948. *Synthesis, Absolute Configuration, and Ring-fission of* cis- *and* trans-*Homocaronic Acid: Their Configurative Relation to Natural Terpenes.*

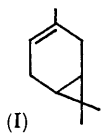
By L. Crombie, J. Crossley, and D. A. Mitchard.

(±)-*cis*- and (±)-*trans*-Chrysanthemic acid yield the expected homochrysanthemic acids on Arndt–Eistert homologation: in the (±)-*cis*-case rearrangement to a cyclobutane, as has been alleged, does not occur. Oxidation of these acids gives (±)-*cis*- and (±)-*trans*-homocaronic acid. Widmark's views on Simonsen's results are confirmed. Earlier specimens of the alleged *cis*-acid were 3,3-dimethylbutene-1,4-dicarboxylic acid and the only previous authentic material is the (+)-acid obtained by Widmark's degradation of the (+)-car-3-ene. By synthesis linking them to the chrysanthemic acids, the absolute configurations of (+)- and (−)-*cis*- and (+)- and (−)-*trans*-homocaronic and homochrysanthemic acid are worked out. This also links the assignments for the chrysanthemic acids with that separately arrived at for (+)-car-3-ene and agreement is found.

The absolute configuration of the chrysanthemic acids previously rested on isolating C-2 as pyrocin and degrading the latter [in the case of the natural (+)-*trans*-acid] to (+)-terebic acid. (+)-*trans*-Homochrysanthemic acid is now converted into a lactone in which C-1 of the parent (+)-*trans*-chrysanthemic acid is isolated and recovered, this time as (−)-terebic acid.

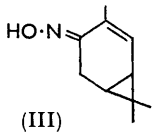
Alkaline fission of the homocaronic esters, which is not complete and does not occur with the free acids, is discussed: it is encountered in ethyl 2-ethoxycarbonylcyclopropylacetate and a case of vinylogous fission is mentioned. In an addendum, the earlier assignment of *trans*-side-chain configuration to natural chrysanthemum dicarboxylic acid from the pyrethrins is confirmed by nuclear magnetic resonance measurements.

From the oxidation products of natural (+)-car-3-ene (I), Simonsen and Rau [1] isolated an acid, m. p. 136—137°, which they regarded as the *cis*-form of homocaronic acid (II). Later, by adding ethyl diazoacetate to 4-methylpent-3-enoic ester and hydrolysing the product with alkali, the same acid was isolated together with a second acid, m. p. 190—191°, which was considered to be the *trans*-form of homocaronic acid.[2] These assignments stood unquestioned until 1957 when Widmark [3] converted natural car-3-ene into its nitrosochloride and thence into the oxime (III). The latter, when oxidised, gave a (+)-acid, m. p. 115—117°. This was esterified with diazomethane to a methyl ester isomeric,

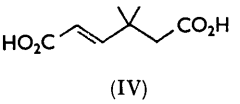


(I)

(II)



(III)



(IV)

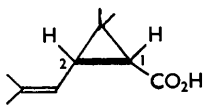
but not identical, with the methyl esters of either of Simonsen's acids,[2] m. p. 136—137° or 190—191°. On hydrolysis with base, however, the new ester gave the acid, m. p. 136—137°, the alleged *cis*-homocaronic acid. Widmark showed that this was in fact 3,3-dimethylbutene-1,4-dicarboxylic acid (IV). His acid, m. p. 115—117°, which formed (±)-terpenylic acid when treated with acid, was therefore considered to be an optically active form of authentic *cis*- or *trans*-homocaronic acid.[3]

The present paper describes the synthesis of authentic *cis*- and *trans*-homocaronic acid in racemic and optically active forms. Their absolute configurations are assigned from their relationship to the chrysanthemic acids. The absolute configurations of the latter

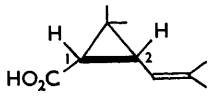
[1] Simonsen and Rau, *J.*, 1923, 549.
[2] Owen and Simonsen, *J.*, 1933, 1225.
[3] Widmark, *Arkiv Kemi*, 1957, **11**, 195.

were worked out earlier [4] and the assignments are now confirmed by a new method. This work also establishes the configurative relationship in absolute terms between natural chrysanthemic acid and (+)-car-3-ene.

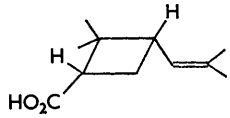
Since Widmark's results [3] show that a homocaronic ester suffers rupture of the cyclopropane ring when heated with alkali, a satisfactory approach seemed to be homologation of appropriate chrysanthemic acids by the Arndt–Eistert technique followed by regulated oxidation of the side-chain. However, in the case of (±)-*cis*-chrysanthemic acid (V–VI),



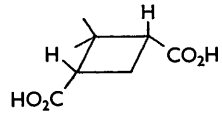
(V) (1*R*,2*S*)



(VI) (1*S*,2*R*)



(VII)



(VIII)

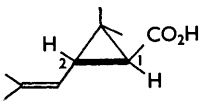
the Arndt–Eistert reaction is said to be abnormal, leading to the cyclobutane (VII) which is oxidised to *cis*-norpinic acid (VIII).[5] This reaction has now been re-examined. The diazo-ketone from (±)-*cis*-chrysanthemic acid chloride was rearranged in the presence of silver oxide and ammonia and converted into the amide. On hydrolysis this was found to give the liquid product described as (VII), together with crystalline material which we identified as (±)-*trans*-homochrysanthemic acid (see below). This latter finding was disturbing, for it indicated that epimerisation at C-1 occurred in the reaction sequence. Although the Arndt–Eistert reaction is usually stereospecific, deviation has been reported.[6] Under more favourable conditions, however (rearrangement of the diazo-ketone in the presence of a silver benzoate–triethylamine catalyst,[6] followed by hydrolysis of the resulting methyl ester), this epimerisation at C-1 could be prevented and the liquid acid was obtained pure, identical with purified material from the amide route.

The liquid acid absorbed one mol. of hydrogen over Adams catalyst and had no high-intensity absorption in the usual ultraviolet range. On ozonolysis it gave acetone and a crystalline dicarboxylic acid, m. p. 176—178°, $\nu_{max.}$ 1706 and 1768 cm.$^{-1}$. The nuclear magnetic spectrum of the methyl ester of this (diazomethane) showed clearly that the two ester groups were not identical (τ 6·35 and 6·39) as required by (VIII) or its *trans*-form. Authentic *cis*-norpinic acid was therefore prepared from α-pinene by the classical method: [7-10] although it had m. p. 176—178° it depressed the m. p. of the product from the Arndt–Eistert reaction some 40° and had different spectral characteristics. There is thus no reason to suppose that the liquid acid is other than (±)-*cis*-homochrysanthemic acid and the dicarboxylic acid, m. p. 176—178°, is therefore (±)-*cis*-homocaronic acid. The remainder of the nuclear magnetic resonance information on the dimethyl ester of the latter, and subsequent reactions, confirm this. Widmark's acid (m. p. 115—117°) has an infrared solution spectrum identical with that of our material and is without doubt one of the optical isomers of *cis*-homocaronic acid as he claims.

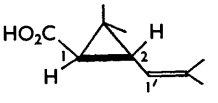
Authentic (±)-*trans*-chrysanthemic acid (IX–X) was then converted into crystalline (±)-*trans*-homochrysanthemic acid by the amide sequence: better yields were obtained by the silver benzoate–triethylamine route,[6] through the methyl ester. This homo-acid absorbed one mol. of hydrogen over a catalyst and on ozonolysis gave acetone and (±)-*trans*-homocaronic acid, m. p. 193—195°, $\nu_{max.}$ 1707 and 1690 cm.$^{-1}$. The latter resisted catalytic hydrogenation, and nuclear magnetic resonance data for the dimethyl ester are consistent with the structure and show that no olefinic protons are present.

[4] Crombie and Harper, *J.*, 1954, 470.
[5] Katsuda, Chikamoto, and Inouye, *Bull. Agric. Chem. Soc. Japan*, 1958, **22**, 185.
[6] Wiberg and Hutton, *J. Amer. Chem. Soc.*, 1956, **78**, 1640.
[7] Baeyer, *Ber.*, 1896, **29**, 22.
[8] Perkin and Simonsen, *J.*, 1909, 1166.
[9] Delepine, *Bull. Soc. chim. France*, 1936, **3**, 1374.
[10] Lauer, Gensler, and Miller, *J. Amer. Chem. Soc.*, 1941, **63**, 1153.

