Selective Synthesis of Optically Pure (+) and (-)-*trans*-Chrysanthemic Acids from (+) Δ^3 -Carene

Sir:

(+) Δ^3 -Carene (I), contained in considerable amounts in turpentine from *Pinus sylvestris* L., *Pinus longifolia* Roxb., Pinaceae etc., has been found no application in chemical synthesis up to date. However, (+) Δ^3 -carene (I) is now

found its utilization by the present authors in selective synthesis of optically pure *trans*-chrysanthemic acids, in particular (+)-*trans*-chrysanthemic acid identical with an acidic component of naturally occurring rethrans.

Keto-aldehyde (II), which had been obtained by Semmler and von Schiller¹⁾ by ozonolysis of I, was cyclized by aldol condensation in the presence of dil. aqueous alkali *p*-toluenesulfonic acid or sodium acetate in acetic

anhydride to give a conjugated ketone, 2-acetyl-6,6-dimethyl-bicyclo [3,1,0]-1-hexene (III) in the yield from 40 to 70%; n_D^{22} 1.4865; $[\alpha]_D^{25} +252^\circ$ (chloroform); $\nu_{\max}$ 1675, 1603, 810 cm^{-1} ; τ 9.15, 8.80, 8.55, 7.8~7.9, 7.65, 7.4, 3.3 p.p.m. (carbontetrachloride); semicarbazone, m.p. 214°C. *Anal.* Found: C, 63.60; H, 7.99; N,

1) F. W. Semmler and H. von Schiller, *Ber.* **60**, 1591 (1927).

20.01. Calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27%.

The conjugated ketone (III) was oxidized with ozone in acetic acid at 5°C. Resulting ozonide was decomposed by heating at 50°C and treated with aqueous alkaline hydrogen peroxide. The reaction product was purified through formation of cyclohexylamine salt, m.p. 197°C, to give pure (+)-*cis*-homocaronic acid (IV), m.p. 115°C, $[\alpha]_D^{25} + 68.6^\circ$ (ethanol). IV was heated in excess acetic anhydride at 140°C for 1 hour, and removal of acetic anhydride under reduced pressure afforded corresponding anhydride (V) as a light brown oil in quantitative yield, $\nu_{\max}$ 2960, 1790, 1750, 1265, 1150, 1090, 1030, 1005, 990, 955 cm^{-1} . UV spectrum revealed no maximum in the range from 200 to 300 $\text{m}\mu$. Therefore there was no doubt concerning the existence of cyclopropane ring in the very anhydride (V). V was treated with 2 moles of methylmagnesium iodide in anhydrous ether under cooling at 30°C and resulting Grignard complex was decomposed with aqueous ammonium chloride. The aqueous layer was acidified with 10% sulfuric acid and extracted with ether. The ether solution was once washed with 5% sodium carbonate and evaporated to afford crystalline γ -lactone (VI) in a very small amount: m.p. 83°C; $\nu_{\max}^{\text{nujol}}$ 1780, 1380, 1260, 1110, 940, 855 cm^{-1} . VI was found to be identical with (+)-pyrocine²⁾ (VI). One of possible explanations for the formation of VI from V could be as follows: attack of Grignard reagent on the carbonyl group just adjacent to cyclopropane ring might afford a lactone (VII), which was hydrolyzed with dil. sulfuric acid to give an intermediate hydroxylic acid (VIII). Dehydration of tertiary hydroxyl group in VIII was very likely to occur, and cyclopropane ring simultaneously opened according to the mechanism proposed formerly by the authors³⁾ to afford an intermediate unsaturated

carboxylic acid (IX), which was thought to have a strong inclination to lactonize by acidic treatment affording VI.

From aqueous sodium carbonate layer from which VI was separated, an oily viscous product was obtained in a considerable amounts by acidification with dil. sulfuric acid. This oily product was treated with a catalytic amount of *p*-toluenesulfonic acid in toluene under refluxing for an hour. The toluene solution was washed with aqueous 5% sodium carbonate. Removal of the solvent under reduced pressure afforded a crystalline δ -lactone (X) in 50% yield: m.p. 83°C (from *n*-hexane); $[\alpha]_D^{25} - 77^\circ$ (chloroform); $\nu_{\max}^{\text{nujol}}$ 1720, 1275, 1100, 1050, 955 cm^{-1} . X was proved to be identical with authentic (–)-dihydrochrysanthemolactone obtained by the Harper's method⁴⁾ from (–)-*cis*-chrysanthemic acid. Treatment of X with dil. sulfuric acid according to the procedure accomplished by Harper⁴⁾ easily gave (–)-*cis*-chrysanthemic acid (XI). Ethyl (–)-*cis*-chrysanthemate (XII), prepared from XI with 2% ethanolic hydrogen chloride, was treated with a catalytic amount of sodium ethoxide in absolute ethanol at 180°C in a sealed tube for 2 hours, and subsequent hydrolysis of the product with potassium hydroxide afforded optically pure (+)-*trans*-chrysanthemic acid (XIII), m.p. 17°C, $[\alpha]_D^{25} + 14^\circ$ (ethanol), in 90% yield. (–)-*trans*-Chrysanthemic acid was also synthesized in fairly good yield from (+)-*f*³-carene in a particular route described below. Treatment of keto-aldehyde (II) with sodium acetate in acetic anhydride at 130°C for 3 hours followed by fractionational separation from conjugated ketone (III) under reduced pressure gave corresponding aldehyde-enol-acetate (XIV); b.p. 87°C/0.4 mm; n_D^{14} 1.4781; $\nu_{\max}$ 2880, 1765, 1720, 1670, 1370, 1220, 1090, 1055, 930 cm^{-1} . XIV was oxidized with ozone in chloroform at –65°C and resulting ozonide was reduced with zinc dust in acetic acid at 20°C. From the neutral part of the reaction

