The Chemistry of Terpenes. Part XVII.[1] Synthesis of (+)-*cis*-Homocaronic Acid (*cis*-3-Carboxymethyl-2,2-dimethylcyclopropanecarboxylic Acid) and Some Related Compounds †‡

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Ozonolysis, in methanol, of (+)-4α-acetoxymethylcar-2-ene (7), decomposition of the ozonide with alkaline hydrogen peroxide, and esterification of the acidic products with diazomethane gave principally dimethyl (+)-*cis*-homocaronate (methyl-*cis*-3-methoxycarbonylmethyl-2,2-dimethylcyclopropanecarboxylate) (4; R = Me) and (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(3-oxobutyl)cyclopropane (9). Also formed were (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-[(1-acetylcyclopropyl)methyl]cyclopropane (10), (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-methoxymethyl-3-oxobutyl)cyclopropane (11) as a pair of epimers, and (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-methylene-3-oxobutyl)cyclopropane (12). (+)-*cis*-1-Methoxycarbonyl-2,2-dimethyl-3-[(2-acetyloxiran-2-yl)methyl]cyclopropane (18) is a precursor of (+)-*cis*-homocaronic ester. Ozonolysis, in methanol, of (+)-4α-acetylcar-2-ene (8) and treatment of the product as described for (7) also yielded (+)-*cis*-homocaronic ester, but the principal product was (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-methoxycarbonylpropyl)cyclopropane (27). Ozonolysis of the ketone (8) in acetic acid or in pyridine gave (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2,2-diacetylethyl)cyclopropane (28), which was oxidised with alkaline hydrogen peroxide to (+)-*cis*-homocaronic acid.

THE insecticidal activity of the esters of (+)-*trans*-chrysanthemic acid, whose absolute configuration is (1),[2] is greater than that of the esters of the (+)-*cis*-form, and both groups are considerably more active than the esters of the enantiomorphic acids.[3] Several

† Preliminary report, W. Cocker, H. St. J. Lauder, and P. V. R. Shannon, *J.C.S. Chem. Comm.*, 1972, 684.

‡ For convenience, throughout this paper non-fused cyclopropane rings have been numbered in conformity with the numbering of (+)-*trans*-chrysanthemic acid (I).

[1] Part XVI, W. Cocker, K. J. Crowley, and K. Srinivasan, *J.C.S. Perkin I*, 1973, 2485.

[2] L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1954, 470.

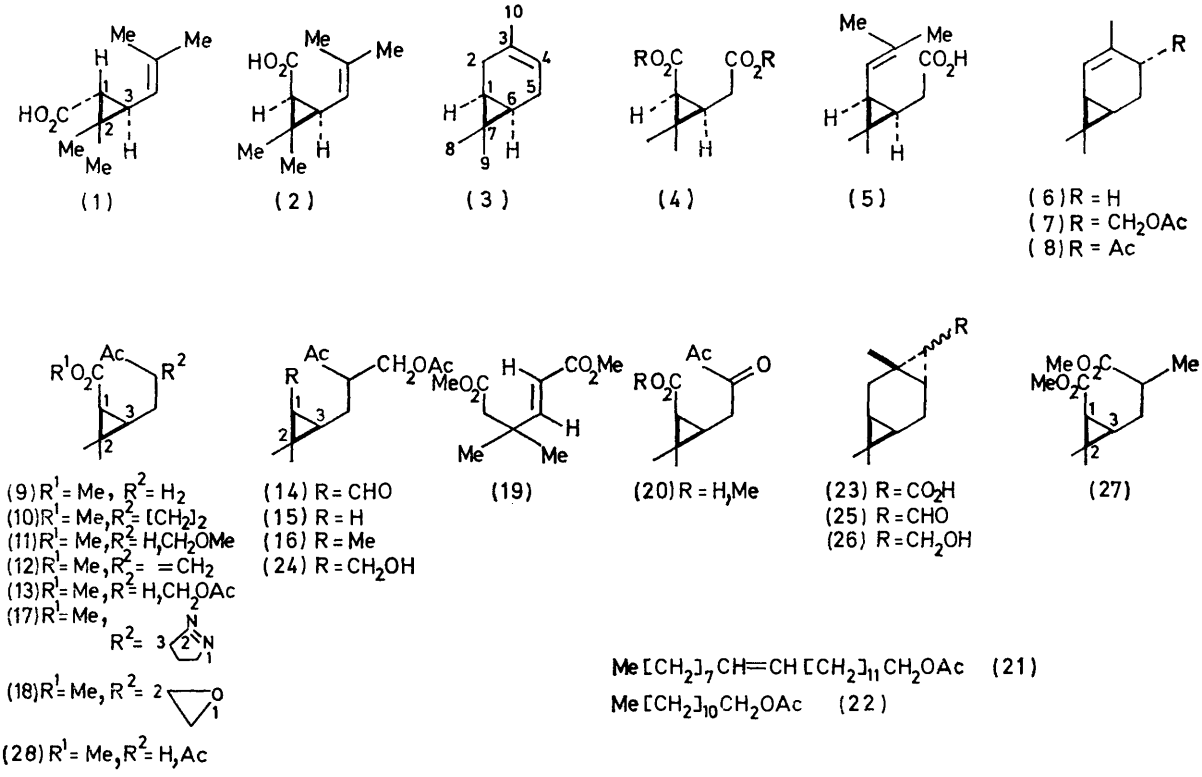
[3] M. Elliott, *Chem. and Ind.*, 1969, 776.

syntheses of chrysanthemic acid have been described. Japanese workers [4] have described a synthesis from (+)-car-3-ene (3) of (+)-*cis*-homocaronic acid (*cis*-3-carboxymethyl-2,2-dimethylcyclopropanecarboxylic acid), of absolute configuration (4; R = H),[5] and its conversion first into (−)-*cis*-chrysanthemic acid (2), and then by inversion of configuration at C(1), into (+)-*trans*-chrysanthemic acid (1). However, in the paper quoted,[4] the authors write the absolute configuration of (+)-car-3-ene (3) as that of its enantiomer. (+)-*trans*-Chrysanthemic acid has also been synthesised [6] from 2-methylbut-3-yn-2-ol, and a method of synthesis of a *cis*-homochrysanthemic acid (5) has been described.[7] The optical properties of starting material and final product were not described verbatim but the formulae used were as in (3) and (5).

(+)-Car-2-ene, whose absolute configuration is (6) [8] would be a convenient starting point for the synthesis of (+)-*cis*-homocaronic acid (4; R = H) [5] and hence of (+)-*trans*-chrysanthemic acid (1). However, (+)-car-2-ene (6) is relatively inaccessible, since it is present in only 5—7% in naturally occurring oils, its isomer (+)-car-3-ene (3) being predominant. While these hydrocarbons can be equilibrated [8,9] giving a mixture containing 40% of (+)-car-2-ene, their separation is tedius.