Attention was then turned to the optically active homocaronic acids and their absolute configuration. (±)-*trans*-Homochrysanthemic acid was resolved [11] with quinine and

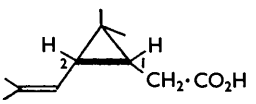


(IX) (1*S*,2*S*)

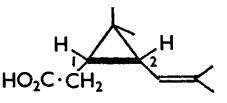


(X) (1*R*,2*R*)

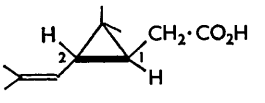
α-methylbenzylamine and on oxidation with permanganate (+)-*trans*-homochrysanthemic acid (XIV) gave (−)-*trans*-homocaronic acid (XVIII), characterised as the 4-bromophenacyl ester, m. p. 107°, $[\alpha]_D^{21}$ −14·7°. Similarly, (−)-*trans*-homochrysanthemic acid



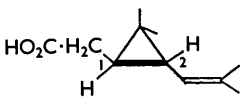
(XI) (1*R*,2*S*)



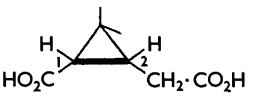
(XII) (1*S*,2*R*)



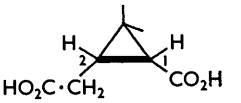
(XIII) (1*S*,2*S*)



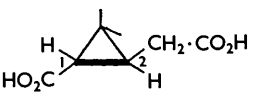
(XIV) (1*R*,2*R*)



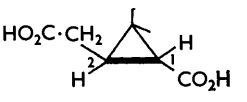
(XV) (1*S*,2*R*)



(XVI) (1*R*,2*S*)



(XVII) (1*S*,2*S*)



(XVIII) (1*R*,2*R*)

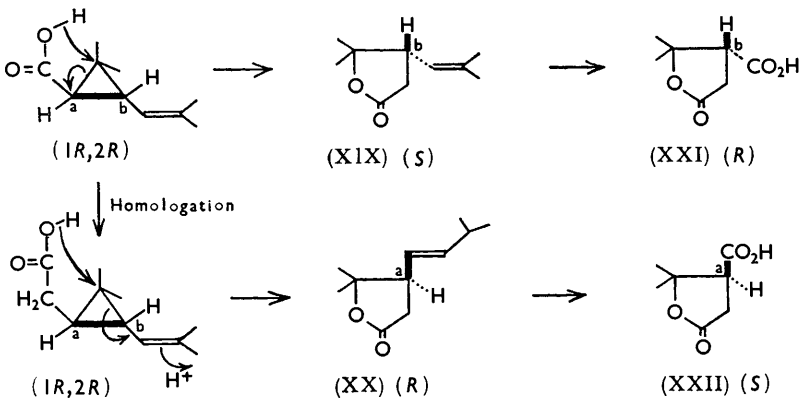
(XIII) gave (+)-*trans*-homocaronic acid (XVII), characterised as the 4-bromophenacyl ester, m. p. 107°, $[\alpha]_D^{21}$ +15·1°. On crystallising together equal parts of the two 4-bromophenacyl esters, the (±)-derivative was obtained. In the *cis*-series, resolution of (±)-*cis*-homochrysanthemic acid was not promising, so (±)-*cis*-chrysanthemic acid was resolved [12] and the enantiomers were severally subjected to Arndt–Eistert homologation. (+)-*cis*-Chrysanthemic acid (V), $[\alpha]_D^{20}$ +40·2°, gave (+)-*cis*-homochrysanthemic acid (XI), $[\alpha]_D^{20}$ +30·7°, and (−)-*cis*-chrysanthemic acid (VI), $[\alpha]_D^{21}$ +41·8°, gave (−)-*cis*-homochrysanthemic acid (XII), $[\alpha]_D^{21}$ −32·1°. The antipodal *cis*-homochrysanthemic acids had identical infrared spectra. Oxidation of (+)-*cis*-homochrysanthemic acid (XI) gave (+)-*cis*-homocaronic acid (XV), $[\alpha]_D^{22}$ +56·6°, the methyl ester of which was gas chromatographically indistinguishable from the ester of Widmark's (+)-degradation product: [3] it formed the biscyclohexylamine salt. The (−)-*cis*-homochrysanthemic acid (XII) gave, on oxidation, (−)-*cis*-homocaronic acid (XVI). When crystallised together, the cyclohexylamine salts of (+)- and (−)-*cis*-homocaronic acid gave the salt of the (±)-acid.

The allocation of absolute configuration to the two *cis*-homocaronic acids follows by their derivation from (+)- and (−)*cis*-chrysanthemic acids (V and VI, respectively).[4,13] In order to make such assignments to the *trans*-compounds it was essential to subject natural (+)-*trans*-chrysanthemic acid (X) [13] to Arndt–Eistert homologation and it was confirmed that it gave (+)-*trans*-homochrysanthemic acid (XIV). Relative to the chrysanthemic acids, then, the absolute configuration of the homocaronic acids is established. The absolute configuration of the chrysanthemic acids themselves were deduced by thermally isomerising (+)-*trans*-chrysanthemic acid (X) into (−)-pyrocin (XIX) which, on ozonolysis, gave (+)-terebic acid (XXI),[4,14] in its turn configuratively linked to D-glyceraldehyde by a

[11] Katsuda and Chikamoto, *Bull. Agric. Chem. Soc. Japan*, 1958, **22**, 330.
[12] Campbell and Harper, *J.*, 1945, 283; *J. Sci. Food Agric.*, 1952, **3**, 189.
[13] Crombie and Elliott, "Chemistry of the Natural Pyrethrins" in "Progress in the Chemistry of Natural Products," 1961, Vol. XIX, p. 120, ed. Zechmeister, Springer-Verlag, Vienna.
[14] Crombie, Harper, and Thompson, *J. Sci. Food Agric.*, 1952, **3**, 189.

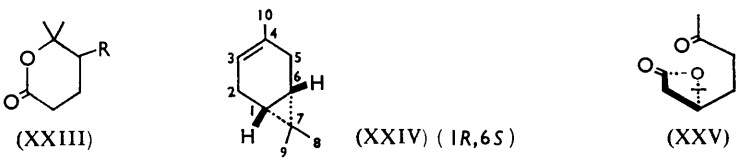
sequence involving (—)-methylsuccinic acid. (+)-*cis*-Chrysanthemic acid gives (+)-pyrocin, so the absolute configuration in the *cis*-series is also known.[4] An interesting confirmation of the assignments has come from a study of the acid-catalysed lactonisation of the homochrysanthemic acids in which the 1- rather than the 2-optical centre is isolated by degradation, as follows.

(±)-*cis*- and (±)-*trans*-Homochrysanthemic acid (or amide) give the same lactone when boiled with acid. It is reported[5] to be the δ-lactone (XXIII; R = $Me_2C{:}CH{\cdot}$), $\nu_{max.}$ 1755 cm.$^{-1}$. In our hands it has $\nu_{max.}$ 1766 cm.$^{-1}$ (pure liquid) but 1752 cm.$^{-1}$ in chloroform: it appeared to be a γ-lactone. Its identity as the γ-lactone (XX and enantiomer) was shown by ozonising it to isobutyraldehyde and (±)-terebic acid (XXI–XXII). According to Katsuda *et al.*[11] ozonisation gives the δ-lactone (XXIII; R = CO_2H), but a synthetic specimen of this has different properties from those reported (see Experimental section). (+)-*trans*-Homochrysanthemic acid gave the (+)-lactone (XX), which on ozonolysis gave (—)-terebic acid (XXII) containing $C_{(a)}$ and enantiomeric with the specimen of (+)-terebic acid obtained when $C_{(b)}$ was isolated by the pyrocin route. (+)-*cis*-Homochrysanthemic



acid similarly gave the (+)-lactone (XX) and hence (—)-terebic acid. This confirms the absolute configurations of the chrysanthemic acids. (+)-*cis*-Chrysanthemic acid is the epimer of (+)-*trans*- at $C_{(b)}$ since (+)-*cis*-homochrysanthemic acid yields the (+)-lactone (XX) when treated with acid.

The absolute configuration of Widmark's acid obtained from natural (+)-car-3-ene through the oxime (III)[3] is thus (XV) and natural (+)-car-3-ene is (XXIV). This links together the absolute configurations of the *trans*-caronic acids, the homocaronic acids, the

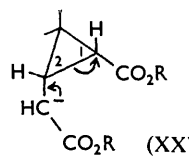


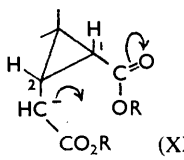
chrysanthemic acids, and car-3-ene. The absolute configuration of natural (+)-car-3-ene has been independently determined by degradation to (+)-homoterpenyl methyl ketone (XXV), which has been further degraded to (—)-terebic acid,[15] and our results lead to the same conclusion (XXIV).

