SYNTHESIS OF ^{14}C LABELLED METALAXYL AND FURALAXYL.

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SUMMARY

The syntheses of the ^{14}C labelled fungicides, metalaxyl and furalaxyl, are described. Sodium 2-[^{14}C]-propionate was brominated at C-2 and esterified with diazomethane to produce methyl 2-bromopropionate. This bromopropionate was reacted with 2,6-dimethylaniline to produce methyl N-(2,6-xylyl)-DL-alaninate which was acylated with either methoxyacetyl chloride or 2-furoyl chloride to produce ^{14}C labelled metalaxyl and furalaxyl respectively.

Keywords: [^{14}C]-metalaxyl, [^{14}C]-furalaxyl

INTRODUCTION

Metalaxyl, 5, methyl N-(2-methoxyacetyl)-N-(2,6-xylyl)-DL-alaninate, (1) and furalaxyl, 6, methyl N-(2-furoyl)-N-(2,6-xylyl)-DL-alaninate, (2) are systemic fungicides suitable for the preventive and curative control of some diseases caused by air and soil born Oomycetes. Both fungicides were evaluated for the control of white rust, Albugo candida Pers. ex. Lev. (Ktze), on rapeseed, Brassica campestris (3). To study their distribution and metabolism by rapeseed plants both fungicides were synthesized with the ^{14}C at the 2 position of the alanine. Details of the syntheses are described in this paper.

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METHODS AND RESULTS

In designing the syntheses, Figure 1, readily available ^{14}C labelled intermediates were desired for generating various methyl N-phenyl alaninate fungicides. Although utilization of $^{14}CH_2N_2$ to

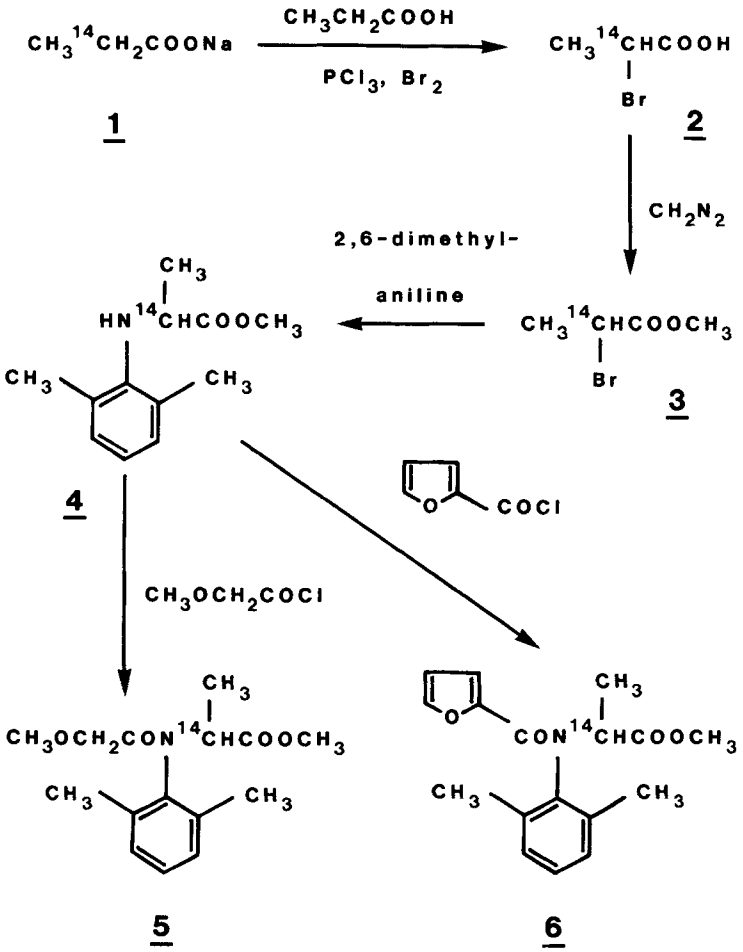

Figure 1. The synthetic pathways for [^{14}C]-labelled metalaxyl and furalaxyl.

esterify the desmethyl fungicides was possible, hydrolysis of the methyl ester could occur in the metabolism of the fungicide with loss of the radiolabel. The reaction between aniline and halopropionate is easier to accomplish than the reaction between alanine and an appropriately substituted aromatic moiety, thus a suitable halopropionate was desired.

Reasoning that there would be equilibrium between free propionic acid and labelled sodium propionate which could then be brominated via the acyl halide intermediate generated in situ, anhydrous sodium 2-[^{14}C]-propionate in propionic acid was brominated with bromine and phosphorus trichloride. The 2-bromopropionic acid was not isolated but was esterified with diazomethane to give the methyl 2-bromopropionate, 3. The bromopropionate was reacted with 2,6-dimethylaniline, which also acted as solvent and proton acceptor, to produce methyl N-(2,6-xylyl)-DL-alaninate, 4. The use of excess 2,6-dimethylaniline also reduced the amount of dialkylation that might occur as an undesirable side reaction. The methyl N-(2,6-xylyl)-DL-alaninate was the key product that could then be acylated with methoxyacetyl chloride or 2-furoyl chloride to produce metalaxyl, 5, or furalaxyl, 6, respectively or other methyl N-acyl-N-(2,6-xylyl)-alaninates.

