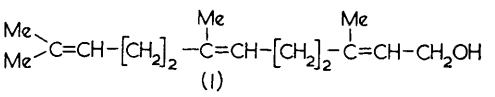
Sesquiterpene Biogenesis

By W. Parker and J. S. Roberts
CHEMISTRY DEPARTMENT, THE UNIVERSITY, GLASGOW
and R. Ramage
CHEMISTRY DEPARTMENT, THE UNIVERSITY, LIVERPOOL

Over the years, the terpenoids have provided a host of challenging problems for the organic chemist. The resultant wide range of acyclic, monocyclic, and fused-ring structures was brilliantly rationalised during the period 1953—1955 by Ruzicka, Eschenmoser, and Heusser,[1a] and by Ruzicka, Eschenmoser, Jeger, and Arigoni[1b] in terms of the Biogenetic Isoprene Rule. Hendrickson[2] in 1959 applied the principles embodied in this rule to a biogenetic correlation of certain sesquiterpenes, but with the ever-increasing diversity of sesquiterpene structures in mind, the time now seems opportune for a critical, comprehensive Review of sesquiterpene biogenesis.

The focal point of sesquiterpene biogenesis is the naturally occurring compound, farnesol (1), whose formation from acetyl CoA, *via* mevalonic acid[3] (2), has found experimental verification.[4–6] For the sake of simplicity, the farnesyl unit is usually considered as having a *trans* central double bond with either a *cis* or *trans* terminal double bond. The latter presumption is permissible in view of the co-occurrence of farnesol and nerolidol[7] (3), and the demonstrated enzymic hydrolysis of farnesyl pyrosphosphate to nerolidol.[8] It should be noted, however, that, on occasion, the use of a farnesyl precursor containing a central *cis* double bond may be necessary to explain certain stereochemical features.



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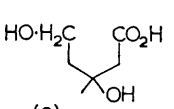

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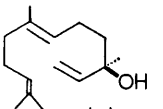


(3)

[1] (*a*) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, 1953, **9**, 357; (*b*) L. Ruzicka, A. Eschenmoser, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890; see also L. Ruzicka, *Proc. Chem. Soc.*, 1959, 341; (*c*) L. Ruzicka, *Pure Appl. Chem.*, 1963, **6**, 493.
[2] J. B. Hendrickson, *Tetrahedron*, 1959, **7**, 82.
[3] D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright, and K. Folkers, *J. Amer. Chem. Soc.*, 1956, **78**, 4499.
[4] B. W. Agranoff, H. Eggerer, U. Henning, and F. Lynen, *J. Amer. Chem. Soc.*, 1959, **81**, 1254.
[5] B. W. Agranoff, H. Eggerer, U. Henning, and F. Lynen, *J. Biol. Chem.*, 1960, **235**, 326.
[6] For an excellent Review, see R. B. Clayton, *Quart. Rev.*, 1965, **19**, 168, 201.
[7] G. Popják, *Tetrahedron Letters*, 1959, No. 19, 19.
[8] D. S. Goodman and G. Popják, *J. Lipid Res.*, 1960, **1**, 286.

The carbon skeletons of virtually all the sesquiterpenes can now be derived[2] by a suitable cyclisation of either *cis*-farnesyl pyrophosphate (4) or *trans*-farnesyl pyrophosphate (5). The initial step in these cyclisations is envisaged (Chart 1) as removal of the pyrophosphate anion accompanied by participation of either the central or terminal double bonds leading to the cations (9)—(14) through the intermediacy of the non-classical cations (6)—(8). It must, of course, be stressed that such representation of a formal charge, either on a particular carbon atom or distributed over a number of atoms, is only a convenient symbolism and should not be taken, at present, as a representation of the enzymic processes involved. In certain cases, the enzyme systems may well produce these complex sesquiterpenes from the pyrophosphate precursor by a partially or even fully concerted process. *Nevertheless, the utility of this scheme in supplying a satisfactory classification of sesquiterpenes cannot be denied.*

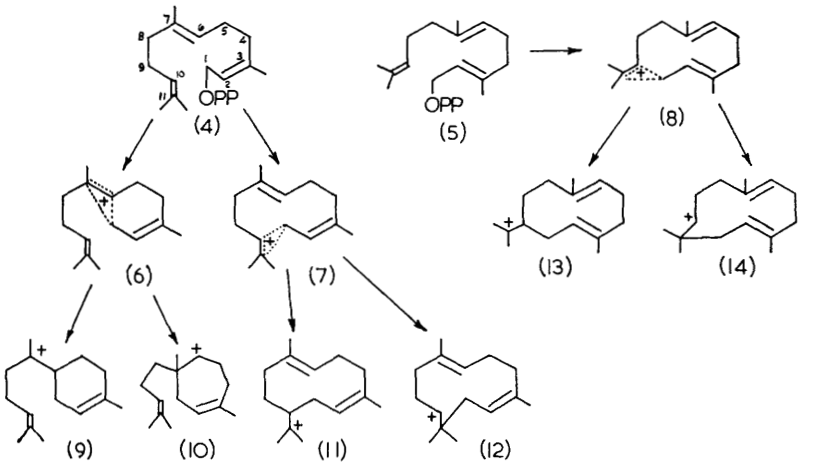
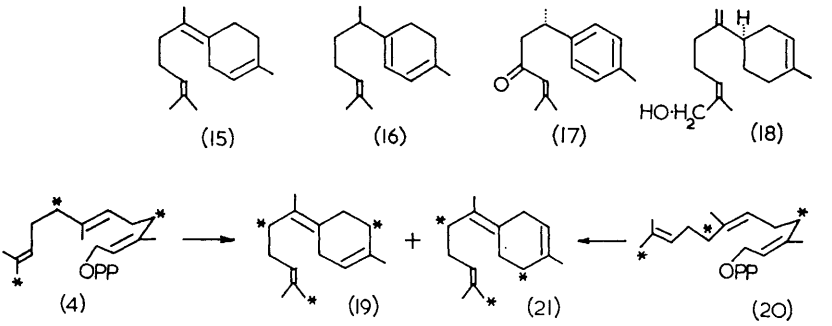


CHART 1.

Monocyclic Six-membered Sesquiterpenes.—In the case of *cis*-farnesyl pyrophosphate (4), interaction of the allylic carbonium ion with the central double bond leads to the monocyclic cations (9) and (10). From a consideration of the steric and electronic factors involved, (9) is favoured and indeed most of the known six-membered monocyclic sesquiterpenes, such as γ-bisabolene (15), γ-curcumene (16), *ar*-turmerone (17), and lanceol (18) can be derived from this cation. Ruzicka[1c] has discussed the hypothetical biogenesis of γ-bisabolene (15), starting from a labelled farnesyl precursor derived from [2-^{14}C]-mevalonic acid. By a series of stereospecific cationic reactions it is possible to arrive at both the labelled γ-bisabolenes (19) and (21) from *trans-cis*-farnesyl pyrophosphate (4) and *cis-cis*-farnesyl pyrophosphate (20). In terms of the resultant labelling pattern(s), this has a profound bearing on those biogenetic suggestions involving the intermediacy of γ-bisabolene.



Humbertiol[9] (22) and calacone[10] (23) are two examples of monocyclic sesquiterpenes with an 'abnormal' ring substitution pattern. Several paper schemes (Chart 2) can be produced for the biogenesis of humbertiol; for example, it could arise from (*a*) condensation of a monoterpene skeleton with a C_5 unit, such as dimethylallyl pyrophosphate, (*b*) fission of a cadinane type sesquiterpene, or (*c*) cyclisation of a *cis*-$\Delta^{6,7}$-farnesyl precursor. The biogenesis of calacone, on the other hand, seems most probable by the addition of a C_5 unit, such as isopentenyl pyrophosphate, to a monoterpene skeleton.

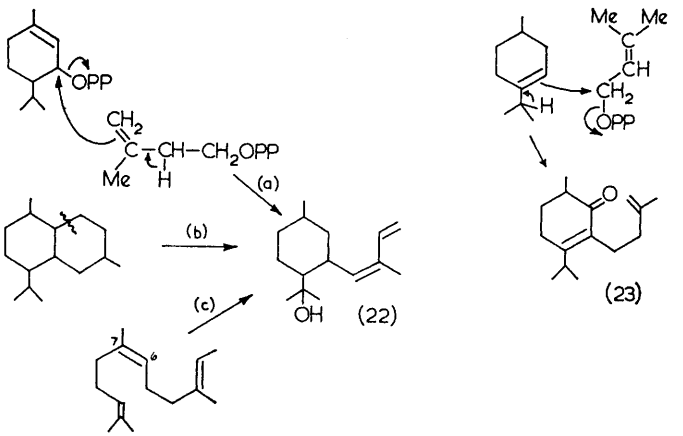


CHART 2.

Cadinane Class.—It can be seen that appropriate cyclisation of cation (9) may lead to the cadinane series of sesquiterpenes [Chart 3, pathway (*a*)]. There are, however, two other possible pathways for the formation of the cadinane skeleton. One of these (*b*) would involve an overall 1,3 hydride shift in cation (11) to cation (24) followed by ring closure, whereas the other (*c*) would require cyclisation of

[9] D. Raulais, D. Billet, C. Mentzer, *Bull. Soc. chim. France*, 1964, 2324.
[10] J. Vrkoč, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1343.

a *cis*-$\Delta^{6,7}$-farnesyl precursor (cf. γ-bisabolene). It is difficult to visualise a definitive tracer experiment which would permit a distinction amongst these three variants, particularly when the possible 'crossover' of γ-bisabolene biogenesis is taken into consideration (see above).

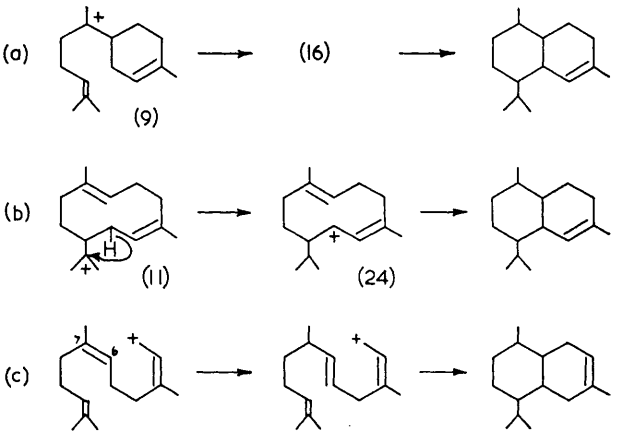
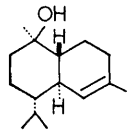


CHART 3.

The majority of cadinane sesquiterpenes have the absolute stereochemistry exemplified by α-cadinol (25) but recently some antipodally related compounds have been isolated such as (−)γ_2-cadinene[11] (26) and khusitone[12] (27), the latter being one of the few C_{14} sesquiterpenes which have been isolated. This antipodal relationship in the sesquiterpenoid field is not unique and an increasing number of examples has been found (see later). Oplopanone[13] (28) is obviously a modified cadinane type. An attempt has been made[14] to correlate the structure of gossypol (29), the toxic yellow pigment of cotton seed, with suggested biogenetic schemes. It was found to incorporate radioactivity from both [1-^{14}C]- and [2-^{14}C]-acetate and partial degradation indicated that the labelling occurred in the predicted positions. A synthesis of gossypol has been recorded[15] in which the two C_{15} units were joined by a phenol oxidative coupling method. The compounds mansonone A (30) and mansonone F (31) are two representatives of six closely related quinonoid sesquiterpenes which have been isolated recently,[16] the latter being the C_{15} analogue of dihydrobiflorin (32).

[11] C. C. Kartha, P. S. Kalsi, A. M. Shaligram, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, 1963, **19**, 241.
[12] K. K. Chakravarti, *Indian J. Chem.*, 1965, **3**, 324.
[13] K. Takeda, H. Minato, and M. Ishikawa, *Chem. Comm.*, 1965, 79; K. Takeda, H. Minato, and M. Ishikawa, *Tetrahedron Supplement*, 1966, **7**, 219.
[14] P. F. Heinstein, F. H. Smith, and S. B. Tove, *J. Biol. Chem.*, 1962, **237**, 2643.
[15] J. D. Edwards and J. L. Cashaw, *J. Amer. Chem. Soc.*, 1957, **79**, 2283.
[16] G. B. Marini Bettòlo, C. G. Casinovi, and C. Galeffi, *Tetrahedron Letters*, 1965, 4857.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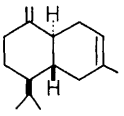
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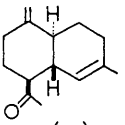
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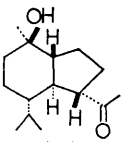
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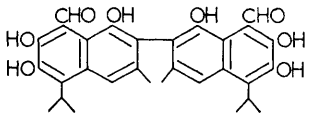
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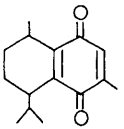
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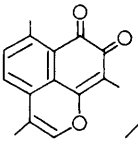
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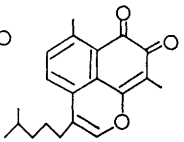
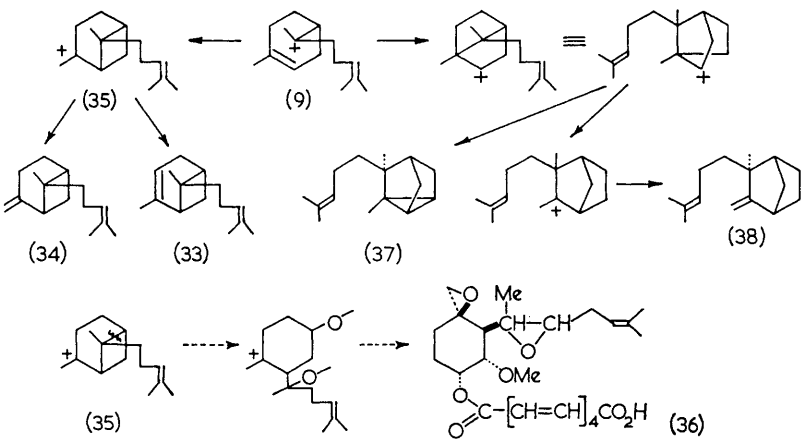

(32)

Bergamotane and Santalane Classes.—The structures of α-[17] and β-[18]bergamotene (33 and 34) suggest that interaction of the cyclic double bond in cation (9) with the carbonium ion can proceed in an electronically favoured fashion, since deprotonation of the resultant cation (35) furnishes these two sesquiterpenes. A plausible biogenetic route to the antibiotic fumagillin[19] (36) involves oxidative fission of the cyclobutane ring in cation (35) as shown. The sterically favoured cyclisation of cation (9), on the other hand, gives rise to α- and β-santalene (37 and 38).


