwas acidified

and extracted with chloroform, and the product divided into acid and neutral fractions by means of bicarbonate. The neutral fraction (3.3 mg.) crystallised to afford unchanged starting material. The acidic fraction was treated with dilute sulphuric acid at room temperature for 3 days. Work-up gave a neutral product, recrystallised to give unchanged l-epigeigerin (2 mg.).

Treatment of Geigerin with Sulphuric Acid: Geigerin was recovered unchanged after treatment with 5% sulphuric acid on the steam bath for 3 hours.

1-Epi-11-epideoxygeigerin (31): To a solution of dihydro-anhydro-8-epiisophotoartemisic lactone (112 mg.) in acetone (5 ml.) was added, under nitrogen, chromous chloride solution (M/1 in N hydrochloric acid; 5 ml.), and the mixture kept tightly stoppered at room temperature for 3 days. Dilution with water and work-up with methylene chloride afforded 1-epi-11-epideoxygeigerin (90 mg.), recrystallised from ethyl acetate - light petroleum: m.p. 127-128°; $[\alpha]_D$, +190° (c, 1.01); λ_{max}, 239 mμ (ε, 16,700); ν_{max}, 1770, 1695, 1642 cm^{-1}. (Found: C, 72.44; H, 8.15. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

Acid Treatment of 1-Epi-11-epideoxygeigerin: 1-Epi-11-epideoxygeigerin (30 mg.) and 5% sulphuric acid (3 ml.) were heated on the steam bath for four hours. Work-up with chloroform gave, on recrystallisation of the product from ethyl acetate - light petroleum, 11-epideoxygeigerin (32) (identified by m.p., mixed m.p. and rotation).

Dihydroisophoto-α-santonic Lactone Oxime (36): Dihydroisophoto-α-santonic lactone[50] (unstable epimer; $[\alpha]_D$, $=46^\circ$; 50 mg.) and hydroxylamine hydrochloride (50 mg.) in ethanol (0.5 ml.) and pyridine (3 drops) were left at room temperature overnight. Removal of the solvent under reduced pressure and recrystallisation from methanol - water afforded the unstable epimer of dihydroisophoto-α-santonic lactone oxime (50 mg.): m.p. ca. 107-113°; $[\alpha]_D$, $+8^\circ$ (c, 1.00; ethanol); ν_{max}, 3630, 1762, 1603 cm^{-1} (chloroform); 3300-3500, 1740, 1668 cm^{-1} (Nujol). (Found: C, 60.2; H, 8.53; N, 4.83. $C_{15}H_{23}NO_4H_2O$ requires C, 60.3; H, 8.35; N, 4.68%.). The compound could not be induced to crystallise from any other solvent.

The stable dihydroisophoto-α-santonic lactone[50] ($[\alpha]_D$, $+39^\circ$), when treated under the same conditions, afforded the stable oxime, recrystallised from methanol - water: m.p. ca. 107-113°; $[\alpha]_D$, $+31^\circ$ (c, 0.90; ethanol); ν_{max},

3640, 1762, 1603 cm^{-1} (chloroform); 3300-3500, 1740, 1668 cm^{-1} (Nujol). (Found: C, 59.6; H, 8.24; N, 4.67%).

The unstable epimer of dihydroisophoto-α-santonic lactone oxime (109 mg.) in ethanol (0.4 ml.) was treated with 4% aqueous potassium hydroxide solution (4 ml.) at room temperature for 6 hours. The solution was then acidified with acetic acid, left for several hours, diluted, and worked up with chloroform. The residue, recrystallised from aqueous methanol, had $[\alpha]_D$, +8° (c, 0.77), identical with that of the starting material.

11-Epideoxygeigerin Oxime (33): 11-Epideoxygeigerin (42 mg.) and hydroxylamine hydrochloride (55 mg.) in ethanol (0.5 ml.) and pyridine (3 drops) were left at room temperature overnight. Dilution, work-up with chloroform, and recrystallisation of the product from ethyl acetate - light petroleum afforded 11-epideoxygeigerin oxime (40 mg.): m.p. 212-216°; $[\alpha]_D$, -97° (c, 0.78); λ_{max}, 241 mμ (ε, 19,000); ν_{max}, 3600, 1765, 1643 cm^{-1}. (Found: C, 68.79; H, 7.68; N, 5.43. $C_{15}H_{21}NO_3$ requires C, 68.5; H, 7.98; N, 5.32%).