In our approach to the synthesis of (+)-*cis*-homocaronic acid (4; R = H) we turned our attention to derivatives of (+)-car-2-ene which can be prepared from (+)-car-3-ene in fair yield. Several such compounds are known, for example (+)-4α-acetoxymethylcar-2-ene (7) [10,11] and (+)-4α-acetylcar-2-ene (8) [12] and its allied acyl derivatives. The 4-substituents were regarded for our purposes as disposable groups.

(+)-4α-Acetoxymethylcar-2-ene (7) was ozonised in methanol at −50°, the ozonide was decomposed with alkaline hydrogen peroxide, and the acidic products were esterfied with diazomethane. In the event, the use of diazomethane led to unexpected products whose formation gave a clue to the reactions involved in the formation of the main product, (+)-*cis*-homocaronic ester (4; R = Me). The mixture of esters, chromatographed on silica, afforded the following volatile products in the order of elution and in the yields (g.l.c.) stated: dimethyl (+)-*cis*-homocaronate (4; R = Me; 35%),



[4] M. Matsui, H. Yoshioka, H. Sakamoto, Y. Yamada, and T. Kitahara, *Agric. and Biol. Chem.* (*Japan*), 1967, **31**, 33; 1965, **29**, 784.

[5] L. Crombie, J. Crossley, and D. A. Mitchard, *J. Chem. Soc.*, 1963, 4957.

[6] R. W. Mills, R. D. Murray, and R. A. Raphael, *Chem. Comm.*, 1971, 555.

[7] T. Sasaki, S. Eguchi, M. Ohno, and T. Oyobe, *Bull. Chem. Soc. Japan*, 1969, **42**, 3582.

[8] W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc.* (*C*), 1966, 41.

[9] G. Ohloff, K. H. Schulte-Elte, and W. Giersch, *Helv. Chim. Acta*, 1965, **48**, 1665.

[10] G. Ohloff, H. Farnow, and W. Philipp, *Annalen*, 1958, **613**, 43.

[11] P. J. Kropp, D. C. Heckert, and T. J. Flautt, *Tetrahedron*, 1968, **24**, 1385.

[12] P. Richter and M. Mühlstädt, *Chem. Ber.*, 1967, **100**, 1892.

(+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(3-oxobutyl)-cyclopropane (9; 26%), (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-[(1-acetylcyclopropyl)methyl]cyclopropane (10; 5·5%), and (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-methoxymethyl-3-oxobutyl)cyclopropane (11; 33%). The last was revealed by g.l.c. as a pair of epimers. Further examination of the mixture of esters by g.l.c.–m.s. additionally revealed the presence of (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-methylene-3-oxobutyl)cyclopropane (12), a key compound in the formation of (+)-*cis*-homocaronic ester (4; R = Me).

Dimethyl (+)-*cis*-homocaronate (4; R = Me) showed ester peaks at 1742 and 1731 cm^{-1} in the i.r., and its cyclopropane protons (1- and 3-H) as a multiplet centred on τ 8·53 in its 100 MHz n.m.r. spectrum. In the presence of tris(dipivaloylmethanato)europium-(III), the signal was resolved revealing a doublet (J 8·5 Hz) for 1-H, as expected of a *cis*-disubstituted cyclopropane.[13] By electron impact mass spectroscopy, the ester gave a weak molecular ion at *m/e* 200 and other ions at 185 (M^+ — Me), 168 (M^+ — MeOH), 140 (M^+ — CO_2Me — H), and 127 (M^+ — CH_2CO_2Me) (base peak). The loss of the butanone side chain is a feature of many of the compounds here described when subjected to electron impact.

Compound (9) had a single carbonyl peak at 1720 cm^{-1} in the i.r. Its n.m.r. spectrum (see Experimental section) was consistent with its structure. Its electron impact mass spectrum showed a very weak molecular ion at *m/e* 198 and other ions at 183 (M^+ — Me) and 140 (M^+ — Me — Ac). The keto-ester (9) and the diester (4; R = Me) showed their molecular ions as base peaks under field ionisation conditions.[14] The keto-ester (9) was identical with a specimen prepared by ozonolysis of (+)-car-2-ene (6).

Compound (10) exhibited ester absorption at 1724 and its cyclopropyl conjugated ketone peak at 1688 cm^{-1} in the i.r. Its 100 MHz n.m.r. spectrum showed one half of a complex A_2B_2 signal at τ 9·28 which can be ascribed to a pair of nearly symmetrical protons of the side chain cyclopropane system. A three-proton multiplet centred on τ 8·92 can be credited to the remaining pair of protons of this cyclopropane system, with overlap of the 3-H signal of the other cyclopropane system. The final cyclopropane proton, 1-H, appeared as a doublet at τ 8·65 (J 8·5 Hz). The mass spectrum of (10) showed the molecular ion at *m/e* 224 and other ions at 209 (M^+ — Me) and 127 (M^+ — $CH_2C[CH_2]_2Ac$). The identity of (10) was confirmed by synthesis as detailed below.

The mixture of epimeric ethers (11) showed carbonyl absorption at 1727 and 1721 cm^{-1} in the i.r. Its 100 MHz n.m.r. spectrum showed split *gem*-dimethyl signals at τ 8·84, a clearly visible but split doublet (J 9 Hz) for 1-H at 8·63, multiplets at 8·24 [$CH_2CH(CH_2OMe)Ac$], 7·40 [$CH(Ac)CH_2OMe$], 6·64 (CH_2OMe), and three 3-proton singlets at 7·92 (Ac), 6·82 (CH_2OMe), and 6·43 (CO_2Me). In the presence of tris-([$^2H_9$]-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)europium-(III), these singlets separated into pairs of equal intensity. A further separation of the 1-H doublet occurred and the *gem*-dimethyl signals separated into four singlets of equal intensity. This effect is consistent with the g.l.c. evidence of a 1 : 1 mixture of epimers about C(2) of the butanone side chain. The g.l.c.–m.s. analysis using the field ionisation technique showed for each epimer a molecular ion as base peak at *m/e* 242; under electron impact ionisation conditions very low intensity ions were seen at *m/e* 211 (M^+ — MeO), 210 (M^+ — MeOH), and 195 (M^+ — Me — MeOH). The relative intensities of the ions of the epimers however differed widely.

Ozonolysis of (+)-4α-acetoxymethylcar-2-ene (7) in acetic acid, followed by decomposition of the ozonide with zinc and esterification of the acid product with diazomethane gave (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-acetoxymethyl-3-oxobutyl)cyclopropane (13). Its keto-group gave a peak at 1721, and its esters at 1739, 1245 (acetate), and 1192 cm^{-1} in the i.r. Its n.m.r. and mass spectra (see Experimental section) were fully in accord with its structure.

