RECENT ASPECTS OF SESQUITERPENOID CHEMISTRY

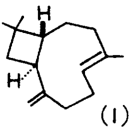
By T. G. HALSALL
(DYSON PERRINS LABORATORY, OXFORD UNIVERSITY)
and D. W. THEOBALD
(MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY, MANCHESTER, 1)

THE sesquiterpenoids were last the subject of a Quarterly Review in 1957.[1] Since then interest in this field has continued and much progress has been made, notably for sesquiterpenoids containing medium-sized rings.

This Review surveys recent developments in the field of those sesquiterpenoids containing nine-, ten-, and eleven-membered carbocyclic rings. As is to be expected with such medium-ring compounds, a rich display of transannular reactions is a prominent feature of their chemistry. A section on the biogenesis of these compounds is also included.

Nine-membered Rings.—*Caryophyllene.* One of the first of these compounds to be studied was the sesquiterpene caryophyllene, isolated from oil of cloves, and studied by Simonsen, Ruzicka, and their co-workers.[2] After some confusion of nomenclature, two substances are now distinguished, caryophyllene (1) and an isomer, isocaryophyllene (2), which differ in the geometry of the endocyclic double bond.

Caryophyllene, $C_{15}H_{24}$, is a doubly unsaturated, and so bicyclic, hydrocarbon. At the time of the previous review of its chemistry, its structure had been established as (1) and the evidence for it was described in detail.[1] Caryophyllene, on treatment with acid, undergoes a number of interesting cyclisations. Among the products are caryolan-1-ol (3) and the hydrocarbon clovene (4).[1]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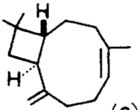
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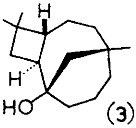

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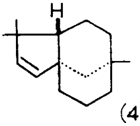
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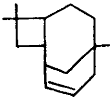
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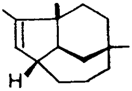
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On more vigorous acid-treatment two other tricyclic hydrocarbons are formed, isoclovene and ψ-clovene. ψ-Clovene has been tentatively given the formula (5), while recent X-ray studies[3] have shown that isoclovene

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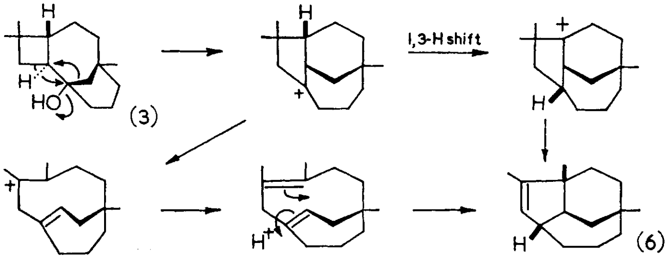
[1] Barton and de Mayo, *Quart. Rev.*, 1957, **11**, 189.

[2] Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, Vol. III, 1952.

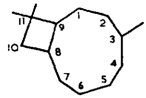
[3] Clunie and Robertson, *Proc. Chem. Soc.*, 1960, 82.

can be represented by (6). The peculiar nature of the conversion of caryolan-1-ol (3) into isoclovene has been observed and the annexed possible routes have been proposed.[3] It is evident from their complexity that this



and related reactions in the caryophyllene series merit further investigation.

Betulenols. A group of compounds related to caryophyllene, the betulenols, isolated from the buds of white birch has been the subject of disagreement between two schools.[4,5] α-Betulenol, $C_{15}H_{24}O$, was shown to be a doubly unsaturated secondary alcohol and therefore bicyclic. Caryophyllane (7) was isolated from the products of hydrogenation, and oxidative degradation gave homocaryophyllenic acid (8), showing that the secondary hydroxyl group cannot be at position 1 or 2. On hydrogenation



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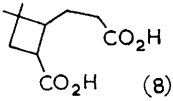
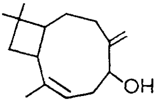


(8)

and oxidation α-betulenol yielded a saturated ketone, $C_{15}H_{26}O$, identical with that prepared from caryophyllene oxide, and this proved that its hydroxyl group must be at position 4. The position of the double bonds followed from the following facts: The infrared spectrum of betulenol indicated an exocyclic methylene system, and the isolation of homocaryophyllenic acid fixes the position of this at 3. The double bonds are not conjugated and there is no indication of a —CH=CH— group in the spectra. Further, the secondary hydroxyl group must be allylic since it is easily hydrogenolysed. These facts enabled α-betulenol to be represented as (9).[5] Similar evidence suggested the formula (10) for β-betulenol.[5]



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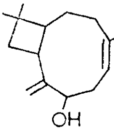

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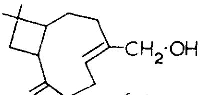

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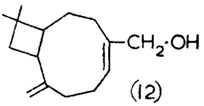

(12)

The facts above suggest that the stereochemistry of the ring junction is that of caryophyllene and it only remains to settle that of the hydroxyl

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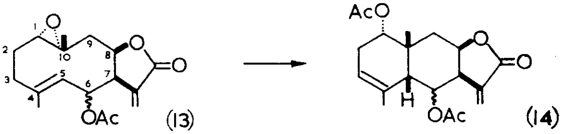
[4] Treibs and Lossner, *Annalen*, 1960, **634**, 124.

