LABELLED ORGANOPHOSPHORUS PESTICIDES. III. SYNTHESIS OF CARBON-14 LABELLED O-(2,6-DICHLORO-4-METHYLPHENYL) O,O-DIMETHYL PHOSPHOROTHIOATE

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SUMMARY

O-(2,6-Dichloro-4-methylphenyl) O,O-dimethyl phosphorothioate (S-3349)(1), a fungicide in soil, was labelled with carbon-14 individually at the aryl methyl and the phenyl ring for use in metabolic studies. The synthetic procedures are illustrated in Fig. 1. 4-Cyano-^{14}C-phenol was quantitatively converted to 4-methyl-^{14}C-phenol (3a) by catalytic hydrogenation using 10% Pd-C as a catalyst. Dichlorination of 3a with chlorine gave 2,6-dichloro-4-methyl-^{14}C-phenol (4a). Condensation of 4a with O,O-dimethyl phosphorochloridothioate gave S-3349-(aryl methyl-^{14}C) (1a) in the overall yield of 22% from potassium cyanide-^{14}C. By the similar procedures, 4-methylphenol-$^{14}C_6$ (3b) was converted to S-3349-(phenyl-$^{14}C_6$)(1b) in 70% yield.

Key Words: Carbon-14, 2,6-Dichloro-4-methylphenol, Organophosphorus Fungicide

INTRODUCTION

O-(2,6-Dichloro-4-methylphenyl) O,O-dimethyl phosphorothioate. (S-3349)(1) is a novel fungicide in soils for the control of plant pests with little toxicity to domestic animals and fishes[1]. It was required to prepare radioactive S-3349 for the investigation of the metabolic fates in mammals and fishes. This report describes the synthesis of this agent labelled with carbon-14 individually at the aryl methyl and the phenyl ring.

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DISCUSSION

In the preceding paper[2] we reported a direct ^{14}C-methylation of 1-bromo-3-methoxybenzene with methyl-^{14}C iodide by a Grignard type of coupling reaction to give an excellent yield of 1-methoxy-3-methyl-^{14}C-benzene which was then converted to 3-methyl-^{14}C-phenol quantitatively. Adaptation of this method to the preparation of 4-methyl-^{14}C analogues was unsuccessful. For example, ^{14}C-methylation of 1-bromo-4-methoxybenzene and 1-bromo-3,5-dichloro-4-methoxybenzene gave the corresponding methyl-^{14}C derivatives in the yields below 40%.

Figure 1 illustrates the procedures which we used for the syntheses of ^{14}C-labelled S-3349 (1a and 1b). By modifying Pichat's method[3], the diazonium salt of 4-aminophenol was allowed to react with potassium [tetracyano-^{14}C-niccolate(II)] to give 4-cyano-^{14}C-phenol in 80% yield. Catalytic hydrogenation of 4-cyano-^{14}C-phenol using 10% palladium-charcoal as a catalyst gave 4-methyl-^{14}C-phenol (3a) in 97% yield. The catalytic hydrogenation was found more effective for the preparation of 3a than Clemmensen reduction reported by Anker[4]

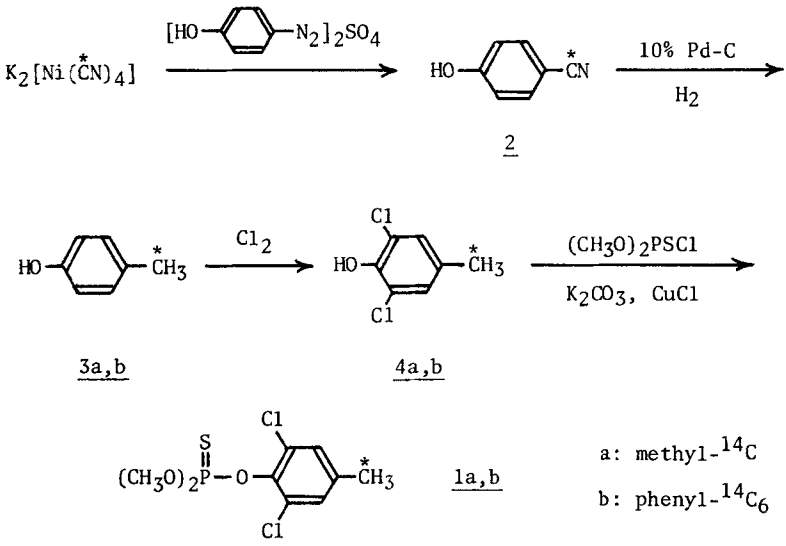

Fig. 1. Scheme for the syntheses of ^{14}C-labelled O-(2,6-dichloro-4-methylphenyl) O,O-dimethy phosphorothioates (1a and 1b)

Dichlorination[5] of 3a with chlorine gave 2,6-dichloro-4-methyl-^{14}C-phenol (4a) in 87% yield. The product, analyzed by radio-thinlayerchromatography (RTLC) and radio-gaschromatography (RGC), contained 2-chloro-4-methyl-^{14}C-phenol (5%) and unidentified by-products (10%) but was used in the next reaction without any purification. To avoid severe side-reactions in this reaction, it seemed necessary to remove the evolved hydrogen chloride from the reaction system by the rapid introduction of chlorine to the surface of the stirred reaction mixture.

