LABELLED ORGANOPHOSPHORUS PESTICIDES. II. SYNTHESIS OF CARBON-14 LABELLED N-*sec*-BUTYL O-ETHYL O-(5-METHYL-2-NITROPHENYL) PHOSPHORAMIDOTHIOATE (CREMART®).

Akira Yoshitake, Fumiaki Shono, Takeshi Kamada and Iwao Nakatsuka,
Institute for Biological Science, Sumitomo Chemical Co., Ltd.,
2-1, 4-Chome, Takatsukasa, Takarazuka-shi, Japan.

Received June 1, 1976
Revised July 2, 1976

SUMMARY

N-sec-Butyl O-ethyl O-(5-methyl-2-nitrophenyl) phosphoramidothioate (Cremart)(I), an organophosphorus herbicide, was labelled with carbon-14 at the aryl methyl group for metabolic studies. The synthetic procedures are shown in Fig. 1. 1-Methoxy-3-methyl-^{14}C-benzene was nitrated with fuming nitric acid-acetic anhydride to give 2-methoxy-4-methyl-^{14}C-1-nitrobenzene which on O-demethylation with boron tribromide gave 5-methyl-^{14}C-2-nitrophenol. Condensation of the latter with N-sec-butyl O-ethyl phosphoramidochloridothioate in the presence of potassium carbonate afforded Cremart-(aryl methyl-^{14}C)(I) in the overall yield of 9.2% from methanol-^{14}C, which had a specific activity of 5.96 mCi/mmole.

Key Words: Carbon-14, 5-Methyl-2-nitrophenol, Organophosphorus Herbicide

INTRODUCTION

N-*sec*-Butyl O-ethyl O-(5-methyl-2-nitrophenyl) phosphoramidothioate (Cremart®)(I), synthesized and developed in our laboratories[1,2], has been evaluated especially as a pre-emergence herbicide controling a broad spectrum of weeds. In the efforts to investigate the metabolic fate in mammals and the mode of decomposition on soils and plants, it has been required to prepare radioactive Cremart. We have already achieved labelling of this agent with ^{3}H or ^{32}P[3]. This report deals with the synthesis of Cremart labelled with carbon-14 at the aryl methyl group.

DISCUSSION

Figure 1 illustrates the overall approach to the preparation of Cremart-(aryl methyl-^{14}C)(I). On the basis of earlier works, we considered that 1-methoxy-3-methyl-^{14}C-benzene (II) was best suited for the starting material. This compound was readily obtained in the overall yield of 70% from methanol-^{14}C by the method described in the preceeding paper[4]; involving iodination of methanol-^{14}C with 57% hydriodic acid followed by Grignard reaction of the resulting methyl-^{14}C iodide with 3-methoxyphenylmagnesium bromide.

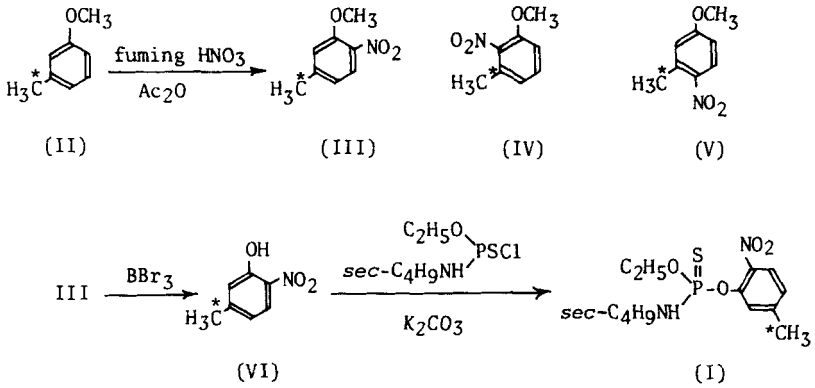

Fig.1. The reaction sequence for the synthesis of Cremart-(aryl methyl-^{14}C)

Attempts to elaborate specifically 2-methoxy-4-methyl-^{14}C-1-nitrobenzene by nitration of II, after protected by sulfonyl group or halogen at C-4 position, followed by removal of the protecting group, were unpromising. Therefore, we employed the direct nitration of II, since it is well known that nitration of anisole or phenol with some nitrating reagents[5-7] gives rise to higher proportions of *ortho*-nitroisomers. After intensive investigations, it was found that treatment of II with fuming nitric acid and acetic anhydride at -5°-0° for 2 hr furnished a mixture of products in the total radiochemical yield of 92%. On the examination by radio-gaschromatography, the mixture was found to consist of 2-methoxy-3-methyl-^{14}C-1-nitrobenzene (III), the nitroisomer (IV) and V together with the starting material (II); the ratio of each product is shown in Table 1. Chromatography of the mixture on silica gel with hexane-ether (10:1

