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STEREOCHEMICAL RELATIONSHIPS IN THE EUDESMANE (SELINANE) GROUP OF SESQUITERPENES

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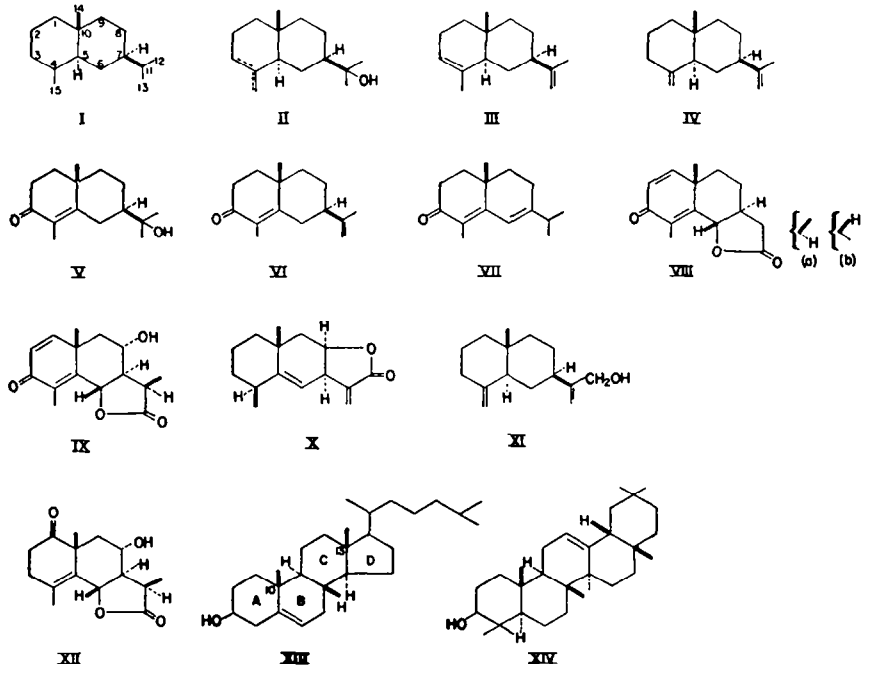
Abstract—The stereochemical correlations in the eudesmane* group of sesquiterpenes are highly ramified. In this article we attempt to summarise the evidence on which the correlations are founded. Most of the classical chemistry of the group of compounds has been reviewed,[1] and some of the more recent developments have been described by Barton and de Mayo.[2]

EUDESMANE has the structure shown in I,[3] and it possesses asymmetric centres at C_4, C_5, C_7 and C_{10}. It is not a naturally occurring compound, but is the parent of a large number of naturally occurring alcohols, ketones, acids and lactones. Introduction of these groups into the parent molecule frequently creates new asymmetric centres,



* For other schemes of nomenclature used in this series see the articles by Kovacs, Herout, Horák, and Sorm, (*Coll. Czech. Chem. Comm.* **21**, 225 ((1956) and Dauben and Hance (*J. Amer. Chem. Soc.* **75**, 3352 (1953)).

[1] (a) Sir John Simonsen and D. H. R. Barton, *The Terpenes* Vol. III, Cambridge Univ. Press (1952); (b) D. H. R. Barton, *Chemistry of Carbon Compounds* (Edited by Rodd) Vol. IIb, p. 630. Elsevier, Amsterdam (1953); (c) A. J. Haagen-Smit, *Fortschr. Chem. Org. Naturstoffe*, **12**, 1 (1955).

[2] D. H. R. Barton and P. de Mayo, *Quart. Rev.* **11**, 189 (1957).

[3] W. Cocker and R. S. Cahn, *Chem. & Ind.* 384 (1955).

particularly at C_6, C_8 and C_{11}. We might mention the following eudesmane derivatives; eudesmol, (II), α- and β-selinenes (III, IV), carissone (V), α-, and β-cyperones (VI, VII), santonin (VIIIa) and 11β (H)-santonin (VIIIb), artemisin (IX), alantolactone (X), sesquibenihiol (XI), and ψ-santonin (XII).

The most important of these asymmetric centres is at C_{10}, comparable with the asymmetric centre at C_{10} in the steroids, e.g. cholesterol (XIII), or triterpenes, e.g. β-amyrin (XIV). It will be shown that without exception all the naturally occurring sesquiterpenes with a eudesmane skeleton, whose stereochemistry is known, possess a 10β-methyl group. In other words the configuration of the 10-methyl group in the 'eudesmanes' and the steroids is identical. As this configuration at C_{10} in the steroids is absolute, it follows that the configuration at C_{10} in the sesquiterpenes is also absolute. It is therefore logical first to trace the relationships at C_{10} of the sesquiterpenoids of the eudesmane type.

It is important to distinguish between the various available proofs of a particular configuration. The least rigorous approach is by analogy; it cannot be termed a proof, although it may provide a good working hypothesis. As an example of this point we can mention the fact that whilst all the known eudesmanes have the 'natural' configuration at C_{10}, the isolation of the 'unnatural' sesquiterpenes of the iresin type,[4] eperuic acid,[5] and cafestol[6] casts some doubt on the universal truth of the hypothesis, even in the eudesmane group. Reasoning by analogy can be applied to asymmetric centres other than C_{10}. It consists in the interpretation of the reactions of the centre in terms of a particular stereochemical configuration. This approach has been greatly facilitated by the development of conformational analysis,[7] and in many cases provides as rigorous a proof as is possible. The use of molecular rotational differences[8] is of considerable importance in the assignment of configuration, and the extension of the method to rotatory dispersion studies[9] has made the method even more valuable. It may be assumed that a rigorous proof of configuration is provided by the method. In the final analysis however a chemical correlation of a compound of unknown configuration with a compound of known configuration provides the ultimate proof.

Configuration at C_{10}

Eudesmol (II). The methyl groups at C_{10} and C_{13} in the steroids are known to be β-orientated.[10] The synthesis[11] of cholesterol (XIII) following essentially the route of the Harvard group of workers uses the laevorotatory unsaturated *trans* decalone (XV) to form rings C and D of the steroid. The angular methyl group in XV therefore

[4] C. Djerassi and S. Burstein, *J. Amer. Chem. Soc.* **80**, 2593 (1958); M. G. Rossmann and W. N. Lipscomb, *Tetrahedron* **4**, 275 (1958); P. Crabbé, S. Burstein, and C. Djerassi, *Bull. Soc. Chim. Belg.* **67**, 632 (1958); L. Caglioti, H. Naef, D. Arigoni, and O. Jeger, *Helv. Chim. Acta* **41**, 2278 (1958).

[5] F. E. King and G. Jones, *J. Chem. Soc.* 658 (1955); J. D. Cocker and T. G. Halsall, *Ibid.* 4262 (1956); C. Djerassi and D. Marshall, *Tetrahedron* **1**, 238 (1957).

[6] H. Bendas and C. Djerassi, *Chem. & Ind.* 1481 (1955); C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **80**, 247 (1958).

[7] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).

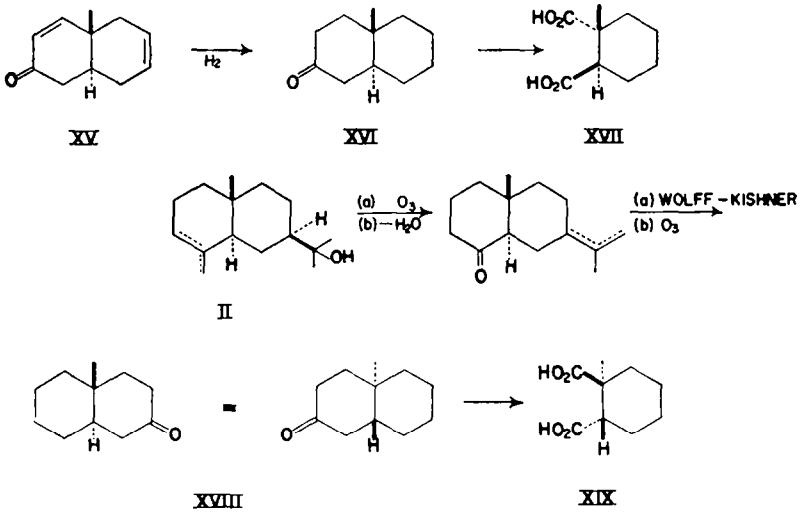
[8] cf. J. A. Mills and W. Klyne, *Progress in Stereochemistry* Vol. I, p. 209. Butterworths, London (1954), where many references are given.

[9] C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Amer. Chem. Soc.* **77**, 4354 (1955); and subsequent papers.

[10] cf. C. W. Shoppee, *Chemistry of the Steroids* p. 23. Butterworths, London (1958).

[11] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952); L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *Ibid.* **76**, 5014 (1954).

corresponds to that at C_{13} in cholesterol and is consequently β-orientated. Reduction of XV affords the saturated ketone (XVI) which on oxidation is converted to the dicarboxylic acid (XVII), and nothing in these reactions can alter the β-orientation of the angular methyl group. With the absolute configuration of these compounds established it is possible to establish the configuration at C_{10} in eudesmol (II), which is converted[12] by the route shown below to the enantiomorphic forms XVIII and XIX of the decalone (XVI) and its related dicarboxylic acid (XVII).



XV XVI XVII

II

XVIII XIX

These experiments make it clear that eudesmol (II) has the 10β-configuration, and consequently the α- and β-selinenes (III) and (IV) respectively, which are closely related to eudesmol, must also have the β-methyl group at C_{10}.

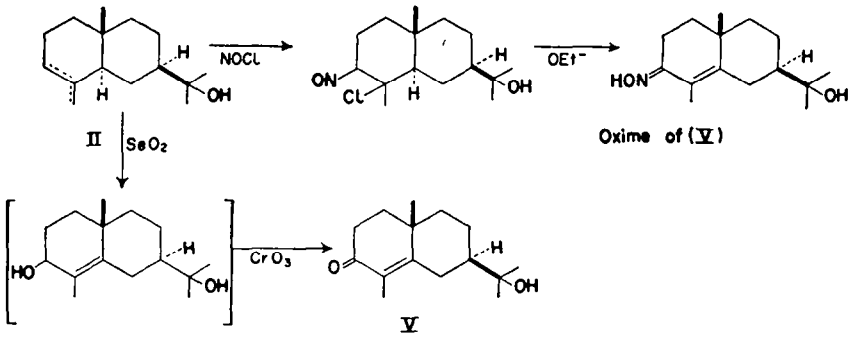
Eudesmol may be considered to be a relay in the correlation of the eudesmane group of sesquiterpenoids with the steroids.

Carissone (V) *and the cyperones* (VI, VII). Carissone (V) has been related[13] to eudesmol (II) and the cyperones (VI, VII) have been related[14] to carissone, by reactions not involving C_{10}. All these compounds thus have the same configuration at C_{10}.