[5] Šorm, Holub, Herout, and Horák, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3730.

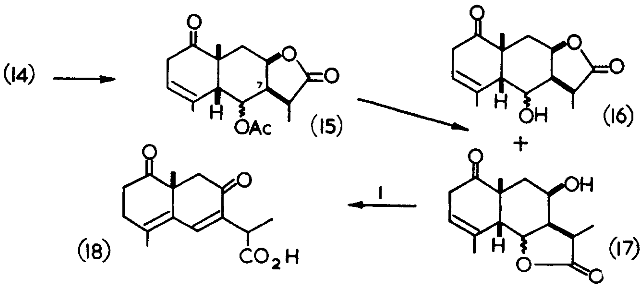
group. Possible cyclisations, parallel to those observed in the caryophyllene series, do not appear to have been investigated. Treibs and Lossner seem to favour the structures (11) and (12) for α- and β-betulenol, respectively.[4]

Ten-membered Rings.—In 1957, the time of the last *Quarterly Reviews* article on sesquiterpenoid chemistry,[1] only one sesquiterpenoid containing a ten-membered carbocyclic structure had been characterised. More than a dozen such substances have now been isolated from natural sources and have been characterised, mainly by Šorm and his colleagues.[6]

Pyrethrosin. The first of these compounds to be characterised was pyrethrosin, which was isolated from *Chrysanthemum cinerariaefolium* in 1891, though its complete structure was not fully determined until recently.[7,8] This compound, $C_{17}H_{22}O_5$, contains two ethylenic linkages (one conjugated with a γ-lactone system) and five oxygen atoms (present as lactone, ether, and acetate). There was no evidence, from either infrared spectra or isotopic exchange, of a free hydroxyl group. Most of the evidence for the structure of pyrethrosin (13) comes from the results of cyclisation. Treatment with acetic anhydride and toluene-*p*-sulphonic acid gave cyclopyrethrosin acetate (14). Selective hydrogenation followed by controlled hydrolysis converted this cyclisation product into an acetoxy-alcohol, which on oxidation yielded the corresponding ketone (15). Hydrolysis of this acetoxy-ketone resulted in two products, one of which (16) could be reacetylated to give back the ketone (15) and so had the lactone system in the original position. The structure of the other product (17) was demonstrated by its conversion into the dienone (18), previously encountered in the santonin series. No dienone could be obtained by



(13) (14)



(15) (16) (17) (18)

Reagents : CrO_3 then base

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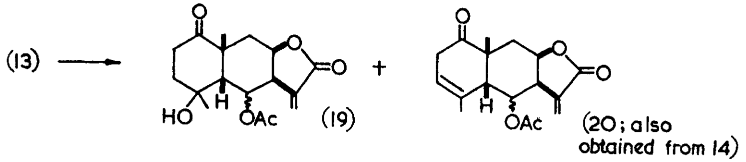
[6] Šorm, Herout, and Sýkora, *Perfumery Essent. Oil Record*, 1959, **50**, 679.

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

[8] Barton, Böckmann, and de Mayo, *J.*, 1960, 2263.

similar treatment of the lactone (16). Since it is this compound which can be related to the compound (14) and so to pyrethrosin, the position of the lactone ring in the latter must be as shown.

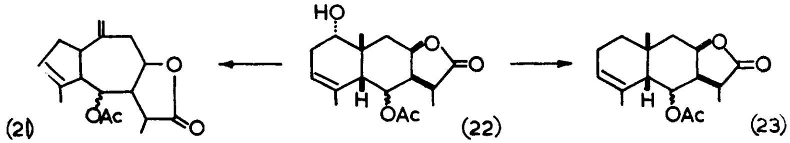
Pyrethrosin and sodium dichromate in aqueous acetic acid at room temperature gave two further bicyclic products (19) and (20), the latter being easily related to cyclopyrethrosin acetate (14). Cyclisation under these mild conditions enabled conclusions to be drawn about the structure



of pyrethrosin itself. The hydroxyl group in (19) established the position of one end of the ethylenic linkage in pyrethrosin, while the carbonyl group marked one end of the oxide ring, for it can be assumed that production of the new carbon–carbon bond was the result of electrophilic attack upon the oxide system involving participation of the π-electrons of the double bond. The other end of the oxide ring must be attached to the carbon atom bearing the methyl group at the ring junction.

The fact that dihydropyrethrosin gave no formaldehyde on ozonolysis showed that the double bond involved in the cyclisations was non-terminal. Confirmation of the presence of a ten-membered ring was obtained by oxidation of a mixture of tetrahydropyrethrosins to β-methyladipic acid.

