BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3582—3585 (1969)

Studies on Reactions of Isoprenoids. VI.[1] Synthesis of *cis*-Homochrysanthemic Acid and Its Derivatives from Δ^3-Carene

Tadashi SASAKI, Shoji EGUCHI, Masatomi OHNO and Takeshi OYOBE

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya

(Received April 18, 1969)

In 1965, Matsui *et al.*[2] reported the synthesis of *trans*-chrysanthemic acid from Δ^3-carene (I) *via* the keto-aldehyde (II) through several steps. Considering the presence of a cyclopropylacetaldehyde in II, it seemed reasonable to attempt the synthesis of homochrysanthemic acid (VII) from II. This paper deals with our results, though our objective (VII) was already prepared from *cis*-chrysanthemic acid by utilizing the Arndt-Eistert homologation in low yields.[3] Since the communication by Matsui *et al.*[2] did not describe the detailed experimental conditions for the preparation of II,[4] we checked the oxidation conditions in three methods. Method 1 involved ozonolysis of I following Semmler and Schiller[4a] to II which was not isolated by Matsui *et al.*[2] We adopted a somewhat modified procedure.[4b] By decomposing the ozonized mixture with hydrogen peroxide in refluxing aqueous acetic acid for 10 hr, 3,3-dimethyl-2-(2-oxopropyl)cyclopropylacetic acid (III) was directly obtained from I in about 10% yield. Method 2 involved a new procedure adopted by Pappas and Keaveney[5] using dimethyl sulfide for decomposition of the intermediated ozonide was applied. The yield of II was 52%. II was readily convertible to III by potassium permanganate in 65% yield. This method seems to be superior to method 1 and the following method 3. Method 3 utilized direct oxidation of I with potassium permanganate in acetone at 10°C; the yield of III was only 15%, many side-products being formed, which were hardly separated from III by repeated *vacuum* distillation.

The conversion of 2-oxopropyl group into isobutenyl was fulfilled by applying the selective Grignard reaction to III and VI followed by dehydration. The keto-ester (VI), obtained from III by the acid-catalyzed esterification or by methylation with diazomethane, was treated with one mole of methylmagnesium iodide and work-up gave methyl 3,3-dimethyl-2-(2-methyl-2-hydroxypropyl)cyclopropylacetate (V). V was also prepared by the methylation of the corresponding IV which was similarly prepared in a 90% yield by the selective Grignard reaction of the keto-acid (III) with two moles of methylmagnesium iodide following the reverse-addition procedure (see Experimental). The results are summarized in Chart 1.

The last step is the dehydration of the hydroxy acid (IV) or hydroxy ester (V). Dehydration of the tertiary hydroxy group in IV and V was very likely to yield isobutenyl group, since a conjugation of the produced double bond with a cyclopropane might favor the desired dehydration,[6] though in IV, simultaneous cyclopropane-ring-opening according to the mechanism proposed by Matsui *et al.*[7] might afford γ-lactone especially in an acidic condition. In fact, when treated with the catalytic amount of *p*-toluenesulfonic acid, IV afforded the known γ-lactone, 4,4-dimethyl-3-(3-methylbut-1-enyl)butanolide (IX);[3] the structure was confirmed by means of analytical and spectral data. A *cis*-relation of the lactone ring to

1) Part V of this series: T. Sasaki, S. Eguchi and T. Ishii, This Bulletin, **42**, 558 (1969).

2) M. Matsui, H. Yoshioka, Y. Yamada, H. Sakamoto and T. Kitahara, *Agr. Biol. Chem. (Tokyo)*, **29**, 784 (1965).

3) L. Crombie, J. Crossley and D. A. Mitchard, *J. Chem. Soc.*, **1963**, 4957 and references cited therein.

4) a) F. W. Semmler and H. von Schiller, *Ber.*, **60**, 1591 (1927); b) Y-R. Naves and A-V. Grampoloff, *Helv. Chim. Acta*, **44**, 637 (1961).

5) J. J. Pappas and W. P. Keaveney, *Tetrahedron Letters*, **1966**, 4273.

6) For example, a successful dehydration of *trans*-δ-hydroxydihydrochrysanthemic acid to chrysanthemic acid by the acid-catalyzed thermal procedure has been reported: M. Matsui and M. Miyano, *Bull. Agr. Chem. Soc.* (Tokyo), **19**, 159 (1955).