(35) (9) (34) (33) (37) (38) (35) (36)

[17] C. S. Narayanan, K. S. Kulkarni, A. S. Vaidya, S. Kanthamani, G. Lakshmi Kumari, B. V. Bapat, S. K. Paknikar, S. N. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, 1964, **20**, 963.

[18] K. S. Kulkarni, S. K. Paknikar, A. S. Vaidya, G. R. Kelkar, R. B. Bates, and S. C. Bhattacharyya, *Tetrahedron Letters*, 1963, 505; K. S. Kulkarni, S. K. Paknikar, and S. C. Bhattacharyya, *Tetrahedron*, 1966, **22**, 1917; T. W. Gibson and W. F. Erman, *Tetrahedron Letters*, 1967, 905.

[19] D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman, and N. J. McCorkindale, *J. Amer. Chem. Soc.*, 1960, **82**, 1005.

Cuparane, Widdrane, Thujopsane, Cedrane and Acorane Classes.—A combination of structural elucidations and thorough chemotaxonomic examination of certain higher plants has permitted an attractive correlation of the above classes of sesquiterpene, involving (Chart 4) the common intermediacy of γ-bisabolene (15). So far, the acorane class is the only one which has not been found to co-exist with at least one of the other four classes.

Enzell and Erdtman[20] suggested that the cuparene skeleton arises from protonation of γ-bisabolene (*i.e.*, 39), followed by cyclisation to the tertiary cation (40), which is the obvious precursor of the two cuprenenes (41)[21] and (42),[22] cuparene (43),[20] and cuparenic acid (44).[20] Recently, two additional members of this class have been isolated,[23] α-cuparenone (45) and β-cuparenone (46), as well as the corresponding alcohols. The main alcoholic constituents of this particular extract, however, were cedrol and widdrol, which is of biogenetic significance. The substituted quinone, helicobasidin (47)[24] clearly belongs to the cuparane class.

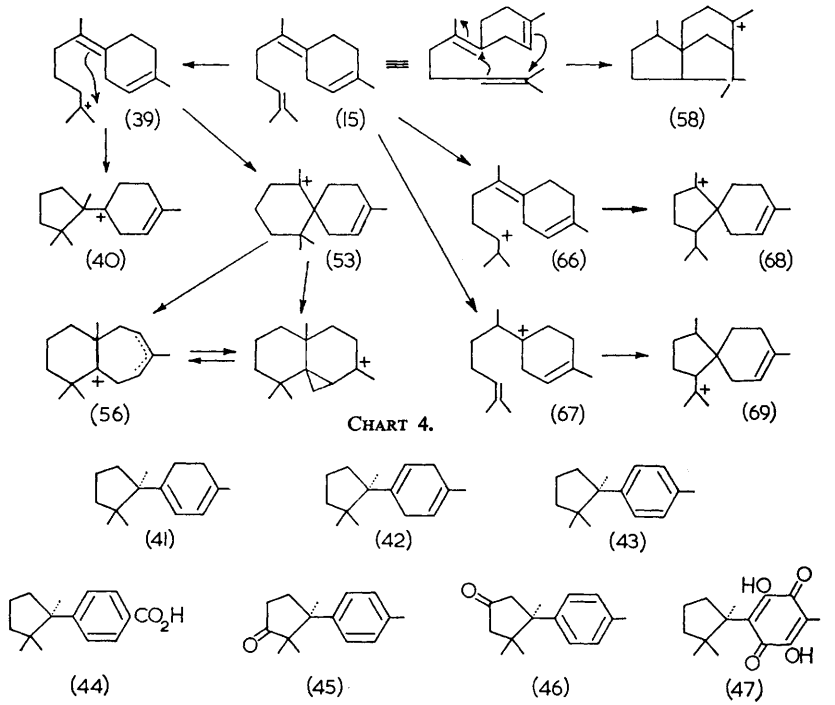
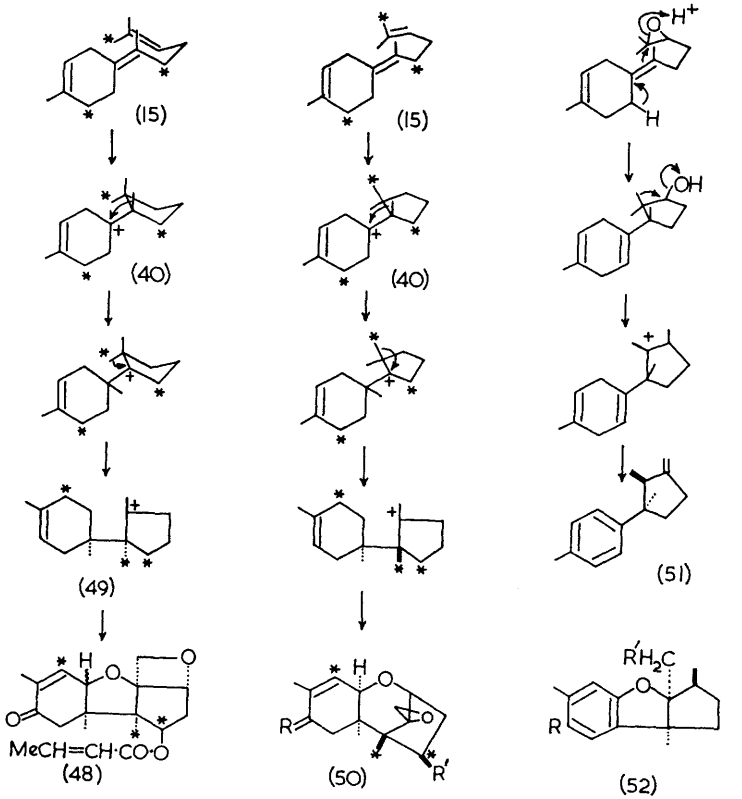


CHART 4.

[20] C. Enzell and H. Erdtman, *Tetrahedron*, 1958, **4**, 361.
[21] T. Nozoe and H. Takeshita, *Tetrahedron Letters*, 1960, No. 23, 14.
[22] W. G. Dauben and P. Oberhänsli, *J. Org. Chem.*, 1966, **31**, 315.
[23] G. L. Chetty and S. Dev, *Tetrahedron Letters*, 1964, 73.
[24] S. Natori, H. Nishikawa, and H. Ogawa, *Chem. and Pharm. Bull. (Japan)*, 1964, **12**, 236.

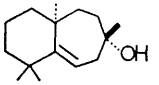
The same cationic intermediate (40) has been suggested as the precursor of the interesting fungal sesquiterpene, trichothecin (48),[25] which is one member of an increasing number of related antibiotics.[26] The suggested genesis of this compound involves two 1,2-methyl migrations, starting from γ-bisabolene with a chair-folded side chain, to give the tertiary cation (49). The elegant tracer experiments conducted by Jones and Lowe,[27] using [1-^{14}C]-acetate and [2-^{14}C]-mevalonate, conclusively demonstrated that the 1,2-methyl shifts did occur, but the *X*-ray[28] and chemical[26] structural determination of the related sesquiterpene, trichodermin (50;R = H_2, R′ = acetyl) suggested a revised structure for trichothecin (*viz.*, 50; R = O, R′ = isocrotonyl). A boat-type folding of the side chain in γ-bisabolene has been postulated[26] to accommodate the stereochemistry and labelling pattern found in this revised structure of trichothecin.



[25] J. Fishman, E. R. H. Jones, G. Lowe, and M. C. Whiting, *J. Chem. Soc.*, 1960, 3948.
[26] W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, 1965, **19**, 1088.
[27] E. R. H. Jones and G. Lowe, *J. Chem. Soc.*, 1960, 3959.
[28] S. Abrahamsson and B. Nilsson, *Proc. Chem. Soc.*, 1964, 188.

The probable biogenesis of the closely related sesquiterpene, laurene (51),[29] isolated from *Laurencia glandulifera*, involves cyclisation of an oxygenated bisabolene and a 1,2-methyl shift, as shown. It has been suggested that debromoaplysin (52; R = H, R′ = H), aplysin (52; R = Br, R′ = H), and aplysinol (52; R = Br, R′ = OH) which are isolated[30] from Sea rat (*Aplysia kurodai Baba*) may be formed from laurene, since Sea rat feeds on *Laurencia glandulifera*.

The alternative cyclisation of cation (39) (Chart 4) gives the spiro-cation (53) which has been suggested by Ramage[31] as the logical precursor of widdrol[32] (54) and thujopsene[33] (55). Using deuterium labelling, Dauben and Friedrich have shown[34] that the *in vitro* interconversion of these two compounds involves the cyclopropane-methylene carbon of thujopsene becoming the allylic methylene carbon of widdrol. They have pointed out that this result, if incorporated into a tracer feeding experiment, could determine whether thujopsene and widdrol are derived from a common intermediary (*viz.*, 56), or whether one is the precursor of the other. A modified scheme for the biogenesis of the cuparane, thujopsane, and widdrane skeletons has been suggested,[24] which involves the cation (56) as a key intermediate. Formed directly from farnesol, rather than *via* γ-bisabolene, (56) can be converted (Chart 4) into the cuparane skeleton by two successive Wagner–Meerwein rearrangements, *viz.*, (56) → (53) → (40). A more detailed analysis of *Thujopsis dolabrata* has revealed[35] the presence of no less than five distinct sesquiterpene types, namely thujopsane, widdrane, cuparane, elemane, and eudesmane, in addition to a C_{14} compound, mayurone[36] (57) which, in fact, is an *in vitro* degradation product of thujopsene.



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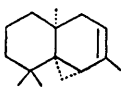

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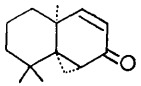
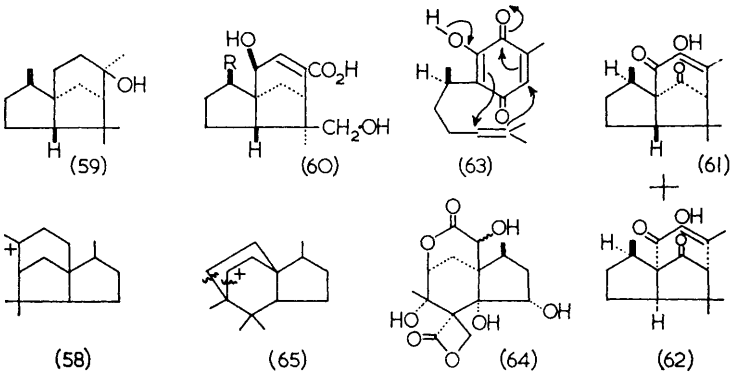


(57)

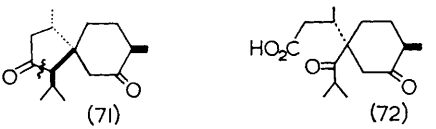
A stereospecific, electronically favoured cyclisation involving all three double bonds of γ-bisabolene could furnish the tricyclic cation (58) (Chart 4) which is the basic skeleton of a class of sesquiterpene exemplified by cedrol[37] (59), shellolic acid[38] (60; R = CO_2H), jalaric acid-B[39] (60; R = CHO) and laksholic acid[40] (60; R = CH_2OH). It has been shown that jalaric acid-B is the naturally

[29] T. Irie, Y. Yasunari, T. Suzuki, N. Imai, E. Kurosawa, and T. Masamune, *Tetrahedron Letters*, 1965, 3619.
[30] S. Yamamura and Y. Hirata, *Tetrahedron*, 1963, **19**, 1485.
[31] R. Ramage, Ph.D. Thesis, Glasgow University, 1961.
[32] C. Enzell, *Acta Chem. Scand.*, 1962, **16**, 1553.
[33] T. Norin, *Acta Chem. Scand.*, 1963, **17**, 738.
[34] W. G. Dauben and L. E. Friedrich, *Tetrahedron Letters*, 1964, 2675.
[35] S. Itˆ, K. Endo, H. Honma, and K. Ota, *Tetrahedron Letters*, 1965, 3777.
[36] G. L. Chetty and S. Dev, *Tetrahedron Letters*, 1965, 3773.
[37] G. Stork and F. H. Clarke, *J. Amer. Chem. Soc.*, 1955, **77**, 1072.
[38] R. C. Cookson, A. Melera, and A. Morrison, *Tetrahedron*, 1962, **18**, 1321.
[39] M. S. Wadia, V. V. Mhaskar, and S. Dev, *Tetrahedron Letters*, 1963, 513.
[40] R. G. Khurana, M. S. Wadia, V. V. Mhaskar, and S. Dev, *Tetrahedron Letters*, 1964, 1537.

occurring compound while shellolic acid and laksholic acid are the products of a Cannizzaro reaction, induced in the isolation procedure. It is of possible biogenetic interest that α- (61) and β-pipitzol (62), the pyrolysis products of perezone[41] (63), not only embody the basic skeleton of the cedrane class of sesquiterpenes but, in the case of α-pipitzol, also the stereochemical features. The probable mechanism of formation of these pyrolysis products has been put forward as shown. The recently adduced structure of anisatin[42] (64) can be formally derived by a Wagner–Meerwein rearrangement of the cedrane cation (58) to cation (65), followed by oxidative fission of either of the bonds shown.