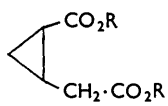
The fission noted by Widmark during alkaline hydrolysis of (+)-*cis*-homocaronic ester has been examined further. As expected, hydrolysis of the (±)-*cis*-methyl ester gave the ester of 3,3-dimethylbutene-1,4-dicarboxylic acid (IV) which could be hydrolysed and hydrogenated to 3,3-dimethyladipic acid. It was noticed that the yield was low, so

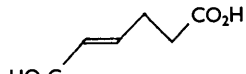
[15] Sandberg, *Arkiv Kemi*, 1960, **16**, 255.

the matter was considered quantitatively. Methyl (±)-*cis*- and (±)-*trans*-homocaronate were each refluxed for 3 hours with 10% methanolic sodium hydroxide, and the whole product was methylated with diazomethane and analysed by gas–liquid chromatography on a polyethyleneglycol adipate column at 160°. The (±)-*cis*-homocaronic ester gave 38·7% of the open-chain ester from (IV) and 61·3% of methyl (±)-*cis*-homocaronate. The (±)-*trans*-ester showed much less cleavage, giving 10·4% of the ester from (IV) and 89·6% of methyl (±)-*trans*-homocaronate. The reason why the unruptured cyclopropane survived was clear for, in quantitative work, on similar boiling with sodium hydroxide the free acids underwent no cleavage to the butene-acid. The carbanion (XXVI) involved in the cleavage is not sufficiently stabilised in the ionised acid and cleavage occurs only with unhydrolysed ester molecules. More cyclopropane cleavage is observed in the case of *cis*-homocaronic ester, and this may be due to a slower hydrolysis of one or both ester groups or to spatial stabilisation by delocalisation of charge in the initial carbanion and in the transition state by involvement of the 1-carboxylic ester grouping (cf. XXVII). The amides and esters of the homochrysanthemic acids apparently resist cleavage with base because there is in them no electron-withdrawing group (cf. C-1 in XXVI) to stabilise the developing negative charge in the transition state leading to ring breakage.


(XXVI)

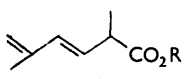

(XXVII)

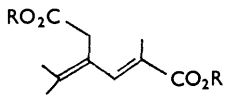

(XXVIII)

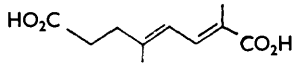

(XXIX)

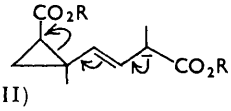
Whilst our work was in progress Ullmann reported that ethyl 2-ethoxycarbonylcyclopropylacetate (XXVIII; R = Et, probably *cis*) was hydrolysed by alkali to the corresponding acid (XXVIII; R = H), m. p. 185—188°.[16,17] In the light of the work above it seemed to us likely that ring cleavage had occurred and that the product was in fact *trans*-2-4,5-dihydromuconic acid (XXIX). Through the kindness of Dr. Ullmann in providing a sample we have shown this to be so.

This type of base-catalysed cyclopropane cleavage also throws light on another matter connected with the chrysanthemic acids. Addition of diazoacetic ester to what is now known [18] to be ethyl 2,5-dimethylhexa-3,5-dienoate (XXX), followed by hydrolysis, gave an acid $C_{14}H_{22}O_4$ originally claimed to be chrysanthemumdicarboxylic acid.[19] Its struc-


(XXX)


(XXXI)


(XXXII)

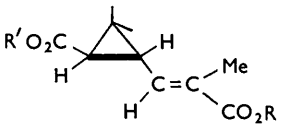

(XXXIII)

ture was later [20] said to be (XXXI) and then shown [18] to be (XXXII). The data available are satisfactorily interpreted by formulating the diester from diazoacetic ester addition as the cyclopropane (XXXIII): when hydrolysed this gives the diene (XXXII) by a vinylogous opening of the above type.

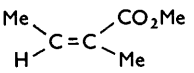
Addendum.—Synthetic evidence supports allocation of the *trans*-configuration to the

[16] Ullmann, *J. Amer. Chem. Soc.*, 1959, **81**, 5386.
[17] Ullmann and Fanshawe, *J. Amer. Chem. Soc.*, 1961, **83**, 2381.
[18] Crombie, Harper, and Sleep, *J.*, 1957, 2743.
[19] Inouye, Shinohara, and Ohno, *Botyu-Kagaku*, 1954, **19**, 35.
[20] Inouye, Takeshita, and Ohno, *Botyu-Kagaku*, 1955, **20**, 102; *Bull. Inst. Chem. Res. Kyoto Univ.*, 1955, **33**, 73.

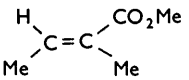
side-chain of natural chrysanthemumdicarboxylic acid (XXXIV; R = R′ = H) and pyrethric acid (XXXIV; R = Me, R′ = H).[13,18] The nuclear magnetic resonance spectrum gives direct evidence on the point. The τ value of the 3-hydrogen in methyl



(XXXIV) (1*R*,2*R*)



(XXXV)



(XXXVI)

angelate (XXXV) is 4·02 and in methyl tiglate (XXXVI) the ester shielding lowers this to 3·27.[21] In methyl chrysanthemate (cf. X) the 1′-hydrogen appears near τ 5·13 (mean value) (see also Hutton and Schaefer [22]). Assuming the shifts in the methyl angelate and tiglate series to apply, one would expect a τ value of ~3·61 in the case of dimethyl chrysanthemumdicarboxylate (XXXIV; R = R′ = Me) and 4·36 if the side-chain were *cis*. The measured value is 3·58, giving strong support to the assignment of the *cis*-side-chain configuration in natural chrysanthemumdicarboxylic and pyrethric acid.

Experimental

Unless otherwise indicated, ultraviolet spectra and optical rotations were determined for ethanol solutions: evaporation signifies evaporation under reduced pressure, and drying refers to the use of anhydrous sodium sulphate.

(±)-cis- *and* (±)-trans-*Chrysanthemoyl Chloride*.—The mixed esters (750 g.) formed by adding ethyl diazoacetate to 2,5-dimethylhexa-2,4-diene [12,23] were hydrolysed with potassium hydroxide in refluxing (3½ hr.) ethanol. Mixed (±)-*cis*- and (±)-*trans*-chrysanthemic acid (593 g.) were obtained. Mixed acids (400 g.) were fractionally crystallised from ethyl acetate to give the (±)-*cis*-acid (90 g.), prisms, m. p. 114—115° (lit.,[24] m. p. 114—115°), and (±)-*trans*-acid (220 g.), needles, m. p. 52—54° (lit.,[25] m. p. 54·5°). The identity and purity of the two compounds were confirmed by infrared comparison with authentic material.

(±)-*trans*-Chrysanthemic acid (100 g.) in light petroleum (b. p. 40—60°) (250 ml.) was treated slowly with thionyl chloride (56 ml.) which had been purified by distillation first from quinoline and then from linseed oil.[26] The solution was kept overnight and the solvent was removed at 20° under reduced pressure. Distillation (frothing usually causes difficulty) gave (±)-*trans*-chrysanthemoyl chloride (82·1 g.), b. p. 113—114°/20 mm., n_D^{23} 1·4856 (lit.,[27] b. p. 100—101°/175 mm., n_D^{20} 1·4856).

In a similar way the (±)-*cis*-acid (30 g.) gave (±)-*cis*-chrysanthemoyl chloride (20·6 g.), b. p. 113—118°/20 mm., n_D^{22} 1·4900 (lit.,[27] b. p. 113—116°/20 mm., n_D^{22} 1·4882).

(±)-trans-*Chrysanthemoyldiazomethane*.—(±)-*trans*-Chrysanthemoyl chloride (37 g.) in dry ether (50 ml.) was added during 1 hr. to a distilled ethereal solution of diazomethane [from methylnitrosourea (120 g.)] at 0° and kept for 3 hr. at 20°. Evaporation gave crude (±)-trans-*chrysanthemoyldiazomethane* (40 g.) which was distilled to give pure material, b. p. 94—96°/1 mm., n_D^{21} 1·5214 (Found: C, 68·4; H, 8·8; N, 14·2. $C_{11}H_{16}N_2O$ requires C, 68·7; H, 8·4; N, 14·55%). About 40% of the material remained undistilled as a high-boiling transparent polymer. The diazo-ketone had $\lambda_{max.}$ 252 (16,450) and 275·5 (14,620) mμ, $\nu_{max.}$ 2110 (·CN_2), 1715 (C=O), 1634 (C=C), and 850 (Me_2C=CH) cm.$^{-1}$.