The evidence for the stereochemistry of cyclopyrethrosin acetate as (14) is as follows. The absolute configuration at position 10 was established as β by isolation of the known dienone (18). When the toluene-*p*-sulphonate of dihydrocyclopyrethrosin was heated with collidine the non-conjugated diene (21) was isolated, which requires that the 1-hydroxyl group should be equatorial.[9] The molecular rotations of the compounds (22) and (23)



showed that the 1-hydroxyl group in compound (22) must be α if the 10-methyl group is β,[10] and this implied a *cis*-ring junction.

Pyrolysis of the benzoate of the second hydroxy-keto-lactone (17) in the gas phase, conditions which favour unimolecular *cis*-elimination,[11] led

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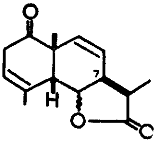
[9] Barton, *Experientia*, 1950, **6**, 316; Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1952, **74**, 2694.

[10] Klyne and Stokes, *J.*, 1954, 1979.

[11] Barton, *J.*, 1949, 2174; de Puy and King, *Chem. Rev.*, 1960, **60**, 431; *J. Amer. Chem. Soc.*, 1961, **83**, 2743.

to the compound (24), containing three vinylic hydrogen atoms. This elimination away from position 7 is only possible if the 7-hydrogen atom and the 8-hydroxyl group are in *trans*-relation to one another.



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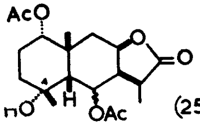


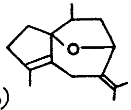
(25)

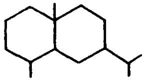
Further, the formation of both the lactones (16) and (17) from (15) is possible only if the side-chain at position 7 is equatorial and thus β.

Dehydration of the compound (25) gave an endocyclic olefin, which suggests that the hydroxyl group at position 4 has an axial and so α-orientation. Provided the acid-catalysed cyclisations are stereospecific, a 4α-hydroxyl group would arise from a *cis*- Δ^4-endocyclic double bond in pyrethrosin, but further work is necessary here before a final conclusion can be reached.

Germacrone. The crystalline sesquiterpenoid germacrone, $C_{15}H_{22}O$, was isolated from *Geranium macrorhizum L.*, and was given structure (26) by Treibs.[12] Recent work[13] necessitates a complete revision of this formula. The rather anomalous infrared and ultraviolet spectra of this substance revealed a conjugated enone system. Hydrogenation on palladium in acetic acid gave a hexahydro-derivative, a saturated ketone, which was reduced to the alcohol, hexahydrogermacrol, $C_{15}H_{30}O$. Germacrone is thus monocyclic.

(26)





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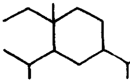
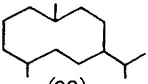


(28)

Direct reduction of germacrone gave germacrol, which on hydrogenation in an acidic medium gave selinane (27), and on dehydration followed by hydrogenation, elemane (28). The infrared spectrum of the parent hydrocarbon (germacrane) differed from that of the perhydro-derivatives of other sesquiterpenoids, and the presence of a ten-membered ring was confirmed by a synthesis of germacrane (29).



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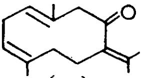

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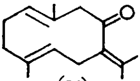

(31)

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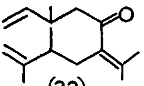
[12] Treibs, *Annalen*, 1952, **576**, 116.

[13] Ognjanoff, Ivanoff, Herout, Horák, Plíva, and Šorm, *Chem. and Ind.*, 1957, 820; Herout and Suchý, *Coll. Czech. Chem. Comm.*, 1958, **23**, 2169, 2175; Herout, Horák, Schneider, and Šorm, *Chem. and Ind.*, 1959, 1089.

Ozonolysis of the unsaturated tetrahydrogermacrone gave one equivalent of acetone and 2,6-dimethyldecanedioic acid, and oxidation with permanganate in acetone yielded lævulic and oxalic acid. These results are compatible with representation of germacrone as either (30) or (31), for both would accommodate the lack of optical activity. The evidence now favours structure (31). In particular, germacrone, like other cyclodecane systems, is susceptible to transannular cyclisations, for example the formation of selinane and elemane mentioned above. Germacrone is also pyrolysed to a monocyclic ketone, β-elemenone (32), during distillation,[14] and when the product of acid isomerisation is hydrogenated a bicyclic ketone (33) is obtained.[15] The formation of these products is accounted for more easily on the basis of structure (31) than of (30), for in the latter case an initial double-bond shift would have to be invoked.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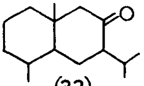
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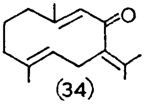
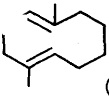

(34)

An isomer of germacrone, isogermacrone, obtained by the action of alkali, has recently been reported, and on the basis of oxidative degradation been given the structure (34).[16]

Costunolide. Costunolide, $C_{15}H_{22}O_2$, is a crystalline, optically active sesquiterpenoid isolated from costus root oil or from *Artemisia balchanorum*, a Russian wormwood species.[17] It contains a γ-lactone ring and three ethylenic linkages and is therefore monocarbocyclic.[18] Preliminary observations, for example, the isolation of 1,6-dimethylnaphthalene on dehydrogenation, and formaldehyde, formic acid, and lævulic acid on ozonolysis, suggested a partial formula (35). Costunolide and dihydrocostunolide both consumed two mol. of perbenzoic acid, showing that one double bond is inert and conjugated with the γ-lactone system; the infrared spectrum showed that it was exocyclic. These results indicated (36) or (37) as the most likely structure for costunolide.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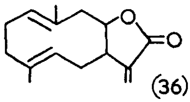
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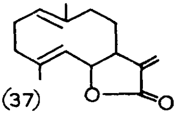
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[14] Ohloff, Farnow, Philipp, and Schade, *Annalen*, 1959, **625**, 206; Ohloff, *Angew. Chem.*, 1959, **71**, 162; Ognjanov, Herout, Horák, and Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2371.