As illustrated in Chart 4, cyclisation of either the secondary cation (66) or the tertiary cation (67), both derivable from γ-bisabolene by protonation, would give the cations (68) and (69), corresponding to the acorane nucleus. A biogenetic derivation of acoric acid[43] (70) can be conceived by oxidative fission of acorone (71) as shown.

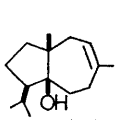


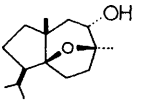
[41] D. A. Archer and R. H. Thomson, *Chem. Comm.*, 1965, 354; F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, and J. Romo, *Tetrahedron Letters*, 1965, 1577; R. B. Bates, S. K. Paknikar, and V. P. Thalacker, *Chem. and Ind.*, 1965, 1793; E. R. Wagner, R. D. Moss, R. M. Brooker, J. P. Heeschen, W. J. Potts, and M. L. Dilling, *Tetrahedron Letters*, 1965, 4233; F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar, and J. Romo, *Tetrahedron*, 1966, **22**, 2387.

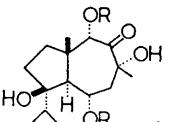
[42] K. Yamada, S. Takada, S. Nakamura, and Y. Hirata, *Tetrahedron Letters*, 1965, 4797.

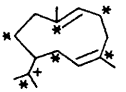
[43] A. J. Birch, F. A. Hochstein, J. A. K. Quartey, and J. P. Turnbull, *J. Chem. Soc.*, 1964, 2923.

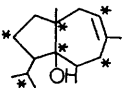
Carotane Class.—The known representatives of this class are carotol (72), daucol[44] (73), and, after a structural revision, laserpitine[45] (74). It is of phylogenetic interest that both carotol and daucol are isolated from one species of the *Umbelliferae* family, while laserpitine is isolated from another species of the same family. One possible biogenetic route to the carotane skeleton would involve a 1,3-hydride shift in cation (11), followed by an anti-Markownikoff cyclisation and subsequent methyl migration. However, a more plausible scheme[46] involves cyclisation of the cation (10) to give (76) followed by an overall 1,3-hydride shift as depicted, and deprotonation to the diene (77). To accommodate the recently determined[47] stereochemistry of carotol and daucol, a stereospecific hydration of (77) is now required. In an elegant tracer study, Souček[46] has degraded carotol produced from [1-^{14}C]-acetate and shown that C(6) and its attached methyl group have 16·6% of the total incorporated activity. This finding is consistent with the suggested scheme starting from cation (10) as shown in the labelling pattern in (78).

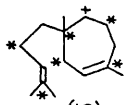

(72)

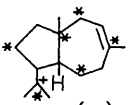

(73)

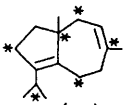

(74)

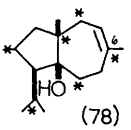

(11)


(75)


(10)


(76)

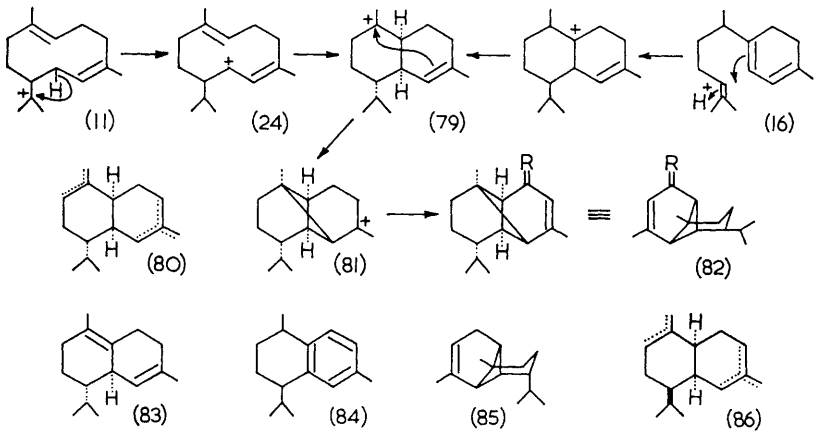

(77)


(78)

Muurolane, Copaane, Amorphane, and Ylangane Classes.—Considering now the outcome of cyclisation of the terminal double bond with the allylic carbonium ion from *cis*-farnesyl pyrophosphate (4), the electronically favoured cation is (11) whereas, from a steric point of view, cation (12) is favoured. Although the former cation was discarded by Hendrickson[2] on the grounds of the strain and non-bonded interactions implicit in its formation, it has since been postulated as the precursor of a number of sesquiterpenes. Thus, an overall 1,3-hydride shift to (24) followed by cyclisation leads to the cation (79) (cf. cadinane sesquiterpenes), the proviso of further internal cyclisation being that this cation is of the *cis*-decalin type. The isolation of the muurolenes[48] (80) with such a *cis* ring junction lends weight to this stipulation. [It could perhaps be argued that this

[44] V. Sýkora, L. Novotný, M. Holub, V. Herout, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 788.
[45] M. Holub, V. Herout, F. Šorm, and A. Línek, *Tetrahedron Letters*, 1965, 1441, 2855; M. Holub, Z. Samek, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1967, **32**, 591.
[46] M. Souček, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2929.
[47] J. Levisalles and H. Rudler, *Bull. Soc. chim. France*, 1964, 2020.
[48] L. Westfelt, *Acta Chem. Scand.*, 1964, **18**, 572.

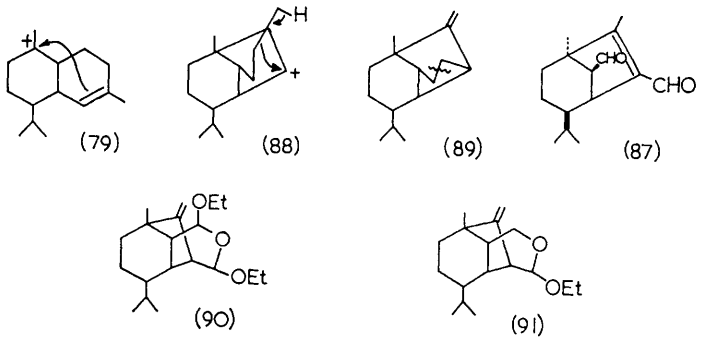
cation can be formed through the intermediacy of an anti-Markownikoff cyclisation of γ-curcumene (16), followed by a 1,2-hydride shift.] The recently determined structures of copaene and the related muskatone[49,50] can be derived from cation (79), by way of an electronically favoured cyclisation leading to the tricyclic cation (81) which on deprotonation yields copaene (82; R = H_2), muskatone (82; R = O) being the product of allylic oxidation. That the biogenetic precursor of copaene is the cation (79) finds credence in its co-occurrence with δ-cadinene (82) and calamenene (84). The sesquiterpene hydrocarbon ylangene[51] (85) differs from copaene only in the configuration of the isopropyl group. The logical precursor of ylangene would be one of the amorphenes[51] (86) which bear the same configurational difference to the muurolenes as copaene does to ylangene.



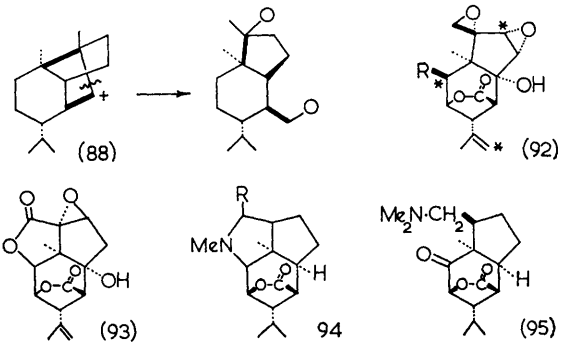
Helminthosporal, Tutin, and Picrotoxin.—The cation (79) has also been suggested as the precursor of the sesquiterpene toxin, helminthosporal[52] (87). Thus, an anti-Markownikoff attack of the double bond on the tertiary carbonium ion gives the secondary cation (88), which can now undergo a Wagner–Meerwein rearrangement, similar to that suggested in the biogenesis of longifolene (see later), followed by deprotonation to give (89). The oxidation sites observed in helminthosporal can be acquired by oxidative cleavage of the bond shown. The final steps in this scheme are substantiated[53] by the isolation of the ethyl acetals of prehelminthosporal (90) and prehelminthosporol[54] (91) and also by

[49] V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, *Tetrahedron*, 1965, **21**, 607.
[50] P. de Mayo, R. E. Williams, G. H. Büchi, and S. H. Feairheller, *Tetrahedron*, 1965, **21**, 619.
[51] O. Motl, V. Herout, and F. Sorm, *Tetrahedron Letters*, 1965, 451; C. H. Heathcock, *J. Amer. Chem. Soc.*, 1966, **88**, 4110; L. Westfelt, *Acta Chem. Scand.*, 1967, **21**, 152.
[52] P. de Mayo, E. Y. Spencer, and R. W. White, *Canad. J. Chem.*, 1963, **41**, 2996.
[53] P. de Mayo, R. E. Williams, and E. Y. Spencer, *Canad. J. Chem.*, 1965, **43**, 1357.
[54] S. Tamura, A. Sakurai, K. Kainuma, and M. Takai, *Agric. Biol. Chem.*, 1963, **27**, 738.

the recent isolation of the unsaturated tricyclic hydrocarbon, sativene[55] (89) itself. The overall biogenetic scheme for helminthosporal has also been verified[56] by a tracer study using [2-^{14}C]-mevalonate which demonstrated that the unsaturated aldehyde carbon atom had 38% of the total incorporated activity.

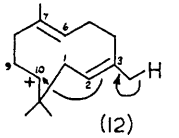


Oxidative fission of the bond shown in (88) (with the isopropyl group axial) leads directly to the gross structure and most of the stereochemical features of tutin[57] (92; R = OH), coriamyrtin[58] (92; R = H), and picrotoxin[59] (93). This plausible biogenetic scheme being assumed, the ^{14}C atoms derived from [2-^{14}C]-mevalonate should be located at the starred positions in tutin. Very closely related to these compounds are the alkaloids dendrine[60] (94; R = $CH_2CO_2CH_3$), dendrobine [61] (94; R = H), and nobiline[61] (95).

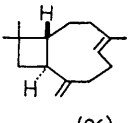


[55] P. de Mayo and R. E. Williams, *J. Amer. Chem. Soc.*, 1965, **87**, 3275.
[56] P. de Mayo, J. R. Robinson, E. Y. Spencer, and R. W. White, *Experientia*, 1962, **18**, 359.
[57] T. Okuda and T. Yoshida, *Tetrahedron Letters*, 1965, 2137, 4191.
[58] T. Okuda and T. Yoshida, *Tetrahedron Letters*, 1964, 439.
[59] H. Conroy, *J. Amer. Chem. Soc.*, 1957, **79**, 5550.
[60] Y. Inubushi and J. Nakano, *Tetrahedron Letters*, 1965, 2723.
[61] S. Yamamura and Y. Hirata, *Tetrahedron Letters*, 1964, 79.

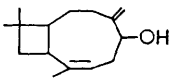
Caryophyllane Class.—Hendrickson[2] has noted that a model of the *cis*-cation (12) shows that the two endocyclic double bonds are not held close enough together to permit internal cyclisation and, in addition, the hydrogen atom on C(1) is held between the cationic site at C(10) and the $\Delta^{6,7}$ double bond, thus excluding cyclisation in this manner. One pathway, therefore, favourable for neutralisation of the cation is a Markownikoff attack of the double bond with concomitant loss of a proton from the C(3) methyl group to give the known stereochemistry of caryophyllene[62] (96). The only other sesquiterpenes with this caryophyllane skeleton are α-betulenol (97a or 97b) and β-betulenol[63,64] (98a or 98b), whose structures still appear in doubt.



