IMPROVED SYNTHESES OF CARBON-14 LABELLED 3-PHENOXYBENZYL [1R,*cis*]- AND [1R,*trans*]-3-(2,2-DICHLOROVINYL)-2,2-DIMETHYLCYCLOPROPANECARBOXYLATES

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SUMMARY

3-Phenoxybenzyl [1R,cis]-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (I) and its [1R,trans]-isomer (II) were labelled with carbon-14 at C-2 position of the dichlorovinyl side chain for metabolic studies. The stereospecific syntheses were achieved according to the reaction scheme shown in Fig. 1. Wittig reaction of methyl [1R,cis]-3-formyl-2,2-dimethylcyclopropanecarboxylate with carbon-^{14}C tetrachloride followed by hydrolysis gave [1R,cis]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (VIa). Chlorination of the acid (VIa) and subsequent treatment of the resulting acid chloride with 3-phenoxybenzyl alcohol afforded 3-phenoxybenzyl [1R,cis]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (I) in the overall yield of 33%. Its [1R,trans]-isomer (II) was also prepared in 35% yield by the similar procedures. The specific activities of I and II were 4.30 and 3.80 mCi/mmole respectively.

Key Words: Carbon-14, Synthetic Pyrethroid, Insecticide.

INTRODUCTION

3-Phenoxybenzyl [1R,1S,*cis,trans*]-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (Permethrin*)(I), synthesized and tested for biological activities by Elliott *et. al.*, has been found to have high insecticidal activities[1,2]. In our laboratory, the metabolic studies of this agent in mammals have been carried out by the use of [1R,*cis*]- and [1R,*trans*]-permethrin-

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* For the practical use, "Permethrin" is a mixture of all stereoisomers concerning the substituents at C-1 and C-3 of the cyclopropane. The system used here to designate stereochemistry is discussed by Elliott *et. al.* (2).

^{14}C labelled in the phenoxybenzyl moiety[3]. In order to further investigate its metabolic fate especially of the cyclopropanecarboxylic acid, [1R,*cis*]- and [1R,*trans*]-permethrin labelled with carbon-14 at the acid moiety were desired.

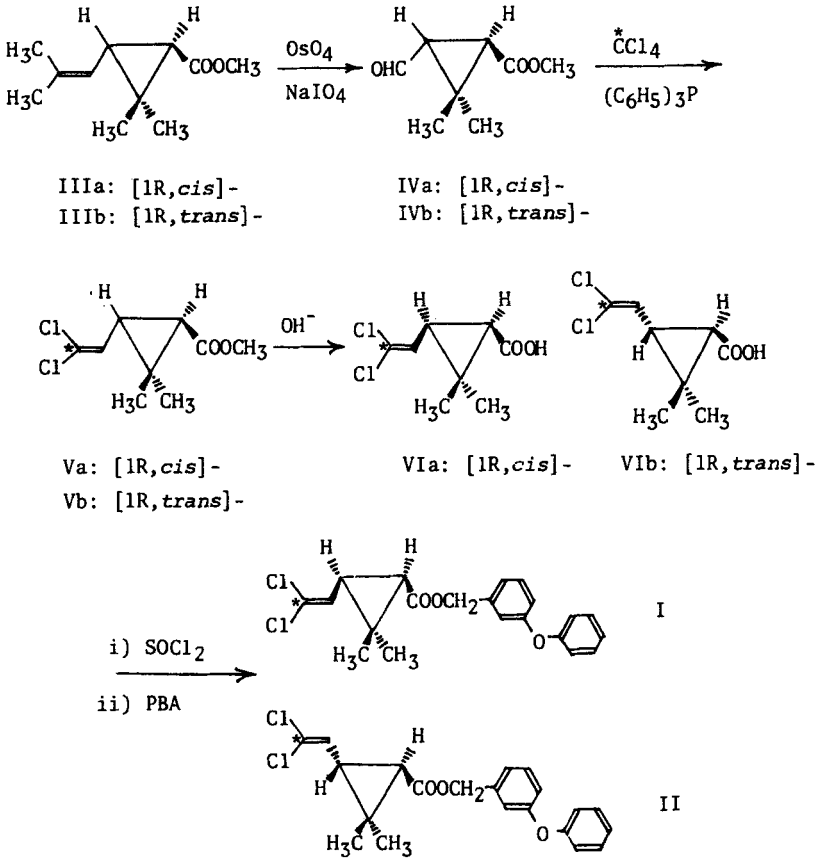
Most recently, Elliott *et. al.* already synthesized these labelled compounds (I and II) for metabolic studies[4]. Their syntheses were carried out by the routes involving Wittig reaction of methyl [1R,*trans*]-3-formyl-2,2-dimethylcyclopropanecarboxylate and also its [1S,*trans*]-isomer with carbon-^{14}C tetrachloride. For the preparation of [1R,*trans*]-permethrin-^{14}C (II), this method is of greater advantage than the conventional other methods[5,6] in terms of stereospecific synthesis. However, their method for the labelling of [1R,*cis*]-permethrin (I) seems rather tedious, since the preparation of the key intermediate, [1R,*cis*]-3-(2,2 dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (VIa) was accomplished only in a poor yield by means of thermal epimerization of the [1S,*trans*]-isomer which was obtained by the Wittig reaction of methyl [1S,*trans*]-3-formyl-2,2-dimethylcyclopropanecarboxylate with carbon-^{14}C tetrachloride.