Table 1. The ratios of nitration products and their retention times (RT) in gas chromatography

product	ratio (%)	RT (min)
2-methoxy-4-methyl-^{14}C-1-nitrobenzene (III)	28.6	9.5
1-methoxy-3-methyl-^{14}C-2-nitrobenzene (IV)	16.9	6.6
4-methoxy-2-methyl-^{14}C-1-nitrobenzene (V)	21.3	8.5
1-methoxy-3-methyl-^{14}C-benzene (II)	25.6	1.8

v/v) gave the desired product (III) in 28% yield from II. Other fractions gave separatly the starting material (II) and a mixture of the nitroisomers (IV and V) in the yields of 24 and 37% respectively. In spite of the relatively lower yield of III, the result seemed satisfactory in our present requirement since not only the starting material (II) but also the nitroisomer (V) could be used for the synthesis of O,O-dimethyl O-(3-methyl-^{14}C-4-nitrophenyl) phosphorothioate (Sumithion®) [4].

2-Methoxy-4-methyl-^{14}C-1-nitrobenzene gave 5-methyl-^{14}C-2-nitrophenol (VI) in nearly quantitative yield when treated with boron tribromide at -5°-0° for 1 hr, and similarly the nitroisomer (IV) was readily converted to the corresponding nitrophenol. In contrast, the nitroisomer (V) could not be O-demethylated with this reagent even under more drastic conditions, and only pyridine hydrochloride [8] was effective to give 3-methyl-^{14}C-4-nitrophenol in 92% yield.

Condensation of 5-methyl-^{14}C-2-nitrophenol with N-*sec*-butyl O-ethyl phosphoramidochloridothioate in the presence of potassium carbonate gave a crude product which was chromatographed on silica gel with benzene to afford Cremart-(aryl methyl-^{14}C) (I) in 50% yield.

EXPERIMENTAL

Radio-gaschromatography was carried out on a Yanako G-80 Chromatograph (Yanagimoto MFG Co., Ltd., Japan) fitted with a thermal conductivity detector and a gasphase counter (counting gas: propane) as a radiodetector. A glass column (1.5 m, 3 mm I.D.) packed with silicone OV-17 (3%) on Chromosorb W (60-80

mesh) was used. Operating conditions: column temperature 130°, N_2 flow rate 25 ml/min, oxidation temperature (with copper oxide) 350°, propane flow rate 50 ml/min. Retention times of the refered materials are shown in Table 1.

1-Methoxy-3-methyl-^{14}C-benzene -- 1-Methoxy-3-methyl-^{14}C-benzene was prepared in 70.0% yield (81.2 mCi) from methanol-^{14}C (116 mCi, 7.15 mmol) by the method described in the preceeding paper[4]. The purity of the product as examined by radio-gaschromatography was radiochemically 99% and chemically 71%; containing methoxybenzene as the main inactive by-product. The product was used for the following reaction without any purification.

2-Methoxy-4-methyl-^{14}C-1-nitrobenzene -- A mixture of fuming nitric acid (950 mg, 15 mmol) and acetic anhydride (3.06 g, 30 mmol) was added dropwise with stirring at -5°-0° during 0.5 hr to 1-methoxy-3-methyl-^{14}C-benzene (81.2 mCi, 5.01 mmol, 16.2 mCi/mmol) and the mixture allowed to react at the same temperature for 2 hr. To the mixture was added ice-water and the slurry extracted with ether. The extract was washed with 10% sodium carbonate solution and then water, dried over sodium sulfate, and evaporated under atomospheric pressure to give an oily residue. The residue, diluted with inactive 2-methoxy-4-methyl-1-nitrobenzene (300 mg, 1.8 mmol), was chromatographed on silica gel and eluted with hexane-ether (10:1 v/v). Evaporation of the first eluate gave the starting material (II)(19.3 mCi, 23.8%). The second eluate was evaporated to give an oily mixture (30.1 mCi) of 1-methoxy-3-methyl-^{14}C-2-nitrobenzene and 4-methoxy-2-methyl-^{14}C-1-nitrobenzene: each ratio as determined by radio-gaschromatography was 42 and 58% respectively. Evaporation of the third eluate gave 2-methoxy-4-methyl-^{14}C-1-nitrobenzene (22.6 mCi, 530 mg, 7.13 mCi/mmol, 27.8%) as yellow needles; the radiochemical purity was 99%; NMR spectrum (δ) in $CDCl_3$: 2.19 (3H, singlet, aryl methyl), 3.94 (3H, singlet, methoxy), 6.80 (1H, quartet, J_{AB}=8 Hz, J_{BC}=3 Hz, C-5 proton), 6.88 (1H, doublet, J_{BC}=3 Hz, C-3 proton) and 7.75 (1H, doublet, J_{AB}=8 Hz, C-6 proton); its IR spectrum was identical with that of the authentic sample.