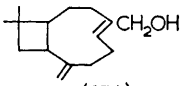
(12)



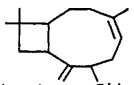
(96)



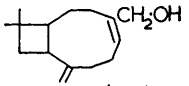
(97a)



(97b)



(98a)

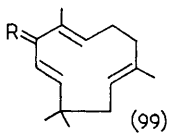


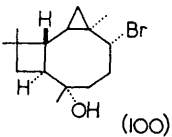
(98b)

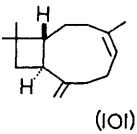
In view of the co-occurrence of humulene with caryophyllene in Nature, it was not unreasonable of Hendrickson to suggest that they originate from the same intermediate cationic species (12). Thus, simple deprotonation from C(9) would furnish the gross skeleton of humulene with a *trans* disubstituted double bond. Until 1963 the stereochemistry of the two trisubstituted double bonds in humulene had not been positively elucidated, but according to Hendrickson's scheme the sesquiterpene would have a *trans-trans-cis* arrangement of the double bonds. However, it has been conclusively shown by *X*-ray analysis[65] of the bis(silver nitrate) adduct of humulene that the double bonds all have *trans* configuration (99; R = H_2). By inference, therefore, humulene is derived from the *trans*-farnesyl cation (14). The same all-*trans* configuration of the double bonds has also been confirmed[66] in zerumbone (99; R = O). This naturally raises the question as to whether caryophyllene could come from the same intermediate (14). Perhaps the fact[67] that caryophyllene is not isolated as such from benzene extraction of oil of cloves but only by steam distillation of the cloves is significant. Sutherland has shown[68] recently that humulene, on

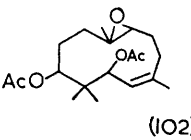
[62] D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 1954, 4665.
[63] M. Holub, V. Herout, M. Horák, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3730.
[64] W. Treibs and G. Lossner, *Annalen*, 1960, **634**, 124.
[65] A. T. McPhail, R. I. Reed, and G. A. Sim, *Chem. and Ind.*, 1964, 976; J. A. Hartsuck and I. C. Paul, *Chem. and Ind.*, 1964, 977.
[66] N. P. Damodaran and S. Dev, *Tetrahedron Letters*, 1965, 1977.
[67] Y. R. Naves, *Helv. Chim. Acta*, 1948, **31**, 378; cf. Y. R. Naves, *Bull. Soc. chim. France*, 1960, 1517.
[68] J. M. Greenwood, J. K. Sutherland, and A. Torre, *Chem. Comm.*, 1965, 410; F. H. Allen and D. Rogers, *Chem. Comm.*, 1966, 582.

treatment with *N*-bromosuccinimide in aqueous acetone gives a 20% yield of the hydroxy-bromo-compound (100), which can be elaborated in two steps to caryophyllene. The structure of the naturally occurring isocaryophyllene (101) might suggest a *cis*-$\Delta^{6,7}$-farnesyl precursor, but the sesquiterpene may, in fact, be an artefact of the isolation procedure since it is known to be the more stable isomer. Caucalol diacetate[69] (102) is the first example of a highly oxygenated eleven-membered ring sesquiterpene, whose stereochemistry about the tri-substituted double bond suggests its genesis from (12).


(99)

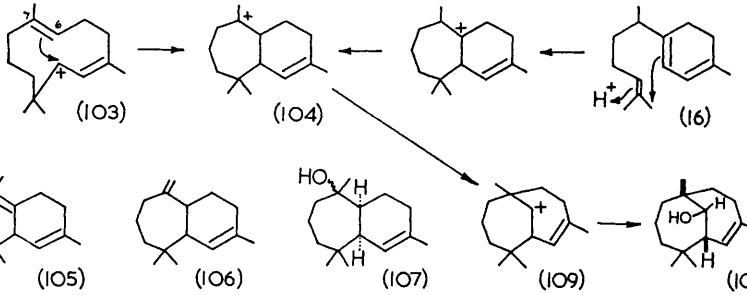

(100)


(101)


(102)

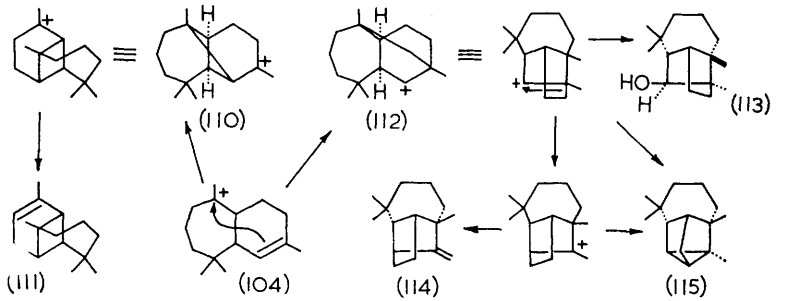
Himachalane and Allohimachalane Classes.—To accommodate the structures of these two types of sesquiterpene, a 1,3-hydride shift in cation (12) is suggested. The resultant cation (103) can now undergo an easy cyclisation with the $\Delta^{6,7}$ double bond to give the tertiary cation (104). Simple deprotonation yields the two isomeric α- (105) and β-himachalenes[70] (106) while solvent attack gives himachalol[71] (107). [As in the case of the suggested precursor of copaene, this intermediate cation (104) could conceivably be formed from γ-curcumene (16), as shown.] The isolation of allohimachalol (108) indicates that a Wagner–Meerwein rearrangement is also possible, giving the bridged cation (109) which can then undergo solvent capture. Solvolysis of the toluene-*p*-sulphonate of allohimachalol produces[71] the following mixture: (105) 3%, (106) 15%, (107) 24%, and (108) 34%.

Longipinane, Longifolane, and Longibornane Classes.—By analogy with the formation of copaene (see earlier), an electronically favoured cyclisation of the

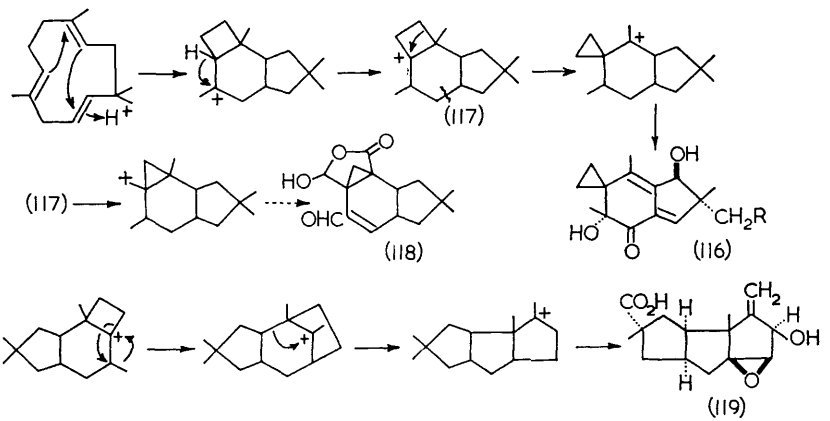

(103) (104) (16) (105) (106) (107) (109) (108)

[69] S. Sasaki, Y. Itagaki, H. Moriyama, K. Nakanishi, E. Watanabe, and T. Aoyama, *Tetrahedron Letters*, 1966, 623.
[70] T. C. Joseph and S. Dev, *Tetrahedron Letters*, 1961, 216.
[71] S. C. Bisarya and S. Dev, *Tetrahedron Letters*, 1964, 3761.

cation (104) would give the tricyclic cation (110) which on deprotonation yields α-longipinene[72] (111). The sterically controlled cyclisation of cation (104) to (112) has been postulated as the probable route to the longifolane skeleton. Solvent attack on this cation gives longiborneol[71] (113), whereas a Wagner–Meerwein shift, followed by deprotonation, gives longifolene[73] (114) and longicyclene[74] (115) respectively. The biogenetic scheme for longifolene has been partially verified[75] by tracer studies using [1-^{14}C]-acetate which showed that the exomethylene group had incorporated virtually no activity.



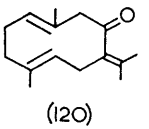
Illudin, Marasmic Acid and Hirsutic Acid.—Cyclisation of *trans*-farnesyl pyrophosphate (5) would furnish cations (13) and (14). The postulate of cation (14) as the precursor of humulene has already been dealt with. An interesting suggestion has been offered[76] for the biogenesis of the fungal metabolites, illudin S (lampterol) (116; R = OH), and illudin M (116; R = H). In the manner shown,



[72] H. Erdtman and L. Westfelt, *Acta Chem. Scand.*, 1963, **17**, 2351; L. Westfelt, *Acta Chem. Scand.*, 1967, **21**, 159.
[73] R. H. Moffett and D. Rogers, *Chem. and Ind.*, 1953, 916.
[74] U. R. Nayak and S. Dev, *Tetrahedron Letters*, 1963, 243.
[75] W. Sandermann and K. Bruns, *Tetrahedron Letters*, 1962, 261.
[76] T. C. McMorris and M. Anchel, *J. Amer. Chem. Soc.*, 1965, **87**, 1594; K. Nakanishi, M. Ohashi, M. Tada, and Y. Yamada, *Tetrahedron*, 1965, **21**, 1231.

cyclisation of humulene followed by a hydride shift would give the cation (117) which, by a final ring contraction, yields the gross structure of these two sesquiterpenes. The same cyclobutyl cation (117) could be an intermediate in the formation of the antibiotic marasmic acid[77] (118) and also hirsutic acid C (119).[78]

Germacrane Class.—Oxidative modification of cation (13) generates all the known ten-membered ring sesquiterpenes with the germacrane skeleton, *e.g.*, germacrone[79] (120), linderane[80] (121), costunolide[81] (122), parthenolide[82] (123), pyrethrosin[83] (124), and arctiopicrin[84] (125). The acid-catalysed cyclisation and pyrolysis products of this group of sesquiterpenes will be referred to later in connection with the biogenetically related eudesmane, elemane, and guaiane classes.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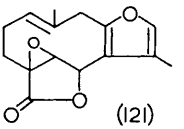
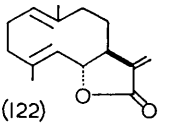
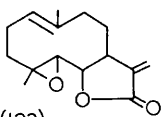
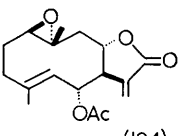
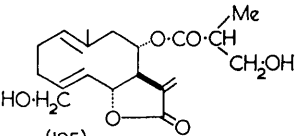

(121)


(122)


(123)



(124)

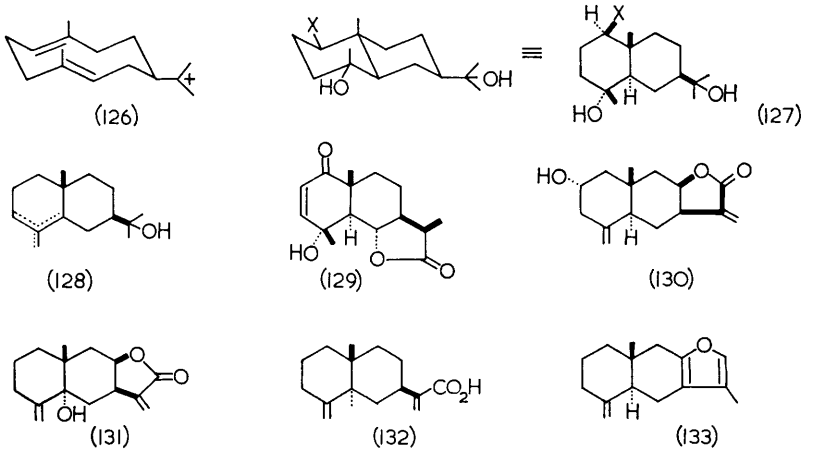


(125)

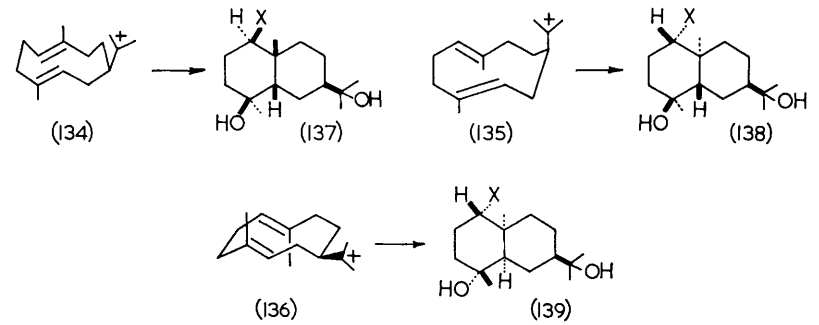
Eudesmane Class.—The two double bonds of cation (13; *i.e.*, 126) are ideally juxtaposed for transannular cyclisations in a *trans*- antiparallel fashion to give the eudesmane series. Thus, a stereospecific Markownikoff-orientated cyclisation, as shown, gives the hypothetical precursor (127) of this series, where X is some electrophile. This hypothesis has been substantiated by the isolation of cryptomeridiol[85] (127; X = H), which has been found to co-occur with the eudesmols[86] (128) and guaiol (see later). Most of the eudesmane sesquiterpenes

[77] J. J. Dugan, P. de Mayo, M. Nisbet, and M. Anchel, *J. Amer. Chem. Soc.*, 1965, **87**, 2768; J. J. Dugan, P. de Mayo, M. Nisbet, J. R. Robinson, and M. Anchel, *J. Amer. Chem. Soc.*, 1966, **88**, 2838.
[78] F. W. Comer, F. McCapra, I. H. Qureshi, J. Trotter, and A. I. Scott, *Chem. Comm.*, 1965, 310.
[79] V. Herout, M. Horák, B. Schneider, and F. Šorm, *Chem. and Ind.*, 1959, 1089.
[80] K. Takeda, H. Minato, and I. Horibe, *Tetrahedron*, 1963, **19**, 2307.
[81] A. S. Rao, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, 1960, **9**, 275; cf. M. Suchý, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1966, **31**, 2899.
[82] T. R. Govindachari, B. S. Joshi, and V. N. Kamat, *Tetrahedron*, 1965, **21**, 1509.
[83] D. H. R. Barton, O. C. Böckmann, and P. de Mayo, *J. Chem. Soc.*, 1960, 2263; S. Iriuchijima and S. Tamura, *Tetrahedron Letters*, 1967, 1965.
[84] M. Suchý, V. Herout, F. Šorm, P. de Mayo, A. N. Starratt, and J. B. Stothers, *Tetrahedron Letters*, 1964, 3907.
[85] M. Sumimoto, H. Ito, H. Hirai, and K. Wada, *Chem. and Ind.*, 1963, 780.
[86] P. Rudman, *Chem. and Ind.*, 1964, 808.

have the absolute stereochemistry depicted in (127) and in many cases further oxidation of the cation framework has taken place, resulting in the large body of lactone and furano-derivatives of this class, *e.g.*, vulgarin[87] (129), ivalin[88] (130), telekin[89] (131), costic acid[90] (132), and atractylon[91] (133).



