TECHNICAL NOTE

Labelling of a New Fungicide with ^3H and ^{14}C

—Synthesis of S-*n*-Butyl S'-*p*-*tert*-Butylbenzyl- ^{14}C N-3-Pyridyldithiocarbonimide (Denmert®)—†

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S-*n*-Butyl S'-*p*-*tert*-butylbenzyl N-3-pyridyldithiocarbonimide (Denmert®) (I) exhibits fungicidal activities against powdery mildew fungi^{1),2)}. The metabolic studies of the agent in mammals and plants required Denmert labelled with radioisotopes at some different moieties of the molecule. The synthesis of Den-

mart-(pyridyl-5- ^3H) was already reported in the preceding paper³⁾. This report deals with the synthesis of Denmert labelled with ^{14}C at the benzyl carbon of the *p*-*tert*-butylbenzyl moiety.

The overall approach to the synthesis of Denmert-(benzyl- ^{14}C) (I) is shown in Fig. 1.

An attempt to prepare the ethereal solution

Fig. 1

of *p*-*tert*-butylphenylmagnesium bromide (II) was failed because of the insolubility of the reagent (II) in ether. However, the reagent (II) was readily prepared in tetrahydrofuran and carbonated with carbon- ^{14}C dioxide at -20° to

give *p*-*tert*-butylbenzoic- ^{14}C acid (III) in 95% yield. Direct reduction of III, without esterification, with lithium aluminum hydride in ether afforded *p*-*tert*-butylbenzyl- ^{14}C alcohol in nearly quantitative yield. Subsequently, the benzyl- ^{14}C alcohol was effectively chlorinated with thionyl chloride, giving *p*-*tert*-butylbenzyl- ^{14}C chloride (IV) in 97% yield.

Condensation of IV with S-*n*-butyl N-3-pyridyldithiocarbamate (V)⁴⁾ was carried out by employing 8% potassium hydroxide solution as

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a base, and Denmert-(benzyl- ^{14}C) (I) was obtained in 63% yield after purification by column chromatography; the overall yield being 58% based on barium carbonate- ^{14}C and the specific activity of I being 8.01 mCi/mmol.

1. *p*-tert-Butylbenzoic- ^{14}C Acid (III)

Into a flask fitted with a reflux condenser and a dropping funnel were placed magnesium turnings (260 mg, 11 mmol) and anhydrous tetrahydrofuran (5 ml). To the mixture was added dropwise with stirring a solution of *p*-tert-butylbromobenzene (2.13 g, 10 mmol) in anhydrous tetrahydrofuran (8 ml), during the addition the mixture being gently refluxed. After the complete addition, the mixture was refluxed for 1 hr to give a solution of *p*-tert-butylphenylmagnesium bromide(II). The solution (9 ml) was placed to a flask, which was connected to a vacuum manifold, frozen, and evacuated. To the frozen mixture was introduced carbon- ^{14}C dioxide which was liberated from barium carbonate- ^{14}C (40 mCi, 4.8 mmol). The mixture was warmed to -20° and stirred for 1 hr. After the addition of 5% hydrochloric acid, the acidic mixture was extracted with ether. The extract was then re-extracted with 5% sodium carbonate solution. The aqueous extract 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 *p*-tert-butylbenzoic- ^{14}C acid (III) (37.8 mCi, 4.5 mmol) which had the radiochemical purity of 99% on TLC (silica gel, hexane/ether=1/1).

2. *p*-tert-Butylbenzyl- ^{14}C -Chloride (IV)

A mixture of *p*-tert-butylbenzoic- ^{14}C acid (37.8 mCi, 4.5 mmol), lithium aluminum hydride (600 mg) and anhydrous ether (80 ml) was refluxed for 2.5 hr. After cooling, the excess reagent was decomposed with water and then the slurry was extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to afford *p*-tert-butylbenzyl- ^{14}C alcohol (37.7 mCi, purity: 98%

on silica gel TLC with benzene/ethyl acetate=4/1). A solution of *p*-tert-butylbenzyl- ^{14}C alcohol and thionyl chloride (1.5 ml) in anhydrous ether (5 ml) was heated to reflux for 4 hr. After cooling, the mixture was extracted with ether, and the extract washed with 10% sodium bicarbonate solution and then water. Drying over sodium sulfate, the extract was evaporated to give *p*-tert-butylbenzyl- ^{14}C chloride (IV) (36.5 mCi); the radiochemical purity being 95% on TLC (silica gel, chloroform). The product was employed for the following reaction without any further purification.

3. S-*n*-Butyl S'-*p*-tert-Butylbenzyl- ^{14}C N-3-Pyridyldithiocarbonimide, Denmert-(benzyl- ^{14}C) (I)

To a cooled solution of *p*-tert-butylbenzyl- ^{14}C chloride (36.5 mCi, 4.4 mmol) and S-*n*-butyl N-3-pyridyldithiocarbamate (1.04 g, 4.6 mmol) in methanol (8 ml), in an ice-bath, was added 8% potassium hydroxide solution (2.5 ml). The mixture was stirred at 0° for 7 hr and then taken up in hexane. The solution was washed with water, dried over sodium sulfate, and evaporated to leave an oily residue. Chromatography of the residue on silica gel with hexane-acetone (20/1 v/v) gave Denmert-(benzyl- ^{14}C) (I) (23.0 mCi, 2.87 mmol); the radiochemical and chemical purities being 99% on TLC (silica gel, chloroform, hexane/acetone=4/1, benzene/ethyl acetate=3/1); the IR spectrum (chloroform) being identical in every respect with that of the authentic sample.

References

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