The neutral fraction from this ozonolysis reaction contained several components which were partially separated on a silica column. The aldehyde (14) was rapidly oxidised and was not obtained pure, but it was recognised by its n.m.r. spectrum, its reducing properties, and its ready conversion into the ester (13). Two other components of the neutral fraction, isolated in small yields and purified by preparative g.l.c. were surprisingly (—)-*cis*-2,2-dimethyl-3-(2-acetoxymethyl-3-oxobutyl)-cyclopropane (15) and *cis*-1,2,2-trimethyl-3-(2-acetoxymethyl-3-oxobutyl)cyclopropane (16). Both ketones had peaks at 1740 and 1240 (acetoxy) and 1716 cm^{-1} (keto) in their i.r. spectra.

The 100 MHz n.m.r. spectrum of (15), the compound with the shorter retention time on g.l.c., showed a two-proton singlet at τ 9·57 which we assign to the methylene group (1-H_2) of the cyclopropane. The other cyclopropane proton (3-H) whose presence was inferred from the integral trace between τ 8·8 and 8·2, was hidden under the multiplet from the side chain methylene group. The *gem*-dimethyl group appeared as a singlet at τ 8·98 and the methyl groups of the acetoxy and acetyl groups as singlets at 8·02 and 7·87 respectively. The methine proton and acetoxymethyl methylene group appeared as a quintet and doublet at τ 7·21 and 5·87 respectively. The field ionisation spectrum of (15) showed the molecular ion as base peak at *m/e* 212 and another ion at *m/e* 83 resulting from the loss of $AcCHCH_2OAc$ from the side chain Its electron impact spectrum showed peaks at *m/e* 152 (M^+ — AcOH), 109 (M^+ — AcOH — Ac), and 82 (Me_2C  $C=CH_2)^+$, the last resulting from a McLafferty-type β-cleavage. The structure of (15) is thus beyond doubt.

[13] H. M. Hutton and T. Schaefer, *Canad. J. Chem.*, 1962, **40**, 875.

[14] H. D. Beckley, 'Field Ionisation Mass Spectrometry,' Pergammon, Oxford, 1971.

The i.r. spectrum of (16) was similar to that of (15). Its 100 MHz n.m.r. spectrum showed the cyclopropane protons as a multiplet between τ 9·73 and 9·37, the *gem*-dimethyl group as singlets at 9·14 and 8·99, and the 1-methyl group as a partially obscured doublet (*J* 6 Hz) centred on τ 9·1. The other signals were similar to those of (15). Likewise the mass spectra of (16) were parallel to those of (15), but with ions of 14 mass units greater.

Reaction of compound (13) with trifluoroacetic acid in carbon tetrachloride gave compound (12) in high yield. This αβ-unsaturated ketone had characteristic maxima at 224 and 310 nm (log ε 3·67 and 1·83) in the u.v., and at 1728 (ester), 1680 (C=C–C=O), 1623, and 900 cm^{-1} ($R_2C=CH_2$) in the i.r. Its 60 MHz n.m.r. spectrum revealed the olefinic protons as two singlets at τ 4·33 and 4·12 and the allylic methylene group in the side chain as a doublet (*J* 7 Hz) at τ 7·43, as well as the other expected signals. Its electron impact spectrum showed no molecular ion, but an ion at *m/e* 195 (M^+ — Me) and a major ion at 127 arising from the complete loss of the ketonic side chain. In fact, its mass spectrum was perfectly superimposable on the g.l.c.–m.s. spectrum of the unsaturated ketone present in the mixture of ozonolysis products described earlier.

The unsaturated ketone (12) was also formed (g.l.c.) along with the methyl ethers (11) and other products when the acetoxy-ketone (13) was treated with sodium hydroxide in methanol.

Reaction of the unsaturated ketone (12) with sodium methoxide in methanol gave compound (11) as an equimolar (g.l.c.) mixture of epimers.

Treatment of the unsaturated ketone (12) with diazomethane gave (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-[(3-acetylpyrazolin-3-yl)methyl]cyclopropane (17), presumably as a mixture of epimers. G.l.c. of this was however unsatisfactory owing to its thermal decomposition on the injection block. In the u.v., it showed maxima at 273, 282, and 326·5 nm (log ε 2·08, 2·06, and 2·19) (*cf.* ref. 15), and at 1728 and 1720 (ester and ketone) and 1542 cm^{-1} (N=N) in the i.r. Its 60 MHz n.m.r. spectrum had a triplet (*J* 8 Hz) at τ 5·47 required of the CH_2–N=N group. The signals of the other methylene group of the pyrazoline and the side chain methylene group were merged between τ 7·7 and 8·7. The presence of the triplet at τ 5·47 established the structure (17) since a symmetrical pyrazoline would require a four-proton doublet in this region. The mass spectrum of the pyrazoline was identical with that of the cyclopropane (10) into which it is readily converted photochemically in benzene with acetophenone as sensitiser.

Finally, reaction of the unsaturated ketone (12) with alkaline hydrogen peroxide followed by re-esterification of the acidic product, gave (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-[(2-acetyloxiran-2-yl)methyl]cyclopropane (18) as an equimolar mixture (g.l.c.) of epimers. It showed a maximum at 287·5 nm (log ε 1·47) in the u.v., and maxima in the i.r. at 1720 (ester), 1712 (ketone), and 855 cm^{-1} (epoxide). Its 100 MHz n.m.r. spectrum showed the epoxide methylene protons as a closely spaced multiplet centred on τ 7·18 and the side chain methylene protons as a complex multiplet at τ 7·6—8·1. Careful examination showed that the methoxycarbonyl signal was split into two singlets of equal intensity. On the addition of tris-([$^2H_9$]-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)europium(III), this splitting was intensified and the signals of the acetyl group and the *gem*-dimethyl group appeared as pairs of singlets of equal intensity. As with the epimeric ethers (11), this behaviour is to be expected from differential complexing with each member of the epimeric pair. The mass spectrum under field ionising conditions demonstrated that the molecular ion was at *m/e* 226.

