NOTE

Synthesis of a ^{14}C -Labelled Fungicide,

N-(3,5-dichlorophenyl)-1,2-dimethylcyclopropane-1,2-dicarboximide-
(carbonyl- ^{14}C) (Sumilex®)[†]

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N-(3,5-dichlorophenyl)-1,2-dimethylcyclopropane-1,2-dicarboximide (Sumilex®) (I) is highly effective for controlling plant diseases, for instance, bean Sclerotinia rot and cucumber gray mould¹⁾. Studies on metabolism of Sumilex in plants and mammals required the preparation of a radioactive form of the agent. In this paper, we describe the synthesis of Sumilex-(carbonyl- ^{14}C).

1. Discussion

The synthetic route leading to Sumilex-(carbonyl- ^{14}C) (I) is illustrated in Fig. 1. The key stage in this isotopic synthesis was obviously the formation of dimethyl *cis*-1,2-dimethyl-1,2-cyclopropanedicarboxylate- ^{14}C (II). McCoy reported the preparation of the unlabelled ester by condensation of 2-halopropionate with methyl 2-methylacrylate under basic conditions^{2,3)}. The method was considered to be best applicable for the present work because of the likely good yield, the high stereoselectivity in forming the desired *cis*-isomer and the relative ease of preparing 2-halopropionate-1- ^{14}C . Concerning the stereoselectivity, McCoy indicated that a somewhat

larger reduction in the *cis/trans* ratio of the isomers produced was observed in going from chloro to bromo to iodo propionates. Re-examination of the method in semimicro-scale reaction using several kinds of 2-halopropionates resulted in the conclusion that methyl 2-chloropropionate would give the best yield of the desired *cis*-isomer.

By adapting Ostwald's method⁴⁾ which was employed for the preparation of chloroacetic-1- ^{14}C acid, propionic-1- ^{14}C acid⁵⁾ was chlorinated with chlorine in the presence of catalytic amount of iodine, red phosphorus and phosphorus pentchloride at 70-80° for 9 hr; giving a crude product of 2-chloropropionic-1- ^{14}C acid. Radiogas chromatography (RGC) of the product showed that it consisted of the desired acid (83%), the starting material (14%) and unidentified by-products (3%). Chlorination of the crude 2-chloropropionic-

[†] ^{14}C 標識農薬用殺菌剤 N-(3,5-ジクロロフェニル)-1,2-ジメチルシクロプロパン-1,2-ジカルボキシイミド-(カルボニル- ^{14}C) (スミレックス®) の合成, 吉武彬, 中塚巖, 恒松英明: 住友化学工業(株)生物科学研究所, 665 宝塚市高司4-2-1

Fig. 1 Scheme for the synthesis of Sumilex-(carbonyl- ^{14}C) (I).

1-¹⁴C acid with oxalyl chloride at 50-60° followed by esterification of the resulting acid chloride with methanol at the same temperature gave methyl 2-chloropropionate-1-¹⁴C in 53% radiochemical yield from propionic-1-¹⁴C acid. The radiochemical purity of the product examined by RGC was nearly 90% and methyl propionate-1-¹⁴C (7%) was contained as an active impurity.

Condensation of methyl 2-chloropropionate-1-¹⁴C with methyl 2-methylacrylate was carried out by allowing to react with sodium hydride in boiling toluene to give a mixture of *cis* and *trans* dimethyl 1,2-dimethyl-1,2-cyclopropanedicarboxylates-1-¹⁴C (II) in 66% yield. RGC examination revealed that the *cis/trans* ratio of the ester was 10/1 as expected. Hydrolysis of the esters with 15% sodium hydroxide solution produced a mixture of the corresponding diacids (III) in 72% yield.

Finally, the mixture was allowed to react with 3,5-dichloroaniline by using triethylamine as a catalyst[®] to give Sumilex-(carbonyl-¹⁴C) (I). The final product (18.5 mCi, specific activity: 4.67 mCi/mmol, purity: 99% on radiothinlayerchromatogram) was obtained by recrystallization from hexane-benzene, and the overall yield from propionic-1-¹⁴C acid was 21%.

2. Experimental

2.1 Analysis

The purities of the volatile products were evaluated by RGC which was carried out on a Yanako G-80 chromatograph fitted with a thermal conductivity detector and a gasphase counter (counting gas: propane) as a radio-detector. A glass column (1.5 m, 3mm I.D.) packed with 20% DC-550 on Chromosorb W(60-80 mesh) was used. Column temperature was 90°; carrier gas was helium (30 mL/min). The retention times of the authentic materials were: propionic acid (1.2 min), 2-chloropropionic acid (5.5 min), methyl 2-chloropropionate (2.1 min), dimethyl *cis*-1,2-dimethyl-1,2-cyclopropanedicarboxylate (5.5 min at 140°) and dimethyl *trans*-1,2-dimethyl-1,2-cyclopropanedicarboxylate (4.4 min at 140°).