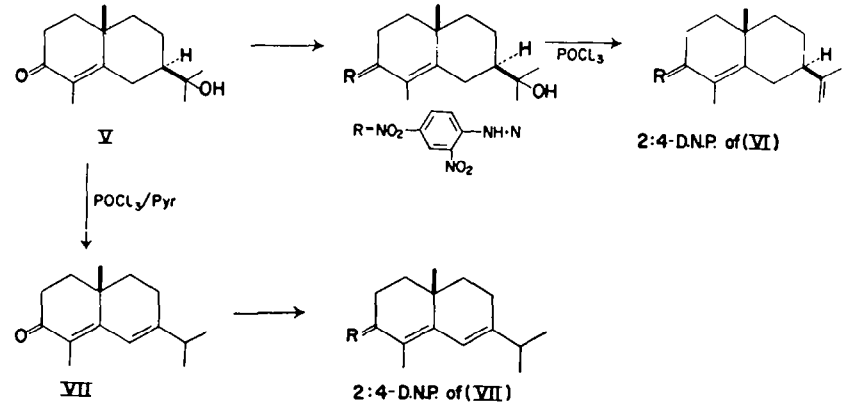
When eudesmol (II) was reacted[13] with nitrosylchloride and the nitroso chloride dehydrochlorinated with sodium ethoxide the oxime of carissone (V) was obtained, but as an oil. Conversion of the oxime to the corresponding 2:4-dinitrophenylhydrazone however gave a crystalline product identical with carissone 2:4-dinitrophenylhydrazone, from which carissone was obtained by reaction with pyruvic acid. Carissone itself was obtained[13] when eudesmol was submitted to successive oxidations with selenium dioxide and chromium trioxide as shown in the reaction sequence below.

Further it has been shown[14] that carissone (V) can be dehydrated, according to the conditions of the reaction, to give either α-cyperone (VI) or β-cyperone (VII), in this way affording a direct correlation between the three ketones. Thus whilst the 2:4-dinitrophenylhydrazone of carissone is dehydrated with phosphorus oxychloride

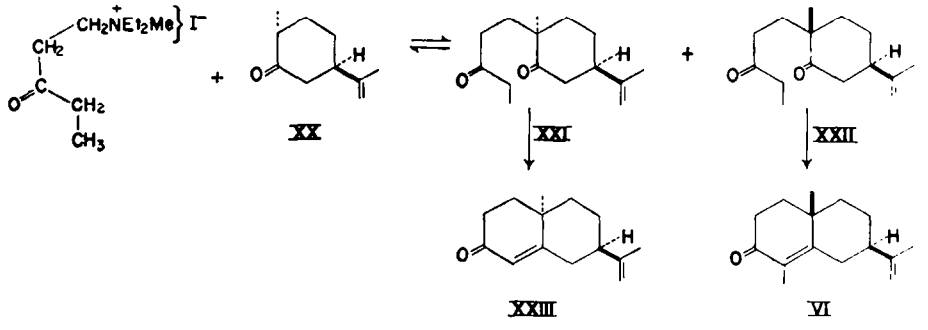
[13] B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold, and R. B. Woodward, *J. Amer. Chem. Soc.* 76, 313 (1954).
[14] W. A. Ayer and W. I. Taylor, *J. Chem. Soc.* 3027 (1955).
[14] D. H. R. Barton and E. J. Tarlton, *J. Chem. Soc.* 3492 (1954).



and pyridine to give the 2:4-dinitrophenylhydrazone of α-cyperone (VI), dehydration of carissone itself gives β-cyperone (VII), identified as its 2:4-dinitrophenylhydrazone.



The assignment of the configuration shown to α-cyperone (VI) was confirmed by its synthesis[15] in the dextrorotatory form from (+)-dihydrocarvone (XX), whose absolute configuration has been established.[16,17] The reactions afford a good example of stereospecific synthesis.



Two products arise from the condensation of dihydrocarvone with 1-diethylamino-pentan-3-one methiodide, namely, natural (+)α-cyperone (VI) and its stereoisomer

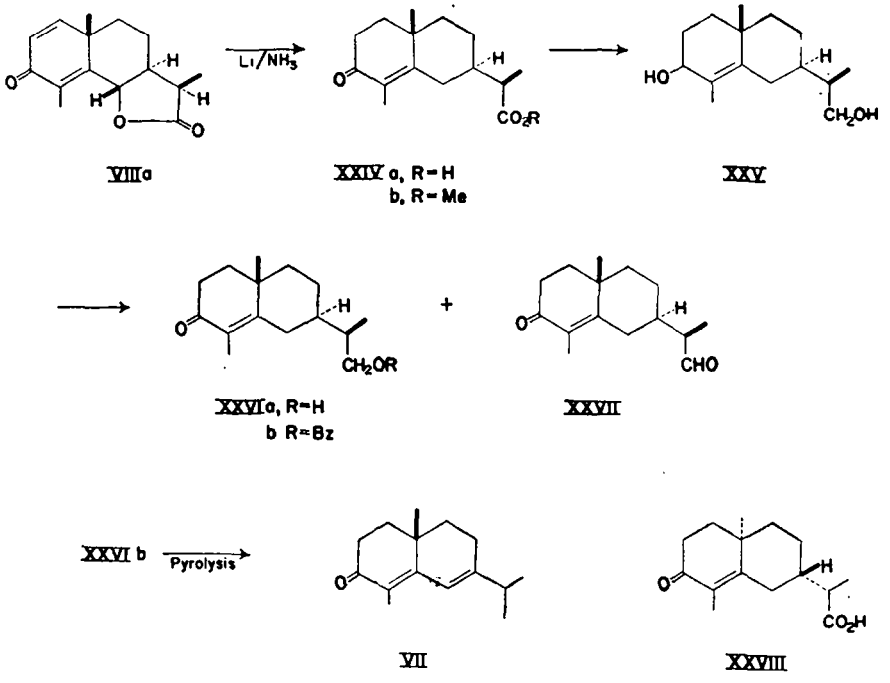
[15] R. Howe and F. J. McQuillin, *J. Chem. Soc.* 2423 (1955).
[16] W. Hückel, *J. Prakt. Chem.* **157**, 225 (1941).
[17] N. L. McNiven and J. Read, *J. Chem. Soc.* 159 (1952).

(XXIII). Of the two intermediate diketones XXI and XXII the former would, on conformational grounds, be expected to be produced the more rapidly, but XXII is thermodynamically more stable than XXI.[18] The formation of XXII, the precursor of natural (+)α-cyperone (VI) undoubtedly arises from a slow equilibration reaction.

It will be noticed that the synthesis also establishes the absolute configuration at C_7 in α-cyperone.

The optical rotatory dispersion curves of carissone and α-cyperone are closely similar to that of 4-methylcholest-4-en-3-one,[19] which confirms the C_{10} configuration shown in (V) and (VI). Synthetic ketones with 7α-(*axial*)-isopropylidene or isopropyl groups show different dispersion curves. As would be expected the dispersion curve of β-cyperone (VII) is similar to that of cholesta-4:6-dien-3-one.

Santonin (VIIIa) *and* 11β(H)-*santonin* (VIIIb). We need not detail here the evidence which demonstrates that these two compounds differ only in configuration at C_{11}. The evidence is given on p. 196. The establishment by chemical methods of the β-methyl configuration at C_{10} in these naturally occurring santonins depends upon the conversion[20] of santonin (VIIIa) to β-cyperone (VII), by the elegant method shown in formulae below.



VIIIa XXIV a, R=H b, R=Me XXV

XXVIa, R=H b R=Bz XXVII

VII XXVIII

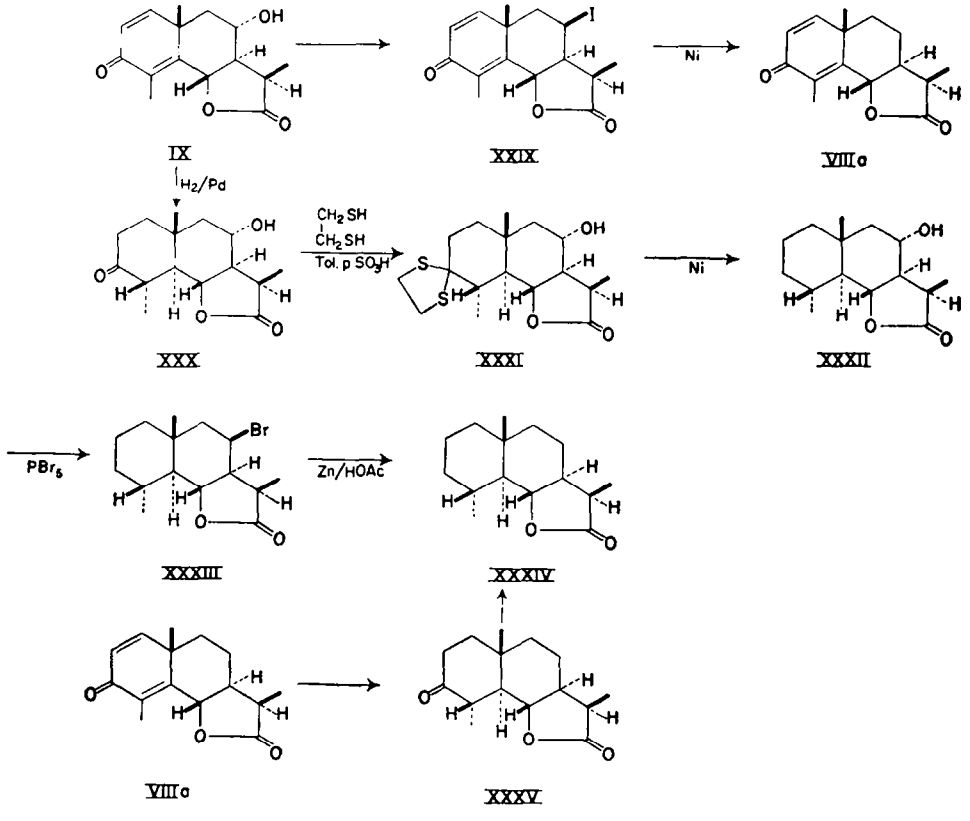
Reduction of santonin (VIIIa) with lithium in liquid ammonia affords the acid (XXIVa). The corresponding ester (XXIVb), when reduced in a mixture of dioxan and ether with lithium aluminium hydride gives the diol (XXV), and this diol undergoes allylic oxidation with manganese dioxide thus affording the ketol (XXVIa), the aldehyde (XXVII) also being produced in this reaction. Pyrolysis of the benzoate

[18] F. J. McQuillin, *J. Chem. Soc.* 528 (1955).
[19] C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); cf. W. Klyne, *J. Chem. Soc.* 3072 (1953).
[20] H. Bruderer, D. Arigoni, and O. Jeger, *Helv. Chim. Acta* **39**, 858 (1956).

(XXVIb) gives β-cyperone (VII) isolated as its 2:4-dinitrophenylhydrazone, but it is probable that α-cyperone (VI) is produced first.