Hydrolysis of the epoxide (18) with alkali of several strengths gave a complex mixture of products. However, its reaction with alkaline hydrogen peroxide followed by esterification of the acidic product with diazomethane gave three compounds (g.l.c.). The principal product was dimethyl (+)-*cis*-homocaronate (4; R = Me) in 51% yield (g.l.c.). A second product was dimethyl *trans*-4,4-dimethylhex-2-enedioate (19) formed in 30% yield (g.l.c.). The third product was not identified. The i.r. spectrum of the αβ-unsaturated ester (19) showed ester absorption, as a broad peak, between 1740 and 1720 and peaks at 1650 and 1020 cm^{-1} (*trans*-CH=$CHCO_2$Me).[16] Its 60 MHz n.m.r. spectrum had a six-proton singlet at τ 8·8 (Me_2C), a singlet at 7·7 (CH_2CO_2Me), three-proton singlets at 6·41 and 6·35 (CO_2Me), and one-proton doublets (*J* 16 Hz) centred at 4·38 and 3·15 (olefinic protons). The coupling constant of the olefinic protons clearly demonstrates their *trans*-arrangement. G.l.c.–m.s. using the electron impact technique, showed weak ions at *m/e* 200 (M^+) and 185 (M^+ — Me) and stronger ions at *m/e* 169 (M^+ — MeO) and 127 ($M^+ - CH_2CO_2Me$) (base peak). These data clearly identify the ester as (19).

We can now consider the mechanisms of the reactions described above. An initial product of the ozonolysis of (+)-4α-acetoxymethylcar-2-ene (7) is probably the keto-acid (13; R^1 = H), or possibly after treatment with alkali, the anion of the keto-acid (13; R^1 = H; R^2 = H,CH_2OH). Each of these can undergo further reaction with base (OH^- or OMe^-), the former giving the anion of the unsaturated keto-acid (12; R^1 = H) and the latter this anion and/or the anion of the keto-acid (9; R^1 = H) (Scheme 1). The methyl esters (9) and (12) were present in the esterified product.

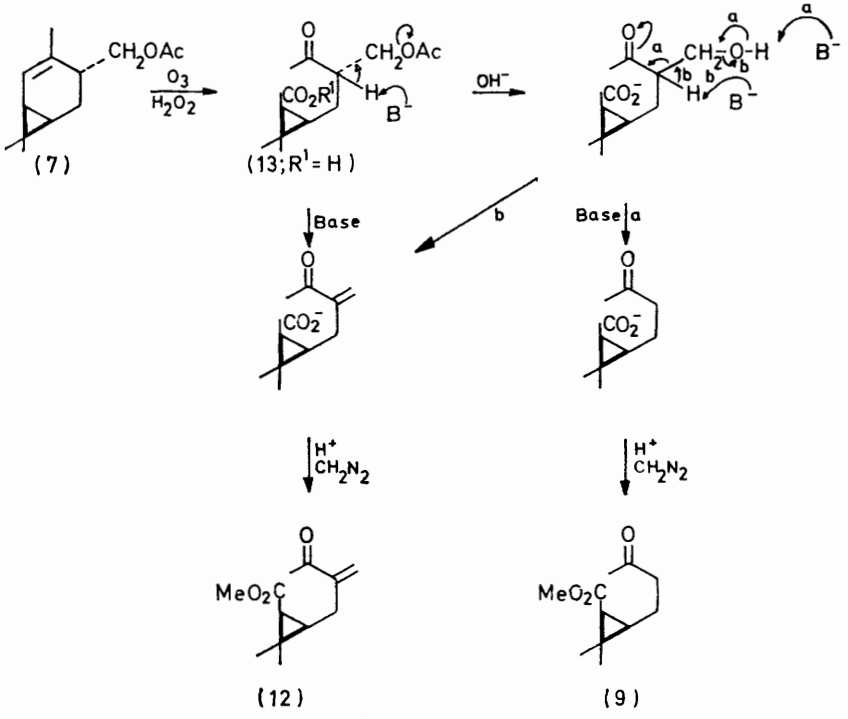
The unsaturated keto-acid (12; R^1 = H) is a key intermediate in the formation of (+)-*cis*-homocaronic acid (4; R = H), since we have demonstrated that its methyl ester (12) can undergo epoxidation with alkaline hydrogen peroxide. We did not isolate the derived epoxide (18) from the mixture of oxidation products,

[15] P. H. Boyle, W. Cocker, R. L. Gordon, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1971, 2127.

[16] J. L. Bellamy, ' The Infrared Spectra of Complex Molecules,' Methuen, London, 2nd edn., 1966, p. 45.

but this is not surprising in view of its ready oxidation to (+)-*cis*-homocaronic acid (**4**; R = H). The question thus arises as to how the epoxide (**18**) is converted into (**4**; R = H). We suggest that the presence of the unsaturated ester (**19**) in the esterified products of the oxidation of the epoxide (**18**) furnishes a clue to the reaction pathway. The formation of (**19**) involves the opening of the cyclopropane system as in the conversion of car-3-en-2-one into eucarvone. (+)-*cis*-Homocaronic ester (**4**; R = Me) does not suffer ring fission under the aqueous alkaline conditions used in the oxidation of the group is lost, frequently as carbon monoxide. In many cases, the carbon deficient group is an alcohol or a ketone. There are however a few cases, as in the formation of (**15**), where cleavage takes place to give an alkyl residue. Thus, for example brassidyl and erucyl acetates (**21**) yield [18] lauryl acetate (**22**) when ozonised.

It is possible that (**15**) may be formed by the decarboxylation of the keto-acid (**13**; R^1 = H). We have not isolated this acid, but we find that the analogous cyclopropane carboxylic acid (**23**) [19] is not decarboxylated when stirred with zinc and acetic acid.



SCHEME 1

epoxide (**18**). This suggests that the diketone (**20**), which would probably afford the anion necessary for cyclopropane isomerisation, is an oxidation product of the epoxide. The diketone (**20**) would undoubtedly afford (+)-*cis*-homocaronic acid (**4**; R = H) on oxidation with hydrogen peroxide.

These mechanistic pathways are shown in Scheme 2.

The bicyclopropane (**10**), found among the esterified oxidation products of (**7**) is obviously an artefact resulting from the use of diazomethane as esterifying agent; it must be formed from the pyrazoline (**17**) derived from the unsaturated ketone (**12**).

The formation of the compounds (**15**) and (**16**) when (+)-4α-acetoxycar-2-ene (**7**) was ozonised in acetic acid was unexpected. They may have been formed on the reduction of the ozonide with zinc or on further reduction of the intermediate aldehyde with this reagent. Many examples of abnormal ozonolysis reactions are known [17] in which the carbon atom of the potential aldehyde

[17] P. S. Bailey, *Chem. Rev.*, 1958, **58**, 925; J. E. Leffler, *ibid.*, 1949, **45**, 399, where many references are given.