(±)-trans-*Homochrysanthemamide*.—Crude (±)-*trans*-chrysanthemoyldiazomethane (16 g.) in dioxan (100 ml.) at 60° was treated with concentrated aqueous ammonia (150 ml.) containing 10% aqueous silver nitrate (36 ml.), and the mixture was refluxed for 3 hr. The volume of the solution was reduced to one-third by distillation and extracted with ether. Drying,

[21] Jackman and Wiley, *J.*, 1960, 2886.
[22] Hutton and Schaefer, *Canad. J. Chem.*, 1962, **40**, 875.
[23] Harper, Reed, and Thompson, *J. Sci. Food Agric.*, 1951, **2**, 94.
[24] Staudinger, Muntwyler, Ruzicka, and Seibt, *Helv. Chim. Acta*, 1924, **7**, 390.
[25] Harper and Reed, *J. Sci. Food Agric.*, 1951, **2**, 418; Reed, Thesis, London, 1950.
[26] Fieser, " Experiments in Organic Chemistry," Heath & Co., Boston, 1957, 3rd edn.
[27] Crombie, Edgar, Harper, Lowe, and Thompson, *J.*, 1950, 3552.

evaporation, and distillation gave (±)-trans-*homochrysanthemamide* (9·8 g.), b. p. 112°/0·02 mm., n_D^{21} 1·4948 (Found: C, 72·8; H, 10·65; N, 7·35. $C_{11}H_{19}NO$ requires C, 72·9; H, 10·55; N, 7·75%). The amide (which partly crystallised) had $\nu_{max.}$ 3356, 3221 ($CO{\cdot}NH_2$), 1660 (amide I), 1631 (amide II), and 847 ($Me_2C{=}CH$) cm.$^{-1}$. The *xanthate derivative* had m. p. 137·5—138° (Found: C, 79·15; H, 7·55. $C_{24}H_{27}NO_2$ requires C, 79·75; H, 7·55%). Examination (infrared) of the crude material before distillation sometimes showed unrearranged diazo-ketone. In such cases more catalyst was added, the rearrangement was repeated, and the isolation then continued as above.

(±)-trans-*Homochrysanthemic Acid* (XIII–XIV).—(*a*) The amide (34 g.) was refluxed for 16 hr. with 10% methanolic sodium hydroxide (100 ml.). The methanol was distilled off and water (100 ml.) was added: after extraction with ether the solution was acidified with 2N-hydrochloric acid and again extracted with ether. The latter extracts were dried and evaporated to 50 ml.; cooling to −70° gave (±)-*trans*-homochrysanthemic acid (20·7 g.), m. p. 69—72°. Recrystallisation from light petroleum (b. p. 40—60°), or chromatography on silica gel and elution with 1 : 20 ethanol–light petroleum, gave the acid, m. p. 80—81° (lit.,[5] m. p. 80—81°) (Found: C, 72·35; H, 10·2%; Equiv., 182·0. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·95%; equiv., 182·3). It had $\nu_{max.}$ (mull) 1701 (CO_2H), 1650 (C:C), and 847 ($Me_2C{:}CH$) cm.$^{-1}$. (±)-*trans*-Homochrysanthemic acid in ethyl acetate absorbed 1·02 ml. of hydrogen over Adams catalyst.

(*b*) The crude (±)-diazo-ketone (18 g.), n_D^{16} 1·5178, prepared as above from chrysanthemic acid (15·2 g.), was converted into (±)-methyl *trans*-homochrysanthemate (8·55 g.), b. p. 54—56°/0·25 mm., n_D^{18} 1·4608, by the method used below for the *cis*-isomer. The catalyst was silver benzoate (6 g.) in triethylamine (60 ml.).[6] The ester was identical (infrared spectrum and gas chromatography on a Dow-Silicone column at 181°) with a specimen made from the acid above with diazomethane. On hydrolysis with methanolic potassium hydroxide the ester (3·4 g.) gave crude acid (1·87 g.) which when crystallised gave (±)-*trans*-homochrysanthemic acid (1·1 g.), identical with the material above (mixed m. p.). The 4-*bromophenacyl ester* had m. p. 33—34° (Found: C, 59·7; H, 5·9; Br, 21·4. $C_{19}H_{23}BrO_3$ requires C, 60·15; H, 6·1; Br, 21·05%), $\nu_{max.}$ 1748 (ester), 1709 (ketone), 1590 (Ph), and 846 ($Me_2C{=}CH$) cm.$^{-1}$.

(*c*) The crude (±)-diazo-ketone (1 g.), collidine (5 ml.), and redistilled benzyl alcohol (5 ml.) were mixed and immersed in a pre-heated bath at 175°.[28] After 15 min. the product was cooled, acidified with 2N-hydrochloric acid, and extracted with ether. Evaporation gave an oily benzyl ester which was hydrolysed with 10% alkali. The acidic product was isolated and distilled (b. p. 105—107°/0·3 mm.). The distillate (0·41 g.) crystallised to give (±)-*trans*-homochrysanthemic acid, needles, m. p. and mixed m. p. 79—80·5° (and infrared identification).

(±)-trans-*Chrysanthemoylmethanol*.—The above crude diazo-ketone (5·1 g.) in dioxan (200 ml.) was treated with 2N-sulphuric acid (130 ml.) and stirred for 1 hr. at 60—65°. The solution was concentrated and extracted with ether. Drying, evaporation, and distillation gave the hydroxymethyl ketone (1·5 g.), b. p. 62—65°/0·25 mm., n_D^{22} 1·4732, $\nu_{max.}$ 3460 (OH) and 1721 (C=O) cm.$^{-1}$. The 2,4-*dinitrophenylhydrazone* had m. p. 153—154° (from methanol) (Found: C, 55·85; H, 6·05; N, 15·75. $C_{17}H_{22}N_4O_5$ requires C, 56·35; H, 6·1; N, 15·45%).

Attempted rearrangement of the diazo-ketone in dioxan with sodium thiosulphate, silver oxide, and sodium hydrogen carbonate in water,[29] with the object of isolating the homochrysanthemic acid directly, gave a mixture of the acid and the hydroxymethyl ketone in rather poor yield.

(±)-cis-*Chrysanthemoyldiazomethane*.—(±)-*cis*-Chrysanthemoyl chloride (34·0 g.) was treated with diazomethane from methylnitrosourea (100 g.) in dry ether, as for the *trans*-compound. The resulting (±)-*cis*-diazo-ketone (32·4 g.), n_D^{20} 1·5118, was normally employed without further purification: it had $\nu_{max.}$ 2110 (CN_2), 1721 (C=O), and 1631 (C=C) cm.$^{-1}$. A specimen had b. p. 80—85°/0·35 mm., n_D^{17} 1·5167.

(±)-cis-*Homochrysanthemamide*.—The crude (±)-*cis*-diazo-ketone (20 g.) in dioxan (100 ml.) was warmed to 60°, and concentrated aqueous ammonia (200 ml.) and 10% aqueous silver nitrate solution (48 ml.) were added. The mixture was refluxed for 3 hr. and then concentrated. Extraction with ether gave an oil which was distilled, to give a fore-run, b. p. 49—90°/0·005 mm., n_D^{19} 1·4770—1·4850, and a main fraction (9·0 g.), b. p. 100—102°/0·005 mm.,

[28] Wilds and Meader, *J. Org. Chem.*, 1948, **13**, 763.
[29] Bachmann and Struve, *Org. Reactions*, 1941, **1**, 38.

which solidified. Crystallisation from light petroleum (b. p. 40—60°) gave (±)-cis-*homochrysanthemamide*, plates, m. p. 73·5—74° (Found: C, 72·7; H, 10·4; N, 7·55. $C_{11}H_{19}NO$ requires C, 72·9; H, 10·45; N, 7·75%). In the infrared (mull) there were $\nu_{max.}$ 3330, 3145 ($CO{\cdot}NH_2$), 1663 (amide I), 1630 (amide II), and 842 ($Me_2C{=}CH$) $cm.^{-1}$. The xanthate derivative had m. p. 149—150° and depressed the m. p. of the derivative of the (±)-*trans*-amide by some 40°.