We now wish to report much improved syntheses of [1R,*cis*]- and [1R,*trans*]-permethrin-^{14}C (I and II).

DISCUSSION

The synthetic procedures used are illustrated in Figure 1. The unlabelled starting materials, methyl [1R,*cis*]-3-formyl-2,2-dimethylcyclopropanecarboxylate (IVa) and its [1R,*trans*]-isomer (IVb) were prepared by oxidation of corresponding optically active methyl chrysanthemates (IIIa and b) with osmium tetroxide and then sodium periodate in 72 and 68% yields respectively. The structures and stereochemistry of these materials were confirmed by comparison with the authentic sample.

For the direct preparation of methyl [1R,*cis*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (Va), we investigated more elaborately Wittig reaction of [1R,*cis*]-aldehyde (IVa) with carbon-^{14}C tetrachloride. In this connection, we attempted to clarify the effects of solvent, temperature, time and molar ratio of the aldehyde (IVa) to carbon tetrachloride on the yield



IIIa: [1R,*cis*]-
IIIb: [1R,*trans*]-

IVa: [1R,*cis*]-
IVb: [1R,*trans*]-

Va: [1R,*cis*]-
Vb: [1R,*trans*]-

VIa: [1R,*cis*]-

VIb: [1R,*trans*]-

I

II

Fig. 1. The reaction sequence for the preparation of [1R,*cis*]- and [1R,*trans*]-permethrin-^{14}C

of the dichlorovinyl ester (Va). Representative results of a number of runs under various conditions are summarized in Table 1. The data suggest that the yield of Va markedly depended upon the reaction solvent used. As pointed out by Elliott[4], in benzene the dichlorovinyl ester (Va) was scarcely produced. However, it was found that the dichlorovinyl ester (Va) could be obtained in reasonable yields (60-76%) when tetrahydrofuran, dichloromethane or dichloroethane was used, and among them tetrahydrofuran seemed to be most suitable for this Wittig reaction. Concerning other elements, it was observed that the reaction time of over 48 hr and the temperature higher than 35° merely led to increase of unfavorable by-products and that the use of the [1R,*cis*]-aldehyde

Table 1. Yields of methyl [1R,*cis*]-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate in Wittig reaction

reaction solvent	reaction time (hr)	reaction temp. (°C)	molar ratio (IVa/CCl_4)	yield[a] (%)
THF[b]	48	35	1.1	76
CH_2Cl_2	48	35	1.1	65
$Cl(CH_2)_2Cl$	48	35	1.1	60
dioxane	48	35	1.1	30
benzene	48	35	1.1	10
THF	24	35	1.1	60
THF	72	35	1.1	67
THF	48	70	1.1	62
THF	48	35	1.5	63
THF	48	35	2.0	50

[a]Yields from carbon tetrachloride.
[b]Tetrahydrofuran.