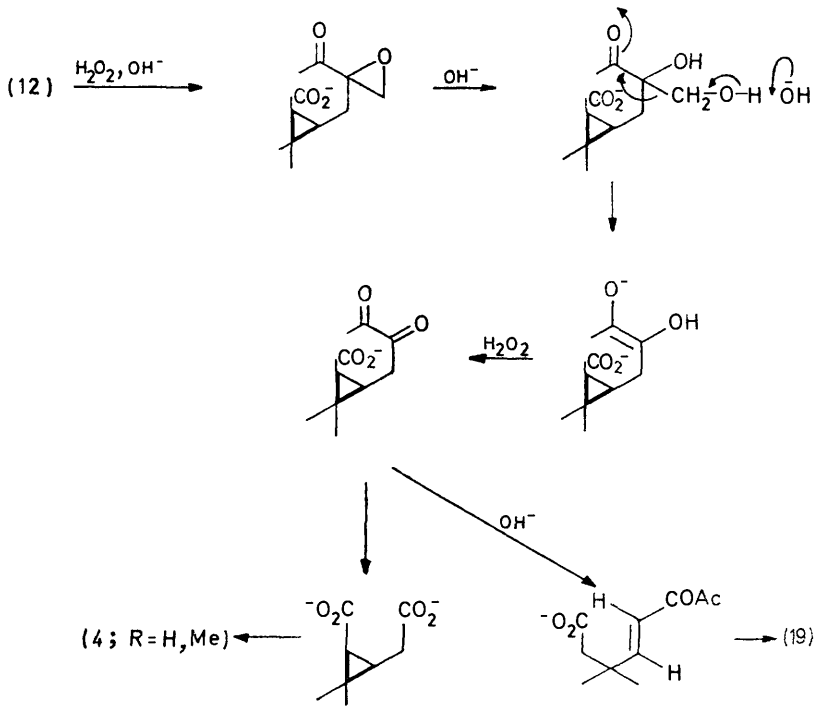
We have found no analogy for the formation of (**16**) in an ozonolysis reaction. It could be formed by a Clemmensen type reduction of the intermediate aldehyde (**14**). Since this is rapidly oxidised we have been unable to test the hypothesis. However, the analogous aldehyde (**25**) [19] is reduced to the methyl compound (**25**, R = Me). The quasi-allylic cyclopropylmethanol (**24**), or its acetate could be an intermediate in the formation of (**16**), but attempted hydrogenolysis of the analogous alcohol (**26**) or its acetate with zinc and acetic acid was unsuccessful. The aldehyde (**25**) is not reduced to (**26**) under these conditions.

Ozonolysis of (+)-4α-acetylcar-2-ene (**8**) in methanol at −50° followed by reaction with alkaline hydrogen peroxide and esterification of the acidic product with diazomethane gave dimethyl (+)-*cis*-homocaronate (**4**; R = Me). The other product was surprisingly, (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2-methoxycarbonyl-

[18] M. Stoll and A. Rouvé, *Helv. Chim. Acta*, 1944, **27**, 950.

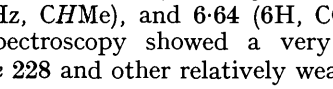
[19] D. A. Baines, W. Cocker, and P. H. Ladwa, unpublished work.

propyl)cyclopropane (27), which had a longer retention time on g.l.c. than (+)-*cis*-homocaronic ester, but was less polar on silica. Its i.r. spectrum showed two ester peaks at 1740 and 1730 cm^{-1}. Its 60 MHz n.m.r. spectrum in CCl_4 had a partially obscured doublet (*J* 8 Hz, *Me*CH) at τ 8·88, singlets at 8·85 and 8·82 (Me_2C), a doublet (*J* 8·5 Hz, 1-H) at 8·63, a triplet (*J* 6 Hz, $CH_2CH[CH_2]_2$) at 8·17, a one-proton multiplet (*J* 6 Hz, *H*CMe) at 7·68, and two singlets at 6·44 and 6·42 (6H, CO_2Me). In [$^2H_6$]benzene the *C*-methyl region was clarified, the *gem*-dimethyl signals appearing *ca.* 10-fold increase in intensity with a drop of 2M-alkali. Its i.r. spectrum had peaks at 1720 (CO_2Me) and 1705 (ketone) and a weak enol maximum at 1590 cm^{-1}. Its 60 MHz n.m.r. spectrum (in CCl_4) had signals at τ 8·87 and 8·82 (Me_2C), 8·8 (obscured multiplet, 3-H), 8·61 (1H, d, *J* 8·5 Hz, 1-H), 7·90 (6H, s, Ac), and 6·45 (CO_2Me). These signals are consistent with compound (28) existing largely as the β-diketo-form in carbon tetrachloride although smaller signals, *e.g.* τ 7·95, indicated the possibility of a minor amount of the enolised form. There was however no recognisable signal of the enolic



SCHEME 2

at τ 9·13 and 8·80 and the CH*Me* appearing as a doublet (*J* 8 Hz) centred at 8·94. Other signals appeared at τ 8·6 (2H, d, *J* 8·5 Hz, 1-H), 7·98 (2H, m, *J* 5 Hz, CH_2), 7·56 (1H, m, *J* 6 Hz, C*H*Me), and 6·64 (6H, CO_2Me). Electron impact spectroscopy showed a very weak molecular ion at *m/e* 228 and other relatively weak ions at 213 (M^+ — Me), 197 (M^+ — MeO), and 196 (M^+ — MeOH). An intense ion at *m/e* 127 arose from the loss of the butyric ester side chain. In early work we concluded wrongly that this ester was the keto- ester (9); they have similar retention times on g.l.c.

Ozonolysis of (+)-4α-acetylcar-2-ene (8) in acetic acid followed by reduction of the product with zinc, and esterification of the acidic fraction with diazomethane gave a complex mixture of products. It was separated into its components on silica. Only one component was identified. This was (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(2,2-diacetylethyl)cyclopropane (28). It gave a violet iron(III) colour. In the u.v. it showed maximum absorption at 288 nm (log ε 2·9) shifted to 307 nm with proton. Its electron impact mass spectrum showed the molecular ion at *m/e* 240 and other signals at 209 (M^+ — MeO), 197 (M^+ — Ac), 180 (M^+ — AcOH), and 127  These data confirm the structure of (28).

The diketone (28) was also the product of ozonolysis of (8) in chloroform containing pyridine.

Hydrolysis of the diketone with sodium hydroxide and re-esterification gave compound (9) as principal product.

Oxidation of the diketone (28) with alkaline hydrogen peroxide gave dimethyl (+)-*cis*-homocaronate (4; R = Me) as the only volatile product.

It is clear from the above data that the formation of the (+)-*cis*-homocaronic ester (4; R = Me) and the keto-ester (9) from (+)-4α-acetylcar-2-ene takes place *via* the diketone (28).

Little is known about the oxidation of 3-substituted

pentane-2,4-diones with alkaline hydrogen peroxide, and we are currently investigating this. Temple [20] in a paper dealing with the oxidation of α-diketones with hydrogen peroxide, suggests that an enol epoxide intervenes, and that β-diketones might be similarly oxidised. Russian workers [21] have shown that dihydroresorcinol affords glutaric acid, and 2-formylcyclohexanone yields cyclopentanecarboxylic acid with this reagent.