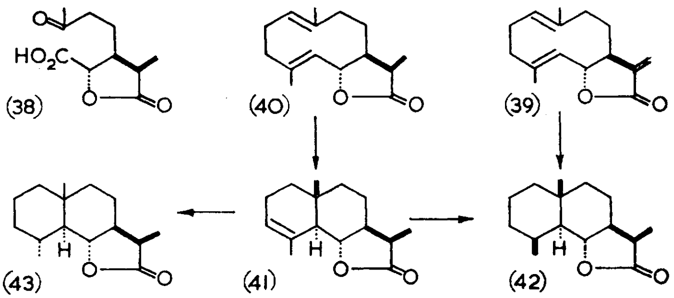
[15] Ognjanov, *Compt. rend. Acad. bulg. Sci.*, 1960, **13**, 51; *Chem. Abs.*, 1961, **56**, 8455h.

[16] Suchý, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1358.

[17] Rao, Varma, Ghosh, and Dutta, *J. Sci. Ind. Res., India*, 1958, **17B**, 228; Benešová, Sýkora, Herout, and Šorm, *Chem. and Ind.*, 1958, 363.

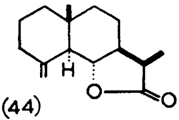
[18] Rao, Kelkar, and Bhattacharyya, *Chem. and Ind.*, 1958, 1359; *Tetrahedron*, 1960, **9**, 275.

The alternative (37) is favoured on the basis of ozonolysis of dihydrocostunolide to the acid (38), which has been prepared from santonin. This also established the absolute configuration of costunolide as (39).


(38) (40) (39)

(43) (41) (42)

Costunolide and its derivatives readily undergo cyclisation to bicyclic compounds in acidic media.[19] For example, dihydrocostunolide (40) in a mixture of acetic anhydride and acetic acid gave the bicyclic lactone (41), which on hydrogenation gave the two known santonin derivatives, "santanolide c" (42) and "santanolide a" (43).[20] Recently the isolation of the unsaturated lactone (44) from the cyclisation has also been reported.[21] These cyclisations confirm the structure of costunolide as (37) and its absolute configuration as (40). If costunolide were represented by (36), then the products would belong to the alantolactone series (45).[22]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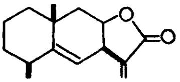
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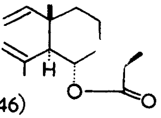
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From the direct pyrolysis of dihydrocostunolide a monocyclic lactone, saussurea lactone (46), has been isolated.[23] This is exactly parallel to the behaviour of germacrone on pyrolysis.

Arctiopicrin. Arctiopicrin, $C_{19}H_{28}O_6$, is isolated from the leaves of *Arctium minus* Bernh. (Compositae) and contains an unsaturated γ-lactone system. Despite its crystallinity, the tendency to oxidative polymerisation made satisfactory elemental analyses difficult to obtain.[24] The main evidence for the structure of arctiopicrin concerns two of the four products

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[19] Herout and Šorm, *Chem. and Ind.*, 1959, 1067; Rao, Kelkar, and Bhattacharyya, *ibid.*, p. 1069.

[20] Kovács, Horák, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1956, **21**, 225; Cocker and McMurry, *J.*, 1956, 4549.

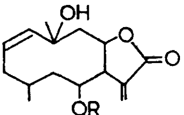
[21] Shaligram, Rao, and Bhattacharyya, *Chem. and Ind.*, 1961, 671.

[22] Tsuda, Tanabe, Iwai, and Funakoshi, *J. Amer. Chem. Soc.*, 1957, **79**, 1009, 5721.

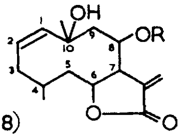
[23] Rao, Paul, Sadgopal, and Bhattacharyya, *Tetrahedron*, 1961, **13**, 319.

[24] Suchý, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1902; Suchý, Horák, Herout, and Šorm, *Chem. and Ind.*, 1957, 894; *Croat. Chem. Acta*, 1957, **29**, 247; Suchý, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 1542.