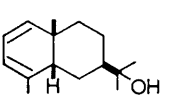
Although the majority of eudesmane (and guaiane) sesquiterpenes can be derived from the 'chair folded' conformation of (13), as depicted in (126), three other conformations (134, 135, and 136) can be invoked to account for the stereochemical features of other members of this class (cf. Nozoe[92]). It should be borne in mind that the classical chemical concepts of strain and steric interactions need not necessarily be the dominant factors in biogenetic schemes, since,



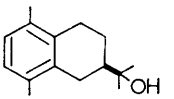
[87] T. A. Geissman and G. A. Ellestad, *J. Org. Chem.*, 1962, **27**, 1855.
[88] W. Herz and G. Högenauer, *J. Org. Chem.*, 1962, **27**, 905.
[89] V. Benešová, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1350.
[90] A. S. Bawdekar and G. R. Kelkar, *Tetrahedron*, 1965, **21**, 1521.
[91] H. Hikino, Y. Hikino, and I. Yoshioka, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 641.
[92] S. Nozoe and C. Kaneko, personal communication.

in vivo, the substrate must concur with the conformational requirements of the particular enzyme(s) involved. The products of a *trans* anti-parallel cyclisation of these three conformers are depicted in the stereostructures (137), (138), and (139) respectively.

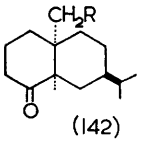
In view of the unusual stereochemistry found in occidentalol[93] (140), conformer (134) seems to be the logical antecedent.[94] Co-occurring with this alcohol is occidol[95] (141), in which a 1,2-methyl migration has taken place. To account for the stereochemistry of the valerane class, exemplified by valeranone[96,97] (142; R = H), kanokonol[97] (142; R = OH), and crytofauronol[98] (143), the intermediate (144) arising from conformer (135) can be formulated. As yet no eudesmane sesquiterpene has been found which might demand the use of conformer (136) as a reasonable precursor.



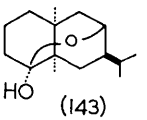
(140)



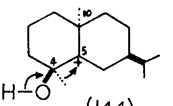
(141)



(142)



(143)



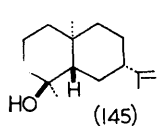
(144)

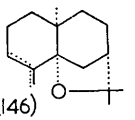
Recently a group of sesquiterpenes has been isolated, *viz.*, intermedeol[99] (145), α- and β-agarofuran[100] (146), and lævojuneol[101] (147), which are antipodally related to the normal eudesmane class. Intermedeol is extracted from a plant source in India, whereas neointermedeol[102] (148) is obtained from the corresponding plant indigenous to Malaya. The stereochemistry at C(4) in the latter compound is anomalous since the configuration of the C(4) hydroxyl group is usually equatorial in the eudesmane series.

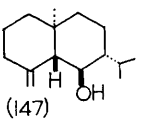
The stereochemistry at C(1) of microcephalin[103] (149) is opposite to that expected (cf. 127) from a *trans*-antiparallel cyclisation of (126). This anomaly can

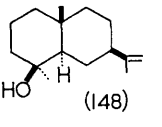
[93] Y. Hirose and T. Nakatsuka, *Bull. Agric. Chem. Soc. Japan*, 1959, **23**, 143.
[94] E. von Rudloff and G. V. Nair, *Canad. J. Chem.*, 1964, **42**, 421.
[95] M. Nakazaki, *Bull. Chem. Soc. Japan*, 1962, **35**, 1387.
[96] W. Klyne, S. C. Bhattacharyya, S. K. Paknikar, C. S. Narayanan, K. S. Kulkarni, J. Křepinský, M. Romaňuk, V. Herout, and F. Šorm, *Tetrahedron Letters*, 1964, 1443.
[97] H. Hikino, Y. Takeshita, Y. Hikino, and T. Takemoto, *Chem. Pharm. Bull.* (*Tokyo*), 1965, **13**, 626.
[98] H. Hikino, Y. Takeshita, Y. Hikino, and T. Takemoto, *Chem. Pharm. Bull.* (*Tokyo*), 1965, **13**, 631.
[99] L. H. Zalkow, V. B. Zalkow, and D. R. Brannon, *Chem. and Ind.*, 1963, 38; cf. R. E. Corbett and R. A. J. Smith, *Tetrahedron Letters*, 1967, 1009.
[100] M. L. Maheshwari, T. C. Jain, R. B. Bates, and S. C. Bhattacharyya, *Tetrahedron*, 1963, **19**, 1079.
[101] S. C. Bhattacharyya, A. S. Rao, and A. M. Shaligram, *Chem. and Ind.*, 1960, 469.
[102] V. B. Zalkow, A. M. Shaligram, and L. H. Zalkow, *Chem. and Ind.*, 1964, 194.
[103] W. Herz, A. Romo de Vivar, and M. V. Lakshmikantham, *J. Org. Chem.*, 1965, **30**, 118.

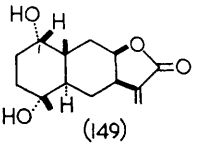
be explained in terms of a ten-membered cationic precursor (150) containing a *cis*-$\Delta^{6,7}$-double bond which on cyclisation would give (151), cf. (149).

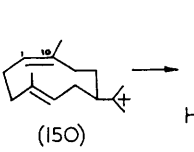

(145)

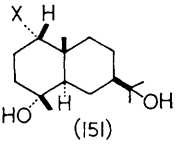

(146)


(147)

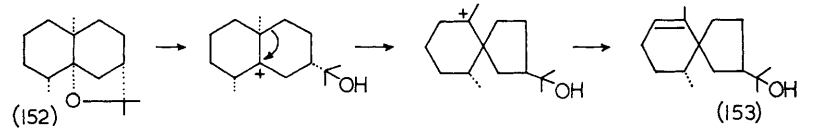

(148)


(149)

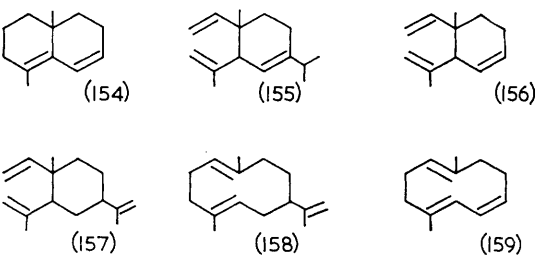

(150)


(151)

A biogenetic scheme has been postulated for the formation of agarospirol[10] (153) which involves a cationic opening of the tetrahydrofuran ring of dihydroagarofuran (152) followed by a Wagner–Meerwein rearrangement and subsequent deprotonation. Significantly, agarospirol is only isolated from fungus-infected wood, whereas the agarofurans are derived from fungus-free wood.

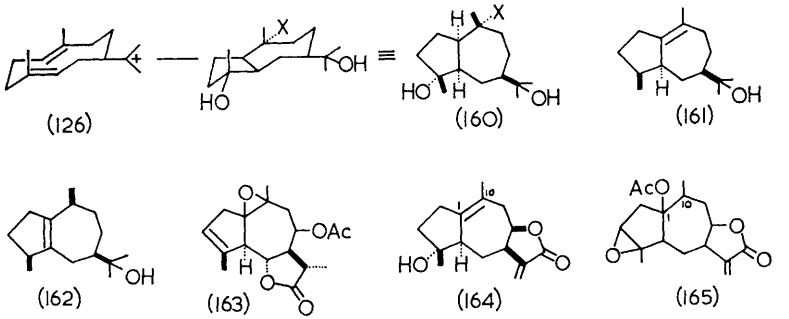

(152) (153)

A possible derivative of the eudesmane class is the optically inactive cogeijerene[105] (154), although its co-occurrence[106] with the racemic α-elemene (155) and geijerene (156) would suggest a relationship to the elemane class. It has been pointed out[106,107] that whereas the naturally occurring optically active β-elemene (157) would probably be derived from an optically active precursor (*e.g.*, 158), the corresponding precursor of the above sesquiterpenes would lack asymmetric centres (*e.g.*, 159).


(154) (155) (156) (157) (158) (159)

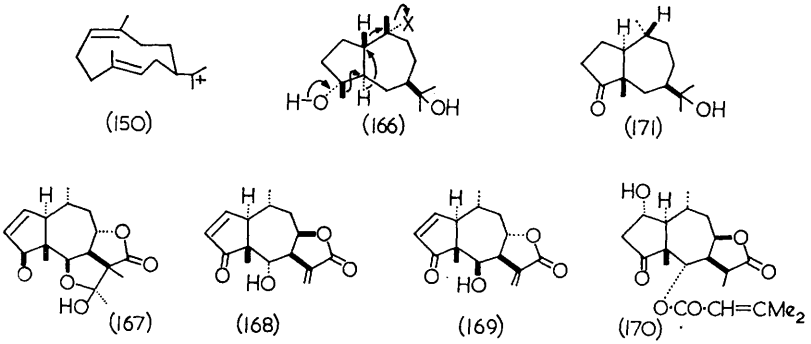
[104] K. R. Varma, M. L. Maheshwari, and S. C. Bhattacharyya, *Tetrahedron*, 1965, **21**, 115.
[105] J. Gough, V. Powell, and M. D. Sutherland, *Tetrahedron Letters*, 1961, 763.
[106] J. Gough and M. D. Sutherland, *Austral. J. Chem.*, 1964, **17**, 1270.
[107] M. D. Sutherland, *Austral. J. Chem.*, 1964, **17**, 75.

Guaiane Class.—As suggested by Hendrickson,[2] an anti-Markownikoff cyclisation of cation (126) generates the guaiane skeleton (160), illustrated by bulnesol[108] (161), guaiol[109] (162), globicin[110] (163), and pseudoivalin[103] (164).



Pseudoivalin is the first guaianolide known to co-occur with an eudesmanolide, *viz.*, microcephalin[111] (149), and the fact that it contains a $\Delta^{1,10}$-double bond could be rationalised in terms of loss of X from (160) followed by subsequent deprotonation. On the other hand, calocephalin[112] (165) co-occurs with pseudoivalin and although its stereochemistry has not yet been determined, it is conceivable that both the C(1) acetoxy-group and C(10) hydrogen atom may be *cis* orientated in which case an *in vivo cis*-elimination would produce pseudoivalin.

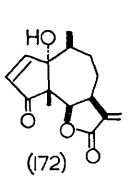
A more attractive scheme which would account for the stereochemistry of the above guaianes and also pseudoguaianolides involves the ten-membered ring cationic precursor with a *cis*-$\Delta^{1,10}$-double bond (150). A *trans* anti-parallel cyclisation gives the intermediate (166) which can undergo a *concerted* loss of

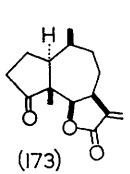


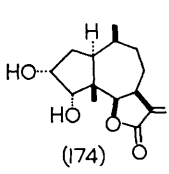
[108] E. J. Eisenbraun, T. George, B. Riniker, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 3648.
[109] K. Takeda and H. Minato, *Tetrahedron Letters*, 1960, **22**, 33.
[110] R. B. Bates, Z. Čekan, V. Prochazka, and V. Herout, *Tetrahedron Letters*, 1963, 1127.
[111] W. Herz, G. Högenauer, and A. Romo de Vivar, *J. Org. Chem.*, 1964, **29**, 1700.
[112] T. J. Batterham, N. K. Hart, and J. A. Lamberton, *Austral. J. Chem.*, 1966, **19**, 143.

