QUARTERLY REVIEWS

RECENT ADVANCES IN SESQUITERPENOID CHEMISTRY

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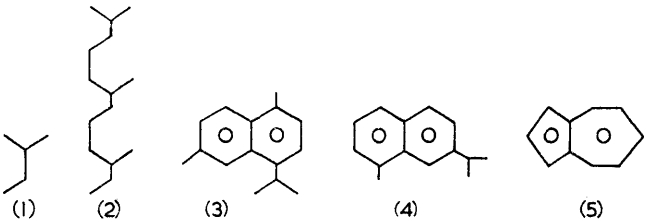
THE chemistry of terpenoid compounds has long been an inspiration to the creative endeavours of the organic chemist. The field of study ranges through mono-, sesqui-, di-, and tri-terpenoids and includes carotenoids and steroids. Even a penta-terpenoid, solanesol, from flue-cured tobacco, has recently been isolated.[1] Apart from their intrinsic interest, terpenoid compounds have provided impetus for theoretical and mechanistic studies and for synthetic investigations.

The best definition of a terpenoid is that it is a compound whose carbon skeleton is either (*a*) theoretically constructed from isoprenoid units (1) or (*b*) has at some stage in its biogenesis had a carbon skeleton so constructed (cf. ref. 2). In the case of sesquiterpenoids the great majority of compounds can be regarded as built up from the union of three isoprenoid residues joined in head-to-tail order (2).



Within the field of sesquiterpenoid chemistry one finds a wide range of oxygenated function, of ring size, and of mechanistic change. If no other type of organic compound were known, organic chemistry would still be a rich and varied field for investigation.

The purpose of the present Review is to deal briefly with established sesquiterpenoid chemistry and treat in more detail the advances of the last decade. The reason for this approach is twofold. First, the extent of the subject is already too large for adequate description in a short review; secondly, earlier work has already been summarised adequately elsewhere.[3]

Sesquiterpenoids can be classified into groups of related compounds

[1] Rowland, Latimer, and Giles, *J. Amer. Chem. Soc.*, 1956, **78**, 4680.
[2] Ruzicka, *Experientia*, 1953, **9**, 357.
[3] Simonsen and Barton, " The Terpenes ", Cambridge Univ. Press, Vol. III, 1952; see also Haagen-Smit, *Fortschr. Chem. org. Naturstoffe*, 1955, **12**, 1.

according to their carbon skeletons. The simplest compounds are aliphatic. Two well-studied and important groups afford respectively cadalene (3) and eudalene (4) on dehydrogenation. A further large group gives on such treatment azulenes (as 5), indicative, in most cases, of a system of fused five- and seven-membered rings. We can also recognise an interesting group of sesquiterpenoids with rings of medium size (9—11-membered).[4] In recent years many sesquiterpenoids of lactonic character have been investigated; these it is convenient to discuss separately although most of them have decalin- or azulene-type carbon skeletons. Tricyclic sesquiterpenoids are common and often present laborious structural problems. Aspects of relative and absolute stereochemistry must also be considered.

Sesquiterpenoids lacking Carbon Rings.—Farnesol (6), which is widely distributed in Nature, is the most important member of this small group. Farnesol and its isomer nerolidol (7) are related in the same way as are geraniol and linaloöl.[5] Farnesol was the first sesquiterpenoid to have its constitution elucidated.[6] In recent years it and its derivatives have been the subject of interesting cyclisations.[7] In so far as cyclic terpenoids may arise in Nature from acyclic or other simpler precursors such experiments are also of considerable biogenetic interest.[8] Simple carbonium-ion theory [9] predicts satisfactorily the products of such cyclisation reactions. The stereochemistry of cyclisation can be discussed along the following lines.[10] Concerted cyclisation of a triene such as (8) should afford a *trans*-fused decalin (9; X = anion). Non-concerted cyclisation to a monocyclic intermediate (10) followed by a concerted ring closure (or its equivalent) should furnish a *cis*-fused decalin (11; X = anion). Several convincing examples of the latter process are known.[11, 12] In the laboratory the cyclisations proceed to give products of mixed stereochemistry and the processes are

[4] Prelog, *J.*, 1950, 420; Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212; Heck and Prelog, *Helv. Chem. Acta*, 1955, **38**, 1541; Brown and Ham, *J. Amer. Chem. Soc.*, 1956, **78**, 2735.

[5] Simonsen and Owen, "The Terpenes", Cambridge Univ. Press, Vol. I, 1947.

[6] Kerschbaum, *Ber.*, 1913, **46**, 1732.

[7] *Inter al.*, Zobrist and Schinz, *Helv. Chim. Acta*, 1949, **32**, 1192; Caliezi and Schinz, *ibid.*, p. 2556; 1950, **33**, 1129; 1952, **35**, 1649; Collin-Asselineau, Lederer, and Polonsky, *Bull. Soc. chim. France*, 1950, 715; Stoll and Commarmont, *Helv. Chim. Acta*, 1949, **32**, 1836; Kappeler, Eschenmoser, and Schinz, *ibid.*, 1953, **36**, 1877; Kappeler, Stauffacher, Eschenmoser, and Schinz, *ibid.*, 1954, **37**, 957; Gamboni, Schinz, and Eschenmoser, *ibid.*, p. 964.

[8] *Inter al.*, Bloch and Rittenberg, *J. Biol. Chem.*, 1945, **159**, 45; Langdon and Bloch, *ibid.*, 1953, **200**, 129; Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023; Clayton and Bloch, *J. Biol. Chem.*, 1956, **218**, 305, 319; Dauben, Abraham, Hotta, Chaikoff, Bradlow, and Soloway, *J. Amer. Chem. Soc.*, 1953, **75**, 3038; Cornforth and Popjak, *Biochem. J.*, 1954, **58**, 403; Popjak, *Arch. Biochem. Biophys.*, 1954, **48**, 102.

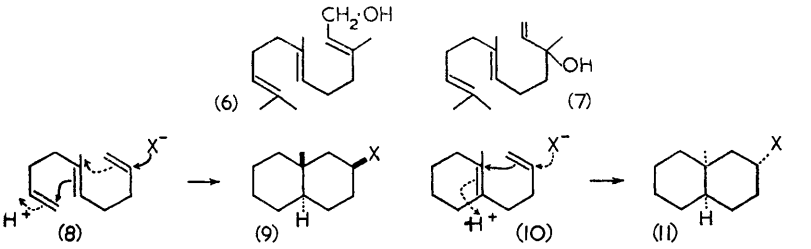
[9] Ingold, "Structure and Mechanism in Organic Chemistry", Bell, London, 1953; Wheland, "Advanced Organic Chemistry", Chapman and Hall, London, 1949.

[10] Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068.

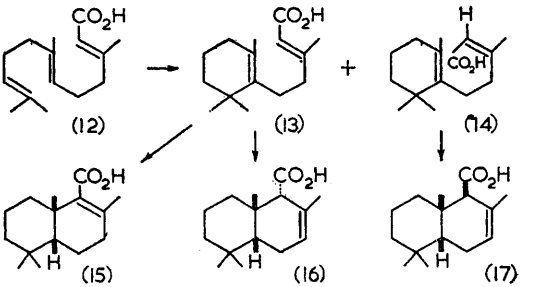
[11] *Inter al.*, Eschenmoser and co-workers, ref. 7; also Eschenmoser, Ruzicka, Jeger, and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890.

[12] Linstead, Wang, Williams, and Errington, *J.*, 1937, 1136; Linstead, Millidge, and Walpole, *J.*, 1937, 1140; Burnop and Linstead, *J.*, 1940, 720.

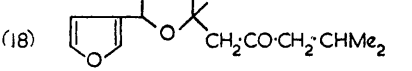
not, in general, fully concerted. For example,[10] treatment of farnesenic acid (12) in benzene solution with boron trifluoride–ether complex affords



the monocyclic derivatives (13) and (14). Cyclisation of the latter at higher temperatures gives three *cis*-decalin derivatives, (15), (16), and (17). Comparable cyclisation processes in Nature appear to be fully concerted.[13] Their imitation still presents, therefore, a challenge.



Amongst more recently investigated non-carbocyclic sesquiterpenoids we may mention ngaione (18) and its enantiomer ipomeamarone.[14] Ngaione comes from the essential oil of *Myoporum acuminatum*, ipomeamarone is found in black-rotted sweet potatoes. The structure (18) is, of course, built up from the usual chain of three isoprenoid residues.



Cadalene-type Sesquiterpenoids.—The chemistry of these substances has for the most part already been adequately reviewed.[3] A number of sesquiterpene hydrocarbons affording cadalene (3) in high yield on dehydrogenation and giving cadinene dihydrochloride (19) on addition of hydrogen chloride, have been reported.[15] The compound known simply as cadinene (from oil of cubebs) has the constitution (20).[16] We may also include in the cadalene

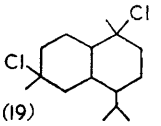
[13] Tchen and Bloch, *J. Amer. Chem. Soc.*, 1956, **78**, 1516.