The rotatory dispersion curve of santonin differs sufficiently from that of cholesta-1:4-dien-3-one its closest steroidal analogue to draw any stereochemical conclusion from it.[19] However the acid (XXVIII) used in the synthesis of the antipode of santonin has a dispersion curve which is almost the mirror image of that of carissone (V). Further support for the presence of 10β-methyl group comes from the dispersion curves of the tetrahydrosantonins (p. 202), and molecular rotation data have also been employed to arrive at the same conclusion.[21]

Artemisin (IX). Artemisin has been shown[22] to be 8α-hydroxysantonin (IX). Two routes were employed for the correlation of this compound with santonin (VIIIa). In the first, artemisin was converted to 8-iodosantonin (XXIX) by the use of triphenylphosphite methiodide, and santonin (VIIIa) was then produced when the

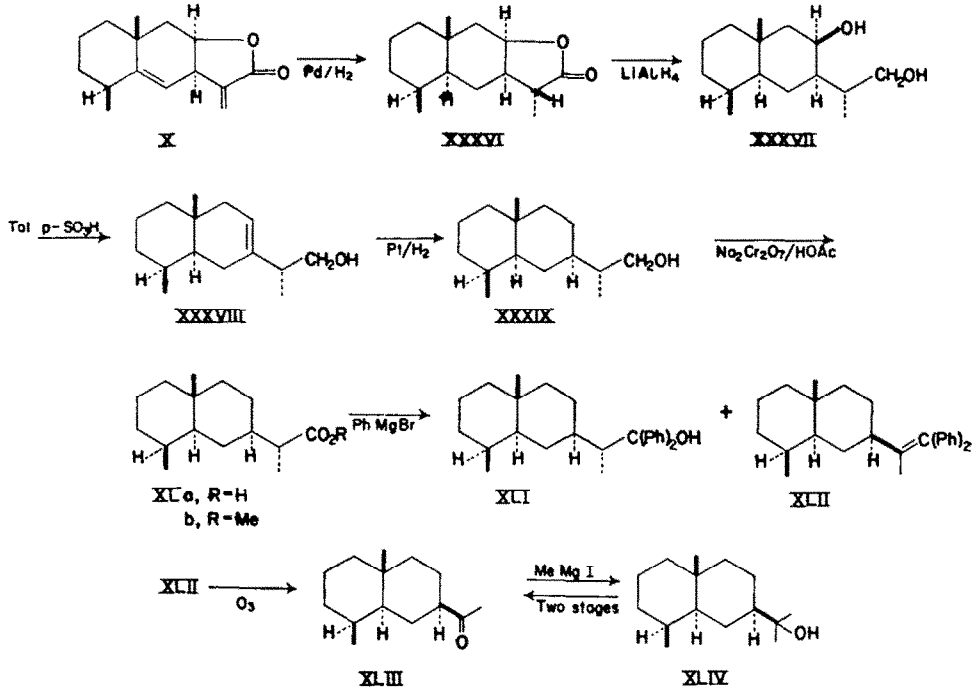


iodo compound was reduced over Raney nickel in pyridine-methanol solution. In the second route artemisin was reduced over palladised charcoal to its tetrahydro compound (XXX), from which the keto group was removed by way of the ethylene

[21] Y. Abe and M. Sumi, *Chem. & Ind.* 253 (1955); E. J. Corey, *J. Amer. Chem. Soc.* 77, 1044 (1955).
[22] M. Sumi, *Pharm. Bull. Japan* 5, 187 (1957); *Proc. Japan Acad.* 33, 153 (1957); *J. Amer. Chem. Soc.* 80 4869 (1958).

thioketal (XXXI) which was desulphurised with Raney nickel. Treatment of the deoxo compound (XXXII) with phosphorous pentabromide afforded the bromo compound (XXXIII), presumably with inversion at C_8, which on reduction with zinc and acetic acid gave a desoxytetrahydrosantonin, namely 5:11α(H), 4:6β(H)-eudesman-6:13-olide (XXXIV). This lactone was also obtained when 3-oxo-5:11α(H), 4:6β(H)-eudesman-6:13-olide (α-tetrahydrosantonin) (XXXV) was reduced *via* its ethylene thioketal. Since the configuration of α-tetrahydrosantonin (XXXV) is known[23] the configuration of tetrahydroartemisin must be that shown in (XXX).

Alantolactone (X). Alantolactone has been converted[24] to dihydroeudesmol (XLIV) by a method which proves that these compounds have the same configuration both at C_{10} and C_7. It will be noticed that we employ the structure X[25] for alantolactone in preference to the alternative structure in which the endocyclic double bond is in the 3:4-position.[26] The former structure seems to us to be more in accord with degradative evidence than the latter.



Alantolactone (X) is readily reduced to its tetrahydro compound, whose structure has been shown to be XXXVI (see pp. 189, 200). The diol (XXXVII), obtained when tetrahydroalantolactone is reduced with lithium aluminium hydride, is dehydrated with toluene *p*-sulphonic acid thus affording the unsaturated compound (XXXVIII). Reduction of the latter gives the saturated alcohol (XXXIX) which on oxidation with dichromate in acetic acid gives the acid (XLa). The corresponding methyl ester (XLb) reacts with phenylmagnesium bromide giving the alcohol (XLI) and the

[23] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956); O. Kovacs, V. Herout, M. Horák and F. Šorm, *Coll. Czech. Chem. Comm.* **21**, 225 (1956); M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955).
[24] K. Tanabe, *Pharm. Bull. Japan* **6**, 214 (1958).
[25] C. Asselineau and S. Bory, *C. R. Acad. Sci., Paris* **246**, 1874 (1958).
[26] K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi, *J. Amer. Chem. Soc.* **79**, 5721 (1957).

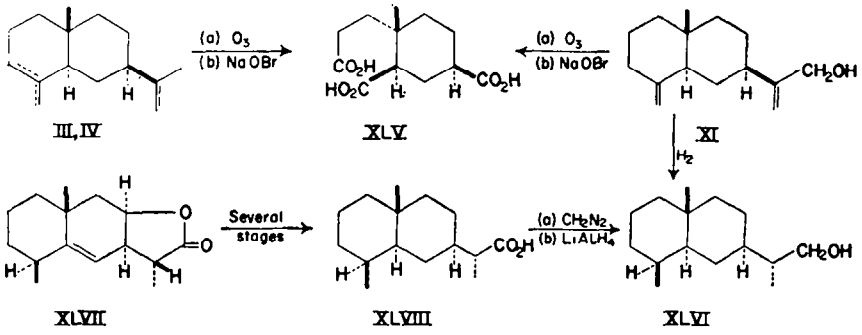
unsaturated compound (XLII). Ozonolysis of the latter compound affords the methyl ketone (XLIII) which may be obtained from dihydroeudesmol (XLIV), and into which it can be converted on reaction with methylmagnesium iodide.

Further evidence of the stereochemistry of alantolactone comes from its correlation with sesquibenihiol (XI).

Sesquibenihiol (Costol) (XI). Recent work[27] has shown that sesquibenihiol is identical with costol, an alcohol isolated from *Saussurea Lappa.*

Almost fifty years ago it was shown[28] that the tricarboxylic acid (XLV) could be obtained by the oxidation of the selinenes, and since the configuration of the selinenes is that shown in III and IV (p. 183), the tricarboxylic acid (XLV) must also have the selinene configuration at C_7 and C_{10}. The same acid has more recently[27,29] been obtained by the oxidation of sesquibenihiol (XI). The configuration of the latter at C_7 and C_{10} is consequently the same as that of the selinenes at these centres.

Sesquibenihiol (XI) has also been related[30] to alantolactone (X). Reduction of sesquibenihiol gives a tetrahydro derivative (XLVI)[27,29] which is identical with an alcohol prepared from dihydroalantolactone (XLVII) *via* the acid (XLVIII).

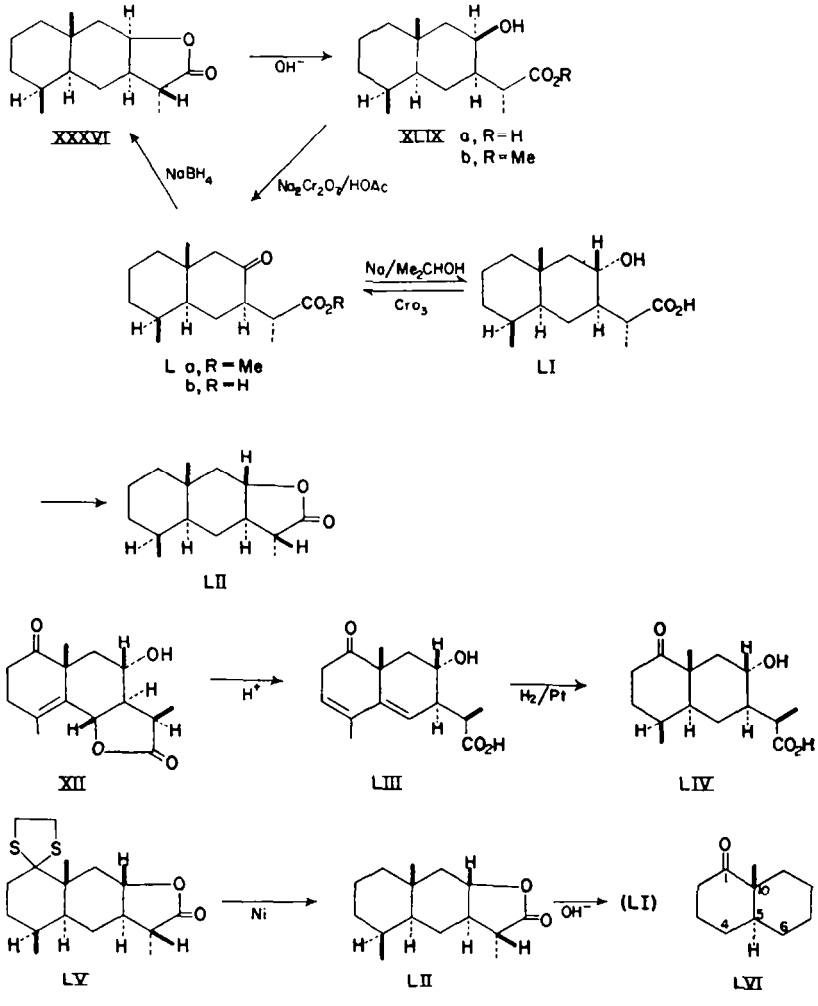


ψ-Santonin (XII). When tetrahydroalantolactone (XXXVI, see pp. 189, 200) is hydrolysed with alkali, and the product carefully neutralised the acid (XLIXa) is obtained, which with diazomethane gives the methyl ester (XLIXb).[26] Oxidation of the ester with dichromate in acetic acid gives the keto ester (La) which is hydrolysed with alkali to the keto acid (Lb). Reduction of the latter with sodium and isopropanol affords the hydroxy-acid (LI), which is lactonised to (LII). On the other hand borohydride reduction of (Lb) gives tetrahydroalantolactone (XXXVI),[26] hence the two lactones XXXVI and LII have opposite configuration at C_8. This will be discussed on p. 195.