HX resulting in the formation of pseudoivalin. In addition a 'non-stop' rearrangement involving loss of X followed by two successive hydride shifts and a methyl shift and subsequent deprotonation gives the stereochemical pattern (171) which is characteristic of the pseudoguaianolides, *e.g.*, tenulin[113] (167), helanalin[144] (168), mexicanin I[115] (169), and flexuosin B[116] (170).

A second group of pseudoguaianolides, *e.g.*, parthenin[117] (172), damsin[117] (173), ambrosiol[118] (174), and hysterin[119] (175), are characterised by a β-oriented C(10) methyl group.


(172)


(173)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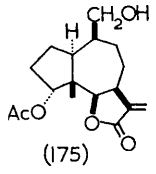
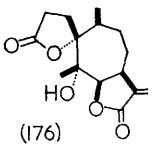
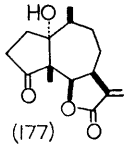
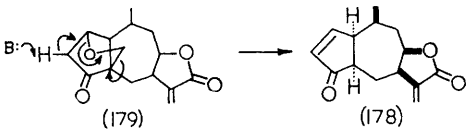

(175)

Recently a modified pseudoguaianolide, psilostachyin[120] (176) has been isolated and an *in vitro* conversion of coronopilin (177) into psilostachyin on treatment with peracetic acid demonstrates their obvious biogenetic relationship.


(176)

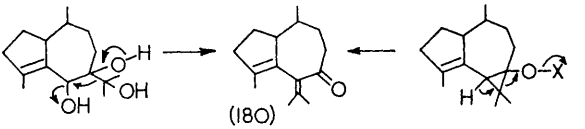

(177)

A biogenetic derivation of mexicanin E[121] (178) has been found in the recent isolation of mexicanin H[122] (179) in which the methyl group at C(5) is attached *via* an oxygen bridge to C(2). A molecule of formaldehyde is readily eliminated from mexicanin H on treatment with base to yield mexicanin E. The mass-spectrum fragmentation pattern of mexicanin H also indicates this breakdown.


(179) (178)

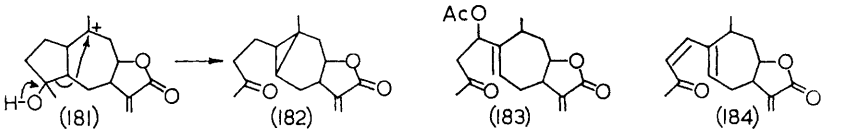
[113] W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Amer. Chem. Soc.*, 1962, **84**, 3857.
[114] W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Amer. Chem. Soc.*, 1963, **85**, 19.
[115] E. Dominguez and J. Romo, *Tetrahedron*, 1963, **19**, 1415.
[116] W. Herz, Y. Kishida, and M. V. Lakshmikantham, *Tetrahedron*, 1964, **20**, 979.
[117] W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem. Soc.*, 1962, **84**, 2601; M. Suchý V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1963, **28**, 2257.
[118] T. J. Mabry, W. Renold, H. E. Miller, and H. B. Kagan, *J. Org. Chem.*, 1966, **31**, 681.
[119] A. Romo de Vivar, E. A. Bratoeff, and T. Ríos, *J. Org. Chem.*, 1966, **31**, 675.
[120] T. J. Mabry, H. E. Miller, H. B. Kagan, and W. Renold, *Tetrahedron*, 1966, **22**, 1139.
[121] J. Romo, A. Romo de Vivar, and W. Herz, *Tetrahedron*, 1964, **19**, 2317; C. N. Caughlan, Mazhar-Ul-Haque, and M. T. Emerson, *Chem. Comm.*, 1966, 151.
[122] J. Romo, A. Romo de Vivar, and P. Joseph-Nathan, *Tetrahedron Letters*, 1966, 1029.

Further modifications the guaiane skeleton can be devised to account for some structurally related sesquiterpenes. The unique structure of zierone[123] (180) has been rationalised either from an oxygenated guaiane or aromadendrane skeleton, by the mechanism shown.



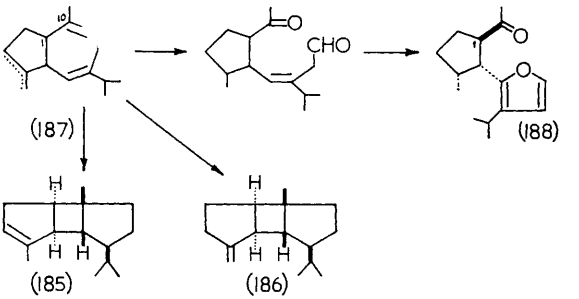
(180)

Rearrangement of the cation (181), derivable from pseudoivalin, could be considered to explain the gross structure of carabrone[124] (182), and a similar type of fission may be operative in the formation of xanthinin (183) and xanthatin[125] (184).



(181) (182) (183) (184)

The structures of α- (185) and β-bourbonene[126] (186) suggest that they could be formally derived by cyclisation of the bicyclic diene (187). The furopelargones[127] [188, epimeric at C(1)] have also been isolated from the same essential oil which makes their suggested biogenesis from an oxidative cleavage between C(9) and C(10) of (187) all the more attractive.

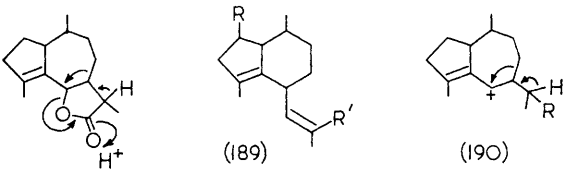


(187) (188) (185) (186)

To accommodate the structures of valerenic acid[128] (189; R = H, R′ = CO_2H) and valerenolic acid[129] (189; R = OH, R′ = CO_2H), a ring B contrac-

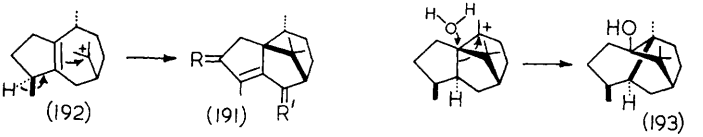
[123] D. H. R. Barton and G. S. Gupta, *J. Chem. Soc.*, 1962, 1961.
[124] H. Minato, S. Nosaka and I. Horibe, *J. Chem. Soc.*, 1964, 5503.
[125] T. A. Geissman, *J. Org. Chem.*, 1962, **27**, 2692; H. Minato and I. Horibe, *J. Chem. Soc.*, 1965, 7009.
[126] J. Křepinský, Z. Samek, and F. Šorm, *Tetrahedron Letters*, 1966, 359; J. Křepinský, Z. Samek, and F. Šorm, *Tetrahedron Letters*, 1966, 3209; J. D. White and D. N. Gupta, *J. Amer. Chem. Soc.*, 1966, **88**, 5364.
[127] G. Lukas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, *Tetrahedron*, 1964, **20**, 1789; G. Büchi and H. Wüest, *J. Amer. Chem. Soc.*, 1965, **87**, 1589.
[128] G. Büchi, T. L. Popper, and D. Stauffacher, *J. Amer. Chem. Soc.*, 1960, **82**, 2962.
[129] J. Křepinský, V. Sýkora, E. Zvonkova, and V. Herout, *Coll. Czech. Chem. Comm.*, 1965, **30**, 553.

tion has been suggested in the manner shown. The isolation of valerenal[130] (189; R = H, R′ = CHO), however, suggests that a more likely intermediate for this type of sesquiterpene would be the cation (190), which can be derived by opening of the cyclopropane ring in α-gurjenene. Although the corresponding alcohol (189; R = H, R′ = CH_2OH) has not as yet been isolated, valerenal could well be the parent compound and the acid and the unreported alcohol Cannizzaro artefacts, induced by the base used in the extraction process (cf. jalaric acid-B, see earlier).



(189) (190)

The sesquiterpenes patchoulenone[131] (191; R = H_2, R′ = O), cyperene[132] (191; R = H_2, R′ = H_2), and isopatchoulen-3-one[133] (cyperotundone) (191; R = O, R′ = H_2), belonging to the revised class name of isopatchoulane, can be formed by nucleophilic attack of the double bond on the cation derivable from epiguaiol (192) which has, itself, been prepared in the laboratory from bulnesol.[134] The revised[135] structure of patchouli alcohol (193) is explained in terms of a Wagner–Meerwein migration with concomitant solvent attack in a cation readily derivable from bulnesol.

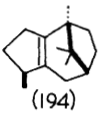


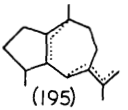
(192) (191) (193)

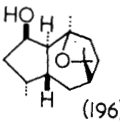
Bulnesol has been shown[134] to undergo *in vitro* transformations which are of biogenetic importance; for example, treatment with alumina and pyridine yields β-patchoulene (194), a degradation product of patchouli alcohol, while the action of acetic and sulphuric acids gives the guaienes (195) and guaiol (162). The unusual stereochemistry of α-kessyl alcohol[136] (196) can readily be explained by an anti-Markownikoff cyclisation of the conformer (134), previously postulated for the formation of occidentalol (see earlier).

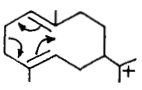
[130] R. B. Bates and S. K. Paknikar, *Chem. and Ind.*, 1965, 1731.
[131] B. Trivedi, O. Motl, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1675.
[132] B. Trivedi, O. Motl, J. Smolíková, and F. Šorm, *Tetrahedron Letters*, 1964, 1197.
[133] H. Hikino, K. Aota, and T. Takemoto, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 628; S. B. Nerali, P. S. Kalsi, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron Letters*, 1965, 4053.
[134] R. B. Bates and R. C. Slagel, *J. Amer. Chem. Soc.*, 1962, **84**, 1307.
[135] M. Dobler, J. D. Dunitz, B. Gubler, H. P. Weber, G. Büchi, and J. Padilla O, *Proc. Chem. Soc.*, 1963, 383.
[136] S. Itô, M. Kodama, T. Nozoe, H. Hikino, Y. Hikino, Y. Takeshita, and T. Takemoto, *Tetrahedron Letters*, 1963, 1787; S. Itô, M. Kodama, T. Nozoe, H. Hikino, Y. Hikino, Y. Takeshita, and T. Takemoto, *Tetrahedron*, 1967, **23**, 553.

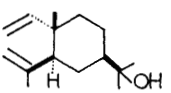
Elemane Class.—A Cope rearrangement of cation (13) has been suggested as a feasible mechanism for the formation of the elemane class of sesquiterpenes, *e.g.*, elemol[137] (197), saussurea lactone[138] (198), and isolinderalactone[139] (199). Since experimental evidence indicates that higher yields of this type of sesquiterpene can be realised if heat is used at any stage in the isolation procedure, doubts have been raised[138,139] as to whether this type exists *per se* in Nature.

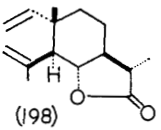

(194)

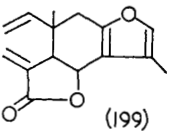

(195)


(196)

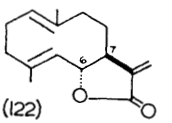

(13)

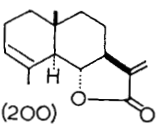

(197)

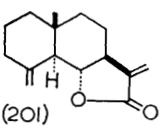

(198)

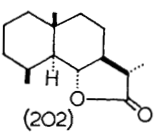

(199)

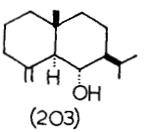
Having considered the genesis of these groups of sesquiterpenes derivable from cation (13), we feel we may digress a little and examine some *in vitro* transannular cyclisations of the germacrane sesquiterpenes which have furnished an experimental basis for the suggested *in vivo* cyclisations described above. Thus, costunolide (122), on treatment with acetic acid, gives rise to the so-called α- (200) and β-cyclocostunolide[140] (201). α-Cyclocostunolide, on catalytic hydrogenation, yields santanolide 'c' (202), the formation of which establishes the stereochemistry of the cyclised product at all the asymmetric centres and by inference at C(6) and C(7) in costunolide itself. This method has provided a means of converting costunolide into the antipode of naturally-occurring juneol[141] (203).


(122)


(200)

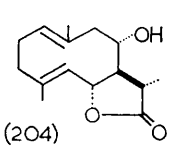

(201)

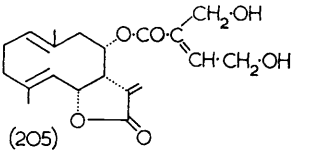

(202)

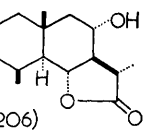

(203)

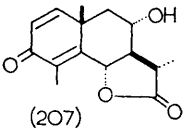
[137] A. D. Wagh, S. K. Paknikar, and S. C. Bhattacharyya, *Tetrahedron*, 1964, **20**, 2647.
[138] A. S. Rao, A. Paul, Sadgopal, and S. C. Bhattacharyya, *Tetrahedron*, 1961, **13**, 319.
[139] K. Takeda, H. Minato, and M. Ishikawa, *J. Chem. Soc.*, 1964, 4578.
[140] G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, 1964, **20**, 2639.
[141] G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, 1964, **20**, 1301.

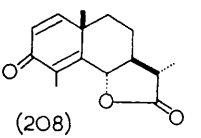
Similarly, arctiopicrin[84] (125), balchanolide[142] (204), and eupatariopicrin[143] (205), after hydrolysis of the side-chain, yield, on hydrogenation in acid medium, the bicyclic derivative (206), which can also be prepared from artemisin (207). Santonin (208) has recently assumed a close association with the germacrane sesquiterpenes through the key rôle which it plays in Corey's brilliantly conceived synthesis[144] of dihydrocostunolide (209).