The low-boiling fore-runs mentioned above were collected from several preparations and united. On careful distillation two products were isolated. The first (and minor) component was recognised as (±)-methyl *cis*-chrysanthemate, b. p. 101—113°/15 mm., n_D^{22} 1·4698, apparently homogeneous as judged by gas–liquid chromatography on Apiezon L at 161° (Found: C, 72·25; H, 10·2. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·95%) (lit.,[25] b. p. 82—83°/7 mm., n_D^{25} 1·4624). The identity of the material was established by comparison of infrared spectra; it absorbed 0·96 ml. of hydrogen on catalytic hydrogenation. The higher-boiling, and major, component of the fore-run had b. p. 76—78°/0·1 mm., n_D^{22} 1·4850, but gas–liquid chromatography showed contamination with about 5% of methyl (±)-*cis*-chrysanthemate. The substance contained no nitrogen but had hydroxyl (3348 $cm.^{-1}$) and ester (1718 and 1691 $cm.^{-1}$) bands, with virtually no absorption at 850 $cm.^{-1}$ which is characteristic of the $Me_2C{=}CH$ group. On hydrolysis and chromatography over silica gel an acid with $\nu_{max.}$ 3378 (hydroxyl) and 1701 (CO_2H) $cm.^{-1}$ was obtained. These results led us to suspect that the by-product was methyl (±)-1′,2′-dihydro-2′-hydroxychrysanthemate. In confirmation, when the acid (0·67 g.) was refluxed with 5% sulphuric acid (15 ml.) for 3 hr. and the neutral products were isolated with ether and distilled (b. p. 88—91°/0·4 mm., n_D^{21} 1·4682; 0·38 g.), the distillate crystallised. Recrystallisation from light petroleum (b. p. 40—60°) gave dihydrochrysanthemo-δ-lactone, m. p. and mixed m. p. 49—51° (and infrared comparison) (lit.,[30] m. p. 50—51°). (±)-Methyl *cis*-1′,2′-dihydro-2′-hydroxychrysanthemate probably originates from the diazomethanolysis of dihydrochrysanthemo-δ-lactone resulting from the acid conditions during the preparation of (±)-*cis*-chrysanthemoyl chloride by the action of thionyl chloride on the acid. The methyl (±)-*cis*-chrysanthemate must come from (±)-*cis*-chrysanthemic acid present as impurity in the acid chloride, which is hydrolysed very rapidly.

(±)-cis-*Homochrysanthemic Acid* (XI–XII).—(*a*) Amide prepared by rearranging (±)-*cis*-chrysanthemoyldiazomethane was distilled but not further purified. The material (12·2 g.) was hydrolysed as for the *trans*-compound and gave acid (5·91 g.), b. p. 87—88°, n_D^{22} 1·4719. In 24 hr., white crystals (2·49 g.), m. p. 64—66°, had been deposited. Crystallisation three times from light petroleum gave (±)-*trans*-homochrysanthemic acid (0·85 g.), m. p. and mixed m. p. 79—80° (and infrared comparison). The cyclohexylamine salt had m. p. 131—133° and the *S*-benzylthiouronium salt, m. p. 129·5—130°.

The liquid remaining after removal of all possible *trans*-material, (±)-*cis*-homochrysanthemic acid (3·42 g.), had $\nu_{max.}$ 1709 (acid) and 851 ($Me_2C{=}CH$) $cm.^{-1}$. When hydrogenated over Adams catalyst in acetic acid the compound absorbed 1·05 mol. of hydrogen. It gave a cyclohexylamine salt, m. p. 133—135°, and an *S*-benzylthiouronium salt, m. p. 144·5—145°. These salts gave m. p. depressions with those of the (±)-*trans*-acid, and their infrared spectra were clearly different. A number of experiments of this kind have been carried out. The one described gave an unusually large amount of (±)-*trans*-impurity but varying quantities were observed on a number of occasions. It is of interest that Matsui and Kitamura [31] must have observed the same thing as they isolated some crystals, m. p. 78—79°. Katsuda *et al.*,[5] who recognised that the crystalline product was (±)-*trans*-homochrysanthemic acid, supposed them to have used impure starting material. We are confident of the purity of our *cis*-acid.

(*b*) Silver benzoate (9·0 g.) was freshly prepared and dried in a vacuum-oven. It was dissolved in triethylamine (90 ml., dried over sodium hydroxide pellets and distilled from barium oxide; b. p. 85—87°).[6] The catalyst solution was rapidly filtered and then added during 12 hr. to a refluxing solution of (±)-*cis*-chrysanthemoyldiazomethane [from the acid (10 g.)] in methanol (100 ml.). Stirring was maintained and moisture excluded. The methanol and triethylamine were distilled off and ether (100 ml.) was added. The ethereal solution was washed with sodium hydrogen carbonate solution, dried, evaporated, and distilled. Successive

[30] Crombie, Harper, and Thompson, *J. Sci. Food Agric.*, 1951, **2**, 421.
[31] Matsui and Kitamura, *Bull. Agric. Chem. Soc. Japan*, 1955, **19**, 42.

fractions were examined by gas–liquid chromatography (Dow-Silicone; 181°). The first fraction contained (±)-methyl *cis*-homochrysanthemate with about 5% of (±)-methyl *cis*-chrysanthemate as impurity, but the bulk (4·12 g.), b. p. 58—60°/0·3 mm., n_D^{20} 1·4663, was free from this. Its infrared spectrum was the same as that of a specimen made by esterifying purified (±)-*cis*-homochrysanthemic acid from the amide route.

The ester (4·0 g.) was refluxed with 10% methanolic sodium hydroxide (40 ml.) for 2 hr. Working up by extraction and distillation gave a first fraction, b. p. 97—103°/0·3 mm., n_D^{20} 1·4799, and the main material, b. p. 111—113°/0·3 mm., n_D^{20} 1·4746. The first fraction slowly deposited a few crystals but these proved to be (±)-*cis*-chrysanthemic acid. No crystalline deposit was obtained from the main fraction on storage and cooling. The infrared spectrum of the (±)-cis-*homochrysanthemic acid* (Found: C, 72·85; H, 9·75. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%) was identical with purified material from the amide route and the *S*-benzylthiouronium salt had m. p. 144·5—145·0° (and mixed m. p. with the specimen above).

(±)-trans-*Homocaronic Acid* (XVII–XVIII).—(*a*) (±)-*trans*-Homochrysanthemic acid (0·767 g.) in chloroform (15 ml.) was ozonised at 0°. The product was evaporated at 5° to give a glass to which water (40 ml.) was added. After 12 hr. at 20° the mixture was steam-distilled into 2,4-dinitrophenylhydrazine reagent. The derivative (100 mg.) was chromatographed from chloroform on bentonite–Celite (1 : 4) and crystallised from ethanol, to give acetone 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 123—125° (and infrared comparison). When kept at 0° the residue from the steam-distillation gave crystals (0·32 g.; m. p. 170—175°) which when crystallised from hot water (charcoal) gave (±)-*trans*-homocaronic acid, m. p. 193—195° (Found: C, 55·7; H, 6·85. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%) (lit.,[2,5] m. p. 190—191°). The acid had $\nu_{max.}$ (mull) 1707 (aliphatic CO_2H) and 1690 (cyclopropane CO_2H) cm.$^{-1}$ and resisted hydrogenation over Adams catalyst in ethyl acetate at atmospheric pressure. The acid (31 mg.) was refluxed for 1 hr. with 10% aqueous sodium hydroxide (1·4 ml.). On cooling, acidification, and storage at 0° for 12 hr., crystals (30 mg.), m. p. 192—194°, were recovered. One crystallisation from water gave (±)-*trans*-homocaronic acid, m. p. and mixed m. p. 193—195°. (±)-*Dimethyl* trans-*homocaronate* (0·74) was obtained by esterifying (±)-*trans*-homocaronic acid (0·85 g.) with diazomethane. It had b. p. 123—125°/15 mm., $n_D^{23.5}$ 1·4465 (Found: C, 60·1; H, 8·2. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·1%), and $\nu_{max.}$ 1736 (aliphatic CO_2Me) and 1724 (cyclopropane CO_2Me) cm.$^{-1}$.

(*b*) (±)-*trans*-Homochrysanthemic acid (1·46 g.) in water (30 ml.) containing potassium hydroxide (0·64 g.) was added to an ice-cold stirred solution of potassium permanganate (4·0 g.) in water (80 ml.) at $<10°$ and the whole was stirred for a further 10—15 min. Ethanol (2 ml.) was added and the solution was acidified and thoroughly extracted with ether. The extracts were dried and on evaporation gave crude (±)-*trans*-homocaronic acid (0·94 g.). Crystallisation from water or nitromethane gave pure acid, m. p. 192—193° (and mixed m. p. and infrared comparison with the specimen above).

(±)-cis-*Homocaronic Acid* (XV–XVI).—(*a*) By an ozonolysis procedure analogous to that for the (±)-*trans*-acid, (±)-*cis*-homochrysanthemic acid (1·03 g.) gave (±)-cis-*homocaronic acid* (0·21 g.), m. p. 167—169°, raised by crystallisation (charcoal) from hot water to 176—178° (Found: C, 55·95; H, 7·2. $C_8H_{12}O_4$ requires C, 55·8; H, 7·05%), $\nu_{max.}$ (mull) 1706 (aliphatic CO_2H) and 1683 (cyclopropane CO_2H) cm.$^{-1}$. Acetone 2,4-dinitrophenylhydrazone (0·676 g.), m. p and mixed m. p. 123—124°, was also formed. On treatment with diazomethane (±)-*cis*-homocaronic acid (0·55 g.) gave the *dimethyl ester* (0·41 g.), b. p. 117—118°/15 mm., n_D^{21} 1·4468 (Found: C, 60·2; H, 8·2%), $\nu_{max.}$ 1739 (aliphatic CO_2Me) and 1724 (cyclopropane CO_2Me) cm.$^{-1}$.