[14] Kubota and Matsuura, *Chem. and Ind.*, 1956, 521; see also Birch, Massy-Westropp, Wright, Kubota, Matsuura, and Sutherland, *ibid.*, 1954, 902.

[15] *Inter al.*, Herout and Šantavy, *Coll. Czech. Chem. Comm.*, 1954, **19**, 118.

[16] Campbell and Soffer, *J. Amer. Chem. Soc.*, 1942, **64**, 417, and references there cited. This refers to material recorded from the dihydrochloride; it may still be inhomogeneous.

group a number of monocyclic sesquiterpenoids which afford the cadalene-type skeleton on cyclisation, or are structurally closely related. Examples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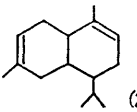
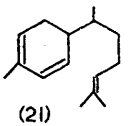

(20)

are zingiberene (21),[17] γ-curcumene (22),[18] and lanceol (23).[19] Also we may mention the cadalene-type dimer gossypol, the pigment of cotton seed.[20]

The interesting sesquiterpene alcohol carotol (24),[21] giving on dehydrogenation the naphthalene (25), may be a member of the cadalene group in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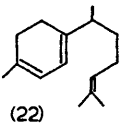
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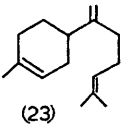
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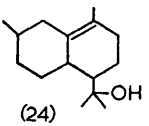
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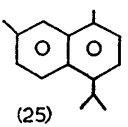
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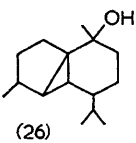
which methyl migration has occurred in the last step of the biosynthesis of the carbon skeleton. The skeleton of carotol can be constructed from three isoprenoid residues, but not if these are linked as in the conventional farnesol chain. An alternative possible biogenesis may be through a spiranic intermediate (see acorone below). Laserpitin, the bitter principle from *Laserpitium latifolium*, has recently been shown to have the same skeleton as carotol.[22] Ledol, isolated from marsh tea oil, was formerly assigned the formula (26) or (27).[23] Recently, this compound and its considered diastereoisomer palustrol have been investigated by Kiryalov [24] and the new constitution (28) has been proposed. The known degradations of ledol [23, 24] could only be explained on the basis of formula (28) if non-Markownikoff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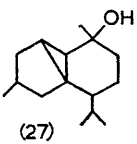
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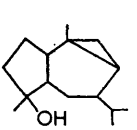

(28)

opening of the *cyclo*propane ring be postulated. In so far as all known *cyclo*propane compounds in the terpenoid series undergo Markownikoff rupture with acid the validity of formula (28) may be doubted.[25] Definite

[17] Eschenmoser and Schinz, *Helv. Chim. Acta*, 1950, **33**, 171.

[18] Batt and Slater, *J.*, 1949, 838; Birch and Mukherji, *ibid.*, p. 2531.

[19] Eschenmoser, Schreiber, and Keller, *Helv. Chim. Acta*, 1951, **34**, 1667; Birch and Murray, *J.*, 1951, 1888.

[20] Adams, Morris, Geissman, Butterbaugh, and Kirkpatrick, *J. Amer. Chem. Soc.*, 1938, **60**, 2193; Edwards and Cashaw, *ibid.*, 1956, **78**, 3224, and references there cited.

[21] Šorm and Urbánek, *Coll. Czech. Chem. Comm.*, 1948, **13**, 49, 420; Šorm and Mleziva, 1949, **14**, 98.

[22] Šorm, Holub, and Herout, *Chem. and Ind.*, 1954, 965.

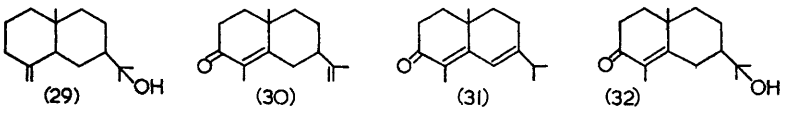
[23] Komppa, cited in ref. 3.

[24] Kiryalov, *Doklady Akad. Nauk S.S.S.R.*, 1948, **61**, 305.

[25] de Mayo, *Perfumery Essent. Oil Record*, 1957, 18.

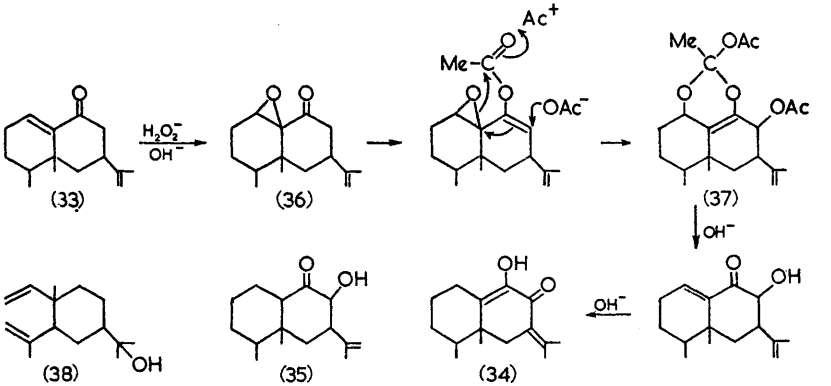
evidence against structure (28) has been provided by Cole and Lahey [26] who were unable to find in the infrared spectrum of ledol the band at 3050 cm.$^{-1}$ characteristic of a methylene group in a three-membered ring.[27]

Eudalene-type Sesquiterpenoids.—These are sesquiterpenoids which afford eudalene (4) on dehydrogenation. Some typical examples are eudesmol (29), from eucalyptus oil, α-(30) and β-cyperone (31), from the tubers of *Cyperus rotundus*,[28] and the related carissone (32).[29] The carbon skeletons of these compounds can be constructed from a farnesol chain.



The position of the angular methyl group in these compounds has been established rigidly by degradation [30] and by synthesis.[31]

The most interesting non-lactonic sesquiterpenoid of the eudalene type is eremophilone (33),[32] for in this compound the angular methyl group occupies an apparently non-isoprenoid position. The constitution of eremophilone can be reconciled with the normal eudalenoid pattern if its



biogenesis involves migration of a methyl group.[33] Similar migrations are, by now, a familiar feature of the chemistry of the higher terpenoids.[34] Eremophilone (33) occurs in the wood oil of *Eremophila mitchelli* together

[26] Lahey and Lamberton, *Austral. J. Chem.*, 1956, **9**, 431.

[27] Cole, *J.*, 1954, 3807, 3810.

[28] Bradfield, Gillam, Hedge, Rao, and Simonsen, *J.*, 1936, 667 ; Bradfield, Pritchard, and Simonsen, *J.*, 1937, 760 ; McQuillin, *J.*, 1955, 528.

[29] Mohr, Schindler, and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 462 ; Barton and Tarlton, *J.*, 1954, 3492.

[30] Plattner, Fürst, and Hellerbach, *Helv. Chim. Acta*, 1947, **30**, 2158.

[31] Howe and McQuillin, *J.*, 1955, 2423. [32] Simonsen *et al.*, cited in ref. 3.

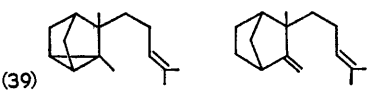
[33] (Sir) Robert Robinson, cited in ref. 3.

[34] Barton, *Chem. and Ind.*, 1948, 638 ; Velluz, Muller, Petit, and Mathieu, *Bull. Soc. chim. France*, 1954, 401 ; Subluskey and Sanderson, *J. Amer. Chem. Soc.*, 1954, **76**, 3512 ; Barton and de Mayo, *J.*, 1953, 3111 ; Allan, Fayez, Spring, and Stevenson, *J.*, 1956, 456, and earlier papers in this series.

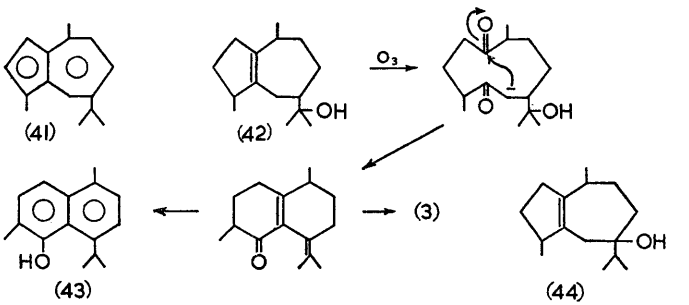
with hydroxyeremophilone (34) [35] and dihydrohydroxyeremophilone (35). One of the most interesting reactions of these compounds is the conversion of eremophilone oxide (36), by digestion with sodium acetate and acetic anhydride followed by hydrolysis with alkali, into hydroxyeremophilone (34). A possible mechanism is indicated in the formulæ; the conversion of the postulated intermediate (37) into (34) by rearrangement of the α-ketol system, etc., is conventional. The constitution assigned to dihydrohydroxyeremophilone has recently been confirmed by *X*-ray analysis.[36]

The sesquiterpene alcohol elemol, obtained from Manila elemi oil, is a monocyclic derivative (38) of the eudesmol carbon skeleton.[37] It will be noted, however, that elemol is not a cyclisation product of farnesol although its skeleton is divisible into isoprenoid residues. It has been suggested [2] that elemol may be formed in Nature by ring fission of a eudesmol-type precursor.

