Cyclopropane Cleavage of Chrysanthemic Acid Relatives to Santolinyl, Artemisyl, and Lavandulyl Structures: Acid-catalysed and Biosynthetic Experiments

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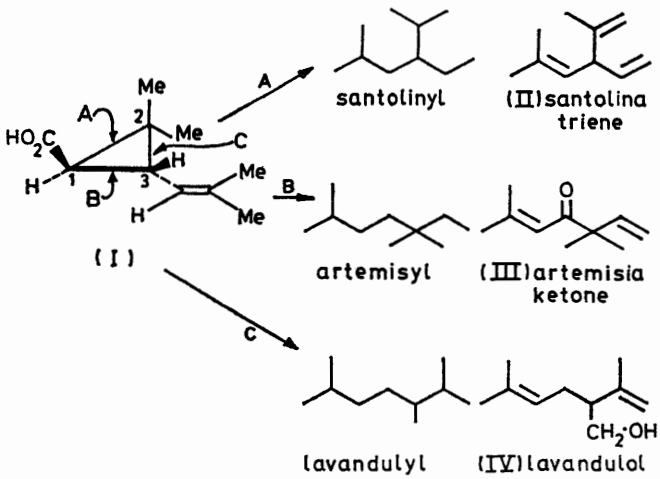
3-Isobutyl-2,2-dimethylcyclopropylmethanol (dihydrochrysanthemyl alcohol) and related compounds undergo acid-catalysed 1,2-cyclopropane (santolinyl) scission; on the other hand, 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropylmethanol (chrysanthemyl alcohol) and various similar compounds undergo 1,3- (artemisyl) cleavage. Introduction of functional groups into the methylpropenyl side-chain in chrysanthemic-type structures allows acid-catalysed cleavage by a 2,3- (lavandulyl) pathway. Certain of the reactions are potentially useful for alkylation with irregular acyclic terpene units, and for specific-atom isolation in biosynthetic work.

Feeding experiments, of *Santolina chamaecyparissus* with ^{14}C-labelled sodium 2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylate (chrysanthemate) and chrysanthemyl phosphates, have been carried out, but no significant incorporation into 3,3,6-trimethylhepta-1,5-dien-4-one (artemisia ketone) has been found. In comparison with incorporations into other monoterpenoids, mevalonic acid is a poor precursor of artemesia ketone.

THE cyclopropane monoterpenoid, 1*R*,3*R*-(+)-*trans*-chrysanthemic acid (I) [1*R*,3*R*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid], the ester of which occurs in pyrethrum flowers (*Chrysanthemum cinerariaefolium* Vis.),[1] has an unusual linkage of isoprene units, which has led to speculation about a possible biogenetic relationship with irregular acyclic terpenes. Formal cleavage of the cyclopropane ring, in the three ways indicated in Scheme 1, leads to 3-ethyl-2,5-dimethylhexyl (santolinyl), 2,5,5-trimethylheptyl (artemisyl), and 2,3,6-trimethylheptyl (lavandulyl) skeletons.



SCHEME 1

The possible, hypothetical conversion into a tail-to-tail monoterpene is relevant to the presqualene–squalene conversion (see later).

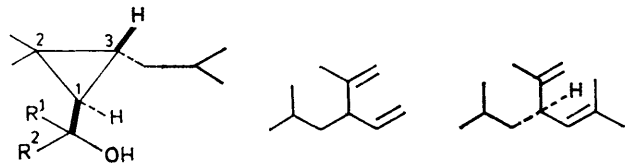
Bates [2] has suggested that chrysanthemyl alcohol (IX), as its pyrophosphate, might give rise to a carbonium ion which could lead to artemisia compounds or santolina triene, and such types occur together in *Santolina chamaecyparissus*.[3,4] In the first part of this paper [5] it is shown that by suitable adjustment of the functional groups in chrysanthemic acid (I), each of the bonds A—C can be made to rupture chemically in carbonium-ion reactions, leading to compounds having santolinyl, artemisyl,† and lavandulyl skeletons. The reactions are also of interest in connection with isolation of specific atoms in biosynthetic work. Since (±)-*trans*- and (±)-*cis*-chrysanthemic acid are accessible [7] compounds and have been optically resolved,[8] certain reactions could be synthetically useful. In the latter part of the paper results obtained from the administration of labelled sodium chrysanthemate and a mixture of chrysanthemyl phosphate and pyrophosphate to *Santolina* plants are described.

The 1,2-cleavage (A) occurs in dihydrochrysanthemyl alcohol derivatives. (±)-*trans*-Dihydrochrysanthemyl alcohol (±)-(V) was resistant to cleavage on heating with small amounts of toluene-*p*-sulphonic acid, but when treated at 0° with thionyl chloride, the santolina diene (±)-(VII) was isolated (39%) by prep. g.l.c. from the mixture of five compounds produced. Distillation of the tertiary alcohol (±)-(VI) [prepared by a Grignard reaction from (±)-*trans*-dihydrochrysanthemic ester], caused decomposition to the diene (±)-(VIII) in 63% yield. The optically active *R*-diene, (−)-(VIII), was made by using 1*R*,3*R*-(−)-methyl *trans*-dihydrochrysanthemate in the Grignard reaction. This retains the 3-centre of the alcohol (VI) and, if formed biosynthetically *via* chrysanthemyl alcohol, the as yet unknown absolute configuration of santolina triene (II) and two

† For an interesting carbonium-ion conversion of the artemisyl into the santolinyl skeleton, see the recent work of Thomas.[6]

[1] L. Crombie and M. Elliott, *Fortschr. Chem. org. Naturstoffe*, 1961, **19**, 120.
[2] R. B. Bates and S. Paknikar, *Tetrahedron Letters*, 1965, 1453.
[3] L. H. Zalkow, D. R. Brannon, and J. W. Uecke, *J. Org. Chem.*, 1964, **29**, 2786.
[4] A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, 1964, 3775; W. Sucrow, *Angew. Chem. Internat. Edn.*, 1968, **7**, 627.
[5] For a preliminary account see L. Crombie, R. P. Houghton, and D. K. Woods, *Tetrahedron Letters*, 1967, 4553.
[6] A. F. Thomas, *Chem. Comm.*, 1970, 1054.
[7] I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 1945, 283; J. Martell and C. Huynh, *Bull. Soc. chim. France*, 1967, 987; M. Julia and A. Guy-Rouault, *ibid.*, p. 1411; E. J. Corey and M. Jautelat, *J. Amer. Chem. Soc.*, 1967, **89**, 3912; R. W. Mills, R. D. H. Murray, and R. A. Raphael, *Chem. Comm.*, 1971, 555.
[8] I. G. M. Campbell and S. H. Harper, *J. Sci. Food Agric.*, 1952, **3**, 183.

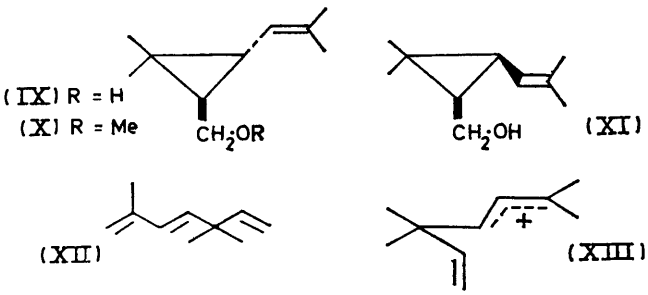
natural relatives mentioned later should be *R*. In these chemical examples, homoallylic carbonium-ion fission proceeds to the tertiary centre causing 1,2-cleavage (A).



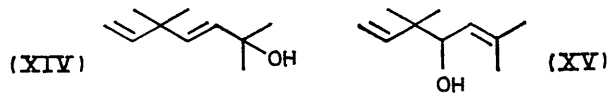
(V) $R^1 = R^2 = H$ (VII) (VIII)
(VI) $R^1 = R^2 = Me$

When the unsaturated 2-methylpropenyl side-chain is unaltered in suitable chrysanthemyl derivatives, 1,3-cleavage (B) occurs in carbonium-ion reactions. Both (±)-*cis*- (XI), and (±)-*trans*- (IX) chrysanthemyl alcohol, and also the methyl ether (X), gave *trans*-artemisia triene [9] (XII) (55—70%) when heated with toluene-*p*-sulphonic acid in benzene. The heptatriene (XII) was also obtained (54%) when the alcohol (IX) was treated with toluene-*p*-sulphonyl chloride in pyridine: thionyl chloride and phosphorus tribromide–pyridine also gave the triene (XII).[10]

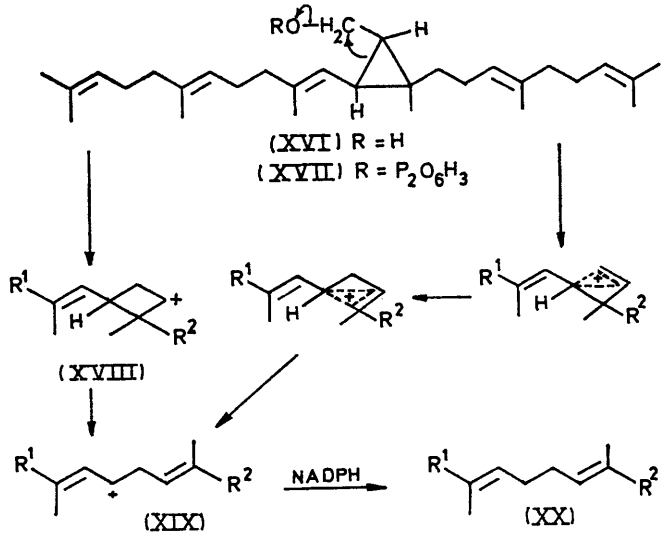
In this type of homoallylic cleavage 1,3-opening (B), giving the tertiary allylic cation (XIII), is preferred to



the 1,2-opening found in the compounds with a saturated side-chain. Only *trans*-triene (XII) was obtained (n.m.r. and i.r.), whether *cis*- or *trans*-chrysanthemyl alcohol was used, and examination of models shows that a transition state leading to *trans*-3-olefin is much less hindered than that leading to *cis*-3-olefin. This is so in both *cis*- and *trans*-cyclopropanes, hindrance being caused by the *gem*-dimethyl group in either case. A similar cleavage leading to triene (XII) has been independently reported with toluene-*p*-sulphonyl chloride–pyridine,[11] and a recent brief report of the solvolysis of the 3,5-dinitrobenzoate of (IX) in aqueous dioxan has appeared.[12] This reaction is reported to give 3,3,6-trimethylhepta-1,4-dien-6-ol (yomogi alcohol) [13] (XIV) (74%), artemisia alcohol (XV) (24%), hydrocarbons (2%), and a trace of chrysanthemyl alcohol. A similar type of carbonium-ion cleavage to that above is thus involved.