Deoxygeigerin Oxime (33): Treated under the same conditions as for 11-epideoxygeigerin oxime, deoxygeigerin afforded deoxygeigerin oxime: m.p. 193-197°; $[\alpha]_D$, -45° (c, 0.68);

λ_{max}, 242 mμ (ε, 19,000); ν_{max}, 3600, 1765, 1642 cm^{-1}. (Found: C, 68.25; H, 7.72; N, 5.26%).

Treatment of 11-Epideoxygeigerin Oxime with Base: 11-Epideoxygeigerin oxime (24 mg.) in ethanol (1 ml.) was treated with 8% aqueous potassium hydroxide solution (1 ml.). The mixture was left at room temperature for four hours, then acidified with acetic acid, left for two hours, diluted and worked up with chloroform. The residue (23 mg.) on evaporation was recrystallised to give unchanged starting material (m.p., mixed m.p., and rotation).

Epianhydrogeigerin Oxime: Epianhydrogeigerin (50 mg.) and hydroxylamine hydrochloride (50 mg.) in ethanol (1 ml.) and pyridine (3 drops) were left at room temperature overnight. Evaporation of the solvent and work-up of the residue with chloroform afforded, on recrystallisation from ethylacetate, epianhydrogeigerin oxime (50 mg.): m.p. 250° (decomp.); $[\alpha]_D$, +11° (c, 0.74; AcOH); λ_{max}, 289 mμ (ε, 26,400); ν_{max}, 1752, 1642, 1600 cm^{-1} (Nujol). (Found: C, 68.96; H, 7.11; N, 5.23. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%).

Anhydrogeigerin Oxime: Anhydrogeigerin, on treatment under the same conditions as for epianhydrogeigerin oxime afforded anhydrogeigerin oxime: m.p. 191-197°; $[\alpha]_D$, -172° (c, 0.71; AcOH); λ_{max}, 288 mμ (ε, 23,000); ν_{max}, 3620, 1763; 1640, 1605 cm^{-1}. (Found: C, 69.07; H, 7.89; N, 5.10%).

Treatment of Epianhydrogeigerin Oxime with Base: Epianhydrogeigerin oxime (21 mg.) was treated with 2% ethanol potassium hydroxide (1 ml.) at room temperature for one hour. The solution was acidified with acetic acid, left for one hour, diluted and worked up with chloroform. The product (17 mg.) on recrystallisation from ethyl acetate was identified as unchanged starting material (m.p., mixed m.p., and rotation).

1-Epigeigerin Methanesulphonate (30; $R=SO_2CH_3$): 1-Epigeigerin (51 mg.) in dry pyridine (1 ml.) was cooled to 0°C, and methanesulphonyl chloride (redistilled; 1 ml.) added dropwise. The mixture was kept in the cold-room (ca. 0°C) overnight, then poured cautiously into ice/water, and worked up with chloroform. The product was filtered in methylene chloride through a short column of alumina (acid; grade III), and recrystallised from benzene - ether

to afford 1-epigeigerin methanesulphonate (35 mg.): m.p. 127-130° (decomp.); $[\alpha]_D$, +77° (c, 0.80); λ_{max}, 236 mμ (ε, 13,000); ν_{max}, 1775, 1710, 1648, 1358, 1180 cm^{-1}.

The analysis, unaffected by several recrystallisations and chromatography, shows this compound to be impure. (Found: C, 57.35; H, 6.64; S, 8.82. $C_{16}H_{22}O_6S$ requires C, 56.13; H, 6.48; S, 9.45%).

Chromous Chloride Reduction of 1-Epigeigerin Methanesulphonate: To a solution of 1-epigeigerin methanesulphonate (35 mg.) in acetone (2 ml.) and acetic acid (1 ml.) was added, under nitrogen, chromous chloride solution (M/1 in N hydrochloric acid; 3 ml.), and the mixture kept tightly stoppered at room temperature overnight. Dilution with water and work up with methylene chloride afforded, on recrystallisation from ethylacetate - light petroleum, 1-epideoxygeigerin (29)(18 mg.): m.p. 128-130°; $[\alpha]_D$, +130° (c, 0.65); λ_{max}, 238 mμ (ε, 14,000); ν_{max}, 1760, 1696, 1645 cm^{-1}. (Found: C, 72.80; H, 8.50. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

Treatment of 1-Epi-11-epideoxygeigerin with Base: To a solution of 1-epi-11-epideoxygeigerin (31) (104 mg.) in ethanol (6 ml.) was added 4% ethanolic potassium hydroxide

(6 ml.). The solution was kept at room temperature for four hours, then acidified, and left for several hours. Work-up with methylene chloride afforded a product which, after four recrystallisations from ether, afforded 1-epideoxygeigerin (29) (49 mg.), identical (m.p., mixed m.p., rotation) with the material obtained from 1-epigeigerin methanesulphonate.