The sesquiterpenoid components of sandal wood oil, α- (39) and β-santalene (40) and their derivatives, can also be regarded as belonging to the eudalene group.[3]



Azulenic Non-lactonic Sesquiterpenoids.—Most of the naturally occurring non-lactonic perhydro-azulenic sesquiterpenoids are related to guaiazulene (41). A typical example is guaiol whose constitution (42) was elucidated



by Plattner and his collaborators.[38] The most significant reaction sequence was that indicated in the formulæ which afforded cadalene (3) and the naphthol (43). The identity of the latter was established by synthesis.

It could have been objected to the constitution (42) that the *tertiary* hydroxyl group might also have been placed as in (44). The correctness of Plattner's formula (42) has been confirmed by pyrolysis of the phenylazo-

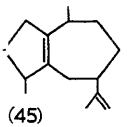
[35] See also Geissman, *J. Amer. Chem. Soc.*, 1953, **75**, 4008.

[36] Grant and Rogers, *Chem. and Ind.*, 1956, 278.

[37] Sýkora, Herout, Pliva, and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 124; Sýkora, Černý, Herout, and Šorm, *ibid.*, p. 566; 1955, **20**, 220.

[38] Plattner and Lemay, *Helv. Chim. Acta*, 1940, **23**, 897; Plattner and Magyar, *ibid.*, 1941, **24**, 191; 1942, **25**, 581.

phenylurethane of guaiol to give a hydrocarbon (45),[39] the presence of the *iso*propenyl grouping being established by the infrared spectrum.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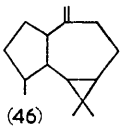
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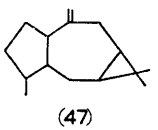
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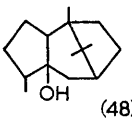
The guaiazulene derivative aromadendrene,[3] the characteristic sesquiterpene of eucalyptus oils, has been related to the alcohol globulol, from *Eucalyptus globulus*, by pyrolysis of the 3 : 5-dinitrobenzoate.[40] Recent work on aromadendrene [41] has led to the proposal of two plausible structures, (46) and (47), for the hydrocarbon, and to the corresponding saturated *tertiary* alcohol formulations for globulol.

Patchouli alcohol, a crystalline constituent of Patchouli oil, was the subject of preliminary investigations in the last century. It is, however, only recently that structural formulæ have been advanced. Treibs [42] proposed the formula (48) mainly on the basis of two important experiments carried out on " patchoulene " (49), the hydrocarbon mixture obtained by acid-catalysed dehydration of the alcohol. Dehydrogenation gave guaiazulene (41), whilst ozonolysis followed by oxidation with potassium permanganate furnished homocamphoric (50) and camphoric acid. Further investigation by Büchi and Erickson [43] has shown that, whilst " patchoulene " is



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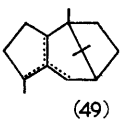
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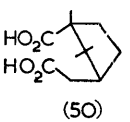
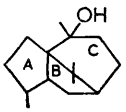
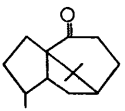


(50)

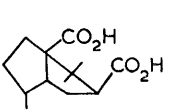
correctly formulated as essentially (49), patchouli alcohol itself has structure (51), its conversion into the hydrocarbon mixture involving a rearrangement. The acetate of patchouli alcohol, prepared by reaction with keten, was pyrolysed and the resulting hydrocarbon oxidised to the nor-ketone (52).



(51)



(52)



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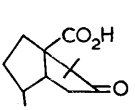


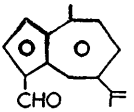
(54)

Further oxidation of the ketone gave a substituted glutaric acid (53), with loss of one carbon atom. This establishes the size of ring C. Further degradation of the acid (53) furnished the ketone (54) whose infrared spectrum showed the keto-group to be contained in a five-membered ring. The size of ring B is, therefore, also established.

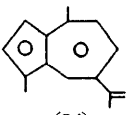
The orange agaric, *Lactarius deliciosus*, contains a number of interesting

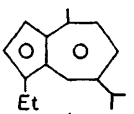
[39] O'Brien, Penfold, Sutherland, and Werner, *Austral. J. Chem.*, 1954, **7**, 298.
[40] Blumann, Cole, Thieberg, and White, *Chem. and Ind.*, 1954, 1426.
[41] Treibs and Barchet, *Annalen*, 1950, **566**, 89 ; Birch and Lahey, *Austral. J. Chem.*, 1953, **6**, 379.
[42] Treibs, *Annalen*, 1949, **564**, 141.
[43] Büchi and Erickson, *J. Amer. Chem. Soc.*, 1956, **78**, 1262.

guaiazulene derivatives. Of these the more important are lactaroviolin (55) and lactarazulene (56).[44] Lactaroviolin (55) is converted into lactarazulene (56) on Wolff–Kishner reduction, whilst on partial hydrogenation the azulene affords guaiazulene (41). Ozonolysis of lactarazulene gives formaldehyde. This evidence establishes the constitution (56) and only leaves unplaced the aldehyde group in lactaroviolin. The correctness of formula (55), suggested by physical data, has been confirmed by conversion of the aldehyde group into —CH(OH)·Me followed by partial hydrogenation. This



(55)

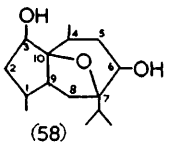

(56)



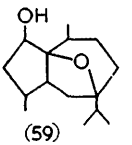
(57)

selectively reduced the *iso*propenyl group and removed the hydroxyl group by hydrogenolysis, thus affording 1-ethyl-4-methyl-7-*iso*propylazulene (57).

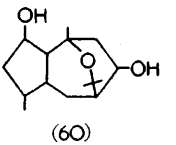
Asahina and Nakanishi[45] isolated from the rhizomes of *Valeriana officinalis* L. var. *latifolia* Miq. a sesquiterpenoid ester which afforded two mols. of acetic acid and a glycol, kessoglycol, on hydrolysis. This glycol and the related alcohol, kessyl alcohol, have been the subject of extensive investigation.[46] Kessoglycol is a derivative of guaiazulene; it has two secondary hydroxyl groups at positions 3 and 6. The remaining structural feature is the position of the ether bridge. Formulæ (58) and (59) have been accepted for some time as representing kessoglycol and kessyl alcohol respectively. Recently the transformations carried out by Ukita[46] have been re-appraised and the structures (60) and (61) proposed for the glycol and its derived alcohol respectively. The new formulæ are in better mechanistic accord with the available evidence.[47]



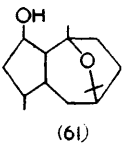
(58)



(59)



(60)



(61)

Of the remaining guaiazulene derivatives partheniol, which occurs as the cinnamate in guayule, has been formulated as (62),[48] whilst linderene, from the oil of *Linderia strychnifolia*, is formulated as (63).[49] The latter structure at least is not, however, firmly established in its finer details.

[44] *Inter al.*, Willstaedt, *Ber.*, 1935, **68**, 333; Šorm, Benešova, and Herout, *Coll. Czech. Chem. Comm.*, 1954, **19**, 357; Šorm, Benešova, Krupička, Šneberk, Dolejš, Herout, and Sicher, *Chem. and Ind.*, 1954, 1511; Plattner and Heilbronner, *Experientia*, 1945, **1**, 233; Plattner, Heilbronner, Schmid, Sandrin, and Fürst, *Chem. and Ind.*, 1954, 1202; Heilbronner and Schmid, *Helv. Chim. Acta*, 1954, **37**, 2018.

[45] Asahina and Nakanishi, *J. Pharm. Soc. Japan*, 1929, **49**, 135.

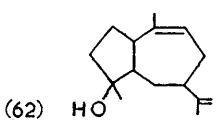
[46] Ukita, *ibid.*, 1944, **64**, 285; 1945, **65**, 458; Treibs, *Annalen*, 1950, **570**, 165.

[47] de Mayo, *Perfumery Essent. Oil Record*, 1957, 18.

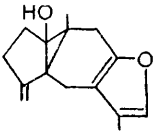
[48] Haagen-Smit and Fong, *J. Amer. Chem. Soc.*, 1948, **70**, 2075.

[49] Takeda, Negata, and Kubota, *Pharm. Bull. (Japan)*, 1953, **1**, 241; Takeda, *ibid.*, p. 244.

Other guaiazulene derivatives of uncertain structure are germacrol,[50] the gurjunenes,[3] himbaccol,[51] and α-chigadmarene.[52]

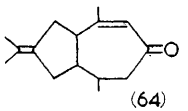


(62)

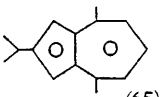


(63)

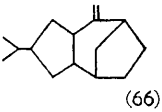
Oil of vetiver contains two stereoisomeric ketones, α- and β-vetivone. Degradational studies have mainly been concerned with β-vetivone (64).[3] Dehydrogenation of suitable derivatives affords vetivazulene (65). The carbon skeleton of this azulene is also based on the farnesol chain. Recently a tricyclic sesquiterpene hydrocarbon, tricyclovetivene (66), has been isolated from the same essential oil,[53] and on dehydrogenation this also affords vetivazulene.