With the recent proposal that the structure of presqualene alcohol is (XVI),[14] and its synthesis [15–17] and identification,* interest has been stimulated in the enzyme-mediated cleavage of the cyclopropane ring which is in an environment similar to that in chrysanthemyl alcohol. The cleavage must follow a less simple pattern than those described herein in order to derive squalene (XX) from the pyrophosphate (XVII), and two possibilities, suggested by van Tamelen,[18] are shown in Scheme 2.† Others [16] have envisaged



SCHEME 2

the cyclobutyl cation (XVIII) an an intermediate, and another suggestion [19] is shown in Scheme 3.

* Undertaken by Professor H. C. Rilling.

† Stereochemical and other requirements are discussed in the papers cited. As pointed out by van Tamelen,[18] the biosynthesis of chrysanthemic acid may proceed along similar lines to that of presqualene alcohol, followed by conversion into the higher oxidation level.

[9] T. Takemoto and T. Nakajima, *Yakugaku Zasshi*, 1957, **77**, 1310.

[10] But *cf.* M. Matsui, Y. Yamashita, M. Miyano, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Agric. Chem. Soc. Japan*, 1956, **20**, 89; Y. Katsuda, T. Chikamato, and Y. Inoue, *ibid.*, 1958, **22**, 185.

[11] R. B. Bates and D. Field, *Tetrahedron Letters*, 1967, 4875.

[12] C. D. Poulter and S. G. Moesinger, Abstracts of Papers, 131st A.C.S. National Meeting, Los Angeles, March 1971, ORGN 43.

[13] K. Yano, S. Hayashi, T. Matsura, and A. W. Burgstahler, *Experientia*, 1970, **26**, 8; B. Willhalm and A. F. Thomas, *Chem. Comm.*, 1969, 1380; W. Sucrow, *Tetrahedron Letters*, 1970, 1431 (*cf.* S. Hayashi, K. Yano, and T. Matsura, *ibid.*, 1968, 6241).

[14] H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, 1969, **91**, 1041; W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, 1970, **18**, 4597.

[15] R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem. Comm.*, 1971, 218.

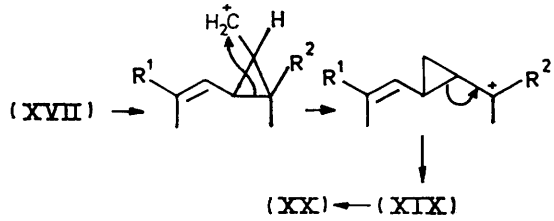
[16] L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, 1971, **93**, 1782.

[17] R. M. Coates and W. H. Robinson, *J. Amer. Chem. Soc.*, 1971, **93**, 1785.

[18] E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, 1971, **93**, 1780.

[19] H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *J. Amer. Chem. Soc.*, 1971, **93**, 1783.

Search for an analogous rearrangement of the chrysanthemyl cation is clearly desirable since such a rearrangement should lead to products derived from the tail-to-tail

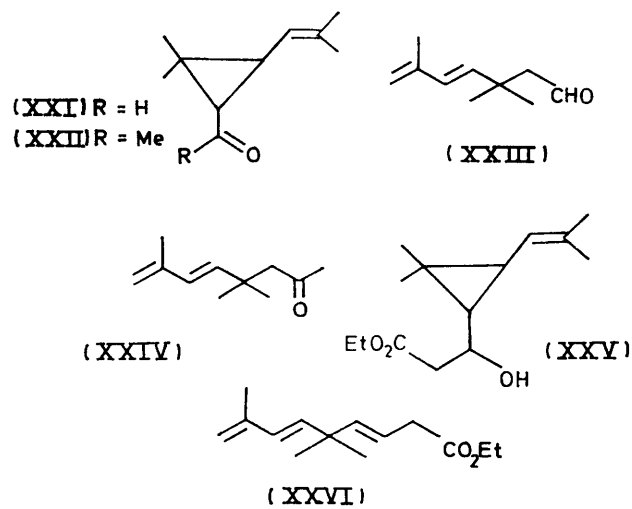


SCHEME 3

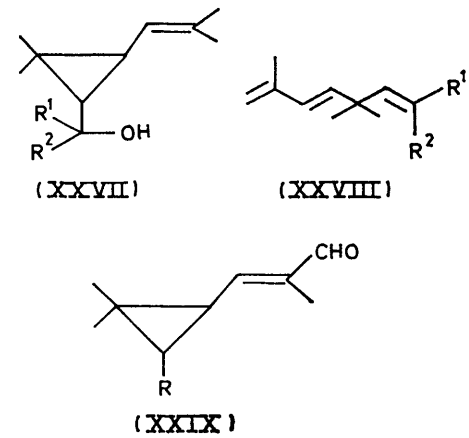
monoterpene carbonium ion (XIX; $R^1 = R^2 = Me$). These have not as yet been reported as natural compounds.

trans-Products, bearing functional groups, of the artemesia-type cleavage (B) are obtained when the aldehyde [20] (XXI) or the ketone [21] (XXII) is heated under reflux with toluene-*p*-sulphonic acid in benzene. The products are the heptadienal (XXIII) (55%) and the octadienone (XXIV) (60%), respectively. The hydroxy-ester (XXV) yields the ethyl nonatrienoate (XXVI).

The possibility of alkylation in synthesis (*cf.* Julia isoprenylation [22]) by an artemisyl or homoartemisyl unit is indicated by the aldehydic and ketonic derivatives, (XXI) and (XXII). For example, a Grignard reaction on methyl (±)-*trans*-chrysanthemate gives the



alcohol (XXVII; $R^1 = R^2 = Me$), which was dehydrated during work-up and distillation to give the octatriene (XXVIII; $R^1 = R^2 = Me$) in 60—70% yield. From the results described before, the dihydro-analogues would give santolinyl derivatives. On the other hand, the side-chain aldehyde compounds (XXIX; R = CH_2·OH or CHO) were resistant to cleavage with toluene-*p*-sulphonic acid under conditions which did not cause extensive decomposition. In these cases the conjugated homoallylic carbonium ion leading to artemisyl cleavage would be destabilised by the aldehyde group in the formylpropenyl side-chain.

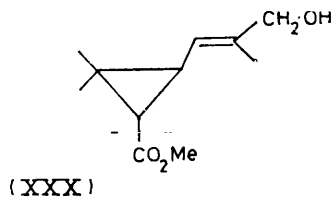


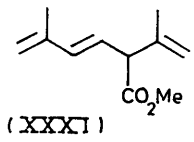
Rupture of the 2,3-cyclopropane bond (C) in chrysanthemyl systems can be induced, with carbonium-ion initiation, by suitable functional groups in the methylpropenyl side-chain. Monoterpenes with a lavandulyl skeleton result. For example, the hydroxy-ester (XXX) (as either the *cis*- or the *trans*-isomer), on heating with toluene-*p*-sulphonic acid gave the *trans*-triene ester [23] (XXXI) (60%), which partially isomerised in light petroleum over basic alumina [apparently *via* a kinetically controlled product, the ester (XXXII)], to the ester [23a] (XXXIII; R = Me). After 30 min of reaction, g.l.c. analysis showed the yields of products to be: (XXXI) 42, (XXXII), 27, and (XXXIII; R = Me) 31%. Basic hydrolysis of the mixture gave the acid [23a] (XXXIII; R = H), which was stable. Rearrangement of the carbonium ion from the optically active *trans*-alcohol, 1*R*,3*R*-(+)-(XXX), gave the *R*-ester (XXXIV), retaining the configuration at C-1 in the parent acid (I). This is the same absolute configuration as natural (−)-*R*-lavandulol,[24] though since lavandulol retains the first formed chiral centre in the postulated presqualene biosynthesis [18] the sequence could be interrupted at this point *in vivo* without passing through a cyclopropane intermediate. Similarly, the diol (XXXV; R^1 = OH, R^2 = Me) gave the triene-ester (XXXI).[23b]

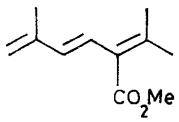
Another lavandulyl type of cleavage was encountered when the *cis*-chrysanthemic diol (XXXVI) was heated with a little toluene-*p*-sulphonic acid in benzene. Here, all three types of fission A, B, and C, as well as trapping of the carbonium ion in the *cis*-structure without cleavage

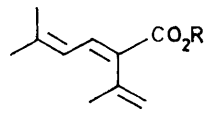
[20] L. Crombie and J. Crossley, *J. Chem. Soc.*, 1963, 4957, 4983.
[21] R. H. Eastman and S. K. Freeman, *J. Amer. Chem. Soc.*, 1955, **77**, 6642.
[22] M. Julia, S. Julia, and R. Guegan, *Bull. Soc. chim. France*, 1960, 1072; S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1968, **90**, 2882.
[23] (*a*) R. H. Wiley, E. Imoto, R. P. Houghton, and P. Veeravagu, *J. Amer. Chem. Soc.*, 1960, **82**, 1413; (*b*) M. Matsui, M. Uchiyama, and H. Yoshioka, *Agric. and Biol. Chem.* (*Japan*), 1963, **27**, 549; M. Matsui, H. Yoshioka, and H. Hirai, *ibid.*, 1964, **28**, 456.
[24] 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, 2nd edition, vol. IIB, Elsevier, 1968, p. 164; M. Souček and L. Dolejš, *Coll. Czech. Chem. Comm.*, 1959, **74**, 3802.