2.2 2-Chloropropionic-1-¹⁴C Acid

To propionic-1-¹⁴C acid which was liberated from sodium propionate-1-¹⁴C (89.6 mCi, 434 mg, 4.52 mmol) in the usual manner⁴⁾ were added propionic acid (222 mg, 3.0 mmol) and propionic anhydride (325 mg, 2.5 mmol), and the mixture refluxed for 30 min. After cooling, to the mixture were added iodine (10 mg), red phosphorus (20 mg) and phosphorus pentchloride (20 mg). Dry chlorine was passed slowly to the mixture under heating at 70-80° for 9 hr to give 2-chloropropionic-1-¹⁴C acid. The product was used for following reaction without any treatment.

2.3 Methyl 2-Chloropropionate-1-¹⁴C

A mixture of 2-chloropropionic-1-¹⁴C acid and oxalyl chloride (1.91 g, 15 mmol) was heated at 50-60° for 3 hr. Evaporation of the excess reagent under reduced pressure (20 mm-Hg) at room temperature gave a residue of 2-chloropropionyl-1-¹⁴C chloride. To the residue was added anhydrous methanol (640 mg, 20 mmol) and the mixture heated at 50-60° for 2 hr. After cooling, water was added to the mixture and the resulting slurry extracted with ether. The ethereal extract was washed with water, 5% sodium carbonate solution and water, successively. The extract dried over sodium sulfate was concentrated under reduced pressure to about 50 mL and then under atmospheric pressure to give methyl 2-chloropropionate-1-¹⁴C (47.4 mCi); the IR spectrum showing an absorption at 1745 cm⁻¹ (ester C=O).

2.4 Dimethyl *cis*-1,2-dimethyl-1,2-cyclopropanedicarboxylate-(carbonyl-¹⁴C) (II)

To a suspension of sodium hydride (290 mg, 12 mmol) in anhydrous toluene (2 mL) was added dropwise with stirring at 100-110° during 30 min a mixture of methyl 2-chloropropionate-1-¹⁴C (47.4 mCi, 6 mmol), methyl 2-chloropropionate (245 mg, 2.0 mmol) and methyl 2-methylacrylate (1.2 g, 12 mmol). After complete addition, the mixture was refluxed for 2 hr. Methanol (1.5 mL) was added dropwise to the mixture under cooling in an ice-bath, then ice-water added, and the

mixture extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to give oily dimethyl 1, 2-dimethyl-1, 2-cyclopropanedicarboxylates-(carbonyl- ^{14}C) (II) (31.4 mCi, 66% yield, *cis/trans* ratio=10/1); the IR spectrum (liquid film) showing the carbonyl absorption at 1720 cm^{-1} and being identical in every respect with the authentic sample (*cis/trans* ratio=9.8/1).

2-5 *cis*-1, 2-Dimethyl-1, 2-cyclopropanedicarboxylic-(carbonyl- ^{14}C) Acid (III)

A mixture of dimethyl 1, 2-dimethyl-1, 2-cyclopropanedicarboxylates-(carbonyl- ^{14}C) (31.4 mCi) and 15% sodium hydroxide solution (10 ml) was heated under reflux for 5 hr. After cooling, the mixture was washed with ether and then acidified with concentrated hydrochloric acid under cooling in an ice-bath. To the mixture was added sodium chloride (2 g) and the mixture extracted with ether. Evaporation of the dried extract gave 1, 2-dimethyl-1, 2-cyclopropanedicarboxylic-(carbonyl- ^{14}C) acids (III) (22.5 mCi, 664 mg, 72% yield, *cis/trans*=11/1); the IR spectrum (nujol) showing absorptions at 1700 (COOH) and $3300\text{--}2600\text{ (COOH)}\text{ cm}^{-1}$.

2-6 N-(3, 5-Dichlorophenyl)-1, 2-dimethylcyclopropane-1, 2-dicaboximide-(carbonyl- ^{14}C) (I)

A mixture of 1, 2-dimethyl-1, 2-cyclopropanedicarboxylic-(carbonyl- ^{14}C) acids (22.5 mCi, 664 mg, 4.2 mmol), 3, 5-dichloroaniline (730 mg, 4.5 mmol) and triethylamine (50 mg) in anhydrous xylene (10 ml) was heated at 140° for 3 hr; during the reaction water formed being azeotropically removed. After cooling, the mixture was taken up in benzene and the

solution washed with 5% hydrochloric acid, 5% sodium carbonate solution and water, successively. After drying over sodium sulfate, the solution was evaporated under reduced pressure to dryness to give a crystalline residue (20.5 mCi). To the residue was added unlabelled Sumilex (160 mg) and recrystallized from hexane-benzene to give Sumilex-(carbonyl- ^{14}C) (I) (18.5 mCi, 1.12 g, 82% yield, 4.67 mCi/mmol); the radiochemical and chemical purities being 99% on radiothinlayerchromatogram on silica gel with benzene and chloroform/methanol (9/1 v/v); mp $165\text{--}166^\circ$; IR spectrum (nujol): $1775, 1715\text{ (C=O)}$, $1590, 1580\text{ (phenyl)}\text{ cm}^{-1}$.

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