(64)

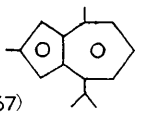


(65)

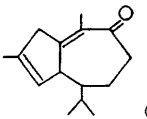


(66)

A new type of azulene skeleton has been detected in the ketone zierone.[54] Dehydrogenation of a derived hydrocarbon affords the novel zierazulene (67), the constitution of which has been confirmed by synthesis. A possible expression for zierone is (68). The carbon skeleton of this compound can be constructed from *iso*prenoid residues but not from a farnesol chain.



(67)



(68)

Medium-ring Sesquiterpenoids.—Few compounds of this class are, as yet, known. The most important and most interesting is the sesquiterpene caryophyllene, the chemistry of which was extensively investigated by Simonsen,[3] Ruzicka,[3] and their colleagues before the war (1939). Other compounds to be mentioned here are the crystalline zerumbone and the liquid humulene, the final details of whose structure still await elucidation. The crystalline lactone, pyrethrosin, with its ten-membered carbon ring, is conveniently considered along with lactones of the decalin class (see below).

The sesquiterpene fraction of oil of cloves is the main source of caryophyllene. In the older literature the terms α-, β- and γ-caryophyllene have been used to designate specific hydrocarbons from this source. Since α-caryophyllene is identical with humulene and γ-caryophyllene is possibly

[50] Treibs, *Annalen*, 1952, **576**, 116.

[51] Birch and Mostyn, *Austral. J. Chem.*, 1955, **8**, 550.

[52] Rao, Dutt, Dev, and Guha, *J. Indian Chem. Soc.*, 1952, **29**, 604, 602.

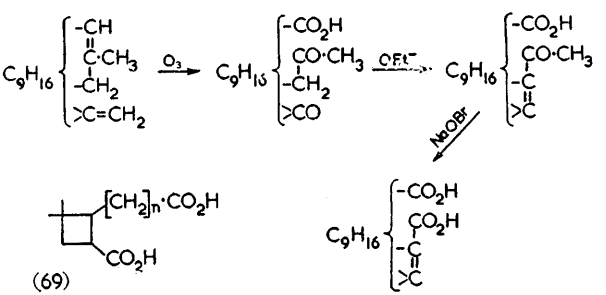
[53] Chiurdoglu and Tullen, *Chem. and Ind.*, 1956, 1094.

[54] Bradfield, Penfold, and Simonsen, *J. Proc. Roy. Soc. New South Wales*, 1933, **67**, 200; Birch, Collins, and Penfold, *Chem. and Ind.*, 1955, 1773.

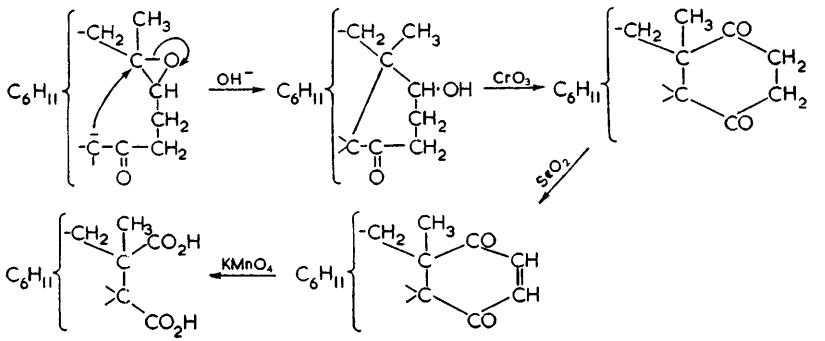
an artefact arising from thermal isomerisation, it is now customary to refer to the main hydrocarbon, β-caryophyllene, simply as caryophyllene and to use the rational name *iso*caryophyllene instead of γ-caryophyllene.

Caryophyllene is principally remarkable for the ease with which it and its derivatives undergo cyclisation. It has the molecular formula $C_{15}H_{24}$ and contains two ethylenic linkages; it is, therefore, bicyclic. Oxidative degradation affords three *cyclo*butane acids: norcaryophyllenic acid (69; n = 0), caryophyllenic acid (69; n = 1), and homocaryophyllenic acid (69; n = 2), all of which have been synthesised.[55]

One of the two ethylenic linkages is present as $>C{=}CH_2$, the other is trisubstituted and, from the degradations shown in the annexed formulæ,[56] is contained in the system $—CH_2—C(CH_3)=CH—$.



The size of the second ring in caryophyllene was for many years a matter of doubt. Evidence on this point was finally forthcoming from two sources. Caryophyllene is smoothly oxidised by hydrogen peroxide to a crystalline



epoxide. This compound retains the $>C{=}CH_2$ of caryophyllene for on further attack by potassium permanganate it affords a crystalline C_{14} epoxy-ketone.[57] The infrared carbonyl frequencies of the epoxy-ketone

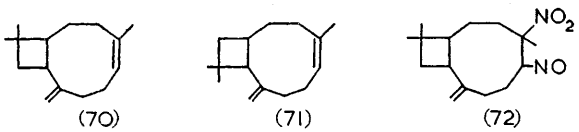
[55] Rydon, *J.*, 1936, 593; 1937, 1340; Campbell and Rydon, *J.*, 1953, 3002; Dawson and Ramage, *J.*, 1950, 3523; 1951, 3382.

[56] Ruzicka and Wind, *Helv. Chim. Acta*, 1931, **14**, 410.

[57] Treibs, *Chem. Ber.*, 1947, **80**, 56.

and of suitable derivatives are best interpreted in terms of a nine-membered ring for caryophyllene.[58] Decisive chemical evidence has been adduced [59] by the reaction sequence outlined, where (A) represents the epoxy-ketone.

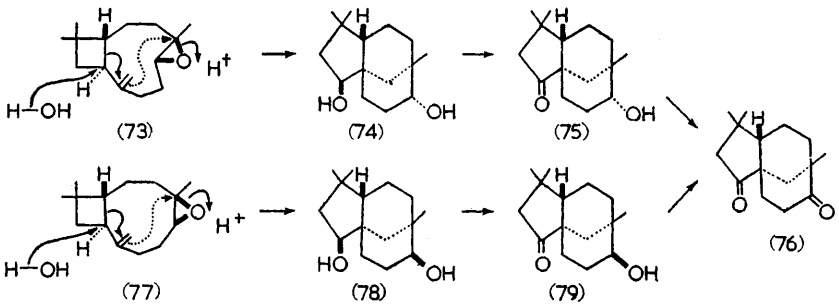
In the formulæ on p. 198 the C_6H_{11} fragment must contain the dimethyl-*cyclo*butane ring. Allowing for this and recognising that the dicarboxylic acid from this sequence is ditertiary shows that the formula for caryophyllene



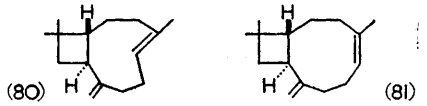
(70) (71) (72)

must be either (70) or (71). The constitutions of caryophyllenic and homocaryophyllenic acids exclude (71), leaving (70) as a formula adequate to explain all the known facts.

The exact nature of " γ-caryophyllene ", now known as *iso*caryophyllene, has been elucidated in the following way.[60] *iso*Caryophyllene is a by-product in the preparation of caryophyllene nitrosite (72) and is formed when the latter is heated in ethanol. On treatment with per-acid *iso*caryophyllene affords a crystalline oxide isomeric with that (see above) from caryophyllene.



Under mild acid conditions, caryophyllene oxide (73) gave a crystalline diol (74) which, when oxidised with chromic acid, afforded first the ketol (75) and then the diketone (76). Similar cyclisation of *iso*caryophyllene oxide gave a stereoisomeric diol (78) oxidised *via* the ketol (79) to the same diketone (76). These experiments show that the two epoxides must be stereo-



isomerides and that therefore caryophyllene and *iso*caryophyllene are simply geometrical isomerides about the endocyclic ethylenic linkage. All the evidence goes to show that caryophyllene is less stable and more reactive

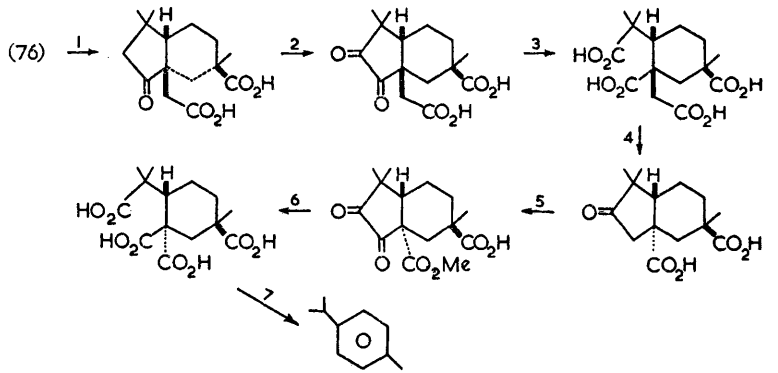
[58] Šorm, Dolejš, and Pliva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 186.