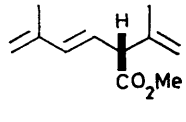
of the cyclopropane ring, are possible courses. Five products were detected by g.l.c. and the major component (47%; isolated by prep. g.l.c.) was the alcohol

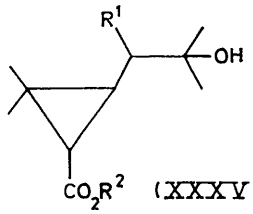

(XXX)


(XXXI)

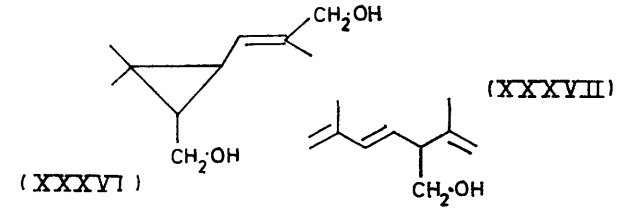

(XXXII)


(XXXIII)


(XXXIV)

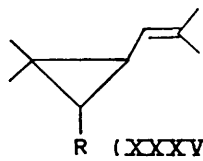

(XXXV)

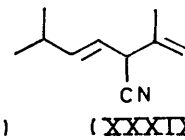
(XXXVII) resulting from lavandulyl cleavage initiated by the allylic carbonium ion.

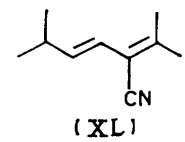

(XXXVI) (XXXVIII)

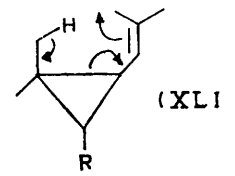
During the preparation of the (±)-*trans*-nitrile (XXXVIII; R = CN)[25] from the (±)-*trans*-amide (XXXVIII; R = CO·NH$_2$) by heating with phosphorus pentoxide, two nitriles (XXXIX) and (XL) were observed in addition to the major product (XXXVIII; R = CN). The (±)-*trans*-nitrile appears not to be the progenitor of the acyclic products as it was unchanged on heating with phosphorus pentoxide or when heated under reflux with toluene-*p*-sulphonic acid in benzene. Although the exact origin of the acyclic nitriles (XXXIX) and (XL) is uncertain, they may arise by pyrolytic fission [*e.g.*, (XLI)], and prototropic shift, in a manner similar to the pyrolytic cleavage of ethyl *cis*- and *trans*-chrysanthemates.[26]

In continuation of these studies of the carbonium-ion-initiated cleavage of the chrysanthemic-type system, we have turned attention to the hypothesis that the process may be involved in the biosynthesis of irregular

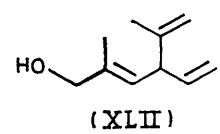

(XXXVIII)

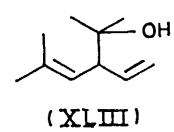

(XXXIX)


(XL)

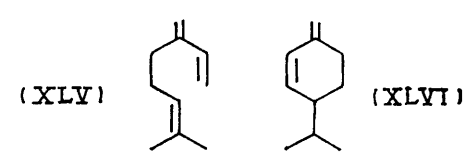

(XLI)

monoterpenoids of the artemesia and santolina type. *Santolina chamaecyparissus* is a shrubby perennial yielding an essential oil containing artemesia ketone [3] (III) and traces of santolina triene [4] (II).* Pin-2(10)-


(XLII)


(XLIII)


(XLIV)


(XLV) (XLVI)

ene (XLIV) and 7-methyl-3-methyleneocta-1,6-diene (XLV) have also been identified in the oil,[4] and we have

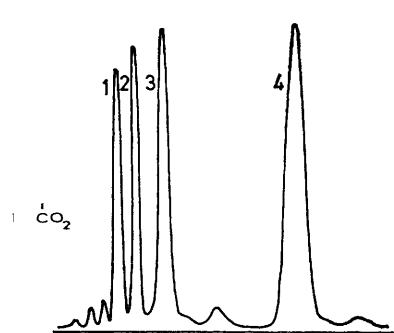


FIGURE 1 Analysis of *S. chamaecyparissus* oil: 1, pin-2(10)-ene and unidentified monoterpene; 2, 7-methyl-3-methyleneocta-1,6-diene; 3, *p*-mentha-1(7),2-diene; 4, artemisia ketone

now characterised the remaining major component (see Figures 1 and 2) as *p*-mentha-1(7),2-diene (XLVI).

* 4-Isopropenyl-2-methylhexa-2,5-dien-1-ol (lyratol) (XLII) has been found in *Cyathocline lyrata*,[27] and the alcohol (XLIII) from *Ormensis multicaulis* [28] has the same skeleton.

[25] S. H. Harper and K. C. Sleep, *J. Sci. Food Agric.*, 1951, **2**, 116.

[26] G. Ohloff, *Tetrahedron Letters*, 1965, 3795.

[27] O. N. Devgan, M. M. Bokadia, A. K. Bose, M. S. Tibbetts, G. K. Trevedi, and K. K. Chakravati, *Tetrahedron Letters*, 1967, 5337; O. N. Devgan, M. M. Bokadia, A. K. Bose, G. K. Trivedi, and K. K. Chakravati, *Tetrahedron*, 1969. **25**, 3217; W. Sucrow, *Tetrahedron Letters*, 1970, 4725.

[28] Y. Chrétien-Bessière, L. Peyron, L. Bénezet, and J. Garnero, *Bull. Soc. chim. France*, 1968, 2018; W. Sucrow, *Tetrahedron Letters*, 1970, 3675.

Chrysanthemic [^{14}C]acid was prepared by the addition of [1-^{14}C]diazoacetic ester to 2,5-dimethylhexa-2,4-diene.[29] After hydrolysis the labelled (±)-*cis*- and

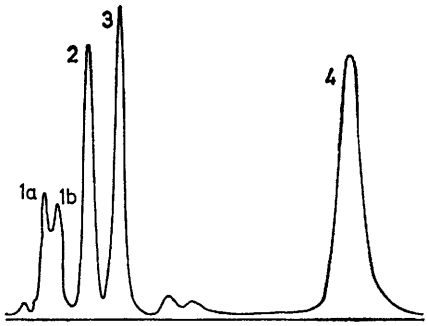
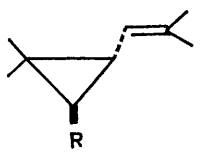


FIGURE 2 Analysis of *S. chamaecyparissus* oil: 1a, pin-2(10)-ene; 1b, unidentified monoterpene; 2, 7-methyl-3-methyleneocta-2,6-diene; 3, *p*-mentha-1(7),2-diene; 4, artemisia ketone

(±)-*trans*-acids were separated chromatographically and the (±)-*trans*-acid was used in the feeding experiments. Part of the *trans*-[^{14}C]acid (XLVII) was



(XLVII) R = $^{14}CO_2H$
(XLVIII) R = $^{14}CH_2OH$
(IL) R = $^{14}CH_2O{\cdot}PO_3^{2-}$ or $^{14}CH_2O{\cdot}P_2O_6^{3-}$

reduced to give [CH_2-^{14}C]*trans*-chrysanthemyl alcohol, which was converted [30] into a mixture of chrysanthemyl phosphate and pyrophosphate. This was not separated but used directly for administration as the sodium salt. The phosphates could be reconverted into chrysanthemyl alcohol by treatment with lithium aluminium hydride (in an experiment with unlabelled material).

Cuttings of *S. chamaecyparissus* were planted and grown for 3 months and the labelled substrate was administered by wick-feeding to a group of 15—31 cuttings, which were left for the stated incorporation time (see the Table). All precursors were administered in neutral aqueous solution. The plant material was then steam distilled and the essential oil (which may at this stage contain steam-volatile precursors or degradation products) was isolated.

Sodium [^{14}C]acetate was incorporated evenly but poorly into g.l.c. fractions 1 and 2 [collected together; pin-2(10)-ene, unidentified material, and 7-methyl-3-methyleneocta-1,6-diene], fraction 3 [*p*-mentha-1(7),2-diene], and fraction 4 (artemisia ketone). Better overall incorporation was obtained with sodium [2-^{14}C]-mevalonate: the *p*-mentha-1(7),2-diene fraction was most labelled, but the incorporation into the artemisia ketone fraction was low, and after purification by p.l.c. the activity fell to *ca.* $\frac{1}{8}$ of its original value.

Sodium [*carboxy*-^{14}C]chrysanthemate was then incorporated into three groups of plants for 24, 40, and 64 h. The distribution of radioactivity into all the fractions was low and comparatively even. In one of the experiments (no. 4) the artemisia ketone fraction (g.l.c.) was again purified by p.l.c., and the activity fell to *ca.* $\frac{1}{10}$ of the original value. Experiments 6 and 7 were run simultaneously and with smaller cuttings than the earlier series. Improved incorporations of sodium [2-^{14}C]mevalonate into all four terpene fractions separated were now found, but again the poorest was for the artemisia ketone fraction. Purification (p.l.c.), however, only lowered the activity by just over half. In the [^{14}C]chrysanthemyl phosphates experiment (no. 7), labelled precursor or its breakdown products badly contaminated the g.l.c. fractions and radiochemical data for the latter are not recorded. Instead, fraction 4 was collected, purified by p.l.c., and finally converted into the crystalline semicarbazone of artemisia

Administration of [^{14}C]labelled substrates to *Santolina chamaecyparissus* plants

Expt. no.	Labelled substrate	*t*/h [a]	Activity (mCi) [b]	No. of plants	Av. wt./plant (g)	Wt. of oil (g)	Incorp. (%) [c]	Scaled activity (d.p.m. mg^{-1}) [d] in g.l.c. fractions: 1 [e]	2 [f]	3 [g]	4 [h]	artemisia ketone [i]
1 [l]	Sodium [1-^{14}C]acetate	96	0·1	31	8·9	0·67	0·19	41 [k]		48	59	
2 [l]	Sodium [2-^{14}C]mevalonate	40	0·1	31	14·1	1·47	1·26	216		578	41	7·05
3 [l]	Sodium [*carboxy*-^{14}C]chrysanthemate	24	0·034	15	16·2	0·83	1·98	74		32	71	
4 [l]	Sodium [*carboxy*-^{14}C]chrysanthemate	40	0·067	31	16·1	1·67		49		43	51	5·5
5 [l]	Sodium [*carboxy*-^{14}C]chrysanthemate	64	0·034	15	15·8	1·03	2·08	15		20	24	
6 [m]	Sodium [2-^{14}C]mevalonate	40	0·1	30	2·2	1·45	3·81	2546	900	1720	261	120
7 [m]	[CH_2-^{14}C]Chrysanthemyl phosphates	24	0·027	20	3·7	1·25	0·38					0·6 [j]

[a] Incorporation time. [b] Total activity of administered sample. [c] Incorporation of original tracer in crude oil, which may include original tracer and breakdown products. [d] Activity is scaled to be equivalent to an administration of 0·1 mCi of tracer. [e] Pin-2(10)-ene and unidentified monoterpene. [f] 7-Methyl-3-methyleneocta-1,6-diene. [g] *p*-Mentha-1(7),2-diene. [h] Artemisia ketone. [i] Artemisia ketone, after further purification by p.l.c. [j] Artemisia ketone purified and counted as the crystalline semicarbazone. [k] Fractions 1 and 2 were not separated in Expts. 1—5. [l] G.l.c. column: 5 ft × $\frac{1}{8}$ in, 10% PEGA on Chromosorb W, 80°. [m] G.l.c. column: 5 ft × $\frac{1}{8}$ in, 30% DEGS on Chromosorb P, 80°.