We prepared 3-methyl-, 3-ethyl-, 3-allyl-, and 3-benzyl-pentane-2,4-dione for the dual purpose of studying their n.m.r. spectra and reaction with alkaline hydrogen peroxide. We can say at this stage that a major product, if not the principal product of the oxidations was, respectively, acetic acid, propionic acid, but-3-enoic acid, and phenylacetic acid. The formation of these oxidation products is strictly analogous to the production of *cis*-homocaronic acid from the diketone (28). It should be added that acetic acid was a product of all the oxidations.

3-Allyl- and 3-benzyl-pentane-2,4-dione can be considered to be electronically analogous to (28) which possesses a quasi-allyl system. These substituted acetylacetones and also the corresponding 3-methyl- and 3-ethyl-derivatives show by n.m.r., varying amounts of enolic proton in carbon tetrachloride and in [$^2H_6$]-benzene. It is not clear why (28) is apparently so weakly enolised in the solvents mentioned.

The formation of the ester (27) by the ozonolysis, in methanol, of (+)-4α-acetylcar-2-ene (8) is being further investigated. However an analogy is the conversion [22] of 2-acetylcyclohexanone into 2-methylheptanedioic acid, albeit in minor yield, with hydrogen peroxide.

EXPERIMENTAL

U.v. spectra were measured in ethanol, i.r. spectra as liquid films, and n.m.r. spectra either at 60 or 100 MHz in carbon tetrachloride, unless otherwise stated. $[\alpha]_D$ Was measured in chloroform. Analytical g.l.c. was carried out on a 2 m × 3 mm, 20% Carbowax 20 M on Chromosorb W column at 150° and on a 2 m × 3 mm, 3% O.V.1 on Chromosorb W column at 120°. Detailed mass and i.r. spectral data are given in Supplementary Publication No. 20855 (17 pp., 1 microfiche).* Field ionisation mass spectra were obtained using a field-ion source supplied by Varian Associates on a Varian CH5 spectrometer. The abundance of the ions is given to the nearest percent.

(+)-4α-*Acetoxymethylcar-2-ene* (7).—Paraformaldehyde (120 g) was treated with (+)-car-3-ene (3) (544 g; $[\alpha]_D^{20}$ +12·4°) in glacial acetic acid (544 g) as previously described.[10,11] The steam-volatile oil was distilled under reduced pressure to remove (+)-car-3-ene (230 g), and the residue, consisting (g.l.c.) mainly of the required ester (7) and the corresponding alcohol was set aside overnight with acetic anhydride (80 ml) and pyridine (170 ml). The mixture was added to water (500 ml), extracted with ether, and the extract was washed with water, hydrochloric acid (10%), and water. The product (295 g) consisting (g.l.c.) of (+)-car-3-ene (2·3%), the required ester (7) (73%), and a number of substances [23] in minor proportions (24·7%) was fractionated through a spinning band column. (+)-4α-Acetoxymethylcar-2-ene (7) (94 g), which distilled (96% purity by g.l.c.) at 70—75° and 0·2 mmHg had $[\alpha]_D^{20}$ +133·6° (*c* 1·0), n_D^{20} 1·4756 (*cf.* ref. 10), τ (60 MHz) 9·13 and 8·93 (6H, 2s, Me_2C), 8·27 (3H, s, MeC=C), 8·0 (3H, s, Ac), 6·02 (2H, d, *J* 8 Hz, CH_2OAc), and 4·48 (1H, s, HC=C).

Ozonolysis of (+)-4α-*Acetoxymethylcar-2-ene* (7).—Ozonised oxygen was passed into a solution of the ester (10·1 g) in methanol (60 ml), kept at −50°, until the solution had a pale blue colour. Hydrogen peroxide (40 ml; 32%) was then carefully added, the mixture was refluxed for 2 h, cooled to 0°, stirred, and treated with sodium hydroxide (40 ml; 33%) which was added dropwise. The solution was stirred at 20° overnight, carefully acidified with dilute sulphuric acid (5%), extracted with ether, and the extract was separated into neutral (2·5 g) and acid fractions (7·3 g). The gummy neutral fraction was not further investigated. The acid fraction was treated in methanol with ethereal diazomethane, the solution was washed with 5% sodium hydrogen carbonate solution, then with water, dried, and distilled giving an oil (2·25 g), b.p. 68—75° at 0·15 mmHg. The product of three reactions (6·58 g) was chromatographed on silica and eluted with mixtures of light petroleum and increasing quantities of ether. The following esters were found in succeeding fractions. Dimethyl (+)-*cis*-homocaronate (4; R = Me) (1·49 g) was an oil, b.p. 68° at 0·4 mmHg, $[\alpha]_D^{20}$ +42·8° (*c* 1·0), n_D^{20} 1·4473 (*cf.* ref. 5), τ (60 MHz) 8·83 and 8·76 (6H, 2s, Mc_2C), 8·53 (2H, m, 1- and 3-H), 7·29 (2H, d, *J* 7 Hz, CH_2CO_2Me), 6·34 (3H, s, CH_2CO_2-*Me*), and 6·3 (3H, s, CO_2Me) (Found: C, 60·3; H, 8·0. Calc for $C_{10}H_{16}O_4$: C, 60·0; H, 8·05%). (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(3-*oxobutyl*)*cyclopropane* (9) was an oil (0·7 g), b.p. 80° at 0·4 mmHg, $[\alpha]_D^{20}$ +27·4° (*c* 2·0), n_D^{20} 1·4542, τ (60 MHz) 8·5—9·1 (2H, m, 1- and 3-H), 8·8 and 8·93 (6H, 2s, Me_2C), 8·04 (2H, m, CH_2CH_2Ac), 7·91 (3H, s, Ac), 7·7 (2H, d, *J* 6 Hz, CH_2Ac), and 6·37 (3H, s, CO_2Me) (Found: C, 66·5; H, 9·1. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·15%). (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-[(1-*acetylcyclopropyl*)*methyl*]*cyclopropane* (10) was an oil (0·2 g) (93% pure by g.l.c.). Its physical constants are given later. (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2-*methoxymethyl*-3-*oxobutyl*)*cyclopropane* (11) was an oil (1·11 g), b.p. 106° at 0·4 mmHg, $[\alpha]_D^{20}$ +22·4 (*c* 1·0), n_D^{20} 1·4582, which on g.l.c. showed the presence of two compounds in equal proportions. G.l.c.–m.s. confirmed the presence of two epimers (Found: C, 64·3; H, 9·3. $C_{13}H_{22}O_4$ requires C, 64·4; H, 9·15%).