[59] Barton and Lindsey, *J.*, 1951, 2988.

[60] Aebi, Barton, and Lindsey, *J.*, 1953, 3124; see also Ramage and Whitehead, *J.*, 1954, 4336.

towards electrophilic reagents than its isomer. Caryophyllene is, therefore, the *trans*-isomer (80) [61] and *iso*caryophyllene the *cis*-derivative (81).

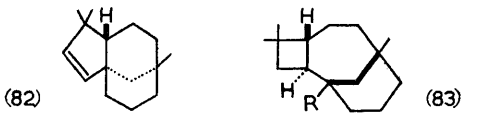
The constitution of the diketone (76) has been rigidly established [62] by the degradational sequence shown leading finally to *p*-cymene. The configurations of the epoxide rings are based on conformational analysis [60, 62]



Reagents: 1, CrO_3; 2, SeO_2; 3, H_2O_2–OH^-; 4, heat; 5, CH_2N_2, then SeO_2; 6, H_2O_2–OH^-; 7, Pd–C.

of the secondary hydroxyl groups in (74) and (78) and upon other considerations.

A number of acid-catalysed cyclisations of caryophyllene are of considerable interest. The major cyclisation products are clovene (82) and caryolan-1-ol (83; R = OH) (formerly known as β-caryophyllene alcohol). The constitution and stereochemistry of clovene have been firmly established by relating it to the diol (74).[62, 63] The constitution of caryolan-1-ol (83; R = OH) was proposed on chemical evidence [64] and established beyond



question by the very important *X*-ray studies of J. Monteath Robertson and Todd [65] on caryolanyl chloride (83; R = Cl), which is formed from the alcohol with retention of constitution and configuration.[64] The *X*-ray studies were especially important in elucidating the stereochemistry of the tricyclic derivatives of caryophyllene and of the ring junction in caryophyllene itself.[66] The conversion of the bridgehead alcohol (83; R = OH)

[61] *Inter al.*, Prelog, Schenker, and Küng, *Helv. Chim. Acta*, 1953, **36**, 471; Prelog, Schenker, and Günthard, *ibid.*, 1952, **35**, 1598.

[62] Aebi, Barton, Burgstahler, and Lindsey, *J.*, 1954, 4659.

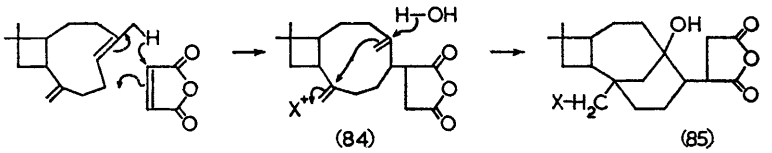
[63] Lutz and Reid, *J.*, 1954, 2265; see also Eschenmoser and Günthard, *Helv. Chim. Acta*, 1951, **34**, 2338.

[64] Barton, Bruun, and Lindsey, *J.*, 1952, 2210.

[65] Robertson and Todd, *J.*, 1955, 1254.

[66] See also Šorm, Jarolim, Streibl, and Dolejš, *Chem. and Ind.*, 1956, 154.

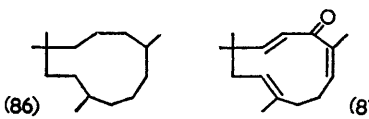
into the chloride is of some mechanistic interest [67] since the change requires the formation of a bridgehead carbonium ion. Presumably the required ion with its flattened (trigonal) geometry is not seriously impeded in the 4 : 3 : 1 system (83). With maleic anhydride caryophyllene forms an adduct which is not of the usual Diels–Alder type : [3] its constitution has been shown to be (84). The adduct cyclises with electrophilic reagents



(84) (85)

(X = Br or H) to furnish yet another type (85 ; X = Br or H) of tricyclic caryophyllene derivative.[68]

Humulene (α-caryophyllene), from oil of hops, is closely related to caryophyllene but differs in being monocyclic, in containing three ethylenic linkages, and in being optically inactive. Hexahydrohumulene (humulane) is undoubtedly 1 : 1 : 4 : 8-tetramethyl*cyclo*undecane (86) and it has been synthesised.[69] The exact location of the three ethylenic linkages within the framework (86) is still a matter for final decision.[70]



(86) (87)

Zerumbone is an interesting ketone isolated from wild ginger.[71] Its structure (87) has recently been elucidated and its relation to humulene made apparent.[72] On treatment with alkali zerumbone is cleaved to give ethyl methyl ketone as the sole volatile fragment. This fact, together with the conversion of zerumbone into humulane and ozonolysis to give *as*-dimethylsuccinic and lævulic acid, serve to establish the constitution.

Miscellaneous Non-lactonic Sesquiterpenoids.—We discuss here several compounds not conveniently considered in the previous sections. The sesquiterpene cedrene, from cedar-wood oil, is a good example of the difficulties of structural work when no useful dehydrogenation products can

[67] Applequist and Roberts, *Chem. Rev.*, 1954, **54**, 1065 ; Doering, Levitz, Sayigh, Sprecher, and Whelan, *J. Amer. Chem. Soc.*, 1953, **75**, 1008 ; Fawcett, *Chem. Rev.*, 1950, **47**, 219.

[68] Nickon, *J. Amer. Chem. Soc.*, 1955, **77**, 1190.

[69] Šorm, Mleziva, and Arnold, *Coll. Czech. Chem. Comm.*, 1949, **14**, 693 ; Sorm, Mleziva, Arnold, and Pliva, *ibid.*, p. 699 ; Herout, Streibl, Mleziva, and Sorm, *ibid.*, p. 716 ; Sorm, Streibl, Pliva, and Herout, *ibid.*, 1952, **16**, 639 ; Šorm, Streibl, Jarolim, Novotny, Dolejs, and Herout, *ibid.*, 1954, **19**, 570 ; Clemo and Harris, *J.*, 1951, 22 ; 1952, 655 ; Harris, *J.*, 1953, 184.

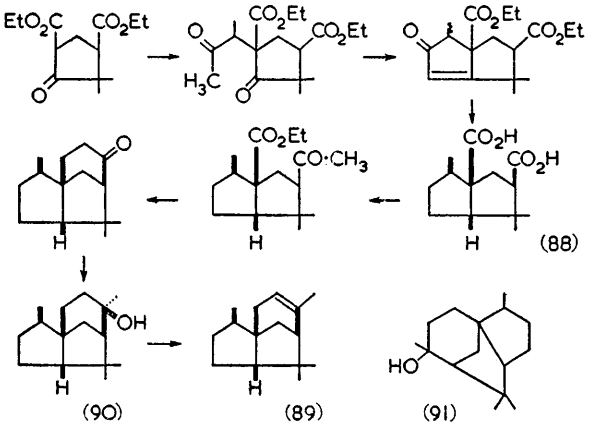
[70] Harris, ref. 69 ; Fawcett and Harris, *J.*, 1954, 2669, 2673 ; Clarke and Ramage, *J.*, 1954, 4345.

[71] Varier, *Proc. Indian Acad. Sci.*, 1944, **20**, *A*, 257.

[72] Dev, *Chem. and Ind.*, 1956, 1051 ; see also Balakrishnan, Razdan, and Bhattacharyya, *Perfumery Essent. Oil Record*, 1956, 274.

be obtained. Cedrene is tricyclic and contains one ethylenic linkage present as the grouping —CH=CMe—.[3] The related *tertiary* alcohol cedrol, containing the system —CH_2·CMe(OH)—, occurs along with cedrene.

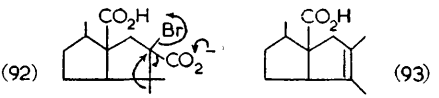
A key degradation product in the chemistry of cedrene was norcedrenedicarboxylic acid obtained—with loss of two carbon atoms—by various oxidation procedures. For some years this acid was regarded as a succinic acid, but eventually critical interpretation [73] based on the extensive work of Plattner and his collaborators [74] showed that this compound must be



of the glutaric acid type (88) and thus made possible the deduction of the expression (89) for cedrene. All structural arguments have been decisively confirmed by the brilliant synthesis of cedrol (90), and hence cedrene (89), carried out by Stork and Clarke [75] along the lines illustrated.

The possible biogenetic relation between cedrol and the cadalene group of sesquiterpenoids (see above) is indicated by rewriting formula (90) in the form (91).

An interesting transformation in the chemistry of cedrene, which initially led to difficulties of interpretation,[3] is the dehydrobromination with



rearrangement of monobromonorcedrenedicarboxylic acid (92) in alkaline solution to give the acid (93). The reaction is essentially a *neo*pentyl solvolysis.[73]

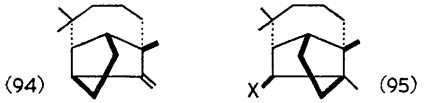
Longifolene, from Indian turpentine, is another tricyclic sesquiterpene with only one ethylenic linkage. The compound was studied extensively

[73] Stork and Breslow, *J. Amer. Chem. Soc.*, 1953, **75**, 3291, 3292.