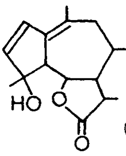
A, B, C, and D obtained by hydrogenation in ethanol. The compound C, m.p. 134°, $C_{19}H_{32}O_6$, gave on hydrolysis a volatile acid, identified as β-hydroxy-α-methylpropionic acid, and a product, tetrahydroarctiolide, $C_{15}H_{26}O_4$, m.p. 145°, that was oxidised by chromium trioxide to a hydroxy-keto-lactone, $C_{15}H_{24}O_4$, m.p. 138°. This showed that arctiopicrin was an ester of β-hydroxy-α-methylpropionic acid and arctiolide, a monocyclic diol-lactone containing two double bonds. Hydrolysis of compound B gave a hydroxy-lactone, $C_{15}H_{26}O_3$, which was oxidised to a keto-lactone, $C_{15}H_{24}O_3$. Therefore the secondary hydroxyl group of arctiopicrin is esterified, while the other (tertiary) hydroxyl group is probably allylic, as shown by its tendency to hydrogenolysis. These results suggest structures (47) or (48) for arctiopicrin.



(47)



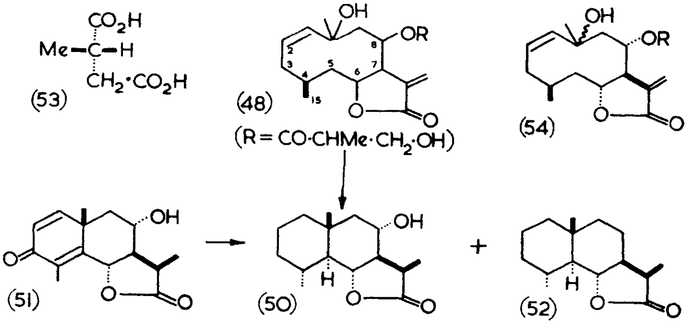
(48)
(R=CO·CHMe·CH₂·OH)



(49)

The position of the γ-lactone ring with respect to the esterified hydroxyl group was inferred by a not very convincing analogy with matricin (49), in which a characteristic shift of the infrared lactone-carbonyl absorption band is also observed;[25] this occurs with a carbonyl or ester group adjacent to the lactone ring. However, the alkaline conditions involved in these reactions left the positions of the esterified hydroxyl group and the lactone group undecided. The position of the tertiary hydroxyl group was deduced from infrared spectral properties of an unsaturated keto-lactone, $C_{15}H_{22}O_3$, m.p. 119°, that was obtained by the dehydration of the hydroxy-keto-lactone, $C_{15}H_{24}O_4$, m.p. 138°. A trisubstituted ethylenic group and an $\alpha\beta$-unsaturated carbonyl group were detected.

The decision between structures (47) and (48) in favour of the latter rested upon a chemical and stereochemical correlation. Hydrogenation



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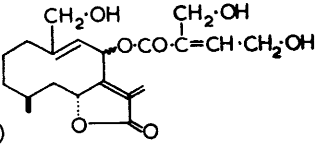
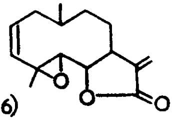
[25] Čekan, Herout, and Šorm, *Chem. and Ind.*, 1956, 1234.

of arctiopicrin on palladium in acetic acid gave the hydroxy-lactone (50), which was also obtained stereospecifically from artemisin (51).[26] This confirms the structure (48) for arctiopicrin, and establishes its absolute configuration at positions 6, 7, and 8 as that in artemisin. It is unlikely that the reduction of artemisin involves a configurational change at position 6 or 7 since the original configuration is preserved in the santonin derivative (52). The configuration at position 4 follows from the isolation of *L*(—)-methylsuccinic acid (53) on oxidation of polymeric arctiopicrin, on the assumption that this acid is derived from the carbon atoms at positions 2, 3, 4, 5, and 15.

Arctiopicrin has therefore structure (54), the configuration at position 10 remaining to be determined. The cyclisation of arctiopicrin probably involves migration of the 1,2-double bond to the 4,5-position at some stage during the hydrogenation in an acidic medium.[27] It is interesting that no such reaction has been observed with another closely related substance cnicin (55)[28] or with parthenolide (56).



(55)



(56)

Parthenolide. The evidence for the structures of the cyclodecane sesquiterpenoids discussed above leans heavily on the products of transannular cyclisation. Where these do not occur, a different approach is necessary. That of oxidative degradation is illustrated in the case of parthenolide (56).[29] This is a crystalline compound, $C_{15}H_{20}O_3$, isolated from *Chrysanthemum parthenium* (L.) Bernh. It contains a γ-lactone system conjugated with an exocyclic methylene group, and like other such compounds the tendency to form polymers complicates accurate analysis. The presence of a second double bond was established by the preparation of an oxide from dihydroparthenolide, itself obtained by hydrogenating parthenolide on platinum in methanol. Complete hydrogenation of parthenolide gave a hexahydro-derivative, $C_{15}H_{26}O_3$, which contained a free hydroxyl group, whereas parthenolide itself had no active hydrogen. This indicates that one oxygen atom is present as an epoxy-group, and that parthenolide is monocyclic. Ozonolysis assisted in fixing the relative positions of these functional groups, (57)—(60).