(*b*) By the method used for oxidising the (±)-*trans*-acid with permanganate, (±)-*cis*-homochrysanthemic acid (0·5 g.) gave (±)-*cis*-homocaronic acid (0·12 g.), m. p. 177—178° and mixed m. p. with the above specimen. On one occasion (±)-*cis*-homochrysanthemic acid (3·42 g.) gave (±)-*cis*-homocaronic acid (0·48 g.) in a form of m. p. 155—156° (unaltered by three crystallisations), but the infrared mull spectrum of this was identical with that of the higher-melting form.

Resolution of (±)-trans-*Homochrysanthemic Acid.*[11]—Quinine trihydrate (37·8 g.) in warm ethanol (40 ml.) was added to (±)-*trans*-homochrysanthemic acid (18 g.) in ethanol (25 ml.) and kept at 20° for 48 hr. Filtration gave the impure quinine salt of (−)-*trans*-homochrysanthemic acid and this, when crystallised seven times from aqueous ethanol (1 : 1), gave a salt, m. p. 106—107°, $[\alpha]_D^{20}$ −118° (*c* 1·98). On decomposition with hydrochloric acid this gave

(−)-*trans*-homochrysanthemic acid (XIII) (1·5 g.), b. p. 91—96°/0·05 mm., n_D^{19} 1·4705, $[\alpha]_D^{18}$ −30·6° ± 0·6° (*c* 2·94).

Water (25 ml.) was added to the filtrate from which the (−)-*trans*-salt had initially crystallised. After 1 hr. at 0° an optically impure salt of the (+)-*trans*-acid (17·7 g.) separated {m. p. 69—87°, $[\alpha]_D^{20}$ −74·3° (*c* 3·55)}. Decomposition gave optically impure (+)-*trans*-homochrysanthemic acid (6·8 g.).

(−)-α-Methylbenzylamine (4·7 g.), b. p. 74°/15 mm., $[\alpha]_D^{20}$ −36·57°, was added to a suspension of this acid in water–ethanol (30 ml.; 3 : 2). On storage at 20° the impure (−)-base (+)-*trans*-acid salt (8·2 g.), m. p. 110—115°, $[\alpha]_D^{19}$ −12·0°, separated and was crystallised five times from water–ethanol (3 : 2) to give the pure salt, m. p. 123—124°, $[\alpha]_D^{21}$ +9·5° (*c* 0·22). On decomposition, (+)-*trans*-homochrysanthemic acid (XIV) (0·99 g.), b. p. 97—100°/0·05 mm., n_D^{19} 1·4710, $[\alpha]_D^{20}$ +30·0° ± 0·4° (*c* 2·15), was obtained. Equal weights of (+)- and (−)-*trans*-homochrysanthemic acid were mixed: the mixture solidified: one crystallisation from light petroleum gave the (±)-*trans* acid, m. p. and mixed m. p. 80—81° {lit.,[11] for (−)-*trans*-homochrysanthemic acid, b. p. 107°/3 mm., $[\alpha]_D^{16}$ −23·3° (*c* 3·00), n_D^{20} 1·4718, and for the (+)-*trans*-form, b. p. 114°/3·5 mm., $[\alpha]_D^{16}$ +23·8° (*c* 2·94), n_D^{20} 1·4718}. The less soluble quinine salt is reported [11] to give the (+)-acid.

(+)-trans-*Homochrysanthemic Acid from* (+)-trans-*Chrysanthemic Acid.*—A mixture of crude acids (60 g.) from hydrolysis of the natural pyrethrins was a gift from Dr. M. Elliott. The oil was extracted with light petroleum (2 × 200 ml.). Evaporation of the petroleum gave a liquid which partly crystallised to give chrysanthemumdicarboxylic acid (9 g.), m. p. 160—164°. The remainder of the petroleum extract was treated with diazomethane and distilled, to give methyl (+)-*trans*-chrysanthemate (20 g.), b. p. 96—110°/15 mm., n_D^{22} 1·4620, an intermediate fraction (6·5 g.), b. p. 110—142°/15 mm., n_D^{22} 1·4650—1·4701, and then dimethyl (+)-*trans*-chrysanthemumdicarboxylate (15·3 g.), b. p. 142—160°/15 mm., n_D^{22} 1·4817. The identity of the two products was verified by comparison of the infrared spectra with authentic material. The monocarboxylic ester had $\nu_{max.}$ 1725 (CO_2Me) and 856 ($Me_2C{:}CH$) $cm.^{-1}$ and the dicarboxylic ester had $\nu_{max.}$ 1742 (CO_2Me), 1712 (α-unsaturated CO_2Me), and 1645 (conj. C=C) $cm.^{-1}$. Redistillation of the monomethyl ester gave material, b. p. 98—99°/17 mm., $n_D^{24.5}$ 1·4600, $[\alpha]_D^{22}$ +20·6° ± 0·6° (*c* 1·21). On hydrolysis of the ester (14·72 g.) for 4 hr. with 10% methanolic potassium hydroxide, (+)-*trans*-chrysanthemic acid (9·75 g.), b. p. 144—147°/16 mm., n_D^{24} 1·4759, $[\alpha]_D^{23}$ +14·3° ± 0·5° (*c* 1·16), was obtained {lit.,[32] $[\alpha]_D^{22}$ +14·2° (*c* 2·77)}.

The acid (6·0 g.) was converted by the thionyl chloride technique into the acid chloride (3·9 g.), b. p. 111—112°/18 mm., n_D^{22} 1·4830, which, by the technique above, was converted into (+)-*trans*-homochrysanthemamide (1·67 g.), b. p. 100—115°/0·2 mm., n_D^{21} 1·4945, $[\alpha]_D^{23}$ 21·8° ± 1° (*c* 0·96), and then into (+)-*trans*-homochrysanthemic acid (XIV), b. p. 102—103°/0·8 mm., n_D^{17} 1·4716, $[\alpha]_D^{19}$ +29·8° ± 0·43° (*c* 2·34), whose infrared spectrum was identical with that of the specimen obtained from the resolution {lit.,[11] b. p. 114°/3·5 mm., n_D^{22} 1·4718, $[\alpha]_D^{16}$ +23·8° (*c* 2·94)}.

(+)- *and* (−)-trans-*Homocaronic Acid.*—(+)-*trans*-Homochrysanthemic acid (0·95 g.), $[\alpha]_D^{20}$ +30·0°, was oxidised with potassium permanganate as described above, and gave (−)-*trans*-homocaronic acid (XVIII) (0·17 g.) which, after chromatography (twice) on silica gel from chloroform, was partly crystalline and had $[\alpha]_D^{20}$ −27·0° (*c* 0·61). It was converted into the *bis*-4-*bromophenacyl ester*, m. p. 105—107° (from ethanol), $[\alpha]_D^{21}$ −14·7° ± 0·2° (*c* 0·245 in acetone) (Found: C, 50·9; H, 4·25. $C_{24}H_{22}Br_2O_6$ requires C, 50·9; H, 3·95%).

(−)-*trans*-Homochrysanthemic acid (0·19 g.), $[\alpha]_D^{19.5}$ −30·6°, similarly gave (+)-*trans*-homocaronic acid (XVII), partly crystalline, $[\alpha]_D^{19.5}$ +26·7° ± 0·6°. The *bis*-4-*bromophenacyl ester* formed needles (from ethanol), m. p. 105—107°, $[\alpha]_D^{21}$ +15·1° ± 0·2° (*c* 0·181 in acetone) (Found: C, 50·85; H, 3·95%). The infrared spectra of the (+)- and the (−)-ester were identical. On crystallising equal weights together from ethanol the (±)-ester was isolated, having m. p. and mixed m. p. 105—107°.

Resolution of (±)-cis-*Chrysanthemic Acid.*—The (±)-*cis*-acid (55 g.) in ethanol (150 ml.) at 70° was treated with quinine trihydrate. Filtration and repeated crystallisation from 80% aqueous ethanol gave quinine salt, m. p. 127—131°, $[\alpha]_D^{20}$ −105·5°, which, decomposed, gave (±)-*cis*-chrysanthemic acid, m. p. 41—43°, $[\alpha]_D^{20}$ +40·2° ± 0·4° (*c* 2·18) {lit.,[12] m. p. 127—135°, $[\alpha]_D$ −103·5°, for the salt; and m. p. 40—42°, $[\alpha]_D^{22}$ +40·8°, for the acid}. The salt recovered

[32] Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 177.

from the filtrate gave (−)-*cis*-chrysanthemic acid, $[\alpha]_D^{26}$ −23·6° (*c* 1·87), which was further resolved with (+)-α-methylbenzylamine. Crystallisations from ethanol–water (1 : 1) gave the (+)-α-methylbenzylamine (−)-acid *salt*, m. p. 127—132°, $[\alpha]_D^{22}$ +7·5°. On decomposition (−)-*cis*-chrysanthemic acid, b. p. 115—120°/15 mm., n_D^{22} 1·4858, $[\alpha]_D^{21}$ −41·8° ± 1·0° (*c* 0·99), was obtained {lit.,[15] $[\alpha]_D^{20}$ −40·8° (*c* 1·52)}.