[74] Plattner, Kusserow, and Kläui, *Helv. Chim. Acta*, 1942, **25**, 1345; Plattner, Fürst, Eschenmoser, Keller, Kläui, Meyer, and Rosner, *ibid.*, 1953, **36**, 1845, and references there cited.

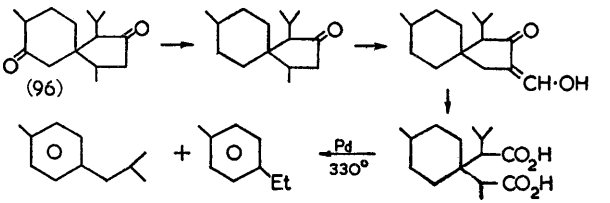
[75] Stork and Clarke, *J. Amer. Chem. Soc.*, 1955, **77**, 1072.

by Simonsen and his collaborators [76] and later by others.[77] However, it proved difficult to break down the ring system and the correct constitution (94) was only elucidated by the excellent *X*-ray work of Moffett and Rogers [78]



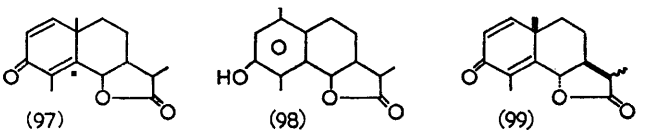
on the longifolene hydrohalides (95 ; X = halogen). It is still desirable, of course, that the proposed structure should be confirmed by further chemical evidence.

Recently Šorm and his collaborators [79] have elucidated the constitution of acorone, a diketone isolated from sweet flag oil. This has been shown to be a carbocyclic spiran (96) ; the discovery is especially important since



it is the first example to be found in Nature. The spiran character of the diketone is strikingly revealed by the formation of both cadalene and 1 : 7-dimethyl-4-*iso*propylnaphthalene on dehydrogenation of a suitable derivative. The same point is illustrated in the transformations formalised here.

Lactonic Sesquiterpenoids based on Decalin.—The most important compound of this type is santonin (97). This has been the subject of investigation for more than a century [3] and even now provides the basis for much



interesting research. One of the most characteristic reactions of santonin is its ease of aromatisation under acid conditions to desmotroposantonin (98). It was this rearrangement which impeded the recognition of the correct santonin structure for many years.[80] The constitution of santonin has been

[76] Simonsen, *J.*, 1923, 2642 ; Bradfield, Francis, and Simonsen, *J.*, 1934, 188.

[77] Dupont, Dulou, Naffa, and Ourisson, *Bull. Soc. chim. France*, 1954, 1075 ; Naffa and Ourisson, *ibid.*, p. 1115 ; Zeiss and Arakawa, *J. Amer. Chem. Soc.*, 1954, **76**, 1653.

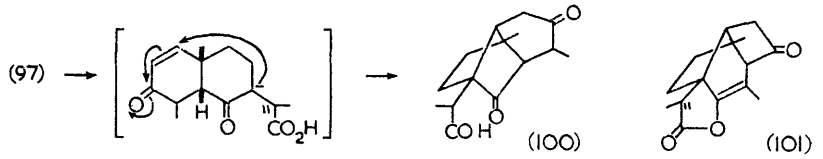
[78] Moffett and Rogers, *Chem. and Ind.*, 1953, 916.

[79] Sykora, Herout, Pliva, and Šorm, *Chem. and Ind.*, 1956, 1231.

[80] Clemo, Haworth, and Walton, *J.*, 1929, 2368 ; 1930, 1110 ; Clemo and Haworth, *J.*, 1930, 2579.

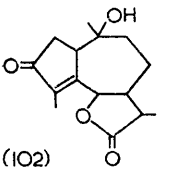
confirmed by synthesis [81] and the stereochemistry almost completely elucidated [82] as in (99).

Santonin undergoes many reactions of theoretical interest. In the space available only two of these can be discussed. On prolonged treatment with alkali santonin is converted into santonic acid (100) by the internal Michael reaction indicated.[83] Treatment with acetic acid followed by heating at



260—300° gives santonide and parasantonide. Both compounds have the formula (101) and differ in configuration at C_{11}.[82, 83] A mechanism for this interesting rearrangement has been proposed.[83]

Santonin, like other *cyclo*hexadienones, is sensitive to light. Amongst the many irradiation products described in the earlier literature [3] the most important are photosantonic acid, whose constitution is still under investigation, and the so-called *iso*photosantonic acid. The latter, which is produced from santonin in yields of up to 35% on irradiation with ultraviolet light in aqueous acetic acid, contains an $\alpha\beta$-unsaturated *cyclo*pentenone ring and has the constitution (102).[84] Ozonolysis affords acetic acid and, with loss of water, a bis-γ-lactone. The carbon skeleton has been confirmed by conversion of a derivative into chamazulene.[84]



Amongst other lactones of the decalin type there should be mentioned artemisin (103) [3, 85a] and ψ-santonin (104).[3, 85b] Although ψ-santonin is not a *cyclo*hexadienone, nevertheless with 55% sulphuric acid it is readily aromatised to desmotropo-ψ-santonin (105), the reaction proceeding through the diene (106) and the conjugated dienone (107) as indicated. The hydroxyl

[81] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1954, **30**, 116, 119; *J. Amer. Chem. Soc.*, 1953, **75**, 2567; 1956, **78**, 1416.

[82] *Inter al.*, Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Abe, Miki, Sumi, and Toga, *ibid.*, 1956, 953; cf. also Miki, *J. Pharm. Soc. Japan*, 1955, **75**, 416.

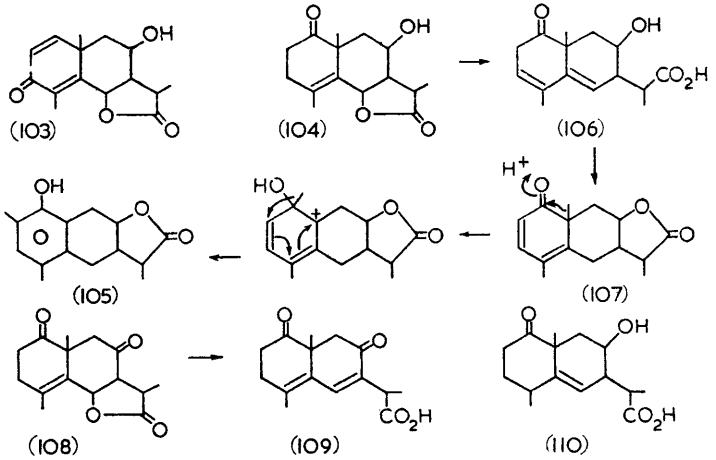
[83] Woodward, Brutschy, and Baer, *J. Amer. Chem. Soc.*, 1948, **70**, 4216; Woodward and Kovach, *ibid.*, 1950, **72**, 1009.

[84] Barton, de Mayo, and Shafiq, *J.*, 1957, 929.

[85a] Sumi, *Proc. Jap. Acad.*, 1956, **32**, 684.

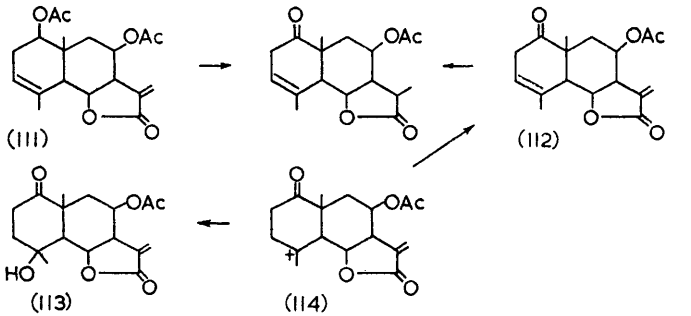
[85b] Chopra, Cocker, Cross, Edward, Hayes, and Hutchison, *J.*, 1955, 588; Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828, and references there cited; Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 2451; Dauben, Hance, and Hayes, *ibid.*, p. 4609, and references there cited.

group, double bond, and lactone group of ψ-santonin have been inter-related by oxidation of ψ-santonin to the corresponding diketone (108), which on mild treatment with a base gives the conjugated dienone (109). The



allylic-lactone character of ψ-santonin is demonstrated by its ease of hydrogenolysis to the acid (110).

The interesting sesquiterpenoid lactone pyrethrosin was first isolated in 1891 from *Chrysanthemum cinerariæfolium*. It has recently been shown to represent a new type of monocarbocyclic sesquiterpenoid.[86] Pyrethrosin contains two ethylenic linkages (one of which is conjugated with a γ-lactone grouping), an acetoxyl group, and a cyclic ethereal oxygen atom. It is, therefore, monocarbocyclic. When heated with acetic anhydride and

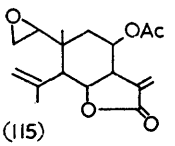


toluene-*p*-sulphonic acid, pyrethrosin is converted into *cyclo*pyrethrosin acetate (111), the structure of which has been proved, *inter al.*, by conversion into the diketone (109).