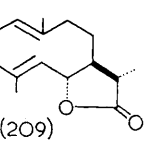

(204)


(205)

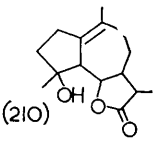

(206)

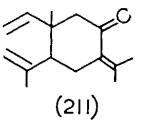

(207)


(208)

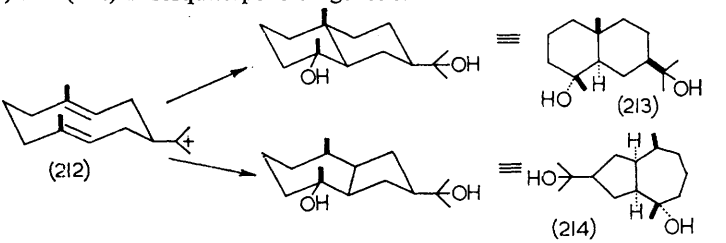

(209)

So far, the only reported *in vitro* cyclisation resulting in a guaiane skeleton is that of parthenolide[82] (123). Thus dihydroparthenolide, on treatment with boron trifluoride ether complex, yields the hydroxy-lactone (210). The Cope rearrangement of some of the germacrane sesquiterpenes to form the elemane series has also been observed, *e.g.*, dihydrocostunolide (209), on pyrolysis, affords saussurea lactone[138] (198), while germacrone, on similar treatment, gives β-elemenone[145] (211).


(210)

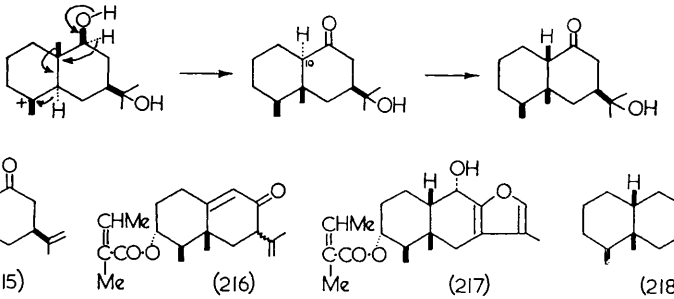

(211)

Eremophilane Class.—A double-bond migration in cation (13) giving cation (212), followed by analogous concerted cyclisations to those postulated for cation (13) itself, result in the formation of two more hypothetical intermediates (213) and (214) in sesquiterpene biogenesis.

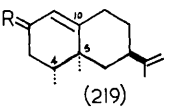

(212) (213) (214)

[142] V. Herout, M. Suchý, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 2612.
[143] M. Suchý, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1715.
[144] E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, 1965, **87**, 5736.
[145] G. Ohloff, H. Farnow, W. Philipp, and G. Schnade, *Annalen*, 1959, **625**, 206.

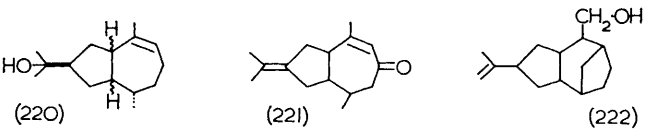
The intermediate (213) has been postulated[146,147] as the ideal precursor for the eremophilane series, *e.g.*, eremophilone[147] (215), petasin[148] (216), furanopetasin[149] (217), and eremophilenolide[150] (218). As illustrated, the scheme involves a series of 1,2-shifts with a final epimerisation of the C(10) hydrogen, resulting in the stereochemistry characteristic of this group.



Nootkatone (219; R = O) and valencene (219; R = H_2), isolated[151] from grapefruit peel, have been correlated with a C(7) epimer of the eremophilane series, but their biogenesis seems to be more closely related to the valerane sesquiterpenes (see earlier) where the C(10) methyl rather than the C(4) methyl group has migrated to C(5).

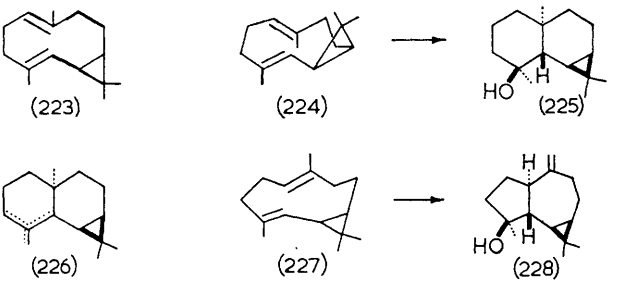


Vetivane Class.—The intermediate (214) is the obvious precursor of the vetivane type of sesquiterpenes, *e.g.*, hinesol[152] (220) and β-vetivone[153] (221), and may also be the antecedent of tricyclovetivenol[154] (222).

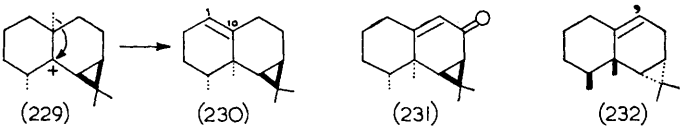


[146] R. Robinson; cf. A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 1939, 87.
[147] L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 6354.
[148] D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 4337.
[149] L. Novotný, Ch. Tabačíkova-Wlotzká, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1922.
[150] L. Novotný, J. Jizba, V. Herout, F. Šorm, L. H. Zalkow, S. Hu, and C. Djerassi, *Tetrahedron*, 1963, **19**, 1101.
[151] W. D. MacLeod, jun., *Tetrahedron Letters*, 1965, 4779.
[152] W. Z. Chow, O. Motl, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1962, **27**, 1914.
[153] A. St. Pfau and P. A. Plattner, *Helv. Chim. Acta*, 1940, **23**, 768.
[154] G. Chiurdoglu and J. Decot, *Tetrahedron*, 1958, **4**, 1.

Maaliane, Aristolane, and Aromadendrane Classes.—The skeletons of these three closely-related groups of sesquiterpenes contain a *gem*-dimethyl cyclopropane ring, and it has been postulated[155] that they have their origin in a common precursor, *viz.*, (223), which can arise from 1,3-deprotonation of cation (8). A consideration of the various conformers of (223) and the corresponding compound with a *cis*-$\Delta^{4,5}$-double bond, can lead to a rationalisation of the main stereochemical features of these groups, *e.g.*, a Markownikoff-oriented cyclisation of conformer (224) would lead to maaliol[156] (225) and the maalienes (226), whereas an anti-Markownikoff cyclisation of conformer (227) yields spathulenol[157] (228).

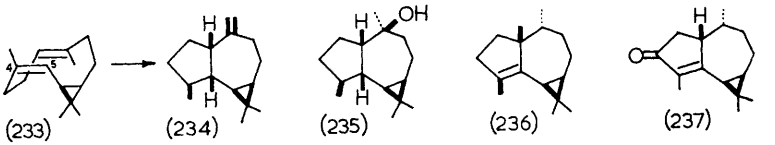


In a similar fashion to the 1,2-migrations suggested in the genesis of the eremophilane group, the maaliane cation (229) would yield 1(10)-aristolene[155–158] (230) (previously named β-gurjenene and calarene) and aristolone[159] (231). The enantiomer of 9-aristolene, α-ferulene (232), has recently been isolated.[160]

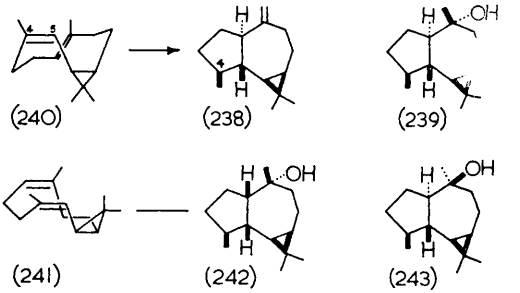


An anti-Markownikoff cyclisation of conformer (233) in which the $\Delta^{4,5}$-double bond is *cis* produces the skeletons of alloaromadendrene[161] (234), viridiflorol[161] (235), α-gurjenene[162] (236), and cyclocolarenone[163] (237).

[155] J. Streith, P. Pesnelle, and G. Ourisson, *Bull. Soc. chim. France*, 1963, 518.
[156] G. Büchi, M. Schach v. Wittenau, and D. M. White, *J. Amer. Chem. Soc.*, 1959, **81**, 1968.
[157] R. C. Bowyer and P. R. Jefferies, *Chem. and Ind.*, 1963, 1245.
[158] J. Vrkoč, J. Křepinský, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1964, **29**, 795
[159] S. Furukawa, *J. Pharm. Soc. Japan*, 1961, **81**, 570.
[160] S. Carboni, A. Da Settimo, V. Malaguzzi, A. Marsili, and P. L. Pacini, *Tetrahedron Letters*, 1965, 3017.
[161] Cf. G. Büchi, S. W. Chow, T. Matsuura, T. L. Popper, H. H. Rennhard, and M. Schach v. Wittenau, *Tetrahedron Letters*, 1959, **6**, 14.
[162] M. Palmade, P. Pesnelle, J. Streith, and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1950.
[163] G. Büchi and H. J. E. Loewenthal, *Proc. Chem. Soc.*, 1962, 280; G. Büchi, J. M. Kauffman, and H. J. E. Loewenthal, *J. Amer. Chem. Soc.*, 1966, **88**, 3403.

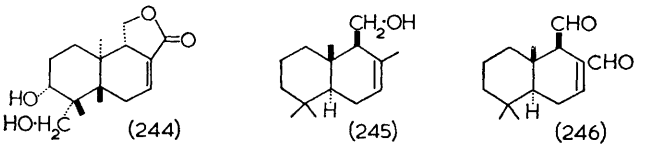


Aromadendrene[161] (238) and globulol[161] (239) could arise from a cyclisation of yet another conformer (240) with a *cis* double bond, and finally conformer (241), in which both double bonds are *cis*, can lead to ledol (242).[161]



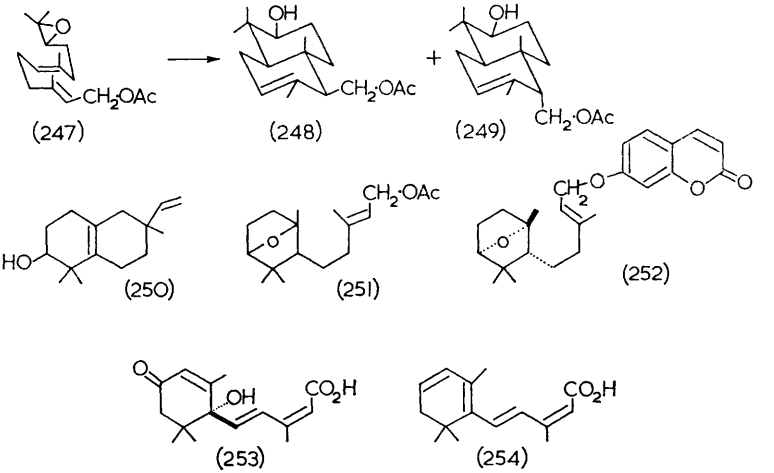
However, this approach fails when a hypothetical precursor of palustrol[161] (243) is sought, since a model of the required conformer indicates that the two double bonds are spatially remote, although it should be pointed out that the structure and stereochemistry of this compound have not been positively correlated with the other members of the aromadendrane group. It is of biogenetic significance that of the two *Dipterocarpus* species so far examined,[155] one yields predominantly caryophyllene and humulene while the other yields predominantly aromadendrene, alloaromadendrene, and α- and β-gurjenene, but no maaliene.

Bicyclofarnesol Class.—Although the majority of sesquiterpenes can be derived by the cyclisation processes outlined above, a well-defined group of sesquiterpenes has been isolated which indubitably are derived by a 'non-stop' *trans*-antiparallel cyclisation of farnesyl pyrophosphate, *e.g.*, iresin[164] (244), drimenol[165] (245), and polygodial[166] (246). It was suggested initially that they may in fact be degraded di- and tri-terpenes, but iresin has been shown to have the opposite stereochemistry from that found in most higher terpenes and steroids, although drimenol has been shown to possess the conventional absolute stereochemistry.



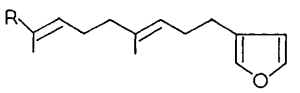
[164] C. Djerassi and S. Burnstein, *Tetrahedron*, 1959, **7**, 37.
[165] H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.*, 1959, 3322.
[166] C. S. Barnes and J. W. Loder, *Austral. J. Chem.*, 1962, **15**, 322.

Van Tamelen and his co-workers have shown[167] that treatment of the terminal monoepoxide of *trans-trans*-farnesyl acetate (247) with boron trifluoride ether complex or mineral acids gives a reasonable yield of the stereoisomers (248) and (249) in the ratio of 5·5 : 1. Oxidation to the corresponding acetoxy-ketones followed by reduction of the thioketals gives *dl*-drimenol and *dl*-epidrimenol respectively. Two by-products of this cyclisation have spectral properties consistent with (250) and (251) respectively. These structures are of biogenetic interest since the ring B moiety in (250) is found in diterpenes such as pimaric acid and rimuene and the second structure (251) is very reminiscent of the naturally occurring farnesiferol C[168] (252). Abscisin II[169] (253), an abscission-accelerating plant hormone, can be derived simply from a farnesyl precursor by direct cyclisation of the $\Delta^{6,7}$ and $\Delta^{10,11}$ double bonds. The structure of abscisin II has been confirmed synthetically[170] by photo-oxidation of the diene (254); this may have a biogenetic implication.