The hydroxy-acid (LI) may be obtained from ψ-santonin as follows.[31] ψ-Santonic acid (LIII), an acid catalysed rearrangement product of ψ-santonin,[32] is readily reduced to its tetrahydro derivative (LIV),[32,33] from which the keto group is removed *via* the ethylene thioketal (LV). The desoxy compound (LII) was however produced

[27] V. Benešová, V. Sýkora, V. Herout, and F. Šorm, *Chem. & Ind.* 363 (1958).
[28] F. W. Semmler and F. Risse, *Ber. Dtsch. Chem. Ges.* **46**, 599 (1913).
[29] S. Katsura, *J. Chem. Soc. Japan* **63**, 1460 (1942).
[30] T. Ukita and S. Nakazawa, *Pharm. Bull. Japan* **2**, 239 (1954).
[31] W. Cocker and T. B. H. McMurry, *Proc. Chem. Soc.* 147 (1958).
[32] G. R. Clemo and W. Cocker, *J. Chem. Soc.* 30 (1946); N. M. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurry, and E. R. Stuart, *Ibid.* 1828 (1956).
[33] W. Cocker and C. Lipman, *J. Chem. Soc.* 1170 (1949).

as a gum, but the corresponding acid was obtained as a highly crystalline compound identical with LI. None of these reactions involve C_{10} consequently ψ-santonin and alantolactone have the same β-methyl configuration at this centre.



Comparison of the rotatory dispersion curves[19,34] of tetrahydro-ψ-santonic acid (LIV) and *trans* 10-methyldecal-1-one (LVI) supports the configuration of ψ-santonin. The rotatory dispersion curves of ψ-santonin and ψ-santonic acid cannot supply any information in the absence of suitable model compounds for comparison.

We can now summarise the foregoing correlations in Chart I.

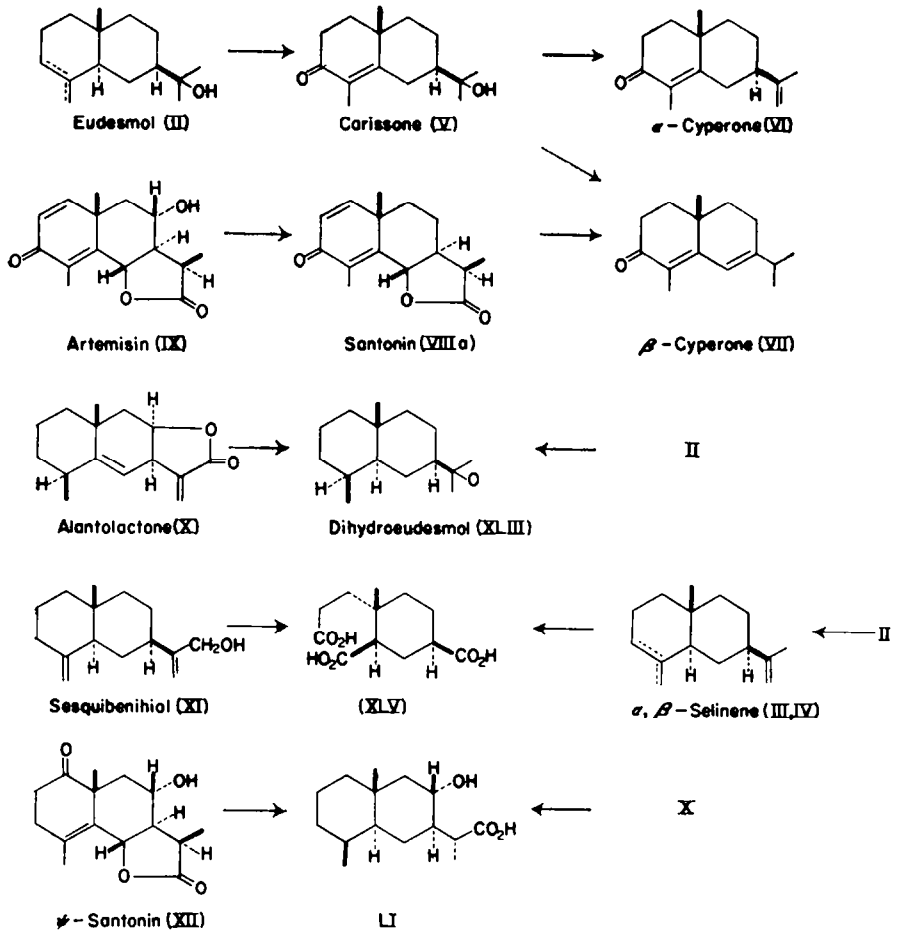
Configuration at C_4

Alantolactone (X). Alantolactone (X) and isoalantolactone (LVII) afford the same tetrahydro derivative XXXVI, which must therefore possess the same configuration at C_4 as alantolactone. This configuration has been established in an ingenious manner. Dihydroisoalantolactone (LVIII) can be converted[35] to its

[34] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).

3-hydroxy derivative (LIX) which on hydrogenation gives 3-hydroxytetrahydroalantolactone (LX). Oxidation of the latter with dichromate in acetic acid affords 3-oxotetrahydroalantolactone (LXI) in which the 4-methyl group is axial (β) since this centre

Chart I



undergoes inversion with alkaline alumina[36,cf.23] giving the lactone (LXII) in which the methyl is equatorial (α). Now, when the keto group is removed from the ketolactones LXI and LXII by way of their thioketals the deoxolactones XXXVI, which is tetrahydroalantolactone, and LXIII are respectively obtained. Obviously therefore alantolactone has the axial 4β-methyl group, shown in (X).

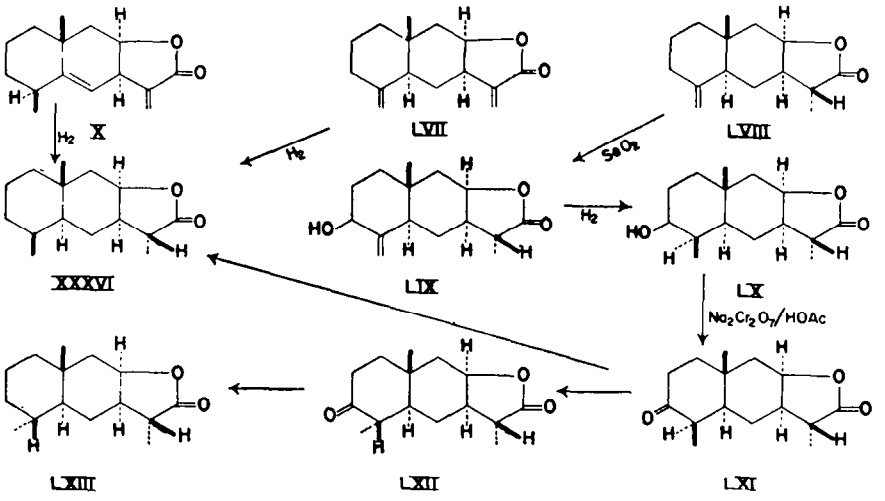
Configuration at C_5

Whilst a number of eudesmanes have an asymmetric centre at C_5, in others this centre becomes of importance after reduction. Of the former type mention can be made of eudesmol (II), the selinenes (III, IV), and sesquibenihiol (XI).

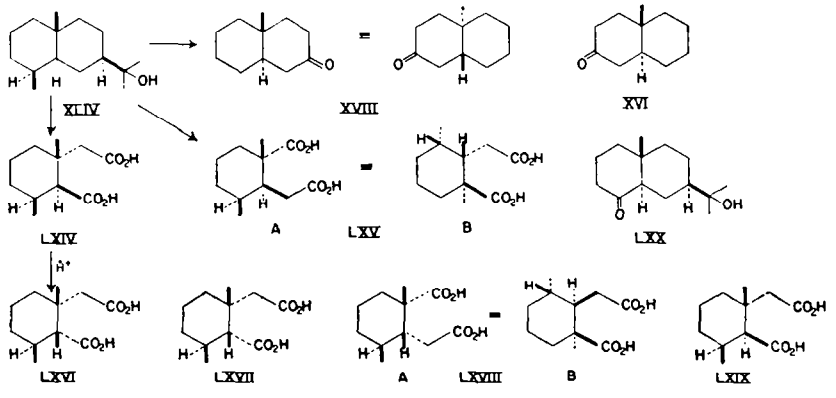
It was shown earlier (p. 183), that eudesmol can be converted to the *trans* decalone

[35] H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan* **74**, 738 (1954).
[36] K. Tanabe, *Pharm. Bull. Japan* **6**, 218 (1958).

(XVIII), the enantiomorph of XVI, a compound of known absolute configuration. It follows from this evidence that eudesmol and hence the selinenes and sesquibenihiol are *trans* decalin derivatives with αH at C_5.



The *trans* ring junction is supported by consideration of the molecular rotations of the dicarboxylic acids (LXIV) and (LXV), oxidation products of dihydroeudesmol,[38] and the acid epimerisation product (LXVI) obtained from LXIV.[39] If the ring junction is *trans*, and we consider the methyl groups and the hydrogen to be equivalent, then obviously LXIV and LXV (written as LXVB) are of the same stereochemical type. As expected on this formulation they have similar positive rotations, whilst LXVI has a negative rotation. If however the ring junction were *cis* then the dicarboxylic acids would be LXVII, LXVIII and LXIX respectively. These formulations cannot be accepted since LXVIII (written as LXVIIIB) is enantiomeric with LXVII and hence these two acids should have rotations of opposite, not the same, sign.



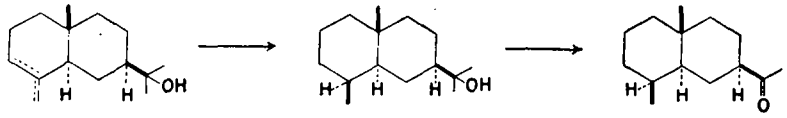
[37] W. Klyne, *J. Chem. Soc.* 3072 (1953).
[38] L. Ruzicka, P. A. Plattner, and A. Fürst, *Helv. Chim. Acta* **25**, 1364 (1942); P. A. Plattner, A. Fürst, and J. Hellerbach, *Ibid.* **30**, 2158 (1947).
[39] D. H. R. Barton, *Chem. & Ind.* 664 (1953); *J. Chem. Soc.* 1027 (1953).

It has also been shown[40] that the ketol (LXX) derived from eudesmol by oxidation is stable to alkali as would be expected of a *trans* A/B ring junction.

Configuration at C_7

In all the eudesmanes where the configuration at C_7 is known, the isopropyl group is β-equatorial.

We have mentioned earlier that dihydroeudesmol (XLIV) is converted in two stages to the ketone (XLIII) which is unaffected by alkali.[12] The isopropyl group must therefore be equatorial, and since the decalin system is *trans* fused the isopropyl group must have also the β-configuration. From the evidence described earlier in this review, it is clear that the selinenes (III, IV), carissone (V), α-cyperone (VI), alantolactone (X), and ψ-santonin (XII), which have been related (Chart I) to eudesmol by reactions not involving C_7, must have the β-(equatorial)-isopropyl group at this centre.



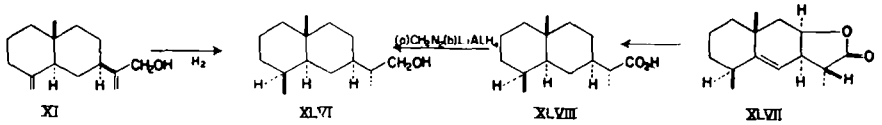
II XLIV XLIII

The configuration at C_7 in alantolactone is confirmed by the stability to alkali of the keto-acid (Lb) and ester (La), obtained[26] from tetrahydroalantolactone (XXXVI).