5-Methyl-^{14}C-2-nitrophenol -- To a solution of 2-methoxy-4-methyl-^{14}C-1-nitro-

benzene (22.6 mCi, 530 mg, 3.25 mmol) and unlabelled 2-methoxy-4-methyl-1-nitrobenzene (160 mg, 1.0 mmol) in anhydrous dichloromethane (5 ml) was added boron tribromide (250 mg, 10 mmol) at -5° under stirring. The mixture was stirred at 0° for 1 hr and to the mixture added ice-water. The mixture was extracted with ether. The extract was washed with water and re-extracted with 10% sodium hydroxide solution. The basic solution was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and evaporated to give 5-methyl-^{14}C-2-nitrophenol (22.0 mCi, 600 mg, 97.3%) as yellow needles; its radiochemical purity was 95%; NMR spectrum (δ) $CDCl_3$: 2.44 (3H, singlet, aryl methyl), 6.83 (1H, quartet, J_{AB}=8 Hz, J_{BC}=3 Hz, C-4 proton), 6.96(1H, doublet, J_{BC}=3 Hz, C-6 proton), 8.00 (1H, doublet, J_{AB}=8 Hz, C-3 proton) and 10.3 (1H, broad singlet, OH); its IR spectrum was identical with that of the unlabelled authentic sample.

N-*sec*-Butyl O-Ethyl O-(5-Methyl-^{14}C-2-nitrophenyl) Phosphoramidothioate (I) -- To a stirred solution of 5-methyl-^{14}C-2-nitrophenol (22.0 mCi, 600 mg, 3.92 mmol) in methyl isobutyl ketone (10 ml) was added potassium carbonate (360 mg, 2.6 mmol) and the mixture heated at 30° for 8 hr. After addition of γ-picoline (400 mg, 4.3 mmol) at room temperature, the mixture was cooled in an ice-bath to -5° and to the mixture added dropwise N-*sec*-butyl O-ethyl phosphoramidochloridothioate (930 mg, 4.3 mmol). The mixture was stirred at 30° for 1 hr and then at 60° for 6 hr. After further addition of the reagent (210 mg, 1.0 mmol), the mixture was stirred at 60° for 1 hr. After cooling, the mixture was poured into ice-water and extracted with benzene. The extract was washed with 5% sodium hydroxide solution, 10% hydrochloric acid and water successively. The dried extract was evaporated to give an oily residue which was chromatographed on a column of silica gel and eluted with benzene. Evaporation of the main fractions gave N-*sec*-butyl O-ethyl O-(5-methyl-^{14}C-2-nitrophenyl) phosphoramidothioate (I) (10.8 mCi, 601 mg, 5.96 mCi/mmol, 49.1%); its purity was 98% both radiochemically and chemically. The labelled compound was identical in every respect with the unlabelled authentic sample.

3-Methyl-^{14}C-4-nitrophenol -- A mixture of 4-methoxy-2-methyl-^{14}C-1-nitrobenzene and 1-methoxy-3-methyl-^{14}C-2-nitrobenzene (total 24.0 mCi, the former 58%) was taken up in anhydrous benzene and the solvent was removed azeotropically under atomospheric pressure to remove the moisture. To the dried mixture was added pyridine hydrochloride (2.0 g), and the mixture heated in an oil bath to 220° and stirred for 20 min. After cooling, the mixture was diluted with water and extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated under reduced pressure to give an oily residue. Chromatography of the residue on silica gel with hexane-ether (9/1 v/v) gave 3-methyl-^{14}C-4-nitrophenol (10.3 mCi, 262 mg, 6.00 mCi/mmol) which was identical in all respect with the authentic sample. From the former fractions 3-methyl-^{14}C-2-nitrophenol (9.61 mCi, 243 mg) was obtained.

ACKNOWLEDGEMENT

The authors wish to thank Dr. H. Yoshioka and Mr. K. Mukai for helpful discussions and providing the unlabelled authentic materials used in this work.

REFERNCES

1. Satomi T., Mukai K., Mine A., Hino N., Tateshi K. and Hirano M. - Ger. Offen. 2,147,873 (1972).
2. Ueda M. - Japan Pesticide Information (Tokyo) 23: 23 (1975).
3. Hazue M., Yoshitake A., Kawahara K. and Endo M. - Research Report: unpublished
4. Yoshitake A., Kawahara K., Kamada T. and Endo M. - J. Labelled Compounds & Radiopharmaceuticals: preceeding paper.
5. Norman R.O.C. and Radda G.K. - J. Chem. Soc.: 3030 (1961).
6. Bunton C.A., Hughes E.D., Ingold C.K., Jacobs D.H.I., Jones M.H., Minkoff P. and Reed R.I. - J. Chem. Soc.:2628 (1950).
7. Kovacic P. and Hiller J.J., Jr. - J. Org. Chem. 30: 2871 (1965).
8. Filler R., Khan B.T. and Mcmullen C.W. - J. Org. Chem. 27: 4660 (1962).