Treatment of 1-Epideoxygeigerin with Acid: 1-Epideoxygeogerin (29) (25 mg.) and 5% sulphuric acid (2.5 ml.) were heated on the steam bath for twelve hours. Work-up with methylene chloride and three recrystallisations from ethyl acetate - light petroleum afforded deoxygeigerin (24) (m.p. and mixed m.p. identical).

11-Epideoxygeigerin O-Methyloxime (44): 11-Epideoxygeigerin (79 mg.) and methoxyamine hydrochloride (97 mg.) were dissolved in ethanol (1 ml.) and pyridine (7 drops) and the solution was left at room temperature for 24 hours. Dilution with water and work up with methylene chloride afforded a crystalline product (82 mg.). Recrystallisation from methylene chloride - light petroleum afforded 11-epideoxygeigerin O-methyloxime: m.p. 162-163°, $[\alpha]_D$, -87° (c, 0.90); λ_{max}, 248 mμ (ε,20,000); ν_{max}, 1765, 1625 cm^{-1}. (Found: C, 69.10; H, 8.30. $C_{16}H_{23}NO_3$

requires C, 69.28; H, 8.36%).

Deoxygeigerin O-Methyloxime (45): Deoxygeigerin, on treatment under the same conditions as for 11-epideoxygeigerin O-methyloxime afforded deoxygeigerin O-methyloxime (recrystallised from methylene chloride - light petroleum, b.p. 40°-60°): m.p. 107-109°; $[\alpha]_D$, -21° (c, 1.12); λ_{max}, 249 mμ (ε, 20,000); ν_{max}, 1762, 1622 cm^{-1}. (Found: C, 69.49; H, 8.54%).

Treatment of 11-Epideoxygeigerin O-Methyloxime (44) with Base: To a solution of 11-epideoxygeigerin O-methyloxime (20 mg.) in ethanol (1 ml.) was added 8% ethanolic potassium hydroxide (1 ml.). The mixture was left at room temperature for four hours, then acidified with acetic acid, left at room temperature for several hours, and worked up with chloroform. The product, on recrystallisation from light petroleum (b.p. 60°-80° and b.p. 40°-60°), was obviously a mixture. One component, separated mechanically and recrystallised from methylene chloride - light petroleum (b.p. 40°-60°), was identified as deoxygeigerin O-methyloxime (45) (m.p. and mixed m.p.).

Dihydro-1-epi-11-epideoxygeigerin (39): 1-Epi-11-Epideoxygeigerin (31) (75 mg.) in ethanol (8 ml.) was hydrogenated

over 10% palladium-charcoal (50 mg.) (uptake, 1.1 mole-equivalent). Dihydro-1-epi-11-epideoxygeigerin was recrystallised from ethyl acetate - light petroleum: m.p. 135-137°; $[\alpha]_D$, -103° (c, 1.06); ν_{max}, 1765, 1735 cm^{-1}. (Found: C, 71.86; H, 9.12. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

Treatment of Dihydro-1-epi-11-epideoxygeigerin with Base: Dihydro-1-epi-11-epideoxygeigerin (60 mg.) was treated with 2% ethanolic potassium hydroxide (5 ml.) at room temperature for three hours. Acidification and work-up with methylene chloride afforded a product which crystallised with difficulty. After several recrystallisations it had m.p. 115-125°C, and $[\alpha]_D$, -85° (c, 0.40), but too little reminaed to purify further.

Dihydro-1-epideoxygeigerin (40): 1-Epideoxygeigerin (29) (14 mg.) in ethanol (5 ml.) was hydrogenated over 10% palladium-charcoal. The product was recrystallised from ethyl acetate - light petroleum or from ether to afford dihydro-1-epideoxygeigerin: m.p. 128-132°; $[\alpha]_D$, -79° (c, 0.95).

Treatment of dihydro-1-epideoxygeigerin with ethanolic potassium hydroxide for three hours at room temperature

afforded, after several recrystallisations, a product, m.p. 115-125°, m.p. undepressed on admixture with the compound of similar melting point obtained from dihydro-1-epi-11-epideoxygeigerin. There was insufficient material for further purification or characterisation.