XXXVI La, R=Me b, R=H

It may be argued that inversion at C_7 could have taken place in the formation of the keto-acid (La) and ester (Lb) from the tetrahydroalantolactone (XXXVI), but this is obviously incorrect since tetrahydroalantolactone is reformed when the keto-acid (Lb) is reduced with sodium borohydride.

The configuration at C_7 of sesquibenihiol (XI) is proved by its reduction to the saturated alcohol[27,29] (XLVI) which may also be obtained from dihydroalantolactone (XLVII). Chart I shows that santonin (VIIIa), and artemisin (IX) have the same



XI XLVI XLVIII XLVII

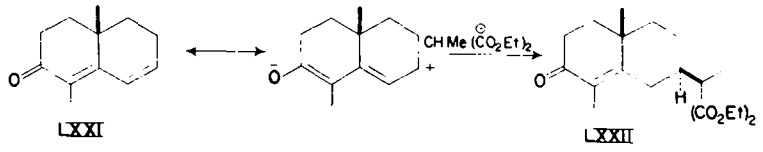
configuration at C_7. Whilst their conversion to β-cyperone (VII) probably proceeds[14] *via* α-cyperone (VI), proof is lacking. However stereospecific synthesis[41] of the

[40] A. J. Birch and K. M. C. Mostyn, *Aust. J. Chem.* **7**, 301 (1954).

[41] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *Proc. Japan Acad.* **28**, 425 (1952); **29**, 113 (1953); **30**, 116, 119 (1954); *J. Amer. Chem. Soc.* **75**, 2567 (1953); cf. M. Matsui, K. Toki, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Chem. Soc. Japan* **27**, 5 (1954); W. Cocker, *Ann. Rep.* **51**, 208 (1954); W. Cocker and J. T. Edward, *Ibid.* **52**, 191 (1955).

santonins VIIIa and VIIIb makes it clear that these compounds afford no exception to the usual configuration at C_7.

In this synthesis the conjugated unsaturated lactone (LXXI)[42] adds the methylmalonic ester anion so that it takes up the more stable equatorial position,[43] thus affording (LXXII). This is the stage in the synthesis which determines the stereochemistry at C_7 in santonin, and we need not here consider the remainder of the synthesis, which does not further concern this centre.



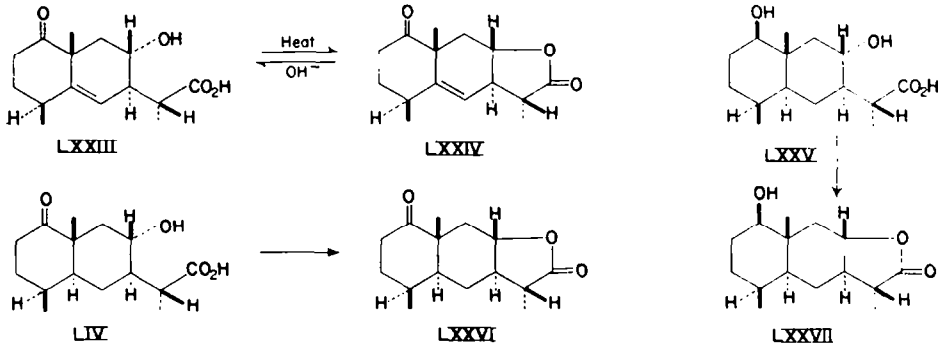
LXXI LXXII

Configuration at C_8

Artemisin (IX), *Alantolactone* (X), *and ψ-Santonin* (XII). In artemisin (IX), and in ψ-santonin (XII), the hydroxyl group at C_8 is α-(equatorial), whilst in alantolactone (X) the lactone ring is β-fused.

Both artemisin[22] and ψ-santonin[44] can be esterified without difficulty, which suggests equatorial hydroxyl. In addition there is a strong positive shift[22] in molecular rotation in proceeding from santonin (VIIIa) to its 8-hydroxy derivative artemisin (IX), and on acetylation of the latter there is a further positive rotational shift. Such shifts indicate[45] α-orientation of the hydroxyl in question.

Further light on the configuration at C_8 in ψ-santonin is thrown by a consideration of the lactonisation of dihydro-ψ-santonin (LXXIII) in which C_8 has the same configuration as its parent. The lactonisation, which affords LXXIV, takes place with considerable negative increment in molecular rotation. Similarly tetrahydro-ψ-santonic acid (LIV) and hexahydro-ψ-santonic acid (LXXV) undergo lactonisation to the anhydro compounds LXXVI and LXXVII respectively with negative incremental changes in molecular rotation.[32]

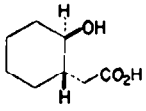


LXXIII LXXIV LXXV

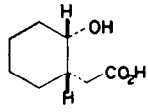
LIV LXXVI LXXVII

[42] F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952).
[43] R. B. Woodward and P. Yates, *Chem. & Ind.* 1391 (1954); J. W. Ralls, *J. Amer. Chem. Soc.* 75, 2123 (1953).
[44] N. M. Chopra, W. Cocker, B. E. Cross, J. T. Edward, D. H. Hayes, and H. P. Hutchison, *J. Chem. Soc.* 588 (1955).
[45] W. Klyne and W. M. Stokes, *J. Chem. Soc.* 1979 (1954); D. H. R. Barton and A. Nickon, *Ibid.* 4665 (1954).
[46] N. M. Chopra, W. Cocker, and J. T. Edward, *Chem. & Ind.* 1535 (1954).

In reinterpreting Hudson's lactone rule, Klyne[47] has shown that in a hydroxy-acid such as (LXXVIII) oriented as shown, lactonisation takes place with positive increment in molecular rotation, and conversely the hydroxy acid (LXXIX) lactonises with negative change in molecular rotation. The ψ-santonin derivatives mentioned above behave in a similar manner to (LXXIX) and hence they have α-hydroxyl at C_8

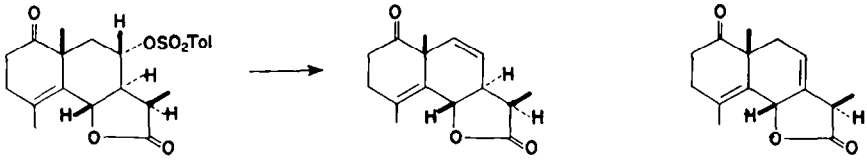


LXXVIII



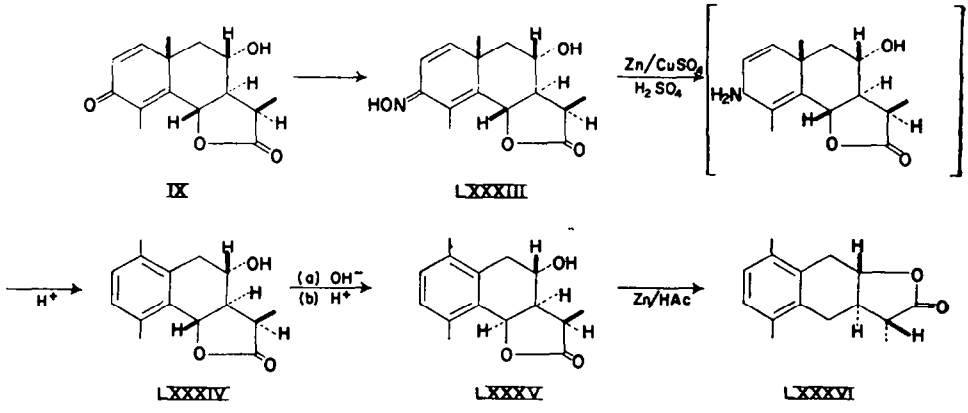
LXXIX

Similar conclusions about the configuration at C_8 in ψ-santonin have been reached by Dauben and Hance,[48] who showed that the tosyl ester of ψ-santonin (LXXX) undergoes ready base catalysed elimination of toluene sulphonic acid to give LXXXI, rather than LXXXII. Since *trans* elimination takes place, it can be assumed that the C_8 tosyloxy group and C_7 hydrogen have *cis* relationship. Consequently the hydroxyl at C_8 is α-orientated, since the C_7 hydrogen is α-orientated (see p. 192).



LXXX LXXXI LXXXII

It has also been shown[49] that ψ-santonin (XII) and artemisin (IX) have the same configuration at C_8. Artemisin oxime (LXXXIII) is reduced in acid solution to give the *trans* lactone hypoartemisin (LXXXIV), by a reaction similar to the conversion[50] of santonin to hyposantonin. Hypoartemisin is converted to isohypoartemisin, the *cis* lactone (LXXXV), by hydrolysis with alkali and acidification of the sodium salt. This is analogous to the conversion of hypo- to isohyposantonin.[50] The *cis* lactones

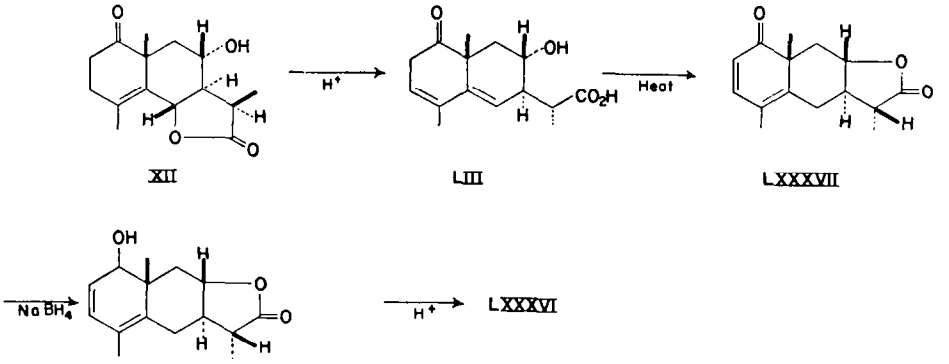


IX LXXXIII

LXXXIV LXXXV LXXXVI

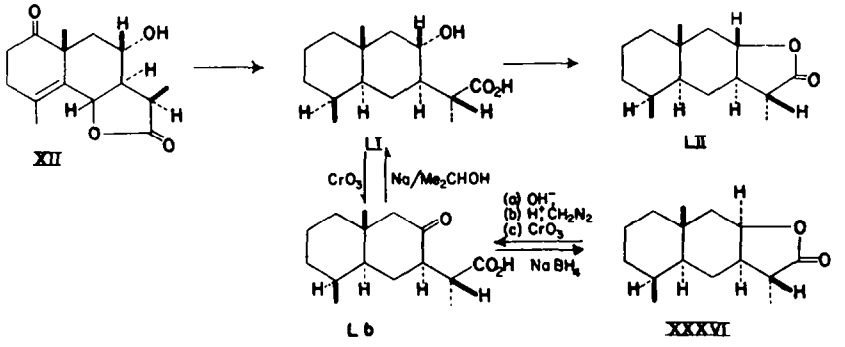
[47] W. Klyne, *Chem. & Ind.* 1198 (1954).
[48] W. G. Dauben and P. D. Hance, *J. Amer. Chem. Soc.* 77, 606 (1955).
[49] M. Sumi, W. G. Dauben, and W. K. Hayes, *J. Amer. Chem. Soc.* 80, 5704 (1958).
[50] Ref. 1a, p. 252.