Condensation of 4a with O,O-dimethyl phosphorochloridothioate in the presence of potassium carbonate and cuprous chloride[1] yielded crude S-3349-(aryl methyl-^{14}C) (1a) in 63% yield. The product was intensively purified by column chromatography followed by recrystallization to give 1a in 33% yield.

S-3349-(phenyl-$^{14}C_6$) (1b) was prepared from 4-methylphenol-$^{14}C_6$ (3b) by the similar methods described above. Dichlorination of 3b with chlorine gave 2,6-dichloro-4-methylphenol-$^{14}C_6$ (4b) in 73% yield after the purification by column chromatography. Condensation of 4b with O,O-dimethyl phosphorochloridothioate gave a crude product which was purified by column chromatography to yield 1b in 95% yield. In the condensation reaction, it was considered that the high purity of 4b as compared to 4a gave rise to the improved yield of 1b.

EXPERIMENTAL

RGC was carried out on a GC-5A Chromatograph (Shimadzu Co., Ltd., Japan) equipped with a Gas Proportional Counter Model 894 (Packard Instrument Co., Inc.). A glass column (2 m, 3 mm I.D.) packed with Silicone OV-17 (3%) on Chromosorb was used for the analyses of 4-cyanophenol and 4-methylphenol. Operating condition: column temperature 150°, He 34 ml/min, H_2 75 ml/min (detector FID), oxidation temperature 350°, propane 50 ml/min. Retention times: 4-cyanophenol 7.6 min, 4-methylphenol 2.3 min. A column (1.5 m, 3 mm I.D.) with Silicone DC-200 (10%) on Chromosorb was used for the analysis of 2,6-dichloro-4-methylphenol; column temperature 105°, He 30 ml/min, H_2 65 ml/min; retention times: 4-methylphenol 3.5 min, 2-chloro-4-methylphenol 4.5 min, 2,6-dichloro-4-methylphenol 13 min.

4-Cyano-^{14}C-phenol (2) -- To a stirred solution of potassium cyanide-^{14}C (100 mCi, 325 mg, 5.0 mmol) in water (4 ml) was added a solution of nickel sulfate ($6H_2O$) (224 mg, 0.85 mmol) in water (3 ml) at room temperature. The solution was heated at 90° for 30 min and then cooled to room temperature. To the solution, maintained below 30° and rapidly stirred, was added over a period of 1 hr a filtered solution of 4-hydroxybenzenediazonium sulfate. The diazonium solution was prepared by adding a solution of sodium nitrite (400 mg, 5.7 mmol) in water (4 ml) to a stirred solution of 4-aminophenol (610 mg, 5.6 mmol) in 35% sulfuric acid (8 ml) below 0°, stirring the mixture at 0° for 1 hr, and adding an aqueous suspension of calcium carbonate to the mixture as required to keep the mixture at pH 6.0. Following the addition of the diazonium solution, the mixture was heated at 85-90° for 2 hr, then cooled, and adjusted to pH 4.0 with concentrated hydrochloric acid. The mixture was extracted with ether, and the extract washed with water and dried over sodium sulfate. Evaporation of the solvent gave a crude product, which was chromatographed on silica gel with hexane-ether (4:1 v/v). Evaporation of the main fractions gave 4-cyano-^{14}C-phenol (80.0 mCi, 475 mg, 80%); IR νmax (nujol): 3250 (OH), 2250 (CN), 1605 cm^{-1} (phenyl); radiochemical purity 99% on RGC and RTLC (silica gel, $CHCl_3/CH_3OH$=10/1 v/v, R_f-value 0.40).