7) M. Matsui, H. Yoshioka and H. Hirai, *Agr. Biol. Chem. (Tokyo)*, **28**, 456 (1964).

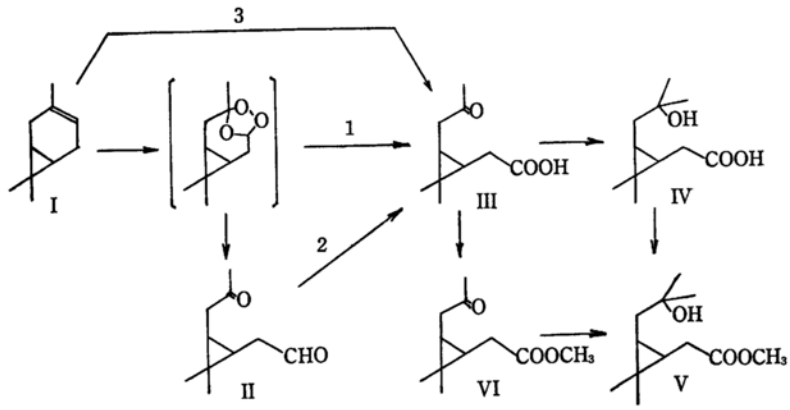

Chart 1

the isopropyl group was demonstrated by the coupling constants of two vinyl protons at 4.53 τ (J= 6.0 and 7.5 Hz) in its NMR spectrum ($CDCl_3$).[8] However, when IV was treated with phosphorus oxychloride in dry pyridine at 0°C, the product was characterized as a seven-membered lactone X on the basis of analytical and spectral data. The formation of IX was also recognized on treatment with phosphorus oxychloride even when a small amount of pyridine was used. At all events, homochrysanthemic acid seems more labile against acid than chrysanthemic acid, and the direct conversion of IV to homochrysanthemic acid was unsuccessful. From the results, dehydration of the hydroxy-ester (V) was investigated. When V was treated with *p*-toluenesulfonic acid in refluxing toluene for 4 hr,

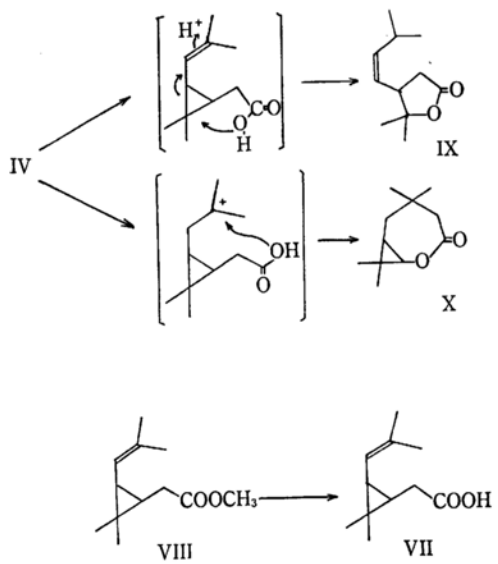

Chart 2

8) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco (1964), p. 85.

the product was found to be a mixture of methyl homochrysanthemate (VIII) and homochrysanthemic acid (VII) produced by hydrolysis of the former. The best method for dehydration of V to VIII was the treatment of V in dry pyridine with phosphorus oxychloride at 0°C. Pure VIII was obtained in a 51% yield. The acid (VII) was obtained by the alkaline hydrolysis of VIII in an 85% yield. The results are summarized in Chart 2.

Experimental

All melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. Boiling points were also not corrected. The microanalyses were performed on a Yanagimoto CHN Corder, Model MT-1, while the IR spectra were obtained on a JASCO Model IR-S spectrophotometer. The NMR spectra were recorded with a Varian A-60 and/or a Jeolco MINIMAR spectrometer using TMS as an internal standard. Chemical shifts were reported in τ values, designating singlet signals as s, doublet as d, triplet as t, multiplet as m. Ozonization was carried out with a Nippon-Ozone Ozonyzer, Model 0-1-2, controlling the reaction with bromination test and thin layer chromatography (TLC).