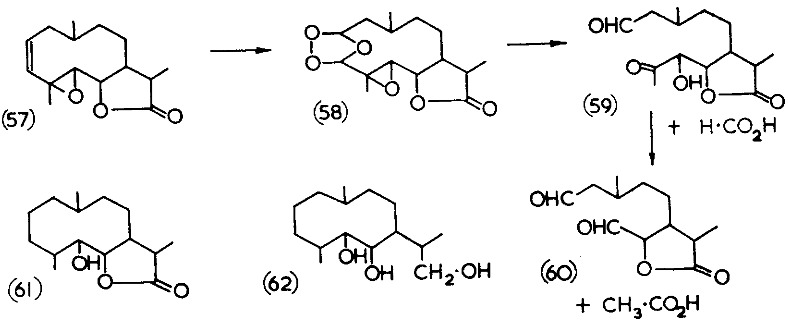
[26] Sumi, *Proc. Japan Acad.*, 1956, **32**, 684; *J. Amer. Chem. Soc.*, 1958, **80**, 4869.

[27] Braude and Linstead, *J.*, 1954, 3544; Fukushima and Gallagher, *J. Amer. Chem. Soc.*, 1955, **77**, 139.

[28] Šorm, Benešová, Herout, and Suchý, *Tetrahedron Letters*, 1959, No. 10, 5; Suchý, Benešová, Herout, and Šorm, *Chem. Ber.*, 1960, **93**, 2449.

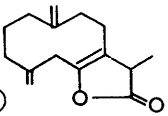
[29] Herout, Souček, and Šorm, *Chem. and Ind.*, 1959, 1069; *Coll. Czech. Chem. Comm.*, 1961, 803.

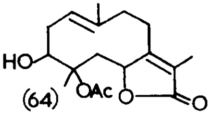
Oxidation of parthenolide (56) and dihydroparthenolide (57) with nitric acid in the presence of vanadium salts gave a mixture of acids, from which β-methyladipic acid was isolated, demonstrating that at least four carbon atoms of the cyclodecane ring carry no oxygen and indicating that the oxide ring was three-membered.

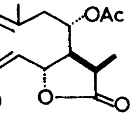


Further evidence for the location of the functional groups comes from the fact that hexahydroparthenolide (61) is easily oxidised to a saturated ketone and that the triol (62) obtained by the reduction of hexahydroparthenolide with lithium aluminium hydride consumed one mol. of sodium periodate. There has been no report of cyclisation of parthenolide under the conditions used with pyrethrosin or arctiopicrin; and the stereochemistry of parthenolide has not yet been settled.

Various. Other sesquiterpenoids with a skeleton based upon a ten-membered ring include aristolactone (63),[30] on which more work is needed, gafrinin (64),[31] acetylbalchanolide (65),[32] balchanolide and isobalchanolide (possibly a pair of geometrical isomers[33]), and millefolide.[31]


(63)


(64)


(65)

Spectral contributions. The geometry of the endocyclic double bonds in these sesquiterpenes is not established by the chemical evidence available, especially since the cyclisations reported involve acidic media and hydrogenation catalysts. It is difficult to see a purely chemical approach to this problem. If, as is believed, these compounds arise biogenetically from *trans*-farnesol, then a *trans-trans*-geometry would be expected. The only direct evidence for this comes from nuclear magnetic resonance data.

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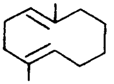
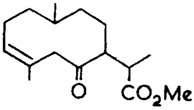
[30] Steele, Stenlake, and Williams, *Chem. and Ind.*, 1959, 1384; *J.*, 1959, 3289.
[31] de Villiers, *J.*, 1961, 2049.
[32] Hochmannová, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1826.
[33] Herout, Suchý, and Šorm, *Coll. Czech. Chem. Comm.*, 1961, 26, 2612.

It has been stated[34] that there is a small but definite dependence of the frequencies of the methyl protons on the geometry of systems of the type $A{\cdot}CH_2{\cdot}CMe{=}CH{\cdot}CH_2{\cdot}B$. The shift of frequency between the *trans*- and *cis*-relations of the vinylic hydrogen atom and methyl group is about 0·07 τ. Examination of the spectra of costunolide (39) and germacrone (31) indicates that both the endocyclic double bonds are *trans* in these compounds. The abnormally high τ values for the methyl groups in the trisubstituted system $MeR{\cdot}C{=}CHR'$ of germacrone and costunolide are attributed to shielding of the absorbing methyl protons by the π-electrons of the second double bond; this shielding cannot occur in pyrethrosin (13).[34]

Transannular effects are also evident in the ultraviolet spectra of these sesquiterpenes. Germacrol and costunolide (39) show extremely high end-absorptions ϵ_{2100} $10^{4{\cdot}16}$ and ϵ_{2130} $10^{4{\cdot}12}$, respectively. Comparison with tetrahydrogermacrone and germacrone diepoxide shows that this is due to two trisubstituted ethylene groups disposed as in the general structure (66). Compounds with only one such ethylenic linkage (67) show an end absorption typical of a trisubstituted ethylene group in a six-membered ring. The anomaly probably arises from the geometry of the cyclodecane ring in permitting electron delocalisation between adjacent but non-conjugated double bonds.[30,35]


(66)



(67)

Eleven-membered Rings.—Sesquiterpenoids with eleven-membered carbocyclic rings were well known before any ten-membered rings compounds were authenticated. The structures of these compounds, humulene and the related ketone zerumbone, have only recently been completely settled with the help of nuclear magnetic resonance spectroscopy.