Hydrogenation of 11-Epideoxygeigerin: 11-Epideoxygeigerin (50 mg.) in ethanol (8 ml.) was hydrogenated over 10% palladium-charcoal (80 mg.) until hydrogen absorption ceased. Even after chromatography and repeated recrystallisations, the product melted over a 20-30° range, and was obviously a mixture, presumably of C_4-epimers: m.p. ca. 105-130°; $[\alpha]_D$, +12° (c, 0.38); ν_{max}, 1762, 1735 cm^{-1}. (Found: C, 71.91; H, 8.96. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

Treatment of the Mixture of Dihydro-11-epideoxygeigerins with Base: The crystalline mixture of dihydro-11-epideoxygeigerins (43 mg.) was treated with 2% ethanolic potassium hydroxide (6 ml.) at room temperature for two hours. The solution was acidified, left for several hours, diluted, and worked up with methylene chloride. The product was a crystalline mixture, which was separated into two components by use of their differing solubilities

in ether. The minor product (41) (more soluble) was recrystallised from ether - light petroleum: m.p. 139-144°C (too little for further characterisation). The major product (42) (less soluble) was recrystallised from ether: m.p. 220-222° (undepressed on admixture with dihydrodeoxygeigerin); $[\alpha]_D$, +140° (c, 0.23).

Dihydrodeoxygeigerin (42): Deoxygeigerin (50 mg.) in ethanol (8 ml.) was hydrogenated over 10% palladium-charcoal (60 mg.) until hydrogen absorption ceased (1.1 mole-equivalent; 30 minutes). The product, recrystallised from ethyl acetate - light petroleum, afforded dihydrodeoxygeigerin: m.p. 219-221°; $[\alpha]_D$, +137° (c, 0.71); ν_{max}, 1765, 1736 cm^{-1}. (Found: C, 72.13; H, 9.00. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

Treatment of Dihydrodeoxygeigerin with Base: Dihydrodeoxygeigerin (21 mg.) was treated with 2% ethanolic potassium hydroxide (4 ml.) at room temperature for two hours. The solution was acidified, left for several hours, diluted, and worked up with methylene chloride. The product was a mixture which, separated on the basis of solubility in ether, afforded two compounds: the minor product (41), recrystallised from ether - light petroleum: m.p. 139-144°,

undepressed on admixture with the compound of similar melting point obtained from dihydro-11-epideoxygeigerin; the major product (42), recrystallised from ether: m.p. 219-222°, undepressed on admixture with the corresponding compound from dihydro-11-epideoxygeigerin.

Acetoxylation of Deoxygeigerin: To a solution of deoxygeigerin (52 mg.) and lead tetra-acetate (400 mg.) in glacial acetic acid (6 ml.) and acetic anhydride (1 ml.) was added boron trifluoride etherate (1 ml.) and the solution kept at room temperature for 18 hours. Water was added and the mixture worked up with chloroform. The residue (66 mg.) on evaporation of the solvent crystallised spontaneously; it was recrystallised from ethyl acetate to afford 2-acetoxydeoxygeigerin (62): 44 mg. (ca. 70% theor.); m.p. 190-207°; $[\alpha]_D$, +49° (c, 0.70); λ_{max}, 240 mμ (ε, 14,000); ν_{max}, 1773, 1755, 1722, 1647, 1245 cm^{-1}. (Found: C, 66.73; H, 7.20. $C_{17}H_{22}O_5$ requires C, 66.7; H, 7.18%). NMR (in $CDCl_3$): peaks at τ values of: 5.68; 4.45 and 4.34 (doublet); 7.80; 8.97 and 8.89 (doublet); 8.72 and 8.62 (doublet).

Reduction of 2-Acetoxydeoxygeigerin with Chromous Chloride: To a solution of 2-acetoxydeoxygeigerin (50 mg.) in acetone

(5 ml.) and glacial acetic acid (1 ml.) was added, under nitrogen, chromous chloride solution (M/1 in N hydrochloric acid; 3 ml.), and the mixture was kept well-stoppered at room temperature overnight. Dilution with water, work-up with chloroform and recrystallisation of the product from ethyl acetate - light petroleum afforded deoxygeigerin (35 mg.).