The acid-catalysed formation of *cyclo*pyrethrosin acetate from pyrethrosin necessarily involves fission of the ethereal ring. The conditions of the reaction are, however, so drastic that it would be unwise to make definite

[86] Barton and de Mayo, *J.*, 1957, 150.

structural proposals for pyrethrosin itself on this evidence alone. Fortunately pyrethrosin is also cyclised under the very mild conditions of oxidation with sodium dichromate in aqueous acetic acid at room temperature. Two products, (112) and (113), are formed in the oxidation. The former of these has been related to *cyclo*pyrethrosin acetate in the manner indicated. Now if one considers the mechanism of the chromic acid oxidation, this must surely be electrophilic attack upon the ethereal ring with participation of the π-electrons of the non-conjugated ethylenic linkages in the formation of the new carbon–carbon bond, thus producing the carbonium ion (114). By proton loss the latter would afford the unsaturated ketone (112), whilst by reaction with the water present in the medium it would afford the tertiary alcohol (113). The ketone group of the ion (114) therefore indicates one end of the ethereal ring and the positive charge one end of the ethylenic linkage. These considerations allow only three possible formulæ, (115), (116), and (117), for pyrethrosin. The first two can be rejected since pyrethrosin contains only one grouping of the type ($>C{=}CH_2$). The correct formula for pyrethrosin must, therefore, be (117).



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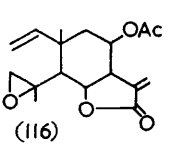

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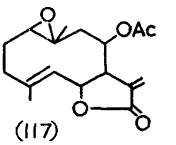

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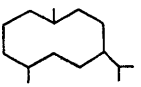


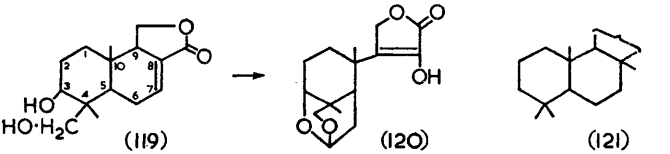
(118)

The ring structure of pyrethrosin may well be of some biogenetic significance since, if one unites a ten-membered ring as in (118), it is possible by establishing different bonds across the ring to construct the carbon skeletons of most of the bicyclic sesquiterpenoids. The cyclisation reactions of pyrethrosin itself already illustrate this point experimentally.

The lactones so far discussed have been derivatives of eudalene or, in the case of pyrethrosin, could be cyclised to such a skeleton. Recently an interesting lactone has been discovered which, although a decalin derivative, belongs to a different series. Iresin (119), from *Iresine colosioides*, is an unsaturated lactonic glycol [87] giving a benzylidene derivative. Dehydrogenation afforded 1 : 5-dimethylnaphthalene and 1 : 5-dimethyl-2-naphthol. Ozonolysis of iresin furnished an internal acetal (120). On the basis of this and other evidence the constitution (119) was proposed. Djerassi and his colleagues [87] have, however, been careful to point out that an alternative structure with the angular methyl at $C_{(5)}$ instead of $C_{(10)}$ is also possible on the evidence so far adduced. In any case iresin is an important compound

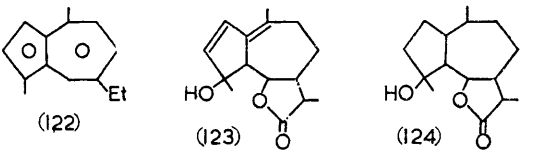
[87] Djerassi, Sengupta, Herran, and Walls, *J. Amer. Chem. Soc.*, 1954, **76**, 2966; Djerassi, Rittel, Nussbaum, Donovan, and Herran, *ibid.*, p. 6410; Djerassi and Rittel, *ibid.*, 1957, **79**, 3528. We thank Professor Carl Djerassi for his kindness in sending us a copy of the last paper before its publication.

since it represents a sesquiterpenoid chain cyclised in a manner characteristic of the first two rings (see 121) of the di- and tri-terpenoids. If the Me *is* at $C_{(5)}$ this would be the result of a trivial migration *after* cyclisation.



(119) (120) (121)

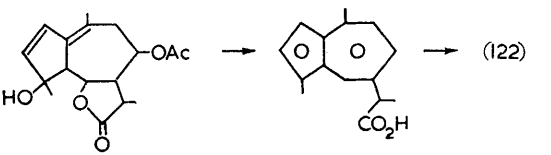
Lactonic Sesquiterpenoids based on Perhydroazulene.—The chemistry of these interesting compounds has only recently received serious attention. One group of azulenic lactones can be described as " chamazulene-precursors ". This is because of the facility with which they afford chamazulene (122) [88] even under such mild conditions as steam-distillation. Wormwood has been extensively investigated [89] and the blue azulene of oil of wormwood identified as chamazulene (122). The oil also contains an interesting yellow dihydrochamazulene, known as chamazulenogen, which is converted into chamazulene merely on exposure to air. The original chamazulene precursor



(122) (123) (124)

in wormwood is artabsin (123).[90] On steam-distillation, particularly in the presence of a trace of acid, this is changed into chamazulene. The proposed constitution is supported by, *inter al.*, conversion by hydrogenation into the hydroxy-lactone (124), obtained earlier from arborescin (see below).

Šorm and his colleagues [89] have also investigated the chamazulene precursors of oil of chamomile. From this source matricin (125) was isolated. In faintly acid solution at about 50° this lactone afforded guaiazulenic acid (126) obtained earlier by Stahl [91] from yarrow and, later, also from chamomile. At somewhat higher temperatures this is decarboxylated to chamazulene.



[88] Meisels and Weizmann, *J. Amer. Chem. Soc.*, 1953, **75**, 3865; Šorm, Herout, and Takeda, *Chem. Listy*, 1954, **48**, 281; Novak, Šorm, and Sicher, *ibid.*, p. 1648.

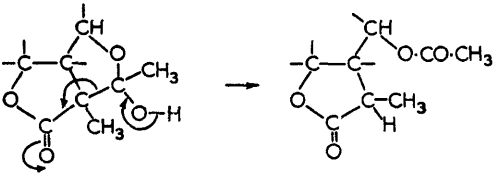
[89] Šorm, Vonasek, and Herout, *Coll. Czech. Chem. Comm.*, 1949, **14**, 91; Herout and Šorm, *ibid.*, 1953, **18**, 854; Ćekan, Herout, and Šorm, *ibid.*, 1954, **19**, 798; Šorm, Novotný, and Herout, *Chem. and Ind.*, 1955, 569; cf. Schenck and Schuster, *Arch. Pharm.*, 1956, **289**, 1.

[90] Herout, Dolejš, and Šorm, *Chem. and Ind.*, 1956, 1236; Cekan, Herout, and Šorm, *ibid.*, p. 1234.

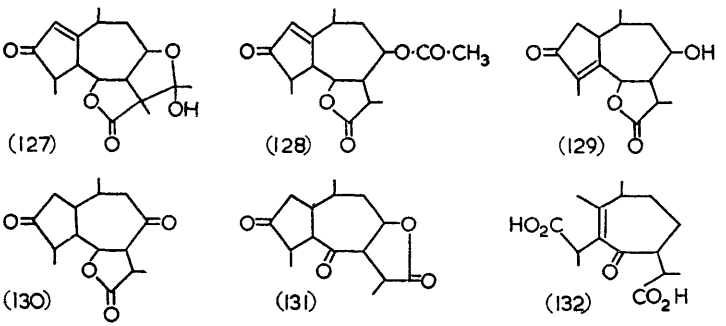
[91] Stahl, *Chem. Ber.*, 1954, **87**, 202, 505, 1626.

The bitter principles of *Artemesia absinthium* have recently [92] been isolated and characterised as anabsinthin, $C_{15}H_{20}O_3$, and absinthin, a substance having the composition $C_{15}H_{20}O_3,\frac{1}{2}H_2O$.

Tenulin and helenalin are the bitter principles of various *Helenium* species. The early work on tenulin [93] has recently been extended.[94] Tenulin affords acetic acid on alkaline hydrolysis. It is also a γ-lactone and contains an $\alpha\beta$-unsaturated *cyclo*pentenone system. Since tenulin has the formula $C_{17}H_{22}O_5$, these facts would appear to account for all the oxygen atoms. However, other evidence discloses the presence of a hydroxyl function and the molecule does not afford acetic acid on acid hydrolysis as does a true acetate. Under very mild alkaline conditions tenulin is isomerised to *iso*tenulin, which does have a true acetate residue but lacks the hydroxyl group. On the grounds of this and other evidence the masking of the acetate function has been explained [94] as illustrated.