Humulene. Humulene, $C_{15}H_{24}$, isolated from oil of hops, is triply unsaturated and its hexahydro-derivative was shown by synthesis to be 1,1,4,8-tetramethylcycloundecane.[36] Location of the double bonds was a more difficult problem. Oxidative degradation of dihydrohumulene led to the isolation of $\alpha\alpha$-dimethylsuccinic acid, $\beta\beta$-dimethyladipic acid, and an unknown keto-acid. Similar treatment of tetrahydrohumulene gave an acid, $C_{15}H_{28}O_4$, whose synthesis confirmed the eleven-membered ring in

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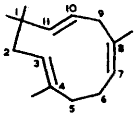
[34] Bates and Gale, *J. Amer. Chem. Soc.*, 1960, **82**, 5749.

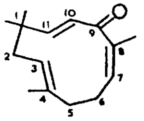
[35] Jones, Mansfield, and Whiting, *J.*, 1956, 4073.

[36] Šorm, Mleziva, Arnold, and Plíva, *Coll. Czech. Chem. Comm.*, 1949, **14**, 699; Herout, Streibl, Mleziva, and Šorm, *ibid.*, p. 716; Šorm, Streibl, Plíva, and Herout, *ibid.*, 1952, **16**, 639; Šorm, Streibl, Jarolim, Novotný, Dolejš, and Herout, *ibid.*, 1954, **19**, 570; Clemo and Harris, *J.*, 1951, 22; 1952, 655; Harris, *J.*, 1953, 184.

humulene.[37] Oxidation of humulene itself gave lævulic acid and its aldehyde, αα-dimethylsuccinic acid, and formaldehyde.[38] This established formula (68) for humulene.



(68)

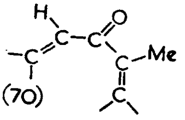


(69)

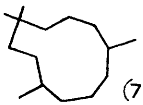
The ultraviolet spectrum of humulene shows that the double bonds are not conjugated, while the infrared spectrum indicated the presence of a trisubstituted ethylene group. Careful ozonolysis of humulene[38] yielded αα-dimethylsuccinic acid and lævulic acid, or, after reduction of the ozonide with lithium aluminium hydride, butane-1,3-diol. In the latter experiment, gas chromatography also revealed the two glycols corresponding to the other fragments.

Though it is always wise to be cautious in accepting the results of ozonolysis, the recent examination of humulene by nuclear magnetic resonance has led unequivocally to the structure (68).[39] In the methyl and the methylene proton region the spectrum is almost identical with that of the related ketone, zerumbone (69), whose chemistry is discussed below. In particular, four methyl groups are evident and all the methylene groups are revealed as allylic. The relative areas of olefinic and saturated protons showed 3·3 olefinic protons, close to the number (4) required by formula (68).

Zerumbone. Zerumbone (69), $C_{15}H_{22}O$, is a monocarbocyclic, crystalline ketone, isolated from the rhizomes of wild ginger.[40] The ultraviolet spectrum indicated the presence of either an αβ-unsaturated carbonyl or a cross-conjugated dienone group. The latter alternative was confirmed when reduction with sodium in alcohol gave tetrahydrozerumbol, $C_{15}H_{28}O$. Further, alkaline treatment of zerumbone resulted in a reverse aldol reaction and the isolation of ethyl methyl ketone, arising from the structural unit (70). Clemmensen reduction of hexahydrozerumbone gave humulane



(70)


(71)

(71), demonstrating the common skeleton of zerumbone and humulene. Ozonolysis of zerumbol, obtained by reducing zerumbone with lithium

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[37] Harris, *J.*, 1953, 184; Fawcett and Harris, *J.*, 1954, 2669, 2673; Clarke and Ramage, *J.*, 1954, 4345.

[38] Hildebrand, Sutherland, and Waters, *Chem. and Ind.*, 1959, 489.

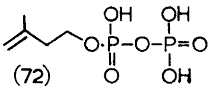
[39] Dev, *Tetrahedron Letters*, 1959, No. 7, 12; *Tetrahedron*, 1960, **9**, 1.

[40] Dev, *Tetrahedron*, 1960, **8**, 171; *Chem. and Ind.*, 1956, 1051.

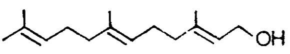
aluminium hydride, gave lævulic acid and αα-dimethylsuccinic acid. These facts suggested the structure (69) for zerumbone, which has been confirmed by nuclear magnetic resonance spectroscopy.[39].