[29] Y. Nishizawa and J. E. Casida, *J. Agric. Food Chem.*, 1965, **13**, 525; F. Acree, C. C. Roan, and F. H. Babers, *J. Econ. Entomol.*, 1954, **47**, 1066. For an alternative labelling see L. Crombie, C. F. Doherty, and G. Pattenden, *J. Chem. Soc.* (*C*), 1970, 1076.

[30] G. Popják, J. W. Cornforth, R. H. Cornforth, R. Ryhage, and De W. S. Goodman, *J. Biol. Chem.*, 1962, **237**, 57; F. Cramer and W. Böhm, *Angew. Chem.*, 1959, **71**, 775.

ketone. The activity of the semicarbazone was nearly zero.

These results with sodium chrysanthemate and with chrysanthemyl phosphates thus provide no direct support for Bates' hypothesis on the origins of artemisia ketone.[2] Nevertheless, caution must be applied in reaching a final conclusion since the results are negative, and general knowledge of the biosynthesis of monoterpenes is limited. The incorporation of [2-^{14}C]mevalonate indicates that it is reaching sites of head-to-tail monoterpene biosynthesis, but its incorporation into artemisia ketone is much more limited. This agrees with the observations of Waller and his colleagues,[31a] who also, like ourselves, found poor incorporation of acetate into monoterpenes in this plant. Low incorporation of [2-^{14}C]mevalonate into artemisia ketone by *Artemisia annua* has been recently reported.[31b]

EXPERIMENTAL

Methyl (±)-trans-3-*Isobutyl*-2,2-*dimethylcyclopropanecarboxylate*.—(±)-*trans*-2,2-Dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylic acid (3·38 g) (chrysanthemic acid) in ethyl acetate was hydrogenated over 5% palladium–barium sulphate (250 mg), and absorbed 1 mol. equiv. of hydrogen. After removal of the catalyst, evaporation gave (±)-*trans*-3-isobutyl-2,2-dimethylcyclopropanecarboxylic acid (dihydrochrysanthemic acid), b.p. 105—106° at 1·5 mmHg, n_D^{22} 1·4469 (lit.,[32] 132° at 10 mmHg, n_D^{20} 1·4482). Esterification with diazomethane gave the methyl (±)-*trans*-carboxylate, b.p. 62—63° at 2 mmHg, n_D^{20} 1·4401 (lit.,[32] 86° at 13 mmHg, n_D^{20} 1·4405). Methyl (−)-*trans*-3-isobutyl-2,2-dimethylcyclopropanecarboxylate was prepared *via* the corresponding acid,[32] b.p. 107—108° at 1·5 mmHg, n_D^{20} 1·4472, $[\alpha]_D^{20}$ −26·5°, in a similar fashion from (+)-*trans*-2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylic acid.

Reaction of Methyl (±)-trans-3-*Isobutyl*-2,2-*dimethylcyclopropanecarboxylate with Methylmagnesium Iodide*.—The *trans*-ester (4·6 g) in ether (25 ml) was added (1 h) to boiling methylmagnesium iodide [from methyl iodide (10·65 g), magnesium (1·8 g), and ether (25 ml)] and the product was heated under reflux overnight. The mixture was cooled in ice, decomposed below 5° by adding aqueous ammonium chloride, and filtered. The ether layer was separated, and the aqueous (chrys) part extracted with ether. The combined extracts were dried, and the solvent was removed to leave *trans*-2-(3-isobutyl-2,2-dimethylcyclopropyl)propan-2-ol (VI), $\nu_{max.}$ 3470 (OH), 1365, and 1145 cm^{-1}, τ 8·6—9·2 (6 × Me). Distillation of this alcohol through a spinning-band column gave 4-*isopropenyl*-2,6-*dimethylhept*-2-*ene* (VIII), b.p. 43·5—44° at 2·0 mmHg, n_D^{22} 1·4453 (Found: C, 86·6; H, 13·45. $C_{12}H_{22}$ requires C, 86·65; H, 13·35%), $\nu_{max.}$ 3060, 1650, 885, and 835 cm^{-1}, τ 5·08 (1H, $J_{3.4}$ 9 Hz, 3-H), 5·4 (C:CH$_2$), 7·07 (1H, q, $J_{3.4} = J_{4.5} = 9$ Hz, 4-H), 8·32 (s) and 8·37 (s) (MeC:CH$_2$, 2-Me, 1-Me), and 9·14 (m, 6.7-Me$_2$).

By a similar method, the (−)-*trans*-methyl ester was transformed into 4*R*—(−)-4-isopropenyl-2,6-dimethylhept-2-ene (VIII), n_D^{20} 1·4445, $[\alpha]_D^{20}$ −32·55 (EtOH) (Found: C, 86·8; H, 13·25%).

[31] (*a*) G. R. Waller, G. M. Frost, D. Burleson, D. Brannon, and L. H. Zalkow, *Phytochemistry*, 1968, **7**, 213; (*b*) D. V. Banthorpe and B. V. Charlwood, *Nature*, 1971, **232**. 285.

4-*Isopropyl*-2,6-*dimethylheptane*.—The (±)-diene (VIII) (332 mg) in ethanol (10 ml) was hydrogenated over 5% palladium–barium sulphate (75 mg) until 2 mol. equiv. of hydrogen had been absorbed. Filtration and evaporation gave 4-*isopropyl*-2,6-*dimethylheptane*, b.p. 63—64° at 14 mmHg, n_D^{22} 1·4197 (Found: C, 84·75; H, 15·25. $C_{12}H_{26}$ requires C, 84·6; H, 15·4%), *m/e* 170, 127, 113, 57, and 43.

(±)-trans-3-*Isobutyl*-2,2-*dimethylcyclopropylmethanol* (V).—A slurry of lithium aluminium hydride (0·6 g) in dry ether (10 ml) was added to methyl (±)-*trans*-3-isobutyl-2,2-dimethylcyclopropanecarboxylate (3·46 g) in dry ether (50 ml) and the solution was heated under reflux for 2 h. After cooling, the mixture was treated with water, and the ether layer was separated. The aqueous portion was washed with ether and the combined organic extracts were dried, concentrated, and distilled, to yield the (±)-*trans*-alcohol (V) (2·25 g), b.p. 46—47° at 1·5 mmHg, $n_D^{18.5}$ 1·4390 (lit.,[32] b.p. 58° at 10 mmHg, n_D^{20} 1·4381).

Reaction of (±)-trans-3-*Isobutyl*-2,2-*dimethylcyclopropylmethanol with Thionyl Chloride*.—A solution of the (±)-*trans*-alcohol (V) (3·12 g) in dry ether (40 ml) was added dropwise during 3 h to a stirred solution of freshly distilled thionyl chloride (2·32 g) in ether (90 ml) at 0°, and stirring was continued for a further 18 h at room temperature. The mixture was washed twice with saturated aqueous sodium carbonate, and then with saturated brine. The organic solution was dried and the ether was evaporated. G.l.c. showed five components, and prep. g.l.c. (10 ft × ⅜ in column; 30% carbowax 20M on Chromosorb P; 150°) gave the major product, 2,5-*dimethyl*-3-*vinylhex*-1-*ene* (VII) (39%), n_D^{23} 1·4293 (Found: C, 86·5; H, 13·25. $C_{10}H_{18}$ requires C, 86·85; H, 13·1%), $\nu_{max.}$ 1650, 1640 (C=C), 915, and 893 (C=CH$_2$) cm^{-1}, τ 4·37 (1H, m, 3-C*H*:CH$_2$), 4·97, 5·2 (3-CH:C*H*$_2$), 5·33 (C*H*$_2$:CMe), 7·3 (1H, q, $J_{3.4} = J_{3.1}$ 8 Hz, 3-H), 8·67 (2H, d, 4-CH$_2$), 8·39 (3H, s, 2-Me), and 9·14 (6H, d, J 6 Hz, 5-Me and 6-H$_3$).

Reduction of (±)-trans-2,2-*Dimethyl*-3-(2-*methylpropenyl*)-*cyclopropanecarboxylic Acid* (I) *with Lithium Aluminium Hydride*.—Reduction of the acid (5·04 g) with a slurry of lithium aluminium hydride (0·9 g) in ether, followed by heating under reflux (2 h) and work-up with water, gave (±)-*trans*-2,2-dimethyl-3-(2-methylpropenyl)cyclopropylmethanol[33] (IX) (2·6 g), b.p. 54—55° at 0·1 mmHg, n_D^{22} 1·4725, identical with material prepared by reduction of the ester, τ 5·15 (1H, C*H*:C), 6·25 (m, C*H*$_2$·OH), 6·82 (1H, exchangeable, OH), 8·35 (6H, *Me*$_2$C:CH·), 8·85 (3-H), and 8·87 and 8·97 (2,2-Me$_2$). When worked-up by decomposition with methyl formate, a mixture of the alcohol and its *formate ester* was obtained. The latter was separated by fractionation (41%; g.l.c. pure) and its structure confirmed spectroscopically; b.p. 80—81° at 1·5 mmHg, n_D^{19} 1·4625, $\nu_{max.}$ 1725 cm^{-1} (Found: C, 72·45; H, 10·05. $C_{11}H_{18}O_2$ requires C, 75·5; H, 9·95%). Use of ethyl acetate gave the *acetate* (35%), b.p. 44—45° at 0·2 mmHg, n_D^{19} 1·4597, $\nu_{max.}$ 1735 cm^{-1} (Found: C, 73·6; H, 10·2. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·25%).