4-Methyl-^{14}C-phenol (3a) -- 4-Cyano-^{14}C-phenol (69.2 mCi, 407 mg, 3.4 mmol) in ethanol (20 ml) was hydrogenated at ordinary pressure and temperature over 10% palladium-charcoal (210 mg) for 3 hr. After further addition of the catalyst (100 mg), the mixture was hydrogenated for further 1.5 hr when the uptake of hydrogen ceased, and the catalyst filtered off. The filtrate was evaporated under reduced pressure, and the residue taken up in ether. The solution was washed with 10% hydrochloric acid, 5% sodium bicarbonate solution and water. After drying over sodium sulfate, the solution was concentrated to give 4-methyl-^{14}C-phenol (67.1 mCi, 356 mg, 97%); radiochemical purity 99% on RGC and RTLC (silica gel, $CHCl_3/CH_3OH$=10/1 v/v, R_f-value 0.51); NMR (δ, $CDCl_3$): 2.23 (3H, s, CH_3), 5.60 (1H, broad s, OH), 6.66 (2H, d, J=8 Hz, aromatic H), 6.94 (2H, d, J=8 Hz, aromatic H).

2,6-Dichloro-4-methyl-^{14}C-phenol (4a) -- To a stirred solution of 4-methyl-^{14}C-phenol (63.7 mCi, 342 mg, 3.2 mmol) in carbon tetrachloride (20 ml) was introduced an excess of chlorine continuously through a gas-inlet tube at room temperature for 30 min. To the mixture was added 10% sodium sulfite solution (30 ml), and the mixture heated under stirring at 80° for 1 hr. After cooling, the mixture was extracted with carbon tetrachloride. The extract was washed with water, dried, and evaporated under reduced pressure to give 2,6-dichloro-4-methyl-^{14}C-phenol (55.2 mCi, radiochemical purity 85%), which was used for the following reaction without any purification.

O-(2,6-Dichloro-4-methyl-^{14}C-phenyl) O,O-Dimethyl Phosphorothioate (1a) -- To a stirred mixture of 2,6-dichloro-4-methyl-^{14}C-phenol (55.2 mCi, ca. 2.3 mmol), potassium carbonate (372 mg, 2.7 mmol) and cuprous chloride (25 mg) in toluene (8 ml) was added a solution of O,O-dimethyl phosphorochloridothioate (434 mg, 3.0 mmol) in toluene (10 ml) at 75-80°, and the mixture heated at 90-100° for 2 hr. After cooling, the precipitates were filtered off and the filtrate diluted with benzene. The solution was washed with 5% sodium hydroxide solution and then water, dried, and evaporated under reduced pressure to leave an oily residue which was chromatographed on silica gel with hexane-ether (98:2 v/v). Evaporation of the main fractions gave a crystalline residue which was diluted with unlabelled S-3349 (64 mg) and recrystallized from methanol to give O-(2,6-dichloro-4-methyl-^{14}C-phenyl) O,O-dimethyl phosphorothioate (15.5 mCi, 288 mg, 16.2 mCi/mmol, 33%); mp and mixed mp 75-77°; purity 99% both radiochemically and chemically. The labelled compound was identical in every respect with the unlabelled authentic sample[1].

2,6-Dichloro-4-methylphenol-$^{14}C_6$ (4b) -- A solution of 4-methylphenol-$^{14}C_6$ (7.48 mCi, 109 mg, 1.0 mmol, The Radiochemical Centre, Amersham) in carbon tetrachloride (7 ml) was reacted with chlorine by the similar method described above. The reaction mixture was washed with water and added to 10% sodium sulfite solution (10 ml). The stirred mixture was heated at 85° for 1 hr, and worked up in the same manner as described above to give a crude product. The product was

purified by column chromatography on silica gel with hexane to give 2,6-dichloro-4-methylphenol-$^{14}C_6$ (5.48 mCi, 131 mg, 73%); radiochemical purity 99% on RGC and RTLC (silica gel, hexane/ether=2/1, R_f-value 0.42); NMR (δ, $CDCl_3$): 2.22 (3H, s, CH_3), 5.63 (1H, s, OH), 7.00 (2H, s, aromatic H).

O-(2,6-Dichloro-4-methylphenyl-$^{14}C_6$) O,O-Dimethyl Phosphorothioate (1b) -- To a stirred mixture of 2,6-dichloro-4-methylphenol-$^{14}C_6$ (5.48 mCi, 131 mg, 0.74 mmol), potassium carbonate (110 mg, 0.80 mmol) and cuprous chloride (5 mg) in toluene (1 ml) was added dropwise a solution of O,O-dimethyl phosphorochloridothioate (127 mg, 0.79 mmol) in toluene (1 ml) at 70-80°, and the mixture heated at 100-110° for 2 hr. After cooling, the mixture was worked up in the same manner as described above to give a crude product. Chromatography of the product on silica gel with hexane-ether (98:2 v/v) gave O-(2,6-dichloro-4-methylphenyl-$^{14}C_6$) O,O-dimethyl phosphorothioate (5.21 mCi, 208 mg, 7.54 mCi/mmol, 95%); mp and mixed mp 75-77°; purity 99% both radiochemically and chemically. The labelled compound was identical in all respects with the unlabelled anthentic sample[1].

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