(but not the *trans*) are reduced with zinc and acetic acid, giving in the case of isohypoartemisin, the linear lactone (LXXXVI). The same lactone was obtained[51] from ψ-santonin (XII) *via* ψ-santonic acid (LIII) and its anhydro compound (LXXXVII).[32,52]



These investigations[49] carried out by Dauben and his co-workers establish the fact that artemisin and ψ-santonin have the same configuration not only at C_8, but also at C_7 and C_{11}.

We have shown earlier (p. 188) that ψ-santonin (XII) has been related[31] to alantolactone (X). We pointed out that ψ-santonin may be converted to the hydroxy-acid (LI), and its lactone (LII), which compounds may also be obtained[26] from tetrahydroalantolactone (XXXVI). The hydroxy acid corresponding to (XXXVI) is oxidised to the keto-acid (Lb), which on reduction with sodium and isopropanol on the one hand affords the hydroxy-acid (LI), whilst on the other hand reduction with sodium borohydride regenerates tetrahydroalantolactone (XXXVI). Since the hydroxy acid (LI) may be reoxidised[53] to the keto-acid (Lb), it is clear that the two lactones XXXVI and LII differ only in configuration at C_8.



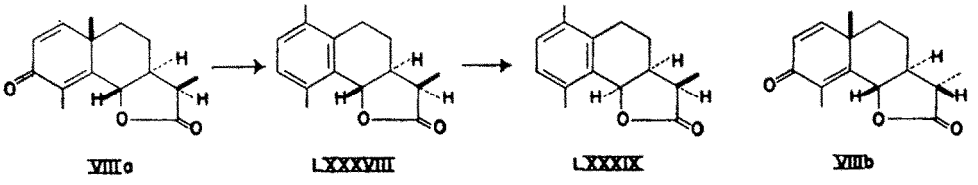
Reduction of a ketone with sodium in an alcohol affords equatorial hydroxyl. The hydroxy-acid (LI) must therefore have α-(equatorial) hydroxyl at C_8, and the lactone LII must consequently be *trans* fused. Sodium borohydride however usually

[51] W. G. Dauben, P. D. Hance, and W. K. Hayes, *J. Amer. Chem. Soc.* 77, 4609 (1955).
[52] W. Cocker, B. E. Cross, and C. Lipman, *J. Chem. Soc.* 959 (1949).
[53] W. Cocker, T. B. H. McMurry and L. O. Hopkins, *J. Chem.* 1998 (1959).

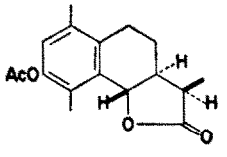
affords axial hydroxyl when the keto group, as in Lb, is hindered. Hence the hydroxy-acid corresponding to tetrahydroalantolactone XXXVI must have β-(axial) hydroxyl at C_8, and tetrahydroalantolactone is thus a *cis* fused lactone.

Configuration at C_{11}

Santonin (VIIIa) *and* 11β(H)-*santonin* (VIIIb). The two santonins mentioned are *trans* fused lactones. This is shown by the fact that santonin may be converted[50] by a series of reactions not involving C_6, to hyposantonin (LXXXVIII), which must have the same lactone ring system as santonin. Gentle alkaline hydrolysis of hyposantonin and acidification of the product however affords a more stable lactone isohyposantonin (LXXXIX), which must therefore be *cis* fused. Epimerisation at C_6 takes place when the sodium salt produced by hydrolysis, is acidified. Again when santonin (VIIIa) is treated[54] under very mild conditions with a mixture of acetic anhydride and acetyl chloride, which cannot affect the lactone ring it affords the acetate of a *trans* fused desmotroposantonin (XC).



VIIIa LXXXVIII LXXXIX VIIIb



XC

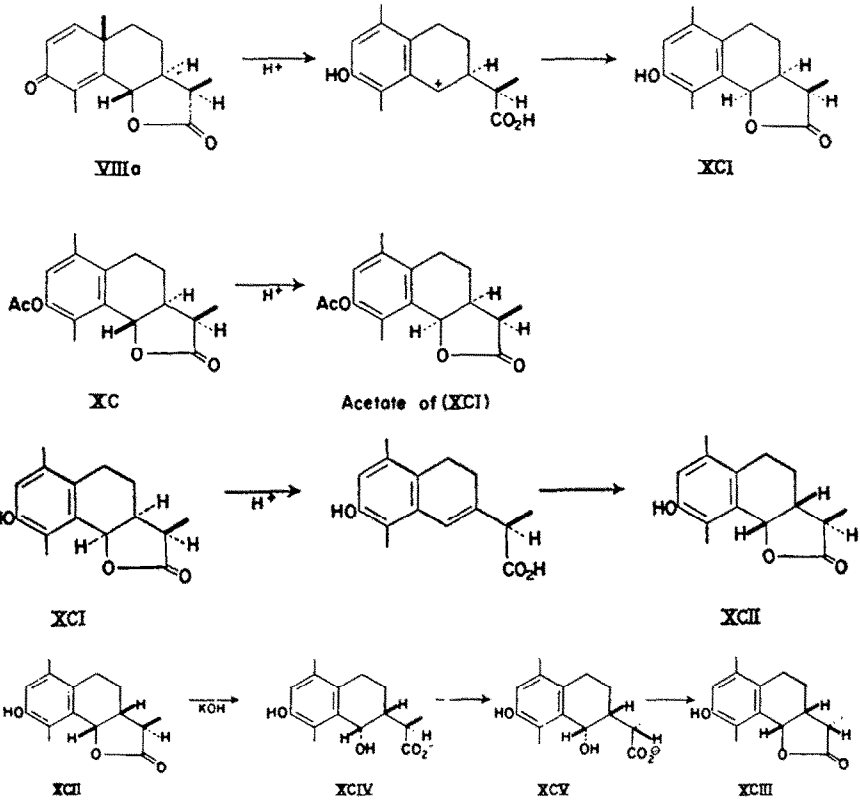
Treatment of santonin (VIIIa) with cold dilute sulphuric acid affords the so-called (—)α-desmotroposantonin (XCI), which is also obtained as its acetate when the acetate (XC) is treated with acid. The only logical deduction from the latter reaction is that (—)α-desmotroposantonin (XCI) is a *cis* fused lactone.[55]

If we accept this view, then in XCI the β-methyl group at C_{11} interacts with the CH_2 at C_8 to a greater degree than its C_{11} epimer, and is thus thermodynamically in the less stable of the two configurations. It can assume the more stable configuration by one of two ways. Either C_{11} can be epimerised leaving C_6 and C_7 unaffected or these centres can be epimerised leaving C_{11} unaffected. In fact when (—)α-desmotroposantonin (XCI) is treated with warm dilute sulphuric acid it undergoes inversion at C_8 and C_7[55] giving (+)β-desmotroposantonin (XCII), in which C_{11} has the more stable configuration.

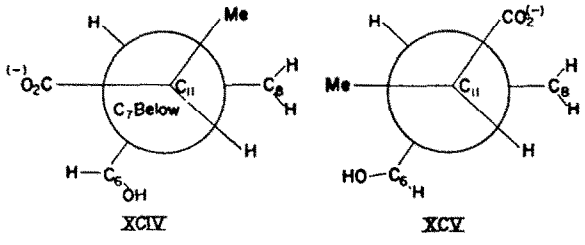
Now when (+)β-desmotroposantonin (XCII) is fused with potassium hydroxide it gives (+)α-desmotroposantonin (XCIII), the enantiomorph of XCI. This change seems to be thermodynamically impossible for in (+)α-desmotroposantonin (XCIII)

[54] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4430 (1955).
[55] Ref. 1(a), pp. 263–269; Huang-Minlon, *J. Amer. Chem. Soc.* **70**, 610 (1948); D. H. R. Barton, *J. Org. Chem.* **15**, 466 (1950).

the methyl group at C_{11} again interacts with the CH_2 at C_8. However it should be remembered[43,56] that during the potash treatment the ion XCIV is present and it is this which undergoes inversion at C_{11} to the more stable ion XCV. Cyclisation of the latter will then afford (+)α-desmotroposantonin (XCIII).



That XCV is the more stable ion is seen in the diagrams below which show that in XCV the CO_2^- group is maximally removed from C_6, the largest group on C_7.

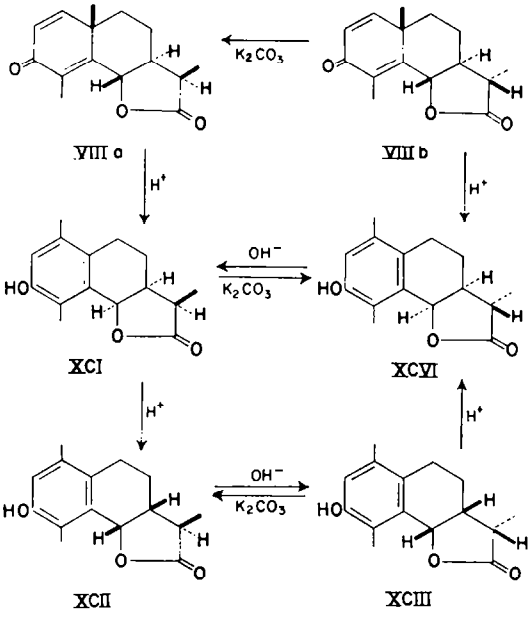


The fact that (+)α-desmotroposantonin XCIII has the more unstable of the two possible configurations at C_{11} is shown as follows: (a) when it is heated with anhydrous potassium carbonate in xylene,[56] under which conditions the lactone remains intact, it affords (+)β-desmotroposantonin (XCII) by epimerisation at C_{11}

[56] N. M. Chopra, W. Cocker, and J. T. Edward, *Chem. & Ind.* 41 (1955).

via the enol, and (b) it affords (—)β-desmotroposantonin (XCVI) when heated with dilute sulphuric acid. Finally, to complete the picture (—)β-desmotroposantonin (XCVI) is (a) obtained from 11β(H)-santonin (VIIIb) with cold dilute acid, (b) is obtained when (—)-α-desmotroposantonin (XCI) is heated with potassium carbonate[56] and (c), it affords (—)α-desmotroposantonin (XCI) when heated with potash.

The full cycle of reactions is shown below and they make it clear that santonin (VIIIa) and 11β(H)-santonin (VIIIb) differ only in configuration at C_{11} and that the former has β-methyl at this centre.



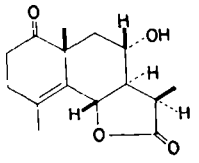
Models show that in both santonin and 11β(H)-santonin, whilst there is no direct interaction between the 11-methyl group and the 8-methylene group, there is greater interference between the 11α-methyl and the lactone carbonyl group than there is in the C_{11} epimer.[54] Hence 11β(H)-santonin has the more unstable lactone. This has been verified experimentally for on heating with anhydrous potassium carbonate,[54] 11β(H)-santonin can be converted to santonin.