(IVa) more than 1.1 equivalents resulted in decreased yields. Thus, allowing to react a 10% excess of IVa with carbon-^{14}C tetrachloride at 35° for 48 hr in a sealed pyrex tube turned out to be the optimum condition for the preparation of [1R,*cis*]-dichlorovinyl-^{14}C ester (Va).

From similar experiments using [1R,*trans*]-aldehyde (IVb), the condition described above was also found to afford the most satisfactory result for the preparation of [1R,*trans*]-dichlorovinyl-^{14}C ester (Vb). In both cases, no epimerizing product could be detected.

Under the above condition, the aldehydes (IVa and b) were converted to the desired dichlorovinyl-^{14}C esters (Va and b) which were immediately hydrolized by potassium hydroxide solution to give [1R,*cis*]- and [1R,*trans*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acids (VIa and b) in overall yields of 39 and 40% from carbon-^{14}C tetrachloride, respectively. These labelled compounds showed identical specific rotations ($[\alpha]_D$ = +32.8 for VIa and +39.8 for VIb) and NMR spectra with those of the unlabelled authentic samples.

Treatment of the acids (VIa and b) with thionyl chloride followed by esterification of the resulting acid chlorides with 3-phenoxybenzyl alcohol gave

[1R,*cis*]- and [1R,*trans*]-permethrin-^{14}C (I and II). After purification by column-chromatography on silica gel, the yields of I and II were 86 and 88% respectively. The final products showed the specific rotations of -1.0° for I and -9.5° for II, and were identical in every respect with the unlabelled authentic samples.

EXPERIMENTAL

The products of Wittig reaction of methyl [1R,*cis*]-3-formyl-2,2-dimethylcyclopropanecarboxylate with carbon tetrachloride were evaluated by gas-chromatography which was carried out on a Yanako G-80 Chromatograph (Yanagimoto MFG Co., Ltd., Japan) fitted with a thermal conductivity detector. A glass column (1 m, 3 mm I.D.) packed with 5% DC QF-1 on Chromosorb W (60-80 mesh) was used. Operating conditions: column temperature 150°, carrier gas helium (50 ml/min). The retention times of the authentic materials were: methyl [1R,*cis*]-3-formyl-2,2-dimethylcyclopropanecarboxylate (2.0 min), methyl [1R,*trans*]-3-formyl-2,2-dimethylcyclopropanecarboxylate (2.3 min), methyl [1R,*cis*]-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (2.5 min) and methyl [1R,*trans*]-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (2.8 min).

Carbon-^{14}C Tetrachloride -- Carbon-^{14}C tetrachloride (specific activity 7.95 mCi/mmol) was purchased from The Radiochemical Centre, Amersham, England, and diluted appropriately with unlabelled carbon tetrachloride.

Methyl [1R,*cis*]-3-Formyl-2,2-dimethylcyclopropanecarboxylate -- A mixture of methyl [1R,*cis*]-chrysanthemate (IIIa)(19.7 g, 104 mmol), osmium tetroxide (100 mg, 0.4 mmol), dioxane (100 ml) and water (35 ml) was stirred at room temperature for 30 min. To the mixture was added sodium periodate (40 g, 190 mmol), and the mixture was heated at 50° for 24 hr under nitrogen stream. After cooling, crystalline precipitates formed were removed by filtration and the filtrate extracted with ether. The extract was washed with 5% sodium carbonate solution and water, then dried over sodium sulfate and evaporated to give a residue. Distillation of the residue at 17 mmHg gave methyl [1R,*cis*]-3-formyl-2,2-

dimethylcyclopropanecarboxylate (12.6 g, 72%); bp 107-112° (17 mmHg); IR spectrum (chloroform): 1730 (ester) and 1705 (CHO) cm^{-1}; NMR spectrum (δ, $CDCl_3$): 1.30 (3H, singlet, CH_3), 1.58 (3H, singlet, CH_3), 1.81 (1H, doublet-doublet, J=6 Hz, J=9 Hz, C-3 proton), 2.13 (1H, doublet, J=9 Hz, C-1 proton), 3.73 (3H, singlet, $COOCH_3$) and 9.76 (1H, J=6 Hz, CHO); $[\alpha]_D^{22°}$=37.5° (c=1.1, CCl_4).