Oxidation of Δ^3-Carene. *Method 1.* Freshly distilled Δ^3-carene (I), bp 66—66.5°C/23.5 mmHg, n_D^{21} 1.4727 (34 g, 0.25 mol) was dissolved in a mixture of 200 m*l* of acetic acid and 10 m*l* of water and ozone was passed through this solution for 10 hr at 8—10°C. After the reaction was over, 200 m*l* of water and 6.33 m*l* of 30% hydrogen peroxide were added and the mixture was refluxed for 2 hr. After cooling, it was extracted with methylene chloride (100 m*l*×5) and the combined extract was washed with water (300 m*l*×3) and dried (Na_2SO_4). Removal of the solvent and distillation afforded 3 g (10%) of 3,3-dimethyl-2-(2-oxopropyl)-acetic acid (III): bp 135—137°C/0.25 mmHg, n_D^{25} 1.4700 (lit,[4b] bp 145—146°C/2 mmHg, n_D^{20} 1.4688).

Method 2. Ozone was passed through a solution of I (68 g, 0.5 mpl) in 300 m*l* of methanol for 17 hr at −60°C under cooling with a dry ice-methanol mixture until bromination test was found negative. After the reaction was over, nitrogen gas was bubbled into the reaction mixture for 5 min at the same temperature and

52 ml (43.5 g, 0.7 mol) of dimethyl sulfide was added with stirring under nitrogen atmosphere. The reaction temperature was allowed to rise gradually to room temperature after removing the cooling bath while stirring was continued. Benzene (500 ml) was added after concentration of methanol solution to *ca.* 100 ml and the benzene layer was wahed with water and dried (Na_2SO_4), and the residue obtained by removal of the solvent was distilled to afford 35 g (40%) of 3,3-dimethyl-2-(2-oxopropyl)cyclopropylacetaldehyde (II) as an oil with a bp 80—83°C/1 mmHg, n_D^{20} 1.4600 (lit,[4b] bp 92-94°C/2 mmHg, n_D^{20} 1.4601).

Method 3. To a stirred solution of I (13.6 g, 0.1 mol) in 100 ml of acetone and 25 ml of water, potassium permanganate (11 g) was added little by little at 5—10°C. After reaction was over, 5 ml of ethanol was added to the reaction mixture in order to decompose the excess potassium permanganate and the resulting precipitates were filtered and washed with acetone (50 ml). The combined filtrate and washings were concentrated and the residue obtained was distilled to give 1.95 g (15%) of III with bp 145—148°C/2 mmHg, n_D^{20} 1.4688 (lit,[4b] bp 145—146°C/2 mmHg).

Oxidation of 3, 3-Dimethyl-2-(2-oxopropyl)cyclopropylacetaldehyde (II) to Keto-carboxylic Acid (III). To a mixture of II (26 g, 0.15 mol), acetone (200 ml), and water (50 ml) was added 22 g of potassium permanganate in small portions with stirring at 5—10°C during 3 hr. Excess potassium permanganate was decomposed with addition of ethanol and the resulting precipitates were filtered and washed with acetone (50 ml). The combined filtrate and washings were concentrated *in vacuo* to *ca.* 100 ml. The residue obtained was extracted with ether after addition of water (100 ml) and the ether layer was dried (Na_2SO_4). Removal of ether gave crude acid (III) which was distilled to afford 17.5 g (65%) of pure III with bp 110—115°C/0.5 mmHg, n_D^{20} 1.4670 (lit,[4b] bp 145—146°C/2 mmHg, n_D^{20} 1.4688).

Reaction of the Keto-carboxylic Acid (III) with Methylmagnesium Iodide. Magnesium (1.366 g, 0.055 g atom) was suspended in 100 ml of dry ether and to this was added an ethereal solution of methyl iodide (7.8 g, 0.055 mol in 50 ml) according to general procedures for preparation of methyl Grignard reagent. To a stirred solution of III (4.6 g, 0.025 mol) in 50 ml of ether was added the Grignard reagent at room temperature very slowly in 3 hr. Stirring was continued overnight, and water was added to produce a turbid solution, to which aqueous ammonium chloride was added. This was acidified with 10% hydrochloric acid and the ether layer was separated and dried (Na_2SO_4). Removal of the solvent left crystalline solids which were recrystallized from *n*-hexane to give 4.51 g (90%) of 3,3-dimethyl-2-(2-methyl-2-hydroxypropyl)cyclopropylacetic acid (IV) as colorless needles with a mp of 87—88°C. IR (KBr) cm^{-1}: 3300 (OH), 3000—2500 and 1680 (COOH) 1150 (-C(-)-O). NMR ($CDCl_3$)τ : 2.90 (2 H, s, COOH and OH), 7.07 (2 H, d, J=7.0 Hz, $-CH_2-$), 8.54 (2 H, d, J=6.0 Hz, $-CH_2-$), 8.72 (6 H, s, $-(HO)C(C\underline{H}_3)_2$), 8.90 and 9.08 (each 3 H, each s, $C(CH_3)_2$), and 9.00—9.32 (*ca.* 2 H, m, cyclopropane ring protons).