2,5,5-*Trimethylhepta*-1. trans-3,6-*triene* (XII).—(±)-*trans*-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropylmethanol (chrysanthemyl alcohol) (2·5 g) in dry benzene containing toluene-*p*-sulphonic acid (25 mg) was heated under reflux (15 min) under nitrogen, so as to remove water azeotropically. The product was cooled, washed twice with saturated

[32] S. H. Harper, *J. Sci. Food Agric.*, 1954, **5**, 529.

[33] Y. Inouye and M. Ohno, *Boytu Kagaku*, 1955, **20**, 149.

sodium carbonate, dried, evaporated, and distilled through a micro-spinning-band column to give 2,5,5-trimethylhepta-1,*trans*-3,6-triene [9] (1·5 g), b.p. 55—56° at 14 mmHg, n_D^{21} 1·4662, $\lambda_{max.}$ 230 nm (ε 14,300), $\nu_{max.}$ (film) 1630, 1608 (C=C), 3080, 880 ($R^1R^2C=CH_2$), 960 (*trans* CH=CH), and 910 ($CH=CH_2$) cm^{-1} (Found: C, 88·2; H, 11·7. Calc. for $C_{10}H_{16}$: C, 88·15; H, 11·85%), τ 4·18 (1H, m, 6-H), 4·2 (2H, q, $J_{3,4}$ 16 Hz, 3- and 4-H), 4·9—5·3 (2H, m, 7-H_2), 5·15 (2H, 1-H_2), 8·22 (2-Me), and 8·87 (5,5-Me_2). On hydrogenation (Pd–$BaSO_4$; ethanol) 3 mol. equiv. of hydrogen were absorbed to give 2,5,5-trimethylheptane, b.p. 65° at 14 mmHg, n_D^{20} 1·4213, M^+, 142, *m/e* 127 and 71. The (±)-*cis*-alcohol (XI) similarly gave 2,5,5-trimethylhepta-1,*trans*-3,6-triene, b.p. 62—63° at 18 mmHg, n_D^{20} 1·4667, identical with that obtained before (g.l.c., n.m.r., u.v., and i.r.).

(±)-*trans*-Chrysanthemyl alcohol (7·7 g) in pyridine (15·8 g) and ether (25 ml) was treated with toluene-*p*-sulphonyl chloride at 0—5°, stirred (3 h), and poured into ice–hydrochloric acid. Work-up gave 2,5,5-trimethylhepta-1,*trans*-3,6-triene (XII) (3·65 g), b.p. 44—45° at 10, n_D^{22} 1·4670 identical with that obtained before.

(±)-*trans*-Chrysanthemyl alcohol (3·08 g) in dry ether was treated with purified thionyl chloride (2·32 g) in ether at 0°. After stirring (18 h), the product was washed with sodium carbonate and worked up. Removal of solvent gave a chlorine-containing liquid; g.l.c. analysis showed seven components. The 2,5,5-trimethylhepta-1,*trans*-3,6-triene peak (*ca.* 40%) was located by mixed g.l.c. Isolation by preparative g.l.c. gave the pure triene identical with the specimens obtained before.

(±)-*trans*-Chrysanthemyl alcohol (3·08 g), dry pyridine (0·1 ml), and benzene (10 ml) were added to phosphorus tribromide (5·42 g), pyridine (0·34 ml), and benzene (10 ml) at −50° and the mixture was stirred at 20° for 18 h. Work-up and distillation, b.p. 44—46° at 1 mmHg, n_D^{19} 1·4895, gave a bromine-containing product which on g.l.c. showed six components. One of these (35%) was isolated and shown to be 2,5,5-trimethylhepta-1,*trans*-3,6-triene.

Acidic Treatment of Methyl (±)-trans-2,2-*Dimethyl*-3-(2-*methylpropenyl*)*cyclopropylmethyl Ether* (X).—The alcohol (3·08 g) was added to sodium (0·46 g) in toluene (100 ml) under reflux and the mixture was stirred and heated under reflux (16 h). Methyl iodide (3·2 g) was added to the cooled product and heating under reflux was continued for 6 h. Work-up gave the (±)-trans-*methyl ether* (X) (2·85 g), b.p. 36—37° at 0·2 mmHg, n_D^{20} 1·4548, $\nu_{max.}$ 1105 cm^{-1} (C–O–C) (Found: C, 78·4; H, 11·75. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%), τ 6·8 (OMe) and 6·72 (CH_2·OMe). Methylation with dimethyl sulphate–potassium carbonate in acetone (18 h, reflux) gave a mixture of alcohol and ether (70 : 30 by g.l.c.): diazomethane–fluoroboric acid gave largely unchanged alcohol.

The methyl ether (2·0 g) was heated for 2 h under nitrogen with benzene (15 ml) containing toluene-*p*-sulphonic acid (25 mg). Work-up gave a liquid (1·15 g) which on distillation gave 2,5,5-trimethylhepta-1, *trans*-3,6-triene (XII), b.p. 44—45° at 10 mmHg, n_D^{20} 1·4680 identical with the specimens obtained before. Under similar conditions (but heating for 6 h), methyl (±)-*trans*-2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylate was unchanged. Heating the pure ester (2 g) with toluene-*p*-sulphonic acid at 130° under vacuum also gave unchanged ester.

2,5,5,7-*Tetramethylocta*-1,trans-3,6-*triene* (XXVIII; $R^1 = R^2 = Me$).—Methyl (±)-*trans*-chrysanthemate (9·1 g) in ether (25 ml) was added to methylmagnesium iodide [from methyl iodide (21·3 g) and magnesium (3·6 g) in ether (50 ml)] and heated under reflux (12 h). Decomposition with aqueous ammonium chloride solution at 0—5° gave 2,5,5,7-*tetramethylocta*-1,trans-3,6-*triene* (4·7 g), b.p. 37—38° at 1·2 mmHg (spinning band), n_D^{19} 1·4750, $\nu_{max.}$ (film) 1630 (C=C), 968 (*trans*-CH=CH), and 878 (C=CH_2) cm^{-1} (Found: C, 87·7; H, 12·35. $C_{12}H_{20}$ requires C, 87·75; H, 12·25%), τ 4·15 (2H, q, $J_{3,4}$ 16 Hz, 3- and 4-H), 4·78br (6-H), 5·2 (2H, 1-H_2), 8·2 (2-Me), 8·35 and 8·42 (6H, both d, *J* 2 Hz, 7-Me and 8-H_3), and 8·85 (5,5-Me_2). On hydrogenation (Pd–$BaSO_4$; ethyl acetate), 3 mol. equiv. of hydrogen were absorbed to give 2,4,4,7-*tetramethyloctane* b.p. 67—68° at 10 mmHg, n_D^{20} 1·4187 (Found: C, 84·35; H, 15·6. $C_{12}H_{26}$ requires C, 84·6; H, 15·4%), M^+, 170.

3,3,6-*Trimethylhepta*-trans-4,6-*dienal* (XXIII).—(±)-*trans*-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarbaldehyde [20] (XXI) (2·0 g; n_D^{20} 1·4771) was heated under reflux for 2 h under nitrogen with toluene-*p*-sulphonic acid (25 mg) in dry benzene (25 ml). Work-up gave 3,3,6-*trimethylhepta*-trans-4,6-*dienal* (XXIII) (1·1 g), b.p. 46—47° at 0·8 mmHg, n_D^{19} 1·4815, $\lambda_{max.}$ 229 nm (12,800), $\nu_{max.}$ (film) 1720 (C=O), 1645, 1610 (C=C), 966 (*trans*-CH=CH), and 882 (C=CH_2) cm^{-1} (Found: C, 78·85; H, 10·55. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%), τ 0·33 (1H, t, $J_{1,2}$ 3 Hz, 1-H), 4·12 (2H, q, $J_{4,5}$ 16 Hz, 4- and 5-H), 5·12 (2H, 7-H_2), 7·69 (2H, d. 2-H_2), 8·20 (6-Me), and 8·81 (3,3-Me_2). The aldehyde absorbed 2 mol. equiv. of hydrogen to give 3,3,6-trimethylheptanal, b.p. 67—68° at 15 mmHg, n_D^{21} 1·4326, $\nu_{max.}$ (film) 1720 (C=O) cm^{-1}.

2,5,5-*Trimethylocta*-1,*trans*-3-*dien*-7-*one* (XXIV).—(±)-*trans*-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarbonyl chloride (14 g) in benzene was added to dimethylcadmium [from magnesium (3·66 g), methyl iodide (21·3 g), and anhydrous cadmium chloride (22·15 g)] in benzene (40 ml) at 40—50°. The mixture was heated under reflux for 1 h and water (40 ml) was added, followed by conc. hydrochloric acid (6·8 ml) in water (10 ml). The mixture was steam distilled. The steam-distillate was extracted with benzene and the benzene extract was dried and distilled through a column packed with helices, b.p. 90—91° at 15 mmHg, n_D^{21} 1·4668 (*ca.* 6 g). G.l.c. showed a mixture of the cyclopropyl methyl ketone (*ca.* 63%) and the open-chain isomer (see later) (*ca.* 37%). Fractionation of the mixture (spinning band) gave 2,2-dimethyl-3-(2-methylpropenyl)cyclopropyl methyl ketone (XXII) (3 g), b.p. 90·8—91·2° at 15 mmHg, n_D^{20} 1·4660 (lit.,[21] 1·4666); semicarbazone, m.p. 161—162° (lit.,[21] 162—163°). The addition of aqueous ammonium chloride at 5° instead of hydrochloric acid, in the above experiment, afforded the ketone (8·2 g) free from ring-cleaved isomer (g.l.c.). Treatment of the ketone (XXII) with toluene-*p*-sulphonic acid in benzene, as before, gave 4,4,7-*trimethylocta*-trans-5,7-*dien*-2-*one* (XXIV), b.p. 86—87° at 14 mmHg, $\lambda_{max.}$ 220 nm (ε 12,900), $\nu_{max.}$ (film) 1735 (C=O), 1640, 1610 (C=C), 966 (*trans*-CH=CH), and 890 (C=CH_2) (Found: C, 79·4; H, 10·75. $C_{11}H_{18}O$ requires C, 79·45; H, 10·9%), τ 4·15 (2H, q, *J* 15 Hz, 5- and 6-H), 5·15 (2H, 8-H_2), 7·61 (2H, 3-H_2), 7·98 (3H, 1-H_3), 8·18 (7-Me), and 8·85 (4,4-Me_2). The *semicarbazone* had m.p. 136° (Found: C, 64·3; H, 9·75; N, 18·6. $C_{12}H_{21}N_3O$ requires C, 64·55; H, 9·5; N, 18·8%). On catalytic hydrogenation (as before) the dienone absorbed 2 mol. equiv. of hydrogen to give 4,4,7-*trimethyloctan*-2-*one*, b.p. 68—69° at 14 mmHg, n_D^{33} 1·4317, $\nu_{max.}$ (film) 1715 (C=O) cm^{-1}. The *semicarbazone* had m.p. 99—100° (Found:

C, 63·3; H, 11·3; N, 18·3. $C_{12}H_{25}N_3O$ requires C, 63·4; H, 11·1; N, 18·5%).