(+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2-*acetoxymethyl*-3-*oxobutyl*)*cyclopropane* (13).—A solution of (+)-4α-acetoxymethylcar-2-ene (7) (10 g) in acetic acid (40 ml) and ethyl acetate (5 ml) was ozonised at 0°. The product was stirred with zinc powder (6 g) for 16 h, filtered, the solution was basified with solid sodium hydrogen carbonate, and extracted with ether. The extract yielded a neutral product (4·27 g), and from the aqueous solution an acidic product (5·48 g) was obtained by acidification and extrac-

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1972, Index Issue.

[20] R. D. Temple, *J. Org. Chem.*, 1970, **35**, 1275.

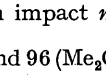
[21] L. P. Vinogradova and S. I. Zav'yalov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1961, 1482 (*Chem. Abs.*, 1962, **56**, 338b).

[22] L. P. Vinogradova, B. A. Rudenko, and S. I. Zav'yalov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1962, 1436 (*Chem. Abs.*, 1963, **58**, 2379b).

[23] J. Chlebicki and B. Burczyk, *Tetrahedron Letters*, 1970, 4775.

tion with ether. The acid fraction was esterified in methanol tion with ether. The acid fraction was esterified in methanol with ethereal diazomethane. The ester product was chromatographed on silica and eluted with light petroleum–ether (9 : 1). The *keto-diester* (13) was obtained as an oil (4·58 g), b.p. 128° at 0·4 mmHg, $[\alpha]_D^{20}$ +3·4° (*c* 0·4), n_D^{20} 1·4595, τ (100 MHz) 9·01 (1H, d, *J* 8 Hz, 3-H), 8·82 (6H, s with sh, Me_2C), 8·62 (1H, d, *J* 8 Hz, 1-H), 8·02 (3H, s, OAc), 7·87 (3H, s, Ac), 6·41 (3H, s, CO_2Me), and 5·95 (2H, t, *J* 2 Hz, CH_2OAc), electron impact *m/e* 211 (M^+ — AcO), 127 [M^+ — $AcCH(CH_2)CH_2OAc$] (Found: C, 62·4; H, 8·2. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%).

The neutral fraction consisted largely of an aldehyde (14), τ 0·24 (1H, d, *J* 5 Hz), which was rapidly oxidised in air to the acid (13; R^1 = H). Oxidation by stirring with an aqueous suspension of silver oxide followed by esterification of the acid product with diazomethane gave an oil consisting (g.l.c.) largely of the ester (13).* This was chromatographed on silica and eluted with light petroleum–ether (85 : 15) giving first a neutral oil (0·49 g) which on g.l.c. showed two components weighted 60 and 40%, corresponding respectively to (15) and (16) in this order of elution. Separation by preparative g.l.c. gave (—)-*cis*-2,2-*dimethyl*-3-(2-*acetoxymethyl*-3-*oxobutyl*)*cyclopropane* (15) as an oil, $[\alpha]_D^{22}$ —33·7° (*c* 1·5), *m/e* 212 (Found: C, 67·8; H, 9·4. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%).

cis-1,2,2-Trimethyl-3-(2-acetoxymethyl-3-oxobutyl)cyclopropane (16) was an oil, obtained in insufficient quantities to determine its rotation, electron impact *m/e* 166 (M^+ — AcOH), 123 (M^+ — AcOH — Ac), and 96 (Me_2C  $C=CH_2)^+$, field ionisation *m/e* 228, 227, 226 (M^+), and 97.

(+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2-*methylene*-3-*oxobutyl*)*cyclopropane* (12).—A solution of the acetoxy-compound (13) (4·58 g) in carbon tetrachloride (10 ml) containing trifluoroacetic acid (3 g) was kept for 18 h at 50—70°. The cooled solution was washed with 5% sodium hydrogen carbonate solution, then with water, dried, chromatographed on silica and eluted with light petroleum–ether (90 : 10). (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2-*methylene*-3-*oxobutyl*)*cyclopropane* (12) was eluted as an oil (2·24 g), b.p. 86—88° at 0·4 mmHg, $[\alpha]_D^{20}$ +5·8° (*c* 1·0), n_D^{20} 1·4696, τ (60 MHz) 8·83 and 8·80 (6H, 2s, Me_2C), 8·67 (1H, s, 1-H), 7·75 (3H, s, Ac), 7·43 (2H, d, *J* 7 Hz, CH_2C=), 6·45 (3H, s, CO_2Me), 4·33 and 4·12 (2H, 2s, H_2C=C) (Found: C, 68·0; H, 8·7. $C_{12}H_{18}O_3$ requires C, 68·5; H, 8·6%).

The unsaturated ketone (12) was also formed (37% by g.l.c.) when the acetate (13) (0·15 g) in methanol (0·5 ml) was stirred with sodium hydroxide solution (0·2 ml; 33%) for 3 h, and the acidic product treated with diazomethane. Other products were the methyl ethers (11) (58% by g.l.c.), and the cyclopropane (10) (2·3%).

Formation of the Epimers of (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2-*methoxymethyl*-3-*oxobutyl*)*cyclopropane* (11) *from the Unsaturated Ketone* (12).—The ketone (0·13 g) in methanol (12 ml) was set aside for 24 h with a solution (2 ml) of sodium (0·25 g) in methanol (25 ml). The solution was shaken with ether, the extract washed with water, dried, and concentrated. The residue was chromatographed on silica and eluted with light petroleum–ether (75 : 25). The product was an equimolar mixture of the epimeric ethers (11) identical with the product described above.

(+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-[(3-*acetyl*-*pyrazolin*-3-*yl*)*methyl*]*cyclopropane* (17).—A solution of the unsaturated ketone (12) (0·23 g) in ether (2 ml) was kept for 4 days with an excess of ethereal diazomethane. Ether was removed under reduced pressure, the residue was chromatographed on silica, and eluted with light petroleum–ether (60 : 40). The *pyrazoline* (17) was an oil (0·11 g), $[\alpha]_D^{20}$ +7·65° (*c* 1·01), n_D^{20} 1·4762, τ (60 MHz) 8·82 (6H, s, Me_2C), 8·7—7·7 (4H, m, CH_2CH_2·N=N and CH_2— ), 8·5 (1H, d, *J* 8·7 Hz, 1-H), 6·3 (3H, s, CO_2Me), and 5·47 (2H, t, *J* 8 Hz, CH_2N=N) (Found: C, 62·1; H, 7·85. $C_{13}H_{20}N_2O_3$ requires C, 61·9; H, 8·0%). Its mass spectrum was identical with that of the cyclopropane (10).