Methyl [1R,*trans*]-3-Formyl-2,2-dimethylcyclopropanecarboxylate -- Oxidation of methyl [1R,*trans*]-chrysanthemate (IIIb) by the same method as described above gave methyl [1R,*trans*]-3-formyl-2,2-dimethylcyclopropanecarboxylate (9.3 g) in 68% yield; bp 108-111° (17 mmHg); IR spectrum (chloroform): 1730 (ester) and 1710 (CHO) cm^{-1}; NMR spectrum (δ, $CDCl_3$): 1.33 (3H, singlet, CH_3), 1.37 (3H, singlet, CH_3), 2.42 (2H, multiplet, C-1 and C-3 protons), 3.68 (3H, singlet, $COOCH_3$) and 9.65 (1H, multiplet, CHO); $[\alpha]_D^{22°}$=13.3° (c=1.0 in CCl_4).

Methyl [1R,*cis*]-3-(2,2-Dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (IVa) -- To a pyrex tube containing triphenylphosphin (3.93 g, 15 mmol), methyl [1R,*cis*]-3-formyl-2,2-dimethylcyclopropanecarboxylate (1.28 g, 7.62 mmol) and anhydrous tetrahydrofuran (13 ml) was added carbon-^{14}C tetrachloride (33.1 mCi, 7.50 mmol, specific activity of about 4.4 mCi/mmol). After cooling to -180°, the tube was sealed in reduced pressure and heated at 35° for 48 hr. The crystalline precipitates produced were removed by filtration and washed with tetrahydrofuran. The filtrate and the washings were combined and evaporated to give a residue (29.5 mCi, radiochemical yield 62.1%) which was identified as methyl [1R,*cis*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate with the radiochemical purity of 95% by radio-gaschromatography and radio-TLC on silica gel (hexane: ethyl acetate= 4:1 v/v). The product was used for the following reaction without any purification.

Methyl [1R,*trans*]-3-(2,2-Dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (IVb) -- Wittig reaction of methyl [1R,*trans*]-3-formyl-2,2-dimethylcyclopropanecarboxylate (1.26 g, 7.50 mmol) with carbon-^{14}C tetrachloride (30.0 mCi, 7.48 mmol, specific activity of about 4.0 mCi/mmol) was carried out under the same

reaction condition as described above for the preparation of IVa to give methyl [1R,*trans*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (IVb) (19.3 mCi, radiochemical yield 64.3%, radiochemical purity 94%). The product was used for the next reaction without any purification.

[1R,*cis*]-3-(2,2-Dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic Acid (Va) -- A mixture of methyl [1R,*cis*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (20.5 mCi, *ca.* 4.77 mmol) and potassium hydroxide (2 g) in methanol (7 ml) was heated to reflux for 1.5 hr. After cooling, the solvent was evaporated under reduced pressure to leave a residue which was dissolved in water (20 ml), and the solution washed with dichloromethane. The aqueous solution was made acidic with 1N hydrochloric acid and extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to give a crystalline residue (13.8 mCi). Chromatography of the residue on silica gel with chloroform-methanol (6:4 v/v) followed by recrystallization from hexane gave [1R,*cis*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (Va)(12.7 mCi, 616 mg, 4.30 mCi/mmol, 61.9%); mp 90-92°; IR spectrum (chloroform) 3400-2500 (COOH) and 1680 cm^{-1}(COOH); NMR spectrum (δ, $CDCl_3$): 1.28 (6H, singlet, 2 CH_3), 1.95 (2H, multiplet, C-1 and C-3 protons), 6.13 (1H, doublet, J=8.5 Hz, vinyl proton) and 11.7 (1H, broad singlet, COOH); $[\alpha]_D^{22°}$= +32.8° (c=1.0, $CHCl_3$).