Ethyl 5,5,8-Trimethylnona-trans-3,trans-6,8-*trienoate* (XXVI).—The aldehyde (XXI) (1·52 g) and ethyl bromoacetate (2·1 g) in dry benzene (14 ml) were added dropwise during 15 min to a stirred suspension of activated zinc (0·8 g) under reflux in dry ether (6 ml) under nitrogen. The mixture was stirred and heated under reflux for 30 min, decomposed with aqueous acetic acid, and worked up to give *ethyl* 3-[(±)-trans-2,2-*dimethyl*-3-(2-*methylpropenyl*)-*cyclopropyl*]-3-*hydroxypropionate* (XXV) (0·8 g), b.p. 72—73° at 1·5 mmHg, n_D^{18} 1·4760, $\nu_{max.}$ (film) 3400 (OH) and 1710 (ester) (Found: C, 70·35; H, 10·2. $C_{14}H_{24}O_3$ requires C, 69·95; H, 10·1%).

The β-hydroxy-ester (1·5 g) was heated under reflux in benzene (15 ml) with toluene-*p*-sulphonic acid (15 mg) for 2 h under nitrogen; water being azeotropically removed. Work-up gave the *trienoate* (XXVI) (200 mg), b.p. 87—88° at 1 mmHg, n_D^{21} 1·4768, $\lambda_{max.}$ 230 nm (ε 16,900), $\nu_{max.}$ (film) 1740 (ester), 1640, 1605 (C=C), and 965 (*trans*-CH=CH) cm^{-1} (Found: C, 75·3; H, 10·2. $C_{14}H_{22}O_2$ requires C, 75·65; H, 9·95%), τ 4·21 (2H, q, $J_{6,7}$ 16 Hz, 6- and 7-H), 4·50 (2H, m, 3- and 4-H), 5·15 (2H, 9-H_2), 7·05 (2H, m, 2-H_2), 8·19 (8-Me), 8·85 (5,5-Me_2), 5·90 and 8·77 (5H, q and t respectively, J 6 Hz, $CH_2{\cdot}CH_3$).

Oxidation of Methyl 2,2-*Dimethyl*-3-(2-*methylpropenyl*)-*cyclopropanecarboxylates with Selenium Dioxide*.—The methyl (±)-*trans*-ester (9·1 g) was heated under reflux (1 h) with selenium dioxide (7·8 g) in anhydrous dioxan (50 ml).[34] Filtration, evaporation, and continuous extraction with light petroleum (b.p. 40—60°) (48 h) gave methyl (±)-*trans*-3-(2-formylpropenyl)-2,2-dimethylcyclopropanecarboxylate (XXIX; R = CO_2Me) (3·2 g), b.p. 110° at 1 mmHg, which had m.p. 54·5° after three crystallisations from light petroleum (b.p. 60—80°) (lit.,[34] m.p. 54°), $\nu_{max.}$ (mull) 1725 (ester) and 1685 (α-unsat. aldehyde) cm^{-1} (Found: C, 67·2; H, 8·25. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2%), τ 0·77 (CHO), 4·00 (C*H*:CMe), 6·35 (OMe), 7·72 (1H, q, $J_{3,1'}$ 8, $J_{3,1}$ 6 Hz, 3-H), 8·16 (CH:C*Me*), 8·28 (1-H), and 8·73 and 8·66 (2,2-Me_2). The 2,4-dinitrophenylhydrazone had m.p. 155—157° (lit.,[34] 157°).

The methyl (+)-*trans*-ester {3·36 g; b.p. 62—63° at 2 mmHg, n_D^{20} 1·4622, $[\alpha]_D^{20}$ +20·6° (EtOH)}, similarly treated with selenium dioxide (2·4 g) and dioxan (20 ml) gave the (+)-*trans*-formyl-ester (XXIX; R = CO_2Me) (0·8 g), b.p. 86—87° at 0·05 mmHg, n_D^{23} 1·4977, $[\alpha]_D^{20}$ +11·5 (EtOH), $\nu_{max.}$ (film) 1735 and 1693 cm^{-1} (Found: C, 67·3; H, 8·2%). N.m.r. resonances were as before. The 2,4-dinitrophenylhydrazone had m.p. 114—116° (lit.,[34] b.p. 130—140° at 1 mmHg, n_D^{19} 1·4970; 2,4-dinitrophenylhydrazone, m.p. 116°).

The methyl (±)-*cis*-ester (9·1 g) and selenium dioxide (6·7 g) similarly gave the (±)-*cis*-formyl-ester (2·7 g), b.p. 113—114° at 1·5 mmHg, n_D^{22} 1·5002, $\nu_{max.}$ (film) 1728 and 1687 cm^{-1} (Found: C, 67·15; H, 8·15%), τ 0·60 (CHO), 3·19 (1H, d, C*H*:CMe), 6·36 (OMe), 7·82 (1H, t, $J_{3,1'} = J_{3,1}$ 6 Hz, 3-H), 8·04 (1H, d, 1-H), 8·20 (CH:C*Me*), and 8·65 and 8·68 (2,2-Me_2). The 2,4-dinitrophenylhydrazone had m.p. 190—192° (lit.,[34] b.p. 140—145° at 17 mmHg, n_D^{21} 1·4994; 2,4-dinitrophenylhydrazone, m.p. 192°).

[34] M. Matsui, M. Miyano, K. Yamashita, H. Kubo, and K. Tomita, *Agric. Biol. Chem.*, 1957, **21**, 22; M. Matsui, M. Miyano, and K. Yamashita, *Proc. Japan Acad.*, 1956, **32**, 352; M. Matsui, Y. Yamada, and M. Nonoyama, *Agric. Biol. Chem.*, 1962, **26**, 351.

The (±)-*trans*- and (±)-*cis*-esters (2 g), heated for 6 h under reflux with toluene-*p*-sulphonic acid (50 mg) in benzene under nitrogen, gave only unchanged starting material. Distillation (1 g) with toluene-*p*-sulphonic acid (50 mg) at 12 mmHg and 145—150° (bath temp.) caused charring.

Reduction of the Formyl-esters (XXIX; R = CO_2Me) *with Sodium Borohydride*.—The methyl (±)-*trans*-formyl-ester [*cf.* (XXIX; R = CO_2Me)] (1·32 g) in methanol (3·5 ml) containing a drop of aqueous 10% sodium hydrogen carbonate was treated with sodium borohydride (75 mg) and stirred for 30 min. The methanol was evaporated, and the residue in ether (5 ml) was shaken quickly with ice-cold hydrochloric acid (5%; 0·5 ml) followed by sodium hydrogen carbonate solution (10%). Drying and distillation gave the *methyl* (±)-trans-3-[2-(*hydroxymethyl*)-*propenyl*]-2,2-*dimethylcyclopropanecarboxylate* (XXX) (0·6 g), b.p. 108—109° at 0·6 mmHg, n_D^{20} 1·4869, $\nu_{max.}$ (film) 3425, 1230, 1075 (OH), and 1735 (ester) cm^{-1} (Found: C, 66·3; H, 9·4. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%), τ 4·90 (1H, d, $J_{3,1'}$ 8 Hz, C*H*:CMe), 6·13 ($CH_2{\cdot}$OH), 6·36 (OMe), 6·8 (OH), 8·02 (1H, q, 3-H), 8·30 (CH:C*Me*), 8·62 (1H, d, $J_{1,3}$ 6 Hz, 1-H), and 8·75 and 8·85 (2,2-Me_2).

The corresponding *methyl* (+)-trans-*hydroxy-ester* (XXX) had n_D^{23} 1·4808, $[\alpha]_D^{20}$ 6·70 (EtOH), $\nu_{max.}$ (film) 1730 cm^{-1} (Found: C, 66·35; H, 9·3%), with n.m.r. data as above.

The methyl (±)-*cis*-formyl-ester (2·64 g) was reduced with sodium borohydride (150 mg) in methanol to give the (±)-cis-*ester* (XXX) (1·4 g), b.p. 117—118° at 0·7 mmHg, n_D^{18} 1·4904, $\nu_{max.}$ (film) 3430, 1230, 1085 (OH), and 1730 (ester) cm^{-1} (Found: C, 67·0; H, 9·2%), τ 4·46 (1H, d, $J_{3,1'}$ 8 Hz, C*H*:CMe), 6·10 ($CH_2{\cdot}$OH), 6·42 (OMe), 7·0 (OH), 8·17 (1H, q, 3-H), 8·31 (CH:C*Me*), 8·4d (1H, $J_{1,2}$ 6 Hz, 1-H), and 8·77 (2,2-Me_2).

Acid-catalysed Cleavage of the Methyl (±)- *and* (+)-trans-*Hydroxy-esters* (XXX).—The (±)-*trans*-hydroxy-ester (2 g) was heated with toluene-*p*-sulphonic acid (50 mg) at 14 mmHg and the distillate was collected, dried, and distilled to give methyl 2-isopropenyl-5-methylhexa-*trans*-3,5-dienoate (XXXI) (1·05 g), b.p. 63—64° at 1·5 mmHg, n_D^{22} 1·4836 (lit.,[23] b.p. 49—50° at 0·65 mmHg, n_D^{20} 1·4820), $\lambda_{max.}$ (EtOH) 230 nm (ε 21,700), $\nu_{max.}$ (film) 1730 (CO_2Me), 1612 (C=C), 965 (conj. *trans*-CH=CH), and 897 (C=CH_2) cm^{-1} (Found: C, 73·15; H, 8·9. Calc. for $C_{11}H_{16}O_2$: C, 73·3; H, 8·95%), τ 4·06 (2H, m, $J_{3,4}$ 16, $J_{2,3}$ 8 Hz, 3- and 4-H), 5·08 and 5·12 (4H, 2 × CH_2=), 6·34 (OMe), 6·34 (2-H), and 8·14 and 8·26 (2 × Me).