The spectrum clearly revealed the *gem*-dimethyl group at position 1 and the two methyl groups at positions 4 and 8. The six protons at positions 2, 5, and 6 were distinct from methyl protons since they are all allylic. Four olefinic protons were revealed, that at position 3 which is not subjected to diamagnetic deshielding by the carbonyl group occurring at higher field strength. No chemical shift was observed between the proton at position 10 and those at positions 7 and 11 which would be expected to be subject to greater deshielding from the carbonyl by conjugative electron displacement. These results in favour of structure (69) for zerumbone were given added weight by a similar study of tetrahydrozerumbone, hexahydrozerumbone, and humulane. It is interesting that as the double bonds are progressively removed, the methyl protons become more and more shielded, possibly owing to increased crowding in the molecule.

Biogenesis.—An interesting feature of sesquiterpene chemistry is the biogenesis of the remarkable variety of structures now known for these natural products. Initial suggestions in this field came from Ruzicka,[41] but recently Hendrickson has considerably developed them on a stereochemical and electronic basis.[42] The fundamental isoprenoid unit involved in terpene biogenesis is isopentenyl pyrophosphate (72) which can condense to farnesol (73), the simplest acyclic sesquiterpene.[43] The farnesol so formed probably has a *trans* central double bond, and the allylic double bond can assume *cis*- or *trans*-configurations by anionotropic interconversion. No oxidation occurs during the cyclisation, so that the most common oxidation state of cyclic sesquiterpenes is that of farnesol (compare the generation of triterpenes from squalene[41]).



(72)



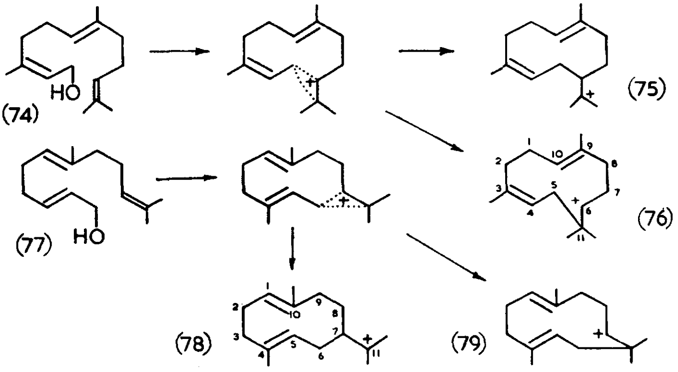
(73)

It is likely[42] that sesquiterpenes arise from 2,3-*cis*-farnesol (74) by way of the cation (75) or (76), or from all-*trans*-farnesol (77) by way of the cation (78) or (79). Models suggest that the cation (75) is much more strained than (76), the latter being preferentially formed with steric control of cyclisation. The cation (78) is sterically and electronically preferred to the cation (79). Thus the sesquiterpenes are probably generated from 2,3-*cis*-farnesol through cation (76) and from all-*trans*-farnesol through cation (78).

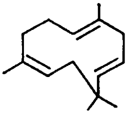
[41] Ruzicka, *Experientia*, 1953, **9**, 364; *Proc. Chem. Soc.*, 1959, 341.

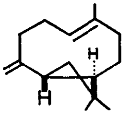
[42] Hendrickson, *Tetrahedron*, 1959, **7**, 82.

[43] Bloch, Rilling, and Amdur, *J. Amer. Chem. Soc.*, 1957, **79**, 2646; Cornforth and Popjak, *Tetrahedron Letters*, 1959, No. 19, 29; Popjak, *ibid.*, p. 19; Lynen, *Angew. Chem.*, 1960, 820.

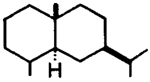


In the cation (76) the disposition of the double bonds does not favour cyclisation and, further, one of the hydrogen atoms at position 5 is turned inside the ring between positions 6 and 10. The loss of a proton yields the humulene skeleton (80) with a *cis-trans-trans*-geometry, while the


(80)



(81)

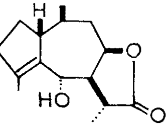


(82)

attack of the 3,4-double bond on the carbon atom at position 6 gives the caryophyllene skeleton (81).

In the cation (78), the parent of the sesquiterpenes with a ten-membered carbocyclic ring, the two double bonds are disposed favourably for cyclisation and there are no hydrogen atoms turned inside the ring. The geometry of the double bonds in this cation suggests that those in the sesquiterpenes with a ten-membered ring are also *trans-trans*. Cyclisation of this cation can be envisaged as giving rise either to the bicyclic sesquiterpenes of the eudesmane series (82)[44] or to the guaiazulene sesquiterpenes (83), for example, geigerin.[45]

Besides cyclisation, however, a direct cyclic movement of electrons may occur resulting in ring fission, (84)→(85).



(83)

(84) (85)

The fact that some reactions of these types have been realised in the

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[44] Cocker and McMurry, *Tetrahedron*, 1960, **8**, 181.

[45] Barton and Pinkey, *Proc. Chem. Soc.*, 1960, 279; Barton and Levisalles, *J.*, 1958, 4518; Huffman, *Experientia*, 1960, **16**, 120.

laboratory lends weight to these biogenetic routes. The cyclisation of pyrethrosin (13) and costunolide (39) may be quoted as examples of acid-catalysed cyclisation; the cyclic electron shift is exemplified in the aprotic cyclisation of germacrone (31) and costunolide (39).