Gathering up the above experimental facts it seems clear that (a) with a *cis* fused butanolide the more stable configuration is the one in which the 11-methyl group is *cis* to the 7-hydrogen atom, and (b) with a *trans* fused butanolide the more stable configuration is the one in which the 11-methyl group is *trans* to the 7-hydrogen atom. Corollaries to these rules are (c) when two *cis* fused butanolides are possible, that in which the 11-methyl group is *cis* to the 7-hydrogen atom will be preferred; and (d) when two *trans* fused butanolides are possible that in which the 11-methyl group is *trans* to the 7-hydrogen atom will be preferred (cf. ψ-santonin below).

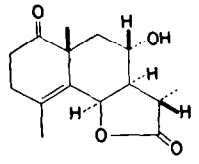
In contrast to the views given above santonin and 11β(H)-santonin have been assigned the opposite configuration at C_{11},[56] but the arguments advanced in support of the hypothesis are dubious. In particular the changed configurations do not explain the reactions of the desmotroposantonins (see p. 196).

Artemisin (IX). We have shown earlier (Chart I) that artemisin is 8-hydroxysantonin. Consequently artemisin has the 11β-methyl group.

ψ-Santonin (XII). We have assigned the 11β-methyl configuration to ψ-santonin,[32] on the following evidence. ψ-Santonin is stable to anhydrous potassium carbonate in boiling xylene and therefore it has the more stable configuration at C_{11}. We can therefore write ψ-santonin as either XII or XCVII, using the rules propounded above.

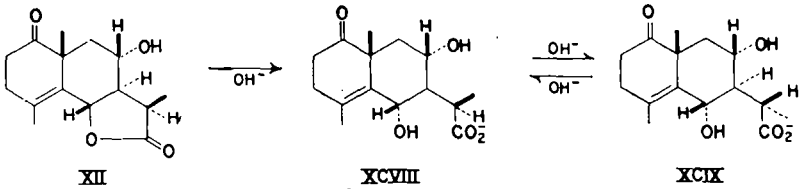


XII

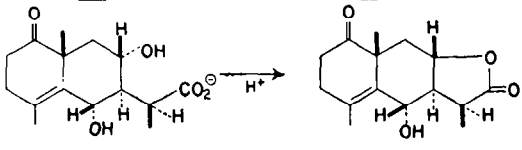


XCVII

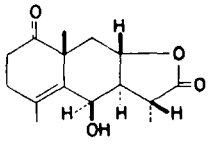
Now when ψ-santonin is heated with potassium hydroxide it gives iso-ψ-santonin,[32] which does not differ from ψ-santonin in its functional groups. On the basis of the preferred structure XII, because of its relationship to santonin, ψ-santonin would be expected with alkali to give the ion XCVIII, which would epimerise at C_{11}[56] to give XCIX, or at least equilibrate with it. On acidification the latter ion would ring-close with the C_8 hydroxyl to give the linear iso-ψ-santonin (C).



XII XCVIII XCIX



C



CI

iso-ψ-Santonin is however stable to potassium carbonate and this is in agreement with the formulation of the lactone as C, which from the rules mentioned above, would be expected to be more stable than its C_{11} epimer. The alternative formulation for ψ-santonin, namely XCVII would lead to the unstable linear iso-ψ-santonin (CI).

Finally as we have already indicated (p. 194), ψ-santonin has been related[49] to artemisin by methods not involving C_{11}, thus showing that ψ-santonin (XII) has the same β-methyl configuration at C_{11} as artemisin, and hence the same as santonin (VIIIa).

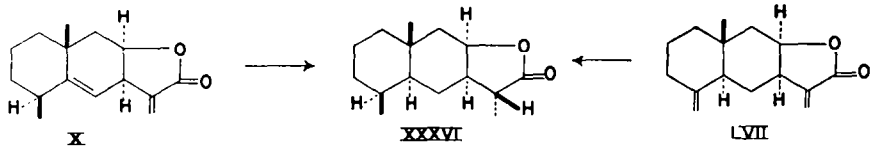
Configuration at C_6 in the lactones

The santonins (VIIIa,b) *artemisin* (IX), *ψ-santonin* (XII). The santonins mentioned have *trans* fused lactone rings; the evidence for this has already been discussed (p. 196). This requirement and the β-orientation of the isopropyl residue at C_7 (p. 192) implies α-linkage of the lactone at C_6. The conversion of artemisin (IX) to santonin without affecting C_6 also implies α-lactone ring fusion in artemisin. Likewise from our discussion of the stereochemistry at C_{11} in ψ-santonin (XII, p. 199) this lactone must also have similar stereochemistry at C_6 to that of the other lactones mentioned.

Stereochemistry of the reduced eudesmanes

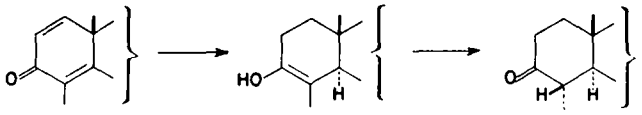
Catalytic reduction of the unsaturated derivatives of eudesmane takes place so that hydrogen adds to the less hindered α-face of the molecule. This is seen in the hydrogenation of eudesmol (II) to give dihydroeudesmol (XLIV), and of both alantolactone (X) and isoalantolactone (LVII) to give tetrahydroalantolactone (XXXVI).

II XLIV



X XXXVI LVII

In cases where there is a 4-en-3-one system as in α-cyperone (VI), santonin (VIIIa), 11β(H)-santonin (VIIIb), and artemisin (IX), the position is complicated by the fact that addition can take place either across the 4:5-double bond, or at the ends of the 4-en-3-one system as a whole. In the latter case the intermediate enol (CII) can rearrange to the stable 4β:5α(H)-system (CIII).



VIIIa CII CIII

1:2 Addition is favoured in non-polar solvents and 1:4-additions in highly polar solvents as noted in the steroid field.[11]

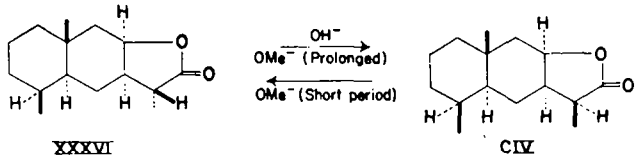
It has been assumed for some time,[39] that dihydroeudesmol could be represented as XLIV. This has recently[58] been proved, by the conversion of tetrahydroalantolactone (XXXVI)[36] whose configuration at C_4 has already been proved (see p. 189), to dihydroeudesmol by reactions not involving C_4. It is clear from these reactions

[57] Y. Abe, T. Miki, M. Sumi, and T. Toga, *Chem. & Ind.* 953 (1956); M. Yanagita and H. Ogura, *J. Org. Chem.* 23, 1268 (1958); cf. W. Cocker and T. B. H. McMurry, *Chem. & Ind.* 1430 (1956).

[58] K. Tanabe, *Pharm. Bull. Japan* 6, 214 (1958).

that alantolactone and isoalantolactone hydrogenate on the α-face of the molecule.

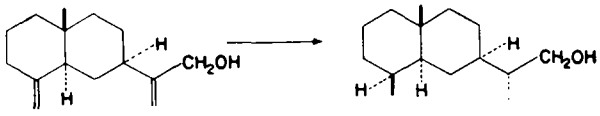
The configuration of the asymmetric centre at C_{11} introduced by hydrogenation of alantolactone (X) or isoalantolactone (LVII) can be deduced[53] from the work of Asselineau *et al.*[59] These workers converted tetrahydroalantolactone (XXXVI) to an isomeric lactone (CIV) by fusion with potassium hydroxide. The conversion can be reversed by a brief treatment with sodium methoxide in methanol, whilst prolonged treatment of tetrahydroalantolactone (XXXVI) with sodium methoxide affords the isomeric lactone (CIV).



XXXVI CIV

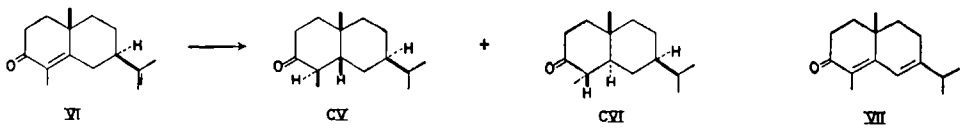
These reactions in which the stereochemistry at C_{11} must be involved, are reminiscent of the chemistry of the *cis* fused lactone rings in the desmotroposantonins (see p. 196). The brief sodium methoxide treatment does not open the lactone ring, but C_{11} is epimerised and the lactone with the more stable configuration at C_{11}, i.e. XXXVI is obtained. Fusion with potassium hydroxide or prolonged treatment with methoxide however affords the more stable (at C_{11}) hydroxy-acid or ester, and these will have configuration at C_{11} corresponding to lactone (CIV), which will consequently be formed on acidification.

Sesquibenihiol (XI). The experiments which related[27,30] sesquibenihiol (XI) to tetrahydroalantolactone (XXXVI, p. 188) make it clear that tetrahydrosesquibenihiol must be XLVI.



XXI XLVI

α-, *and β-Cyperones* (VI, VII). Hydrogenation of α-cyperone (VI) using a palladium-charcoal catalyst in ethanol affords a mixture of the *cis* fused tetrahydro derivative CV and the *trans* isomer CVI in the ratio of 11 to 14.[60] Reduction in



VI CV CVI VII

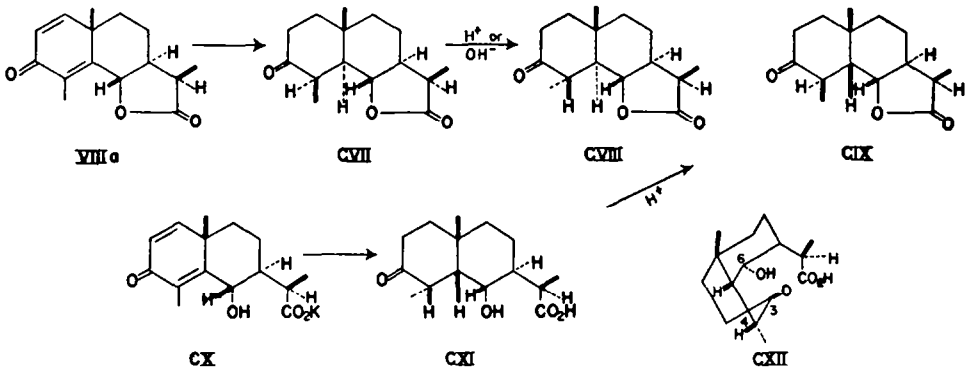
alkaline ethanol gives the *cis* fused tetrahydro derivative, a reaction which involves the enolate.

Reduction of β-cyperone (VII) gives at least some of the *cis* isomer (CV). This must be formed by initial hydrogenation on the α-face of the β-cyperone molecule at the 6:7-double bond followed by desorption from the catalyst and hydrogenation

[59] C. Asselineau, S. Bory, and E. Lederer, *Bull. Soc. Chim. Fr.* 1524 (1955).
[60] R. Howe and F. J. McQuillin, *J. Chem. Soc.* 2670 (1956); 1194 (1958).

of the resulting dihydro compound at the 4:5-double bond from the β-face of the molecule.