In a similar way the (+)-*trans*-hydroxy-ester gave (−)-R-*methyl* 2-*isopropenyl*-5-*methylhexa*-trans-3,5-*dienoate* (XXXI), b.p. 92—93° at 12 mmHg, n_D^{20} 1·4820, $[\alpha]_D^{20}$ −6·8° (EtOH), $\lambda_{max.}$ (EtOH) 230 nm (ε 20,800), $\nu_{max.}$ (film) 1735 (ester), 1635, 1605 (C=C), 965 (conj. *trans*-CH=CH), and 890 (C=CH_2) cm^{-1} (Found: C, 72·95; H, 9·15%). N.m.r. data were closely similar to those above.

Isomerisation of the Ester (XXXI).—The ester (600 mg) was hydrolysed (1 h) with methanolic 10% sodium hydroxide (6 ml) under reflux. Work-up and crystallisation from methanol–water gave 2-isopropenyl-5-methylhexa-2,4-dienoic acid (XXXIII; R = H) (300 mg), m.p. 127—129° (lit.,[23] 130—131°), $\lambda_{max.}$ 276 nm (ε 19,500), $\nu_{max.}$ (mull) 1676 (acid), 1630, 1593 (C=C), and 910 (C=CH_2) cm^{-1}. The acid, esterified with diazomethane, gave the methyl ester, n_D^{21} 1·5244 (lit.,[23] n_D^{22} 1·5251), $\lambda_{max.}$ (EtOH) 287 nm (24,400), $\nu_{max.}$ (film) 1705 (α-unsatd. ester), 1630, 1583 (conj. C=C), and 910 (C=CH_2) cm^{-1}, τ 2·61 (1H, d, $J_{3,4}$

12 Hz, 3-H), 3·87 (1H, d, 4-H), 4·82, 5·23 (CH_2), 6·29 (OMe), and 8·09 and 8·13 (9H, 3 × Me).

The ester (XXXI) in light petroleum (b.p. 40—60°) was left over aluminium oxide (Woelm basic; activity 1) for 30 min and the product was eluted with benzene–methanol (95 : 5). Evaporation left (g.l.c.) unisomerised ester (XXXI), methyl 2-isopropylidene-5-methylhexa-3,5-dienoate (XXXII), and the ester (XXXIII; R = Me) (42 : 27 : 31): products (XXXI) and (XXXIII; R = Me) were identified by mixed g.l.c. with authentic [23] samples. On similar treatment for 70 min the products (XXXII) and (XXXIII; R = Me) only were found, in the proportions 66 : 34. Ester (XXXII) (isolated by prep. g.l.c.) had $\nu_{max.}$ (film) 1705 (α-unsatd. ester), 1635, 1605 (conj. C=C), 965 (*trans*-CH=CH), 905, and 895 ($CH=CH_2$) cm^{-1}, τ 3·85 (2H, q, $J_{3,4}$ 16 Hz, 3- and 4-H), 5·05 (CH_2), 6·30 (OMe), and 8·13 (9H, 3 × Me).

Acid-catalysed Cleavage of Methyl (±)-trans-3-(1,2-*Dihydroxy*-2-*methylpropyl*)-2,2-*dimethylcyclopropanecarboxylate*.—The (±)-*trans*-ketol (XXXV; R^1 = =O, R^2 = H), m.p. 142—143° (lit.,[35] 143—144°) was converted into its methyl ester, m.p. 38—41° (lit.,[35] 41—42°). Reduction with sodium borohydride gave the dihydroxy-ester (XXXV; R^1 = OH, R^2 = Me), b.p. 140—142° at 20 mmHg, n_D^{20} 1·4608, $\nu_{max.}$ (film) 3400 (OH) and 1730 (ester) cm^{-1}. The corresponding dihydroxy-acid had m.p. 198—199° (lit.,[35] 197—199°), and was identical with a specimen made by direct hydroxylation of the acid.

The dihydroxy-ester (XXXV; R^1 = OH, R^2 = Me) (2 g) was heated under reduced pressure with toluene-*p*-sulphonic acid (50 mg) and the distillate was shown by preparative g.l.c. (10% Carbowax 20M on Chromosorb W at 124°) to contain the triene ester (XXXI) (85%), n_D^{20} 1·4840 (Found: C, 73·20; H, 9·0%), identical with the specimen above.

Acidic Treatment of (±)-cis-3-(2-*Hydroxymethylpropenyl*)-2,2-*dimethylcyclopropenylmethanol* (XXXVI).—The *diol* (3·6 g) (see later), b.p. 137—139° at 1 mmHg, $n_D^{20.5}$ 1·5009 (Found: C, 70·45; H, 10·3. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·65%), was prepared by reducing the (2-formylpropenyl) compound (XXIX; R = CO_2Me) (4·9 g) with lithium aluminium hydride in ether. The *cis*-diol (2 g) was heated under reflux in dry benzene (30 ml) containing toluene-*p*-sulphonic acid (25 mg) in a nitrogen atmosphere for 30 min. The product was washed with aqueous sodium carbonate, dried, and evaporated. The oily residue showed five peaks on g.l.c. (20% Carbowax 20M; 140°); the major component, isolated by prep. g.l.c. (30% Carbowax 20M on Chromosorb P, 165°, in a 10 ft glass column), was 2-*isopropenyl*-5-*methylhexa*-trans-3,5-*dien*-1-*ol* (XXXVII) (Found: C, 78·55; H, 10·7. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%), $\nu_{max.}$ 3450, 3100, 1640, and 1610 cm^{-1}, $\lambda_{max.}$ 231 nm (ε 17,000), τ 3·7 (1H, d, $J_{3,4}$ 16 Hz, 4-H), 4·44 (1H, $J_{3,4}$ 16, $J_{2,3}$ 8 Hz, 3-H), 5·1br (4H, 2 × CH_2=), 6·3br (2H, d, CH_2·OH), and 8·17 and 8·28 (2 × Me).

Preparation of the (±)-trans-*Diol* (XXXVI).—Methyl (±)-*trans*-3-(2-formylpropenyl)-2,2-dimethylcyclopropanecarboxylate (4·9 g) in dry ether (25 ml) was treated with a slurry of lithium aluminium hydride (0·99 g) in ether (10 ml), and the mixture heated under reflux for 2 h. After treatment with water, the product was continuously extracted with ether. The ether extracts, after drying and distillation, gave an oil (4·5 g), b.p. 112—118° at 0·5 mmHg, which still showed ester carbonyl absorption. This product was further treated with lithium aluminium hydride as above. The product (2·8 g), b.p. 115—120° at 0·05 mmHg, was the (±)-trans-*diol* (XXXVI) (Found: C, 70·85; H, 10·5. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·65%), $\nu_{max.}$ 3400 and 1660 cm^{-1}, τ 4·82 (1H, d, *J* 7 Hz, C*H*:CMe), 6·02 (2H, s, CH_2OH), 6·1—6·7 (m, CH_2·OH), 8·27 (Me), and 8·84 and 8·92 (2,2-Me_2).

Reaction of (±)-trans-2,2-*Dimethyl*-3-(2-*methylpropenyl*)-*cyclopropanecarboxamide* (XXXVIII; R = CO·NH_2) *with Phosphorus Pentoxide*.—The (±)-*trans*-amide [25] (XXXVIII; R = CO·NH_2), m.p. 128° (10 g), and phosphorus pentoxide (10 g) were heated together at 170° under vacuum. The distillate (6 g) was re-distilled through a spinning-band column, the fraction, b.p. 93·5—94·5° at 10 mmHg, n_D^{20} 1·4700, being collected. G.l.c. indicated three components; these were separated by preparative g.l.c. (10 ft × ⅜ in column; 30% Apiezon L on Chromosorb P; 190°). Thirty-two 150 μl injections enabled three fractions, A (80 mg), B (2 g), and C (120 mg), to be collected. Component A was 2-*isopropenyl*-5-*methylhex*-trans-3-*enonitrile* (XXXIX) (Found: C, 80·35; H, 10·1; N, 9·25. $C_{10}H_{15}N$ requires C, 80·5; H, 10·15; N, 9·4%), $\nu_{max.}$ 2218 (CN), 1650 (C=C), 970 (*trans*-CH=CH), and 905 ($CH=CH_2$) cm^{-1}, τ 4·45 (2H, m, $J_{3,4}$ 16, $J_{2,3}$ = $J_{4,5}$ = 7 Hz, 3- and 4-H), 4·99 (CH_2), 6·3 (1H, d, 2-H), 7·6 (1H, m, 5-H), 8·19 (Me), 8·69 and 9·00 (6H, 5-Me and 6-H_3).

Product B was (±)-*trans*-2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarbonitrile (XXXVIII; R = CN), n_D^{20} 1·4710 (lit.,[25] 1·4700) (Found: C, 80·25; H, 10·0; N, 9·55. Calc. for $C_{10}H_{15}N$: C, 80·5; H, 10·15; N, 9·4%), $\nu_{max.}$ 2250 (CN) and 1640 (C=C) cm^{-1}, τ 5·05 (1H, d, $J_{1',2}$ 8 Hz, C*H*:CMe), 8·25 (CH:CMe_2), and 8·87 and 8·94 (2,2-Me_2).

The final component C was 2-*isopropylidene*-5-*methylhex*-trans-3-*enonitrile* (XL), n_D^{20} 1·4613 (Found: C, 80·55; H, 10·0; N, 9·45. $C_{10}H_{15}N$ requires C, 80·5; H, 10·15; N, 9·4%), $\lambda_{max.}$ 246 (ε 15,310) nm, $\nu_{max.}$ 2215 (CN) and 960 (*trans*-CH=CH) cm^{-1}, τ 3·93 (2H, m, $J_{3,4}$ 15, $J_{4,5}$ 2 Hz, 3- and 4-H), 7·56 (5-H), 7·86 and 8·06 (6H, Me_2C=), and 8·95 (6H, d, 5-Me and 6-H_3).

The (±)-*trans*-nitrile (XXXVIII; R = CN) was unchanged by heating under reflux in benzene for 2 h with toluene-*p*-sulphonic acid, or by heating with phosphorus pentoxide at 170°.