[1R,*trans*]-3-(2,2-Dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (Vb) -- Under the same reaction condition as described above, methyl [1R,*trans*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (19.3 mCi) was hydrolyzed to give [1R,*trans*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (Vb)(12.0 mCi, 658 mg, 3.81 mCi/mmol, 62.1%); mp 55-58°; IR spectrum (chloroform): 3500-2500 (COOH) and 1680 cm^{-1} (COOH); NMR spectrum (δ, $CDCl_3$): 1.22 (3H, singlet, CH_3), 1.33 (3H, singlet, CH_3), 1.56 (1H, doublet, J=5 Hz, C-1 proton), 2.22 (1H, doublet-doublet, J=5 Hz and J=9 Hz, C-3 proton), 5.56 (1H, doublet, J=9 Hz, vinyl proton) and 11.7 (1H, broad singlet, COOH); $[\alpha]_D^{22°}$= +39.8° (c=1.0, $CHCl_3$).

3-Phenoxybenzyl [1R,*cis*]-3-(2,2-Dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (I) -- A mixture of [1R,*cis*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (12.7 mCi, 616 mg, 2.95 mmol) and thionyl chloride (850 mg, 7.1 mmol) in anhydrous dichloromethane (6 ml) was heated at 60° for 2 hr. After removal of the excess of thionyl chloride and the solvent, the residue was taken up in anhydrous toluene (4 ml). The solution was added dropwise at room temperature to a mixture of 3-phenoxybenzyl alcohol (590 mg, 2.95 mmol) and pyridine (470 mg) in anhydrous toluene (5 ml). After complete addition, the mixture was stirred at room temperature for 24 hr. The mixture was poured into water and extracted with benzene. The extract was washed with 1N hydrochloric acid, 5% sodium carbonate solution and water successively, dried over sodium sulfate, and evaporated to give a residue. The residue was subjected to column chromatography on silica gel and eluted with hexane-ether (10:1 v/v). Evaporation of the main fractions gave a crystalline residue which was recrystallized from hexane to afford 3-phenoxybenzyl [1R,*cis*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate ([1R,*cis*]-permethrin-^{14}C)(I) (10.8 mCi, 981 mg, 4.30 mCi/mmol, overall yield 33.3%) as colorless needles; mp 72-73°; IR spectrum (chloroform): 1720 (ester C=O) and 1590 cm^{-1} (phenyl); NMR spectrum (δ, $CDCl_3$): 1.20 (6H, singlet, 2 (CH_3), 1.98 (2H, multiplet, C-1 and C-3 protons), 5.08 (2H, singlet, benzyl protons), 6.30 (1H, doublet-doublet, J=7 and 1 Hz, vinyl proton), 7.10 (9H, multiplet, phenyl protons); $[\alpha]_D^{20°}$ = -1.0° (c=1.0, $CHCl_3$).

3-Phenoxybenzyl [1R,*trans*]-3-(2,2-Dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate (II) -- Esterification of [1R,*trans*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylic acid (12.0 mCi, 658 mg, 3.15 mmol) was carried out by the method described above to give 3-phenoxybenzyl [1R,*trans*]-3-(2,2-dichlorovinyl-2-^{14}C)-2,2-dimethylcyclopropanecarboxylate ([1R,*trans*]-permethrin-^{14}C)(II)(10.5 mCi, 1.08 g, 3.80 mCi/mmol, overall yield 35.0%);

the IR spectrum (chloroform): 1710 (ester C=O) and 1590 cm^{-1}; NMR spectrum (δ, $CDCl_3$): 1.18 (3H, singlet, CH_3), 1.29 (3H, singlet, CH_3), 1.62 (1H, doublet, J=5 Hz, C-1 proton), 2.25 (1H, doublet-doublet, J=5 and 9 Hz, C-3 proton), 5.11

(2H, singlet, benzyl protons), 5.62 (1H, doublet, J=9 Hz, vinyl proton) and 7.22 (9H, multiplet, phenyl protons); $[\alpha]_D^{20°} = -9.5°$ (c=1.0, $CHCl_3$).

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