(+)- *and* (−)-cis-*Homochrysanthemic Acid.*—(+)-*cis*-Chrysanthemic acid (6·1 g.) was converted into the acid chloride and thence, *via* the diazo-ketone, by the silver benzoate–triethylamine method, into methyl (+)-*cis*-homochrysanthemate (1·1 g.), b. p. 58—59°/0·3 mm., n_D^{20} 1·4683, $[\alpha]_D$ +58·8° ± 0·1° (*c* 1·080). The infrared spectrum was closely similar to that of the (±)-ester and mixed gas–liquid chromatography on Dow-Silicone caused no separation. On hydrolysis the (+)-*cis*-acid (XI), $[\alpha]_D^{22}$ +30·7° ± 0·2° (*c* 0·360), n_D^{22} 1·4770 (0·6 g.), was obtained: the infrared spectrum was closely similar to that of the (±)-acid. Another specimen was made from (+)-*cis*-chrysanthemic acid (8·1 g.) by the amide route: the (+)-*cis*-amide had $[\alpha]_D^{20}$ +17·4° ± 0·85° (*c* 1·15), and the (+)-*cis*-acid (0·37 g.), b. p. 97—98°/0·2 mm., $[\alpha]_D^{21}$ + 30·7° ± 0·8° (*c* 0·90).

By the amide route, (−)-*cis*-chrysanthemic acid (7·34 g.) gave (−)-*cis*-homochrysanthemic acid (XII) (1·53 g.), b. p. 113—114°/0·4 mm., n_D^{21} 1·4760, $[\alpha]_D^{22}$ −32·1° ± 0·8° (*c* 1·25). The antipodes had identical infrared spectra and a mixture of equal weights had an infrared spectrum identical with that of (±)-*cis*-homochrysanthemic acid.

(+)- *and* (−)-cis-*Homocaronic Acid.*—Oxidation of (+)-*cis*-homochrysanthemic acid (0·33 g.; from the methyl ester route) by the method employed for the (±)-*cis*-acid gave (+)-*cis*-homocaronic acid (XV) (0·105 g.), $[\alpha]_D^{22}$ +56·6° ± 0·2° (*c* 0·910), semi-crystalline. The biscyclohexylamine salt had m. p. 169—170°, $[\alpha]_D^{18}$ −38·8° ± 3° (*c* 0·465). A second oxidation (material from the amide route) gave biscyclohexylamine salt, m. p. 199—201°, $[\alpha]_D^{20}$ −31·8° ± 0·8° (*c* 0·86). The m. p.s of these salts appear to depend on the conditions of the determination, and polymorphism may occur.

Oxidation of (−)-*cis*-homochrysanthemic acid gave impure (−)-*cis*-homocaronic acid (XVI), semi-crystalline, $[\alpha]_D^{20}$ −27·6° ± 0·5°. The biscyclohexylamine salt had m. p. 199—201°, $[\alpha]_D^{20}$ +32·9° ± 0·8° (*c* 0·56). The (+)- and the (−)-salt had identical infrared spectra. Dissolving them together in methanol and precipitating them with dry acetone gave a product of m. p. 141—142°, undepressed on admixture with authentic (±)-biscyclohexylamine-*cis*-homocaronate.

Widmark purified the homocaronic acid obtained from the oxidation of the oxime (III) by conversion into the biscyclohexylamine salt, m. p. 196—199°, and the acid itself was then isolated with m. p. 115—117° and $[\alpha]_D^{25}$ +62° by regeneration.[3] A specimen of Widmark's acid was methylated with diazomethane. The infrared spectrum was identical with that of our methyl (±)-*cis*-homocaronate and different from our methyl (±)-*trans*-homocaronate. Widmark's ester and our (+)- or (±)-*cis*-ester could not be separated gas chromatographically. The biscyclohexylamine salt prepared from Widmark's acid had m. p. 179—182° (variable), $[\alpha]_D^{22}$ −36° ± 6° (*c* 0·469).

Degradation of α-*Pinene to* cis-*Norpinic Acid.*—α-Pinene was oxidised by permanganate to (±)-*cis*-pinonic acid, needles, m. p. 103—105° (Found: C, 65·25; H, 8·7. Calc. for $C_{10}H_{16}O_2$: C, 65·2; H, 8·75%), $\nu_{max.}$ (mull) 3226s (OH), 1745 (lactone), and 1701 (C=O) cm.$^{-1}$, $\nu_{max.}$ (in $CHCl_3$) 3484w (OH) and 1701s (C=O and CO_2H) (lit.,[7-9] m. p. 103—105°).

This acid was oxidised to (±)-*cis*-pinic acid, m. p. 101·5—102·5 (Found: C, 57·75; H, 7·7. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%), $\nu_{max.}$ (mull) 1709 (CO_2H) and 1664 (CO_2H) cm.$^{-1}$ (lit.,[7] m. p. 101·5—102·5°).

(±)-*cis*-Pinic acid was brominated and converted into hydroxypinic acid, m. p. 189—192°, $\nu_{max.}$ (mull) 3425 (OH), 1718 (CO_2H), and 1704 (CO_2H) cm.$^{-1}$ (lit.,[7,8] m. p. 191—192°). Hydroxypinic acid was oxidised by lead tetra-acetate [10] to *cis*-norpinic acid, needles (from nitromethane), m. p. 175—176° (Found: C, 55·9; H, 7·05. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·05%) (lit.,[7,8] m. p. 175°). The m. p. was depressed to 135—139° on admixture with (±)-*cis*-homocaronic acid and comparison of infrared mull spectra confirmed non-identity. *cis*-Norpinic acid had $\nu_{max.}$ (mull) 1715 (CO_2H) and 1695 (CO_2H) cm.$^{-1}$.

Hydrolysis of (±)-*Dimethyl* cis- *and* trans-*Homocaronate:* 3,3-*dimethylbutene*-1,4-*dicarboxylic acid.*—(*a*) *Preparative.* (±)-Dimethyl *cis*-homocaronate (140 mg.) was refluxed with 10% methanolic potassium hydroxide (5 ml.) for 3 hr. The excess of methanol was distilled off and water (3 ml.) added. The solution was acidified with phosphoric acid and extracted with ether.

The extracts were dried and evaporated to give a solid (106 mg.), m. p. 110—114° (not clear), which when crystallised from hot water (charcoal) gave 3,3-dimethylbutene-1,4-dicarboxylic acid (IV), m. p. 135—137° (Found: C, 55·95; H, 7·0. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·05%), $\nu_{max.}$ (mull) 1705 (saturated CO_2H), 1695 (conjugated CO_2H), 1645 and 985 (*trans*-CH=CH) cm.$^{-1}$ (lit.,[3] m. p. 134—136°). The acid absorbed 0·99 ml. of hydrogen over Adams catalyst in ethyl acetate to give 3,3-dimethyladipic acid, m. p. 86° (from ethyl acetate–light petroleum) (lit.,[33] m. p. 86—87°).

(±)-Dimethyl *trans*-homocaronate (250 mg.), similarly treated, gave crude product (172 mg.), m. p. 175—178°. When crystallised from hot water (±)-*trans*-homocaronic acid, m. p. and mixed m. p. 194—195°, was obtained.

(*b*) *Quantitative examination of products.* The acid or methyl ester (200 mg.) was refluxed for 3 hr. with 10% methanolic potassium hydroxide (10 ml.). Most of the methanol was evaporated and water (15 ml.) was added. Neutral material was removed with ether (10 ml.), the solution was acidified with 2N-hydrochloric acid, and the acids were extracted with ether. The ethereal extracts were added to ethereal diazomethane (excess) and after 30 min. the solution was dried and evaporated. The residue was allowed to attain constant weight in a vacuum-desiccator. It was then dissolved in chloroform and analysed by gas–liquid chromatography on a 6 ft. column containing poly(ethylene glycol) adipate on Celite at 160°. The results for the homocaronic acids and esters are tabulated.