(+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-[(1-*acetylcyclo*-*propyl*)*methyl*]*cyclopropane* (10).—A solution of the pyrazoline (17) (0·11 g) in benzene (220 ml) containing acetophenone (90 mg) was irradiated for 1·5 h through Pyrex with light from a Hanovia medium pressure 200 W lamp. The mixture was chromatographed on silica and eluted with light petroleum–ether (8 : 2) giving the *cyclopropane* (10) (51 mg), b.p. 101° at 0·5 mmHg, $[\alpha]_D^{20}$ +0·02° (*c* 1·02), $[\alpha]_{578}^{22}$ +0·85°, $[\alpha]_{546}^{22}$ 1·6°, $[\alpha]_{436}^{22}$ +8·2°, $[\alpha]_{365}^{22}$ +25·2° (*c* 1·18), n_D^{20} 1·4756, τ (100 MHz) 8·82 (6H, s, Me_2C), 8·08 (3H, s, Ac), and 6·41 (3H, s, CO_2Me) (Found: C, 69·3; H, 9·2. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%). It was identical with the product obtained from the oxidation of (7).

(+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-[(2-*acetyloxir*-*an*-2-*yl*)*methyl*]*cyclopropane* (18).—A solution of the unsaturated ketone (12) (0·21 g) in methanol (1·5 ml) containing hydrogen peroxide (0·6 ml; 30%) was cooled to 0°, stirred, and sodium hydroxide solution (0·4 ml; 15%) was added slowly. Stirring was continued for 0·5 h, the product was extracted with ether, the dried solvent evaporated, the residue was chromatographed on silica, and eluted with light petroleum–ether (80 : 20). The *epoxide* (18) (0·15 g) was obtained as a 1 : 1 mixture (g.l.c.) of epimers, b.p. 105° at 0·6 mmHg, $[\alpha]_D^{20}$ +11·7° (*c* 1·3), n_D^{20} 1·4663, τ (100 MHz) 8·86 and 8·84 (6H, 2s, Me_2C), 8·07 (3H, s, Ac), 8·1—7·6 {2H, m, $CH_2C[O(CH_2)_2]CO$}, 7·18 (2H, m, CH_2O), and 6·43 and 6·41 (3H, 2s, CO_2Me) (Found: C, 63·5; H, 7·9. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

Oxidation of the Epoxide (18).—A mixture of the epoxide (1 g), hydrogen peroxide (4 ml; 30%), sodium hydroxide (4 ml; 33%), and methanol (5 ml) was stirred and refluxed for 3 h. After cooling, the mixture was carefully acidified with 10% sulphuric acid, extracted with ether, the extract dried, and treated with an excess of ethereal diazomethane. Removal of solvent gave a volatile oil (0·6 g) containing (g.l.c.) (4; R = Me, 51%) and (19; 30%). It was chromatographed several times on silica and eluted with light petroleum and increasing amounts of ether. Dimethyl (+)-*cis*-homocaronate (4; R = Me) (0·1 g) was eluted first followed by *dimethyl* trans-4,4-*dimethylhex*-2-*enedioate* (19) which consisted of an oil (70% pure by g.l.c.). It was purified by preparative g.l.c., *m/e* 200 (M^+).

(+)-4α-*Acetylcar*-2-*ene* (8).—(+)-Car-3-ene ($[\alpha]_D^{18}$ +11·1°) was treated with acetic anhydride in the presence of zinc chloride as described in the literature.[12] The ketone (8) was obtained in 82% purity (g.l.c.) by fractionation on a spinning band column and collection at 110—112° and 9

* *Added in proof:* In later experiments, this oxidation was more satisfactorily performed with Brown's or Jones reagent.

mmHg, $[\alpha]_D^{20}$ +402°, n_D^{20} 1·4848 (*cf.* ref. 12), $\nu_{max.}$ 1709 (C=C–C=O), 1660 (C=C), and 836 cm^{-1} (R_2C=CHR), τ (60 MHz) 9·18 and 8·96 (6H, 2s, Me_2C), 8·29 (3H, s, MeC=C), 7·97 (3H, s, Ac), and 4·4 (1H, s, *H*C=C).

Ozonolysis in Methanol of (+)-4α-*Acetylcar-2-ene* (8).—An excess of ozonised oxygen was passed into a solution of the ketone (8) (10 g) in methanol (50 ml) kept at −55°. Hydrogen peroxide (40 ml; 30%) was added, the mixture was stirred for 2·5 h at 0°, sodium hydroxide solution (40 ml; 33%) was slowly added at 0—10°, and the mixture was stirred overnight at room temperature. It was extracted several times with ether, from which a neutral fraction (2·4 g) was isolated as an oil. Acidification of the aqueous liquor and extraction with ether gave an acid fraction which was esterified with diazomethane. G.l.c. of the esters (6·5 g) showed the presence of (+)-*cis*-homocaronic ester (4; R = Me) (30%) and another component. The mixture was chromatographed on silica and eluted with mixtures of light petroleum and ether. (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2-*methoxycarbonylpropyl*)-*cyclopropane* (27) was eluted first as an oil (0·6 g; 86% pure by g.l.c.), $[\alpha]_D^{21}$ +47·9° (*c* 1·25), n_D^{20} 1·4491, *m/e* 228 (M^+).

(+)-*cis*-Homocaronic ester (4; R = Me) (0·25 g) was eluted next, and this was identical with material from earlier preparations of this compound. Although more polar on silica (4; R = Me) has a lower retention time on g.l.c. than the ester (27).

Ozonolysis of (+)-4α-*Acetylcar-2-ene* (8) *in Acetic Acid.*—The ketone (9·7 g) in acetic acid (45 ml) and ethyl acetate (5 ml) was ozonised at 0°, and the product was stirred for 20 h with zinc powder (6 g). The acidic fraction of the product was treated with diazomethane, chromatographed on silica, and eluted with light petroleum–ether (80 : 20). (+)-cis-1-*Methoxycarbonyl*-2,2-*dimethyl*-3-(2,2-*diacetylethyl*)-*cyclopropane* (28) was obtained as an oil (2·6 g), $[\alpha]_D^{21}$ +22·7°, n_D^{21} 1·4671, *m/e* 240 (M^+). It gave a deep violet ferric colour.

Alkaline Hydrolysis of the β-*Diketone* (28).—The diketone (53 mg) was stirred with sodium hydroxide solution (0·2 ml; 5%) for 16 h, and then extracted with ether. The aqueous solution was acidified and the product treated with diazomethane. The principal volatile product (g.l.c.) was (+)-*cis*-1-methoxycarbonyl-2,2-dimethyl-3-(3-oxobutyl)-cyclopropane (9).

Oxidation of the β-*Diketone* (28) *with Alkaline Hydrogen Peroxide.*—The diketone (50 mg) in methanol (0·25 ml) was refluxed for 4 h with hydrogen peroxide (0·2 ml; 30%) and sodium hydroxide (0·2 ml; 30%). Esterification of the acid fraction with diazomethane gave (+)-*cis*-homocaronic ester (4; R = Me) as the only volatile product (g.l.c.).

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