On digestion with sodium hydrogen carbonate solution tenulin and *iso*tenulin are converted into deacetyl*neo*tenulin. The latter contains the system —CO·CMe:C< since on ozonolysis it affords acetic acid. This and other work has led to formulation of tenulin as (127), *iso*tenulin as (128), and deacetyl*neo*tenulin as (129). Recently Braun, Herz, and Rabindrau [95]



have made the interesting observation that deacetyldihydrodehydro*iso*tenulin (130) is cleaved with alkali to a dicarboxylic acid containing an $\alpha\beta$-unsaturated ketone grouping. This reaction is possibly explained better by the formulation (131) for deacetyldehydrodihydro*iso*tenulin, the dicarboxylic acid being

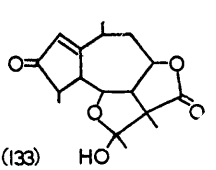
[92] Sorm, Novotny, and Herout, *Chem. and Ind.*, 1955, 569.

[93] Clark, *J. Amer. Chem. Soc.*, 1939, **61**, 1836; 1940, **62**, 597; Ungnade and Hendley, *ibid.*, 1948, **70**, 3921; Ungnade, Hendley, and Dunkel, *ibid.*, 1950, **72**, 3818.

[94] Barton and de Mayo, *J.*, 1956, 142.

[95] Braun, Herz, and Rabindrau, *J. Amer. Chem. Soc.*, 1956, **78**, 4423.

(132). If this is correct then the tenulin formula (127) simply requires revision to (133). The modified formula for tenulin (134) advanced by Braun, Herz, and Rabindrau [95] does not explain the properties of *neo*tenulin ; other evidence of these workers, however, tends to support the position of the lactone ring as in (127).



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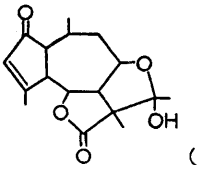
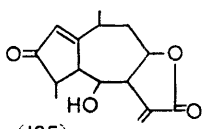


(134)

Helenalin, also obtained from *Helenium* species, is a lactone showing many similarities to deacetyl*iso*tenulin. Earlier work by Adams and Herz [96] had established the presence of a γ-lactone and a secondary hydroxyl group and an $\alpha\beta$-unsaturated *cyclo*pentenone system. Evidence was also provided for the presence of a grouping $>C=CH_2$ and for an azulenic carbon skeleton. Further work by Büchi and Rosenthal [97] has completed the evidence for constitution (135). An isomer of helenalin, *iso*helenalin, was also isolated in these studies and shown to have structure (136). The position of the $\alpha\beta$-unsaturated ketone moiety in these formulæ was based on nuclear magnetic resonance spectra. The position of the secondary hydroxyl group was deduced mainly from the action of base on dehydrotetrahydrohelenalin (137). This afforded a dicarboxylic acid (138), the formation of which can be rationalised as the cleavage of a vinylogous β-diketone system.[97] It is, however, clear that further evidence as to the position of the lactone ring is desirable both for tenulin and for helenalin.



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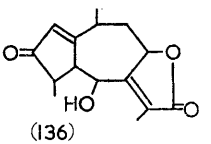

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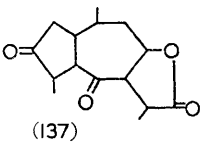

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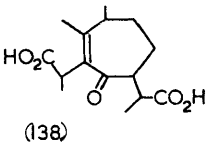

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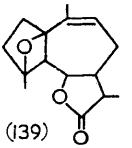
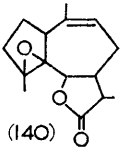
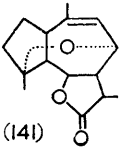


(139)



(140)



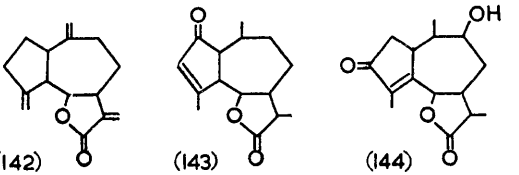
(141)

Arborescin, isolated from *Artemisia arborescens*, is an isomer of artabsin (123).[98] A relation between these two compounds has already been referred to in the text above. The proposed constitution (139) for arborescin [98] contains the unusual feature of a trimethylene oxide ring. Whereas the position of the ethylenic linkage and one terminus of the oxide ring appear

[96] Adams and Herz, *J. Amer. Chem. Soc.*, 1949, **71**, 2546, 2551, 2554.
[97] Büchi and Rosenthal, *ibid.*, 1956, **78**, 3860.
[98] Mazur and Meisels, *Chem. and Ind.*, 1956, 492.

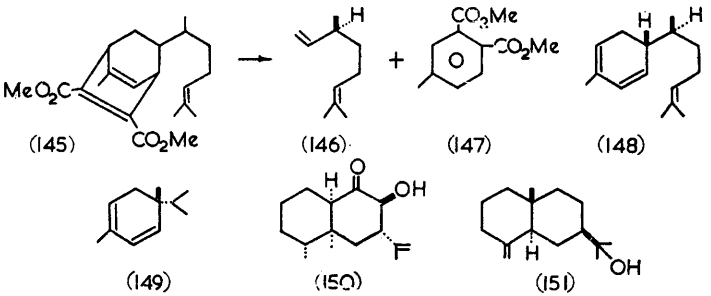
to be well established, some dubiety is attached to the other terminus. Structures such as (140) and (141) still remain to be excluded.

Other sesquiterpenoid lactones for which structures have been proposed are dehydrocostus lactone [99] (142) from costus oil, carpesia lactone [100] (143)



from *Carpesium abrotanoides*, and geigerin [101] (144). The constitution for carpesia lactone may require some revision as to the position of the ketonic function.

Relative and Absolute Stereochemistry of Sesquiterpenoids.—Stereochemical investigations have not been pursued so intensively in sesquiterpenoid compounds as in di- and tri-terpenoids. The methods are, however, the same and we can mention degradation to compounds of known orientation, ring formation, and conformational analysis [102] as important techniques for the solution of these stereochemical problems. The first method also, of course, provides information on absolute configuration. Where degradation



is not convenient, molecular-rotation correlations are often of great help,[103] the basic idea being that like structures embedded in like stereochemical environments make like contributions to molecular rotations.

We may use the stereochemistry of zingiberene (21) as an illustration. The adduct (145) of zingiberene and dimethyl acetylenedicarboxylate affords the (+)-diene (146) as well as the dimethyl methylphthalate (147)

[99] Romanuk, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1956, **21**, 894.

[100] Kariyone and Naito, *J. Pharm. Soc. Japan*, 1955, **75**, 39; Kariyone, Naito, and Chatani, *Pharm. Bull.* (*Japan*), 1954, **2**, 339.

[101] Rimington, *Onderstepoort J. Vet. Sci.*, 1936, **7**, 485; Perold, *J.*, 1957, 47; Barton and Levisalles, unpublished work.

[102] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

[103] Mills, *J.*, 1952, 4976; Klyne, *J.*, 1952, 2916; 1953, 3072; Klyne and Stokes, *J.*, 1954, 1979.

on pyrolysis.[105] The absolute configuration of the diene (146) is known from its relation to citronellal, the (+)-form of the latter affording the (−)-diene.[106] The complete absolute configuration of zingiberene as (148) was then deduced by comparing the molecular rotations of zingiberene and (−)-α-phellandrene (149) whose absolute configuration is known.

In the eudalene group of sesquiterpenoids *trans*-fusion of the rings is general except for dihydrohydroxyeremophilone,[36] the stereochemistry of which is depicted in (150). The absolute configuration of this compound is based on molecular-rotation considerations.[104] Eudesmol has been related to the steroids, which are of known absolute configuration, through an intermediate in the Woodward steroid synthesis.[107] In this way eudesmol has been shown to have the absolute structure (151). The relationship of eudesmol to α- and β-cyperone and to carissone [108] shows that these compounds also have the same type of absolute configuration. Santonin has been converted into β-cyperone, thus establishing its absolute stereochemistry as already indicated in formula (99).[109]

Nothing is, as yet, known about the stereochemistry of the perhydroazulenic sesquiterpenoids, but the known relation of santonin to "*iso*photosantonic acid" must eventually prove helpful.

The stereochemistry of cedrene (89) was established interestingly enough by synthesis ; [75] the absolute configuration is not known. The absolute configuration of caryophyllene (80) is based on extensive molecular-rotation correlations.[110] The stereochemistry of longifolene already given (94) is based on the *X*-ray work and, for the absolute configuration, on molecular-rotation arguments.[111]

[104] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362, and earlier papers.

[105] Eschenmoser and Schinz, *Helv. Chim. Acta*, 1950, **33**, 171.

[106] Arigoni and Jeger, *ibid.*, 1954, **37**, 881.

[107] Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313.

[108] Ayer and Taylor, *J.*, 1955, 3027 ; McQuillin, *J.*, 1955, 528 ; Howe and McQuillin, *J.*, 1955, 2423.

[109] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858.

[110] Barton and Nickon, *J.*, 1954, 4665.

[111] Ourisson, *Bull. Soc. chim. France*, 1955, 895.