2) M. Matsui, T. Ono, S. Kitamura and M. Toyao, *Bull. Chem. Soc. Japan*, **25**, 210 (1952).

3) M. Matsui, H. Yoshioka and H. Hirai, *This Journal*, **28**, 456 (1964).

4) S. H. Harper, and R. A. Thompson, *J. Sci. Food Agric.*, **3**, 233 (1952).

mixture, 2,2-dimethyl-3-*cis*-(2'-oxo)propyl-cyclopropane-1-aldehyde (XV) was obtained in pure state in 80% yield: b.p. 50°C/0.5 mm; n_D^{15} 1.4660; $\nu_{\max}$ 2880, 2770, 1720, 1695, 1165, 1120 cm^{-1} . The aldehyde (XV) was quite easily oxidizable with aqueous alkaline potassium permanganate or even with gaseous oxygen to afford corresponding carboxylic acid (XVI), which was treated with ethereal diazomethane. Distillation of methylated product gave methyl (-)-2,2-dimethyl-3-*cis*-(2'-oxo)propyl-cyclopropane-1-carboxylate (XVII) in 70% yield: b.p. 57°C/0.3 mm; $[\alpha]_D^{14}$ -23.7° (chloroform); $\nu_{\max}$ 2980, 1730, 1440, 1380, 1360, 1250, 1180, 1140, 990, 860 cm^{-1} . A dropwise addition of methylmagnesium iodide in ether to ether solution of the methyl ester (XVII) and subsequent chromatographic purification over alumina afforded methyl (-)-2,2-dimethyl-3-*cis*-(2'-methyl-2'-hydroxy)propyl-cyclopropane-1-carboxylate (XVIII) in 80% yield: $[\alpha]_D^{14}$ -16.1° (chloroform); $\nu_{\max}$ 3640, 2960, 1730, 1440, 1380, 1225, 1175, 1125, 990, 905, 885, 853 cm^{-1} . XVIII was hydrolyzed with methanolic potassium hydroxide, and subsequent lactonization of the acidic product with *p*-toluenesulfonic acid in toluene under reflux afforded crystalline δ -lactone (XIX) which was proved to be identical with authentic (+)-dihydrochrysanthemolactone (XIX), m.p. 83°C, $[\alpha]_D^{18}$ +77° (chloroform). By the same procedures already described XIX was derived to optically pure (-)-*trans*-chrysanthemic acid (XXI), m.p. 17°C, $[\alpha]_D^{25}$ -14° (ethanol). Dehydration of hydroxyl ester (XVIII) with a catalytic amount of *p*-toluenesulfonic acid at 110°C gave methyl *cis*-chrysanthemate (XXIV) in impure state comprising a double bond isomer of methyl (-)-*cis*-chrysanthemate: b.p. 99°C/20 mm; $\nu_{\max}$ 2960, 1730, 1440, 1380, 1200, 1175, 1140, 1075, 885, 850 cm^{-1} .

(+)-*trans*-Chrysanthemic acid (XIII) was also obtainable from (+)-*cis*-chrysanthemic acid (XX) by a selective epimerization at C-3 carbon atom by the method described below. XX was oxidized with excess amount of

aqueous alkaline potassium permanganate at 40°C and then heated at 100°C for 10 minutes. Acidic product, isolated from the reaction mixture, was found to be (+)-2,2-dimethyl-3-*trans*-(1'-oxo-2'-hydroxyl-2'-methyl)-propyl-cyclopropane-1-carboxylic acid (XXIII), m.p. 145.5° (from water), $[\alpha]_D^{15}$ +20° (pyridine), which was identical with one derived from optically pure (+)-*trans*-chrysanthemic acid by oxidation with aqueous alkaline potassium permanganate.⁵⁾

These facts unambiguously revealed occurrence of epimerization at position 3 carbon atom of *cis*-ketol-chrysanthemic acid (XXII)⁶⁾ by treatment with hot aqueous alkali resulting in *trans* configuration between positions 1 and 3 carbon atoms. (+)-*trans*-Ketol-chrysanthemic acid (XXIII) was reduced by the method described by the authors⁷⁾ giving (+)-*trans*-chrysanthemic acid (XIII) in poor yield. The details of these works will be published elsewhere in the near future.

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6) M. Matsui and H. Yoshioka, *This Journal*, 28, 32 (1964).
7) M. Matsui, M. Uchiyama and H. Yoshioka, *This Journal*, 27, 558 (1964).