Santonin (VIIIa) *and* 11β(H)-*Santonin* (VIIIb). The catalytic reduction of santonin has been studied in several schools.[61] All workers are now agreed that the principal products of catalytic reduction of santonin are the two *trans* fused tetrahydrosantonins CVII and CVIII together with a little of the *cis* isomer CIX.[62,63]



Hydrogenation of potassium santoninate (CX) is comparable with the hydrogenation in alkaline ethanol of α-cyperone (VI), and the *cis* fused hydroxy-acid (CXI) is the main product.[64] Ring closure of the hydroxy-acid takes place with epimerisation at C_4 to give CIX. The stability of the hydroxy-acid at C_4 can be explained if ring A exists in the boat conformation CXII, which would be stabilised by hydrogen bonding between the 6α-hydroxyl and the 3-keto group.[62,63] In CXII, the 4α-methyl group is in the more stable equatorial conformation.

Reduction of 11β(H)-santonin (VIIIb) closely parallels the reduction of santonin itself, and the configuration of the 11-methyl group has little influence on the nature of the products formed.[63,65] With palladised charcoal as catalyst 11β(H)-santonin (VIIIb) affords a mixture of the two *trans* fused tetrahydro compounds CXIII and CXIV, together with a smaller quantity of the *cis* fused isomer CXV and the dihydro compound CXVI.

As in the santonin series the tetrahydro compound CXIII is readily converted either under acid or basic conditions to CXIV with equatorial methyl at C_4. The configurations of the santonin and 11β(H)-santonin reduction products were related[63] by conversion of CXIV to the corresponding tetrahydrosantonin (CVIII) by treatment with potassium carbonate in tetralin.[52,66] Also the 3-desoxy compound (CXVII) derived from the tetrahydro 11(βH)-santonin (CXIV) has been epimerised[66] at C_{11} with sodium methoxide (though it is unaffected by potassium carbonate) to CXVIII,

[61] M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955); A. Tahara, *Ibid.* **21**, 442 (1956); M. Yanagita and R. Futaki, *Ibid.* **21**, 949 (1956); M. Yanagita and H. Ogura, *Ibid*, **22**, 1092 (1957); W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956); B. Riniker, Thesis, E.T.H., Zurich (1955); C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); Ö. Kovács, V. Herout, M. Horák, and F. Šorm, *Chem. Listy* **49**, 1856 (1955); *Coll. Czech. Chem. Comm.* **21**, 225 (1956); cf. ref. 1(a), p. 292.

[62] J. C. Banerji, D. H. R. Barton and R. C. Cookson, *J. Chem. Soc.* 5041 (1957).

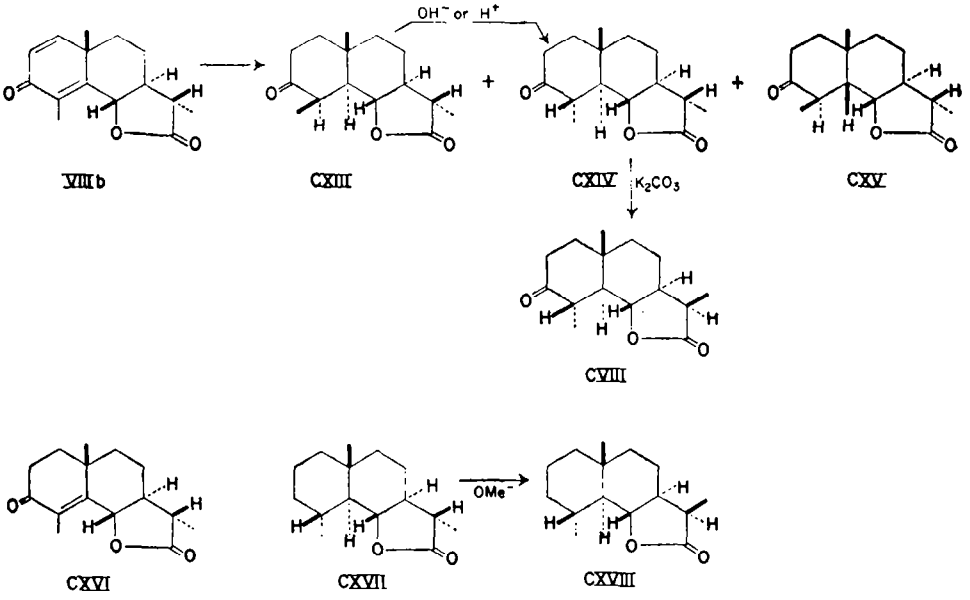
[63] W. Cocker, N. J. H. Dodds, and T. B. H. McMurry, *Tetrahedron* **3**, 160 (1958).

[64] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956).

[65] M. Yanagita and H. Ogura, *J. Org. Chem.* **23**, 1268 (1958).

[66] M. Yanagita and H. Ogura, *J. Org. Chem.* **22**, 1092 (1957).

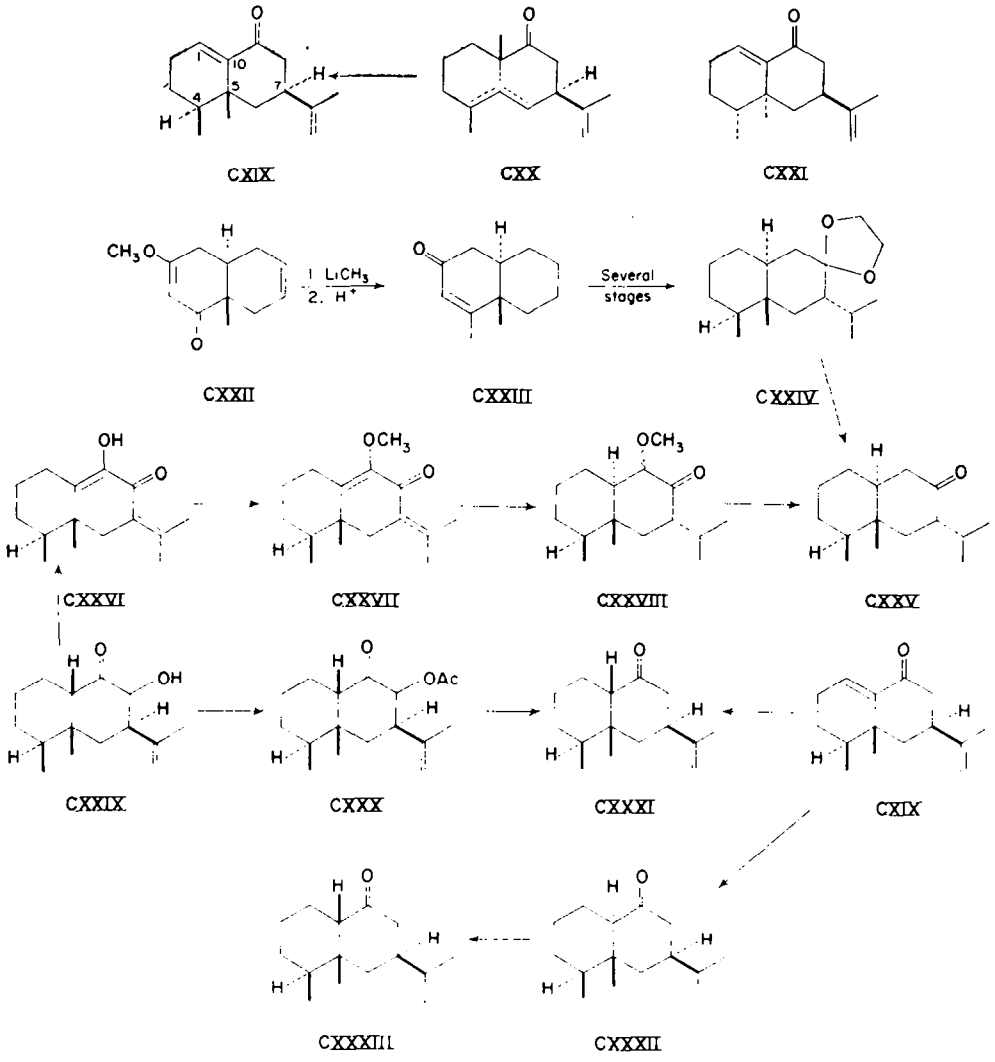
the 3-desoxy compound of the tetrahydrosantonin (CVIII). Such an inversion is expected since as pointed out on p. 198 santonin and its reduced compounds have the more stable configuration at C_{11}.



Eremophilone (CXIX). (Revised, 26 Sept. 1959). Eremophilone is usually looked upon as a member of the eudesmane family, in which the normal isoprene rule is not obeyed. The methyl group is thought[67] to have migrated from C_{10} by a Wagner rearrangement.

The stereochemistry of eremophilone has recently been shown[68,69] to be as in (CXIX), in spite of earlier work[19] which seemed to favour the structure (CXXI). The configuration at C_5 was proved when the dextrorotatory ketone (CXXII), of known absolute configuration[70] was converted to the saturated ketone (CXXV), via (CXXIII) and (CXXIV). The saturated ketone (CXXV) was also obtained from hydroxyeremophilone (CXXVI) by hydrogenation of its methyl ether (CXXVII), equilibration of the resulting ketone with alkali, and demethoxylation of the product (CXXVIII) with calcium in liquid ammonia.[68] Hydroxydihydroeremophilone can be oxidised with bismuth oxide to hydroxyeremophilone (CXXVI) and hence hydroxydihydroeremophilone must have a 5β-methyl group, as in (CXXIX). The orientation of the other asymmetric centres in (CXXIX) follow from an X-ray crystallographic analysis.[71] Hydroxydihydroeremophilone (CXXIX) was converted to its acetate (CXXX) which was reduced with calcium in liquid ammonia to dihydroeremophilone (CXXXI), previously obtained from eremophilone (CXIX) itself. This sequence of reactions cannot involve the centres at C_4, C_5, or C_7 and these must therefore have the same

[67] Sir R. Robinson, cf. A. R. Penfold and Sir J. Simonsen, *J. Chem. Soc.* 87 (1939).
[68] L. H. Zalkow, F. X. Markley and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 2914 (1959).
[69] C. Djerassi, R. Mauli and L. H. Zalkow, *J. Amer. Chem. Soc.* **81**, 3424 (1959).
[70] A. J. Speziale, J. A. Stephens and Q. E. Thompson, *J. Amer. Chem. Soc.* **76**, 5011 (1954).
[71] D. F. Grant and D. Rogers, *Chem. & Ind.* 278 (1956); D. F. Grant, *Acta Cryst.* **10**, 498 (1957).



orientation in eremophilone (CXIX) as in hydroxydihydroeremophilone (CXXIX). Hydrogenation of eremophilone gives the *trans* A/B-fused tetrahydroeremophilone (CXXXII).[19,69] This contains an axial isopropyl group and readily rearranges to give the *cis*-isomer (CXXXIII) where the isopropyl group can be equatorial.