Extraction of Santolina chamaecyparissus (*L.*).—Coarsely chopped leaf and stem of *Santolina chamaecyparissus* (1·75 kg) was steam distilled. The distillate (9 l) was extracted with ether (2 l). The extract was dried and evaporated to yield the essential oil (8·5 g). G.l.c. analyses are shown in Figures 1 and 2. Preparative g.l.c. was on either 10 ft × ⅜ in polyethylene glycol adipate (PEGA) or diethylene glycol succinate (DEGS) columns (Chromosorb P) at 50° with nitrogen as carrier gas (200 ml N_2 min^{-1}) (see Table). The nitrogen was dried before use with liquid air traps. Collection bottles were also cooled in liquid air, and all fractions were distilled after collection.

Identification of Components of Oil from S. chamaecyparissus.—3,3,6-Trimethylhepta-1,5-dien-4-one (artemisia ketone) (III) (fraction 4 in Figures 1 and 2) had $\nu_{max.}$ 1680 (C=O) cm^{-1}, $\lambda_{max.}$ (hexane) 236 nm (ε 13,800), τ (CCl_4) 3·73 (5-H), 4·07 (1H, $J_{1,2}$ 17·5 Hz, 2-H), 4·95 and 4·98 (2H, 1-H_2), 7·90 and 8·12 (6-Me and 7-H_3), and 8·81 (3,3-Me_2). The ketone (38 μl) in ethanol (0·25 ml) and pyridine (0·05 ml) was added to semicarbazide hydrochloride (50 mg)

[35] M. Matsui, M. Uchiyama, and H. Yoshioka, *Agric. Biol. Chem.*, 1963, **27**, 554.

in hot water (0·05 ml), and the mixture heated on a steam-bath for 2 h to give artemisia ketone semicarbazone (37 mg), m.p. 92° [from light petroleum (b.p. 60—80°)] (lit.,[36] 96—97°), *m/e* 209 (M^+), τ ($CDCl_3$) 2·3 (NH), 4·2 (NH_2), 4·58 (1H, m, 5-H), 4·99 and 5·02 (2H, 1-H_2), 5·10 (1H, $J_{1,2}$ 10 and 18 Hz, 2-H), 8·15 and 8·46 (6-Me and 7-H_3), and 8·80 (3,3-Me_2).

p-Mentha-1(10),2-diene (XLVI) (fraction 3), $\lambda_{max.}$ 231 (ε 11,200) nm, τ 3·93 (1H, $J_{2,3}$ 6, $J_{3,4}$ 2 Hz, 3-H), 4·35 (2-H), 5·33 (2H, 10-H_2), 9·09 and 9·11 (6H, both d, $J_{7,8} = J_{7,9}$ 7 Hz, 8- and 9-H_3), *m/e* 136 (M^+) and 93 (100%) (*cf.*, ref. 37), showed an i.r. spectrum identical with that of an authentic specimen,* and similar to that recorded in the literature.[37] It was identical (g.l.c. and spectral comparison) with a major component of the distillate of Canada balsam oil [38] [pin-2-ene and pin-2(10)-ene were also identified].

7-Methyl-3-methyleneocta-1,6-diene (XLV) (fraction 2), $\lambda_{max.}$ (hexane) 224 nm (ε 15,700), τ 3·62 (1H, $J_{1,2}$ 11 and 17 Hz, 2-H), 4·5—5·1 (5H, 1-H_2, 6-H, 3-CH_2), 8·35 and 8·43 (7-Me and 8-H_3), was identified by i.r. comparison with the recorded spectrum.[37]

Fraction 1 was unresolved by g.l.c. (PEGA column), but was seen to have two components by g.l.c. on the DEGS column: that of lower retention time was pin-2(10)-ene (XLIV) (g.l.c. and spectral comparison with an authentic sample); the other was not identified.

Radiochemical Techniques.—In experiments 1—5 (see Table), organic compounds (1—5 mg) were counted in toluene phosphor (15 ml) containing 0·5% 2,5-diphenyloxazole (PPO) and 0·03% 1,4-bis-[2-(4-methyl-5-phenyloxazolyl)]-benzene (dimethyl-POPOP) in low-potassium-glass vials. Samples were swept with nitrogen before counting, except when volatile liquids were to be assayed. Aqueous solutions were counted in a solution (15 ml) prepared from PPO (4 g), dimethyl-POPOP (0·2 g), naphthalene (60 g), methanol (100 ml), and ethylene glycol (20 ml), diluted with dioxan to 1 l. A Packard 3375 liquid scintillation counter was used, with samples kept at 0°, when background of *ca.* 20 counts min^{-1} was achieved at 75% efficiency. Efficiences were determined with both external and internal standards. In experiments 6 and 7, samples were counted in NE-233 phosphor solution (10 ml; Nuclear Enterprises, Edinburgh) at ambient temperature with a Nuclear Enterprises 8310 counter. Background activity was measured at *ca.* 24 counts min^{-1} at 70% efficiency; the internal standard ([^{14}C]n-hexadecane) method was used for efficiency determination.

Administration of Labelled Compounds.—Three-month old *Santolina chamaecyparissus* plants, cuttings from mature specimens, were used in all experiments. Propagation was timed to provide specimens from May to July. Radioactive compounds were administered in aqueous solution *via* unmercerised cotton wicks to woody parts of the stem. After all the solution had been absorbed, a supply of water to the wick was maintained until harvesting. After the required incorporation time (see Table), all plant material above ground level was steam distilled. The essential oil was recovered by continuous ether extraction and stored at −10°. Radiochemical incorporation into the crude oil was measured before separation by prep. g.l.c. The appropriate g.l.c. fractions were collected, distilled, and counted. In some cases, 3,3,6-trimethylhepta-1,5-dien-4-one (artemisia ketone) was further purified by t.l.c., or the semicarbazone was prepared.

Sodium [1-^{14}C]acetate and (±)-[2-^{14}C]mevalonolactone (in benzene solution) were obtained from the Radiochemical Centre, Amersham. The former was fed directly in aqueous solution (0·1 mCi ml^{-1}) (Expt. 1). The latter was evaporated at 50° under nitrogen, and the residue dissolved in N-sodium hydroxide (0·002 ml per 0·1 mCi). The solution (Expts. 2 and 6) was diluted to 1 ml before feeding. Labelled 2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylic acid was prepared from [1-^{14}C]glycine (*vide infra*) and neutralised with aqueous N-sodium hydroxide (Expts. 3—5). 2,2-Dimethyl-3-(2-methylpropenyl)cyclopropylmethanol was converted (*vide infra*) into water-soluble phosphates (Expt. 7).

[carboxy-^{14}C]-(±)-trans-2,2-*Dimethyl*-3(2-*methylpropenyl*-*cyclopropanecarboxylic Acid* (XLVII).—[1-^{14}C]Glycine (0·5 mCi, 41·4 mCi $mmol^{-1}$), glycine (540 mg), hydrogen chloride (1 g), and ethanol (15 ml) were heated under reflux together for 3 h. On cooling, ethyl glycinate hydrochloride precipitated out; this was collected, and dried under vacuum (936 mg). The hydrochloride was shaken with sodium acetate (16 mg), sodium nitrite (800 mg), water (2 ml), and 2,5-dimethylhexa-2,4-diene, keeping the mixture at 15°. Sulphuric acid (10%; 0·1 ml) was added and after reaching equilibrium, the aqueous phase was separated and repeatedly washed with portions (1·5 ml) of 2,5-dimethylhexa-2,4-diene adding 10% sulphuric acid (0·1 ml) with each washing, until the organic phase was no longer coloured. The hexadiene extracts were passed through a column of anhydrous sodium sulphate, and added dropwise during 30 min to 2,5-dimethylhexa-2,4-diene (1 ml) and copper powder (0·5 mg) under reflux. The product was chromatographed on Florisil (1 × 30 in column) and eluted with light petroleum (b.p. 40—60°) until all the hexadiene was removed (t.l.c.). The ethyl ester of the acid (XLVII) was then eluted with ether–light petroleum (b.p. 40—60°) (1 : 4), recovered from solution by evaporation, and was heated under reflux for 2 h in 80% aqueous ethanol (3 ml) containing sodium hydroxide. The mixture was evaporated, acidified, and extracted with ether. The ether extracts were dried and evaporated to yield a solid mixture of (±)-*cis*- and (±)-*trans*-acid (XLVII). This mixture was chromatographed on a column prepared from Celite (50 g) treated with aqueous 10% ammonia saturated with isopropyl acetate (25 ml). Elution with isopropyl acetate (equilibrated with aqueous 10% ammonia) afforded the (±)-*cis*-acid. Elution with ethyl acetate gave the (±)-*trans*-isomer (505 mg after distillation; radiochemical yield 36%).

(±)-trans-2,2-*Dimethyl*-3-(2-*methylpropenyl*)*cyclopropyl*-[^{14}C$_1$]*methanol* (XLVIII).—Lithium aluminium hydride (100 mg) was added in small portions to the foregoing [^{14}C]-acid (280 mg) in dry ether (3 ml), and the mixture was heated under reflux for 2 h. The product was treated with water and dil. hydrochloric acid, and continuously extracted with ether. The dried extract was evaporated. Distillation of the residue gave the cyclopropyl[^{14}C]methanol (212 mg; radiochemical yield 88%).

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Phosphorylation [30] *of* (±)-trans-2,2-*Dimethyl*-3(2-*methylpropenyl*)*cyclopropyl*[^{14}C]*methanol*.—To the cyclopropylmethanol (300 mg) and trichloroacetonitrile (1·3 g) was added bistriethylamine phosphate (1·04 g) in acetonitrile (30 ml) with stirring during 4 h. After a further 2 h at ambient temperature, ether (150 ml) was added, and the mixture was extracted with 0·1N-ammonia (3 × 50 ml) yielding a solution of (±)-*trans*-2,2-dimethyl-3-(2-methylpropenyl)cyclopropylmethyl phosphate and pyrophosphate (IL). Evaporation under reduced pressure gave a residue from which, after drying by azeotropic distillation with benzene, the starting alcohol was regenerated by treatment with lithium aluminium hydride in ether under reflux. In a radiochemical experiment with the alcohol (300 mg; 0·108 mCi), the ammoniacal extracts were concentrated *in vacuo* and diluted to 10 ml with water. This solution (IL) (0·054 mCi; radiochemical yield 50%) was used directly for feeding.

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