	Recovery (%)	3,3-Dimethylbutene diester * (%)	Uncleaved cyclopropane diester (%)
(±)-*trans*-Acid	94·5	nil	100
(±)-*cis*-Acid	95·0	nil	100
(±)-*trans*-Diester	92·5	10·8	89·2
		10·0	90·0
(±)-*cis*-Diester	94·2	42·8	57·2
		39·4	60·6
		40·4	59·6

* Dimethyl 3,3-dimethylbutene-1,4-dicarboxylate. Calibration was made by using known standard mixtures of the esters being analysed.

trans-2,3-*Dihydromuconic Acid*.[34]—*cis,cis*-Muconic acid, m. p. 187—190° (decomp.), was treated with 75% sulphuric acid, to give 3-(carboxymethyl)but-2-enolide, m. p. 112° (lit.,[34] m. p. 111°) and then hydrogenated to 3-(carboxymethyl)butanolide, m. p. 58—60° (lit.,[34] m. p. 60—61°). The lactone was esterified with diazomethane and then refluxed with sodium hydrogen carbonate solution and treated with hydrochloric acid, to give *trans*-dihydromuconic acid, m. p. 187—189°, $\nu_{max.}$ (mull) 1710 (satd. CO_2H), 1691 (conjugated CO_2H), 1657 and 973 (*trans*-CH:CH) cm.$^{-1}$ (lit.,[34] m. p. 191°). Admixture with Dr. Ullmann's sample,[16] m. p. 185—188°, caused no depression of m. p. M. p.s are dependent on the rate of heating: those given were carried out on a Kofler block. Both samples decolorised permanganate solution and their infrared spectra support the identity.

(±)-4,4-*Dimethyl*-3-(3-*methylbut*-1-*enyl*)*butanolide* (cf. XX).—(±)-*trans*-Homochrysanthemamide (2 g.) was refluxed for 4½ hr. with 20% sulphuric acid (10 ml.). The product was extracted with ether, and the ethereal extracts were dried, evaporated, and distilled, to give the *lactone* (1·75 g.), b. p. 78—80°/0·1 mm., n_D^{20} 1·4585, having a characteristic odour (Found: C, 72·35; H, 9·85. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%). The lactone had $\nu_{max.}$ (liq. film) 1766 (γ-lactone) and 1663 (C=C) cm.$^{-1}$. In chloroform, however, it had $\nu_{max.}$ 1752 cm.$^{-1}$. The lactone absorbed 0·99 mol. of hydrogen on catalytic hydrogenation.

(±)-*trans*-Homochrysanthemic acid (3 g.), similarly treated with acid, gave the same lactone (1·92 g.) (infrared spectrum, gas–liquid chromatography on Apiezon grease at 198°). Also (±)-*cis*-homochrysanthemamide (1 g.) gave the same lactone (0·57 g.).

(+)-*trans*-Homochrysanthemamide (1·67 g.), when refluxed with 25% sulphuric acid as above, gave the (+)-butanolide (XX) (0·66 g.), b. p. 90—92°/1·0 mm., n_D^{24} 1·4572, $[\alpha]_D^{19}$ 37·0° ± 0·6° (*c* 1·21). (+)-*cis*-Homochrysanthemamide (1·5 g.) similarly gave the (+)-butanolide (XX), b. p. 81—82°/0·4 mm., n_D^{18} 1·4575, $[\alpha]_D^{19}$ +36·4° ± 0·5° (*c* 2·06). The infrared spectrum was identical with that of the (±)-lactone above.

[33] Rydon, *J.*, 1937, 1340.
[34] Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228.

Ozonolysis of (±)-4,4-*Dimethyl*-3-(3-*methylbut*-1-*enyl*)*butanolide*.—The lactone (298 mg.) was ozonised at 0° for 2 hr. in glacial acetic acid. Zinc dust was added and the mixture was immediately steam-distilled into 2,4-dinitrophenylhydrazine reagent. The derivative (147 mg.) was filtered off and chromatographed on 1 : 4 bentonite–Celite from chloroform, to give, after crystallisation from ethanol, isobutyraldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 182—183°. Infrared spectra confirmed the identification.

The lactone (960 mg.) was again ozonised at 0°, in n-hexane (15 ml.). After evaporation at 5°, water (15 ml.) was added to the glassy residue and the mixture was refluxed for 2 hr. Volatile material was removed by distillation, the volume of the residue being kept at about 10 ml. by addition of water. Finally the solution was concentrated to give crystals (0·38 g.), m. p. 160—165°. Recrystallisation from hot water (charcoal) gave (±)-terebic acid, m. p. and mixed m. p. 175—176° (and infrared comparison). Ozonolysis in ethyl acetate or chloroform gave poorer yields of (±)-terebic acid. Authentic (±)-terebic acid [35] had m. p. 175—176° (Found: C, 53·45; H, 6·3. Calc. for $C_7H_{10}O_4$: C, 53·3; H, 6·35%), $\nu_{max.}$ (mull) 1749 (γ-lactone) cm.$^{-1}$. Methyl terebate had $\nu_{max.}$ (liquid film) 1766 (γ-lactone) and 1740 (CO_2Me) cm.$^{-1}$.

The (+)-lactone (XX) (0·61 g.), ozonised similarly, gave (−)-terebic acid (XXII) (0·23 g.), m. p. 199—201°. Recrystallisation from water gave needles, m. p. 205—206°, $[\alpha]_D^{23}$ −12·25° ± 0·62° (*c* 1·63 in acetone) {lit.,[36] m. p. 201—205°, $[\alpha]_D^{25}$ −13·2° (*c* 3·48 in acetone)}.

Tetrahydro-2,2-*dimethyl*-6-*oxopyran*-3-*carboxylic Acid* (XXIII; R = CO_2H).—This acid was prepared from diethyl α-acetylglutarate and methylmagnesium iodide and had b. p. 113—114°/0·5 mm., n_D^{21} 1·4472, prisms, m. p. 35—36·5°, and gave a 4-*bromophenacyl ester*, plates, m. p. 89—91° (from ethanol) (Found: C, 51·65; H, 4·85. $C_{16}H_{17}BrO_5$ requires C, 52·0; H, 4·65%), and a 4-*phenylphenacyl ester*, plates, m. p. 105—107° (Found: C, 71·55; H, 6·3. $C_{22}H_{22}O_5$ requires C, 72·1; H, 6·05%). The ozonolysis product of Katsuda *et al.*[11] had m. p. 175° and is clearly not this acid: we cannot account for their finding acetone as the other product.

(±)-trans-2′-*Chlorodihydrochrysanthemic Acid*.—(±)-*trans*-Chrysanthemic acid (8 g.) was warmed on a water-bath for 25 min. with concentrated hydrochloric acid (20 ml.). Water (10 ml.) was added and the solution was extracted with ether. Evaporation of the extract gave solid (7·3 g.), m. p. 91—93°, which when crystallised from light petroleum (b. p. 60—80°) gave (±)-*trans*-2′-chlorodihydrochrysanthemic acid, needles, m. p. 93—94·5° (Found: C, 58·5; H, 8·25; Cl, 17·35. Calc. for $C_{10}H_{17}ClO_2$: C, 58·6; H, 8·3; Cl, 17·3%), $\nu_{max.}$ (mull) 1689 (CO_2H) cm.$^{-1}$ (lit.,[37] m. p. 91—92° for material made by a different route). When refluxed with 10% aqueous sodium hydroxide (50 ml.) for 3 hr. the chloro-compound (1 g.) gave a solid (0·81 g.), m. p. 89—90°, extracted with ether after acidification. Recrystallisation from light petroleum (b. p. 60—80°)–ethyl acetate gave (±)-*trans*-dihydro-2′-hydroxychrysanthemic acid,[38] m. p. and mixed m. p. 95·5—96·5° (and infrared comparison).

(±)-*Dimethyl* trans-*Chrysanthemumdicarboxylate* (XXXIV; R = R′ = Me).—Natural acid (isolated above), m. p. 160—164°, was esterified with diazomethane in ether to give the ester, b. p. 150—151°/15 mm., n_D^{22} 1·4830—1·4835 (lit.,[39] b. p. 149°/16 mm.). This was used in the nuclear magnetic resonance work.

We thank Dr. J. W. Lown for the nuclear magnetic resonance information reported, also Dr. M. Elliott, Dr. W. F. Ringh and Benzol Products, Co., U.S.A., Dr. G. F. Ullmann, and Professor G. Widmark for gifts of materials or specimens. Two of us (J. C. and D. A. M.) thank the D.S.I.R. for post-graduate awards.

Department of Chemistry, King's College (University of London), Strand, London W.C.2. [*Received, February 28th*, 1963.]

[35] Simonsen, *J.*, 1907, **91**, 184.
[36] Fredga, *Svensk Papperstidn.*, 1947, **50**, 91.
[37] Matsui, Yamashita, Miyano, Kitamuka, Suzuki, and Hamiro, *Bull. Agric. Chem. Soc. Japan*, 1956, **20**, 90.
[38] Harper and Thompson, *J. Sci. Food and Agric.*, 1952, **5**, 230.
[39] Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 201.