Acetoxylation of Deoxygeigerin with Lead Tetra-acetate-[1-^{14}C]: (i): A solution of sodium [1-^{14}C]-acetate (0.1 millicurie; 0.55 mg.) and lead tetra-acetate (150 mg.) in acetic acid (1 ml.) and acetic anhydride (0.1 ml.) was kept for six hours with occasional heating so that the lead tetra-acetate remained in solution for most of this period, and exchange of [1-^{14}C]-acetate could take place. Deoxygeigerin (20 mg.) and boron trifluoride etherate (0.3 ml.) were then added and the solution was left at room temperature for 22 hours. The solution was diluted with water and worked up with chloroform. The twice-recrystallised 2-acetoxydeogeigerin had an activity of 17,800 counts per minute per mg. The combined mother liquors were diluted with pure inactive geigerin acetate (29 mg.), and the mixture filtered in benzene through a short column of alumina (acid; grade III). After 2

recrystallisations from ethyl acetate - light petroleum the activity was 350 counts per minute per mg.

After 3 recrystallisations: 60 c.p.m./mg.
" 4 " : 60 c.p.m./mg.
" 5 " : 33 c.p.m./mg.
" 6 " : 34 c.p.m./mg.

At this stage too little material remained for further purification. All geigerin acetate mother liquors (except the first) were combined, and converted to the 2,4-dinitrophenylhydrazone. This showed the following activities:

After 3 recrystallisations (ex ethyl acetate-ether): 60 c.p.m./mg.
" 5 " " " 24 c.p.m./mg.
" 7 " " " 22 c.p.m./mg.
" 9 " " " 21 c.p.m./mg.

A count of 34 on geigerin acetate is equivalent to a count of 22 on the 2,4-dinitrophenylhydrazone. This indicates a yield of 0.28%, based on the activity of the 2-acetoxy-deoxygeigerin.

(ii): Sodium [1-^{14}C]-acetate (ca. 0.2 mc.; 1 mg.) and lead tetra-acetate (300 mg.) in glacial acetic acid (2 ml.) and acetic anhydride(0.2 ml.) was warmed for three hours and then left at room temperature overnight. Deoxy-geigerin (80 mg.) and boron trifluoride etherate (0.6 ml.)

were added, and the solution was left at room temperature for seven hours. The reaction was worked up as before. The 2-acetoxydeoxygeigerin had an activity of 17,500 counts per minute per mg.

The mother liquors were diluted with geigerin acetate (80 mg.), passed in benzene solution through a short column of alumina and recrystallised from ethyl acetate - light petroleum:

After	5	recrystallisations	the	activity was	150 c.p.m./mg.
"	7	"	"	"	30 c.p.m./mg.
"	9	"	"	"	21 c.p.m./mg.
"	11	"	"	"	18 c.p.m./mg.
"	13	"	"	"	22 c.p.m./mg.

The final specimen (6 mg.) was converted to the 2,4-dinitrophenylhydrazone by treatment with 2,4-dinitrophenylhydrazine (5 mg.) in aqueous methanolic sulphuric acid. The product was chromatographed in methylene chloride on bentonite-kieselguhr and recrystallised (ethyl acetate - light petroleum). The activity was 12 counts per minute per mg. A count of 20 on geigerin acetate is equivalent to a count of 12.5 on the 2,4-dinitrophenylhydrazone. This indicates a yield of 0.11%.

Control Experiment: A solution of sodium [1-^{14}C]-acetate (ca. 0.1 mc; 0.45 mg.) in glacial acetic acid (1 ml.) and acetic anhydride (0.1 ml.) was warmed for half-an-hour to allow exchange of [1-^{14}C]-acetate. Boron trifluoride etherate (0.3 ml.) and deoxygeigerin (19 mg.; from the same preparation as that used in the acetoxylation experiments) were added, and the mixture was kept at room temperature overnight. The reaction was worked up and the product diluted with geigerin acetate (25 mg.). After three recrystallisations from ethyl acetate - light petroleum the count on 0.5 mg. samples, over a total count of 4,000-5,000 seconds per sample, was indistinguishable from background.

In order to establish that any geigerin present would be acetylated under these conditions, geigerin (50 mg.) was treated with glacial acetic acid (2 ml.), acetic anhydride (0.2 ml.), boron trifluoride etherate (0.6 ml.) and sodium acetate (1 mg.) at room temperature overnight. Dilution with water and work up with chloroform afforded geigerin acetate almost quantitatively (identified by m.p. and infrared spectrum).

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