Found: C, 65.68; H, 10.01%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Esterification of the Hydroxy-carboxylic Acid (IV) to (V). A solution of IV (1 g, 0.005 mol) in ether was treated with an ethereal solution of diazomethane which was prepared from 2 g of nitrosomethylurea and 6 ml of 50% aqueous potassium hydroxide in 50 ml of ether. After standing overnight, ether and excess diazomethane were removed to give pure ester (V) in almost quantitative yield. IR (neat) cm^{-1}: 3550 and 1170 (-C(-)-OH), 1740 and 1029 ($COOCH_3$), and 2910, 1450, 910 and 770. NMR($CDCl_3$) τ: 6.22 (3 H, s, $COOCH_3$), 7.65 (2 H, d, J=7.0 Hz, $-C\underline{H}_2COOCH_3$), 8.24 (1 H, s, OH), 8.53 (2 H, d, J=7.0 Hz, $-CH_2-$), 8.71 (6 H, s, $-(HO)C(C\underline{H}_3)_2$), 8.86 and 9.10 (*ca.* 6 H, each s, $C(CH_3)_2$), and 9.00—9.40 (*ca.* 2 H, m, cyclopropane ring protons).

Found: C, 67.55; H, 10.76%. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35%.

Preparation of the Keto-ester (VI). Treatment of III (8.3 g, 0.045 mol) with an excess diazomethane in ether at room temperature afforded crude (VI) which was distilled to give 8.1 g (92%) of pure VI with a bp of 83—85°C/1 mmHg, n_D^{20} 1.4518 (lit,[4b] bp 98—99°C/2 mmHg, n_D^{20} 1.4518). Treatment of III in refluxing methanol in the presence of a catalytic amount of sulfuric acid afforded also VI in a 50% yield, though some decomposition reactions were unavoidable.

Grignard Reaction of Keto-ester (VI). To a stirred solution of VI (8 g, 0.043 mol) in 50 ml of ether was added slowly the Grignard reagent prepared from 0.945 g (0.043 g atom) of magnesium and 6.11 g (0.043 mol) of methyl iodide in 100 ml of ether. Stirring was continued for 3 hr at room temperature and aqueous ammonium chloride was added to the reaction mixture which was neutralized with 10% hydrochloric acid. The ether layer was separated and the water layer was extracted with ether (30 ml×2). The combined ether layer and extracts were washed with water and dried (Na_2SO_4). After removal of ether, the oily residue was distilled to give 7.74 g of the hydroxy-ester (V), bp 76—80°C/2 mmHg, n_D^{20} 1.4560. Its infrared spectrum (neat) was superimposable on that of V prepared from IV.

Dehydration of the Hydroxy-carboxylic Acid (IV).

a) With p-Toluenesulfonic Acid. A mixture of 0.5 g (0.0025 mol) of IV and 50 mg of *p*-toluenesulfonic acid was dry-distilled to give an oil with a bp of 115—120°C/1 mmHg, which was further purified by chromatography on a silica-gel (Mallinckrodt, 100 Mesh) column eluting with methylene chloride to give 300 mg (66%) of γ-lactone (IX). IR (neat) cm^{-1}: 2980 (CH), 1780 (γ-lactone), and 1660 (C=C). NMR ($CDCl_3$)τ : 4.46 and 4.60 (2 H, q, J=6.5 and 7.5 Hz, -CH=CH-, *cis*), 7.00—7.80 (4 H, m, CH_2 and CH), 8.52 and 8.72 (each 3 H, each s, $C(CH_3)_2$), and 8.96 (6 H, d, J=6.5 Hz, $CH(CH_3)_2$).