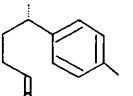


Recently several acyclic sesquiterpenes have been isolated. Dendrolasin (255; R = CH_3), torreyal (255; R = CHO), and neotorreyol (255; R = CH_2OH) co-occur[171] with the bisabolane-type sesquiterpenes, nuciferal (256; R = CH_3, R′ = CHO) and niciferol (256; R = CH_2OH, R′ = CH_3). Ipomeamarone (257) has been shown[172] to incorporate both [2-^{14}C]-acetate and [2-^{14}C]-mevalonate.

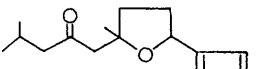
[167] E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Amer. Chem. Soc.*, 1963, **85**, 3295; E. E. van Tamelen and R. M. Coates, *Chem. Comm.*, 1966, 413 and refs. therein.
[168] L. Caglioti, H. Naef, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1959, **42**, 2557.
[169] K. Ohkuma, F. T. Addicott, O. E. Smith, and W. E. Thiessen, *Tetrahedron Letters*, 1965, 2529; J. W. Cornforth, W. Draber, B. V. Milborrow, and G. Ryback, *Chem. Comm.*, 1967, 114.
[170] J. W. Cornforth, B. V. Milborrow, and G. Ryback, *Nature*, 1965, **206**, 715; M. Mousseron-Canet, J-C. Mani, J-P. Dalle, and J-L. Olivé, *Bull. Soc. chim. France*, 1966, 3874.
[171] T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Japan*, 1965, **38**, 381.
[172] T. Akazawa, I. Uritani, and Y. Akazawa, *Arch. Biochem. Biophys.*, 1962, **99**, 52.



(255)

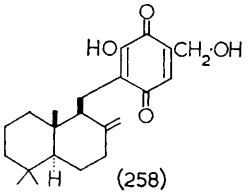


(256)

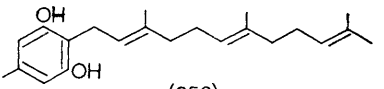


(257)

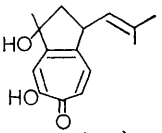
The drimanyl quinone tauranin[173] (258), grifolin[174] (259), and chanootin[175] (260) seem to have a mixed biogenetic origin. Chanootin, which is related to nootkatin (261) and procerin (262), can be derived from condensation[176] of a C_5 unit with β-thujaplicin (263).



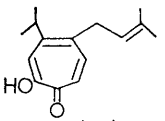
(258)



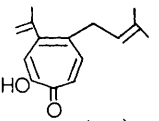
(259)



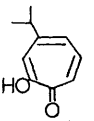
(260)



(261)



(262)



(263)

The overall picture which emerges from this Review is reminiscent of the state of alkaloid biogenesis before the elegant radioactive tracer studies of the schools led by Professors Barton, Battersby, Leete, and Mothes. Although some of the above biogenetic schemes, *e.g.*, those of trichothecin, helminthosporal, carotol, and longifolene have been corroborated by ^{14}C tracer studies, more of this type of verification has yet to appear in print. One reason for the paucity of such corroboration may be the difficulty of tracer feeding and harvesting in the higher plants.

Alternative methods of substantiation of sesquiterpene biogenetic suggestions lie in a chemotaxonomic classification of plants, as advocated by Erdtman,[177] and an extension of the *in vitro* reactions of neryl- and geranyl-diphenylphosphate giving rise to known monoterpenes, as determined by Miller and Wood.[178]

[173] K. Kawashima, K. Nakanishi, and H. Nishikawa, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 796.
[174] T. Goto, H. Kakisawa, and Y. Hirata, *Tetrahedron*, 1963, **19**, 2079.
[175] T. Norin, *Arkiv Kemi*, 1964, **22**, 129.
[176] H. Erdtman, *Progr. Org. Chem.*, 1952, **1**, 22.
[177] H. Erdtman, *Pure Appl. Chem.*, 1963, **6**, 679; cf. C. Steelink and J. C. Spitzer, *Phytochem.*, 1966, **5**, 357; N. G. Bisset, M. A. Diaz, C. Ehret, G. Ourisson, M. Palmade, F. Patil, P. Pesnelle, and J. Streith, *Phytochem.*, 1966, **5**, 865; L. Novotný, J. Toman, F. Starý, A. D. Marquez, V. Herout, and F. Šorm, *Phytochem.*, 1966, **5**, 1281.
[178] J. A. Miller and H. C. S. Wood, *Angew. Chem.*, 1964, **76**, 301.

The work of Haagen-Smit and his co-workers[179] in which isoprenoid compounds were produced from mevalonic acid by the action of enzyme preparations from green peas, could perhaps open the door to an exciting field of investigation parallel with the elegant studies of Cornforth, Popják, Lynen, and Bloch on yeast and mammalian enzymes. The advent of more exacting analytical tools such as the combination of gas–liquid chromatography and mass spectrometry, ^{13}C nuclear magnetic resonance,[180] and improved tissue culture techniques will undoubtedly lead to an even more detailed understanding of terpene biogenesis.

Addendum—Since the completion of this Review, a number of significant papers have been published which contribute to the general picture of sesquiterpene biogenesis, formulae being omitted for brevity.

Laurinterol, a close relative of laurene (51) has been isolated,[181] and its *in vitro* conversion to aplysin (52; R = Br, R′ = H) by treatment with *p*-toluenesulphonic acid has demonstrated their biogenetic relationship.

The structural elucidation of chamigrene[182] [*i.e.*, a deprotonated form of (53)] provides the 'missing link' in the biogenetic scheme for the cuparane, thujopsane, widdrane and cedrane classes. This scheme has now become even more convincing since, not only is chamigrene found to co-occur with representatives of these four classes, but can also be derived from either widdrol (54) or thujopsene (55) by *in vitro* processes.

Herout and co-workers[183] and Westfelt[184] have reported the structures and stereochemistry of the four diastereoisomeric compounds belonging to the cadalane skeleton. Thus, the four sub-groups, which differ in the relative configurations about the ring junction and isopropyl group, should now be termed the cadinane, muurolane, amorphane and bulgarane types. In this context, copaborneol[185] is closely related to copaene by a Wagner-Meerwein rearrangement, while the two cubebenes[186] [cf. cubenol and its C(1) epimer[187]] are representatives of an alternate mode of cyclisation of a cadalene precursor.

A preliminary communication[188] indicates that [2-^{14}C]-mevalonate is incorporated into *Dendrobium nobile* from which radioactive dendrobine (94; R = H) can be isolated. The positions of the radioactive carbons have, however, not yet been rigorously established.

[179] C. J. Pollard, J. Bonner, A. J. Haagen-Smit, and C. C. Nimmo, *Plant Physiol.*, 1966, **41**, 66; cf. L. J. Rogers, S. P. J. Shah, and T. W. Goodwin, *Biochem. J.*, 1966, **99**, 381 and refs. therein.
[180] Cf. M. Tanabe and G. Detre, *J. Amer. Chem. Soc.*, 1966, **88**, 4515.
[181] T. Irie, M. Suzuki, E. Kurosawa, and T. Masamune, *Tetrahedron Letters*, 1966, 1837.
[182] S. Itô, K. Endo, T. Yoshida, M. Yatagai, and M. Kodama, *Chem. Comm.*, 1967, 186.
[183] O. Motl, M. Romaňuk, and V. Herout, *Coll. Czech. Chem. Comm.*, 1966, **31**, 2025; A. Zabza, M. Romaňuk, and V. Herout, *Coll. Czech. Chem. Comm.*, 1966, **31**, 3373; R. Vlahov, M. Holub, I. Ognjanov, and V. Herout, *Coll. Czech. Chem. Comm.*, 1967, **32**, 808; R. Vlahov, M. Holub, and V. Herout, *Coll. Czech. Chem. Comm.*, 1967, **32**, 822.
[184] L. Westfelt, *Acta Chem. Scand.*, 1966, **20**, 2829, 2841, 2852.
[185] M. Kolbe and L. Westfelt, *Acta Chem. Scand.*, 1967, **21**, 585.
[186] Y. Ohta, T. Sakai, and Y. Hirose, *Tetrahedron Letters*, 1966, 6365.
[187] Y. Ohta and Y. Hirose, *Tetrahedron Letters*, 1967, 2073.
[188] M. Yamazaki, M. Matsuo, and K. Arai, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 1058.

The structure of the unusual sesquiterpene, fomannosin has been adduced.[189] By oxidative cleavage of the bond shown, this compound can be formally derived from the cation (117) which has been previously suggested in the biogenesis of the illudins, marasmic acid and hirsutic acid C.

Another example of unusual *cis* ring junction stereochemistry in the eudesmane class has been found in the acetylenic nor-sesquiterpene, chamaecynone,[190] which can best be derived from conformer (134), cf. occidentalol (140). Sutherland and co-workers[191] have shown that the triene, prepared from germacrone (120), undergoes a *trans*-antiparallel cyclisation in the presence of *N*-bromosuccinimide in aqueous acetone to yield a bicyclic derivative which has all the stereochemical features associated with the eudesmane group. The isolation of chamissonin[192] from an *Ambrosia* species provides an interesting example of an uncyclised precursor in a plant species which had previously been characterised only by the presence of pseudoguaianolides. Ivaxillarin[193] and zaluzanin A[194] are representatives of a new type of guaianolide in which a cyclopropane bond has been formed between C(8) and C(10).

The structure of eremoligenol[195] is in accord with the biogenetic derivation of the eremophilane class from the eudesmane class of sesquiterpenes.[147] Whether, in fact, it is necessary to invoke a double bond migration from cation (13) to cation (212) is a moot point.

The complete structural revision of two members of the vetivane class of sesquiterpenes certainly demands a reappraisal of their biogenesis. Thus, α-vetivone[196,197] has been shown to be a double bond isomer of nootkatone (219; R = O) and, as such, should be renamed iso-nootkatone.[197] Its co-occurrence with β-vetivone, now formulated as a spiro(5,4)decane derivative[198] suggests a common biogenetic link similar to that suggested for the biogenesis of agarospirol (153). It is of possible biogenetic significance that valeranone (142; R = H) has been found to co-occur with nardostachone.[199] These findings, therefore, cast reasonable doubt on the structural validity of other supposed members of the vetivane class.

By an unambiguous synthesis of the enantiomer of aromadendrene, Büchi and co-workers[200] have demonstrated that the previously accepted structure of aromadendrene (238) requires alteration with respect to the C(4) methyl group which has now been shown to be in an α configuration. Syntheses of other

[189] J. A. Kepler, M. E. Wall, J. E. Mason, C. Basset, A. T. McPhail, and G. A. Sim, *J. Amer Chem. Soc.*, 1967, **89**, 1260.
[190] T. Nozoe, Y. S. Cheng, and T. Toda, *Tetrahedron Letters*, 1966, 3663.
[191] E. D. Brown, M. D. Solomon, J. K. Sutherland, and A. Torre, *Chem. Comm.*, 1967, 111.
[192] T. A. Geissman, R. J. Turley, and S. Murayama, *J. Org. Chem.*, 1966, **31**, 2269.
[193] W. Herz, V. Sudarsanam, and J. J. Schmid, *J. Org. Chem.*, 1966, **31**, 3232.
[194] J. Romo, A. R. de Vivar, and P. J. Nathan, *Tetrahedron*, 1967, **23**, 29.
[195] H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc.* (*C*), 1966, 1545.
[196] K. Endo and P. de Mayo, *Chem. Comm.*, 1967, 89.
[197] J. A. Marshall and N. H. Andersen, *Tetrahedron Letters*, 1967, 1611.
[198] J. A. Marshall and P. C. Johnson, private communication.
[199] S. D. Sastry, M. L. Maheshwari, K. K. Chakravarti, and S. C. Bhattacharyya, *Perfum. & Essen. Oil Rec.*, 1967, **58**, 154.
[200] G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Amer. Chem. Soc.*, 1966, **88**, 4113.

stereoisomers in this series by the same workers also necessitates the reformulation of alloaromadendrene (234) in a similar manner. Thus, aromadendrene could result from an anti-Markownikoff cyclisation of conformer (227), whereas alloaromadendrene could arise from conformer (224). These stereochemical corrections may, in turn, require a critical reappraisal of the related alcohols, ledol, viridiflorol, palustrol and globulol.

Finally, an extensive screening of plant sources for potential antitumour agents by Kupchan and co-workers has led to the isolation and structural elucidation of the biologically active sesquiterpene lactones, elephantin,[201] elephantopin,[201] euparotin acetate[202] and gaillardin.[203]

[201] S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 1966, **88**, 3674.
[202] S. M. Kupchan, J. C. Hemingway, J. M. Cassady, J. R. Knox, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, 1967, **89**, 465.
[203] S. M. Kupchan, J. M. Cassady, J. E. Kelsey, H. K. Schnoes, D. H. Smith, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 1966, **88**, 5292.