Found: C, 72.58; H, 9.99%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

b) With Phosphorus Oxychloride and Pyridine. To a stirred solution of IV (0.3 g, 0.0015 mol) in 5 ml of dry pyridine was added 0.55 ml of phosphorus oxychloride at 0°C during 30 min and the mixture was stirred for another 2.5 hr. After confirming the termination of reaction by TLC, the reaction mixture was poured onto ice-water and extracted with chloroform (20 ml× 5). The combined chloroform extracts were washed with 5% hydrochloric acid, and then with water several times and dried (Na_2SO_4). Removal of chloroform *in vacuo* afforded 160 mg (59%) of needles of the ε-lactone derivative (X), mp 40—41°C. IR (KBr) cm^{-1}: 2900 (OH), 1712 (ε-lactone) and no OH and C=C bands.

NMR ($CDCl_3$)τ: 6.98—8.20 (4 H, complex m, $-CH_2-\times 2$), 8.49 and 8.55 (6 H, eash s, $-O-C(CH_3)_2$), 8.90 (6 H, s, $C(CH_3)_2$), and *ca.* 8.90—9.21 (*ca.* 2 H, m, cyclopropane ring protons).

Found: C, 72.49; H, 10.22%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

When the amount of pyridine decreased or in the absence of pyridine, the exothermic reaction occurred in the above reaction to result in the formation of the γ-lactone derivative (IX) which was confirmed by infrared specral comparison with a specimen prepared as above.

Dehydration of the Hydroxy-ester (V). *a) With p-Toluenesulfonic Acid.* A solution of V (4.8 g, 0.022 mol) and *p*-toluenesulfonic acid (20 mg) in 50 m*l* of dry toluene was refluxed for 4 hr to give a red solution. Purification of the products by distillation and chromatography on a silica-gel column afforded 0.84 g (24%) of methyl *cis*-homochrysanthemate (VIII) as an oil with a bp of 55—60°C/0.3 mmHg and 2.4 g (50%) of *cis*-homochrysanthemic acid (VII) with a bp of 110—115° C/0.1 mmHg, n_D^{20} 1.4652, both of which were confirmed by infrared spectral comparison with the respective specimen prepared by the following procedure.

b) With Phophorus Oxychloride and Pyridine. Similar procedure to the dehydration of IV was carried out on V (1 g, 0.0046 mol) in 10 m*l* of dry pyridine and phosphorus oxychloride (0.6 m*l*) at 0°C for 3 hr. After pouring onto ice-water, the reaction mixture was extracted with benzene. The benzene extracts were chromatographed on a silica-gel column to give 0.47 g (51%) of methyl *cis*-homochrysanthemate, n_D^{20} 1.4658 (lit.,[3] n_D^{20} 1.4663). IR (neat) cm^{-1}: 1740 and 1065 ($COOCH_3$), 1650 and 840 (CH=C). NMR ($CDCl_3$)τ: 5.18 (1 H, broad d, J=7.5 Hz, -CH=C), 6.37 (3 H, s, $COOCH_3$), 7.37 (2 H, d, J=7.0 Hz, $-C\underline{H}_2-COOCH_3$), 8.07 (*ca.* 1 H, superimposed t, J=*ca.* 7.5 Hz, allylic cyclopropane ring proton), 8.27 and 8.32 (*ca.* 6 H, overlapped s, $C=C(CH_3)_2$), 8.86 and 9.05 (*ca.* 6 H, each s, $C(CH_3)_2$) and *ca.* 8.80—9.23 (*ca.* 1 H, complex m, cyclopropane ring proton).

Found: C, 73.26; H, 10.36%. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%.

***cis*-Homochrysanthemic Acid (VII) by Hydrolysis of Its Ester (VIII).** A suspension of VIII (200 mg) in 5 m*l* of 5% sodium hydroxide was stirred at room temperature for 12 hr. The mixture was acidified with 10% hydrochloric acid and extracted with chloroform (20 m*l*×5). The combined chloroform extract was washed with water and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded 160 mg (85%) of VII as an oil. IR (neat) cm^{-1}: 3100—2729 and 1703 (COOH), 1648 and 840 (CH=C). NMR ($CDCl_3$)τ: −1.25 (1 H, s, COOH), and other signals were almost the same as those of VIII.

Found: C, 72.36; H, 9.90%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.