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectral data were measured in $CDCl_3$ on a Varian HA-100 or T-60 spectrometer and reported in delta units relative to tetramethyl silane at 0.0 units (s=singlet, d=doublet, q=quadruplet, and m=multiplet). Mass spectra were obtained on a AEI MS12 mass spectrometer. Infrared spectra were obtained on a

Beckman IR 8 spectrophotometer. Thin layer chromoatography was carried out on silica gel 60 F254 plates of 0.25 mm thickness and scanned in a Packard 7201 radiochromatogram scanner. Sodium 2-[^{14}C]-propionate was purchased from Amersham Corportion, Oakville, Ontario, Canada.

Methyl 2-[^{14}C]-2-bromopropionate, 3. Sodium 2-[^{14}C]-propionate, 1, (250 uCi, about 0.72 mg) was dissolved in freshly distilled dry propionic acid (515.4 mg, 6.96 mmole). The specific activity of the propionic acid was 20.4 uCi/mmole. The propionic acid was added to dry bromine (1584 mg, 9.96 mmole) and freshly distilled phosphorus trichloride (12 ul, 0.1 mmole) in a flask equipped with a reflux condenser and a calcium chloride drying tube (4). The solution was heated in an oil bath at 85°C for 24 hours before cooling to room temperature. The crude 2-[^{14}C]-bromopropionic acid, 2 (0.98 gms), was dissolved in ethyl ether (20 ml) and an etherial solution of diazomethane, prepared from N-methyl-N-nitroso-p-toluenesulfonamide (5), was added dropwise until the yellow color persisted for 5 minutes. The ether was evaporated to give crude methyl 2-[^{14}C]-2-bromopropionate, 3, (0.93 gms, 5.56 mmole). IR(neat) 1740 (C=O), 1185 (ROC-OCH_3) cm^{-1}. MS 168,166 (M), 137,135 (M-OCH_3), 109,107 (M-$COOCH_3$). NMR(60 MHz) 1.82 (CH_3CH, d, J=6 Hz), 3.75 ($COOCH_3$, s), 4.37 ($CHCH_3$, q, J=6 Hz).

Methyl 2-[^{14}C]-N-(2,6-xylyl)-DL-alaninate, 4. Crude methyl 2-[^{14}C]-2-bromopropionate (0.93g, 5.56 mmole) was added to freshly distilled 2,6-dimethylaniline (1.34 g, 11.1 mmole) and the flask was stoppered and heated in an oil bath for 3 hours at 90°C. A precipitate was formed after cooling to room temperature. A saturated solution of $NaHCO_3$ was added to the reaction mixture

which was then transferred to a separatory funnel and extracted with methylene chloride (3x30 ml). The combined methylene chloride extracts were washed with water (25 ml), dried over Na_2SO_4, filtered and evaporated to about 4 ml. Isolation of the product was done by preparative TLC using ethyl acetate-hexane (1:4 by vol.) as solvent. The product (R_f=0.7) was extracted from the silica gel with methylene chloride which was evaporated to give methyl 2-[^{14}C]-N-(2,6-xylyl)-DL-alaninate, 4, (0.83 g, 4.00 mmole). IR(neat) 3380 (NH), 1735 (C=O), 1137 (CH_3O-COR) cm^{-1}. MS 207 (M), 148 (M-$COOCH_3$), 105 (Ar(CH_3)CH_2). NMR(60 MHz) 1.37 ($C\underline{H}_3CH$, d, J=6 Hz), 2.28 (Ar($C\underline{H}_3$)$_2$, s), 3.63 ($COOC\underline{H}_3$, s), 3.75 (N$\underline{H}$), 3.97 ($C\underline{H}CH_3$, q, J=6 Hz), 7.20 (Ar$\underline{H}_3$, m).

Methyl 2-[^{14}C]-N-(2-methoxyacetyl)-N-(2,6-xylyl)-DL-alaninate, 5. Freshly distilled methoxyacetyl chloride (821 g, 7.61 mmole) was added to methyl 2-[^{14}C]-N-(2,6-xylyl)-DL-alaninate, 4, (0.83 g) and the mixture was left at room temperature for 3 hours. A saturated solution of $NaHCO_3$ was added to the reaction mixture which was then transferred to a separatory funnel and extracted with methylene chloride (3x30 ml). The combined extracts were washed with water (25 ml), dried over Na_2SO_4, filtered and evaporated to leave the crude product which crystallized from ethyl ether-hexane (1:19 by vol.). The mother liquor was purified by preparative TLC using acetone-hexane (1:4 by vol.) to give unreacted 4 plus product 5 (R_f=0.22) which was combined with the first crop of crystals and crystallized from hexane (0.82 g,). A portion of the product was distilled at 125°C using a water aspirator to give 5, (11.8 uCi/mmole) m.p. 70°C, lit. m.p. 71-72°C (6). Found C 64.5, H 7.5, N 5.0, O 23.0 $C_{15}H_{21}NO_4$ requires C 64.5, H 7.6, N 5.0, O 22.9. IR (KBr) 1755 (ester C=O), 1665 (amide C=O) cm^{-1}. MS 279 (M), 234 (M-CH_3OCH_2), 220 (M-$COOCH_3$), 206

($M-CH_3OCH_2CO$), 174 ($M-Ar(CH_3)_2$). NMR (100 Mz) 1.01 ($C\underline{H}_3CH$, d, J=7 Hz), 2.16 ($ArC\underline{H}_3$, s), 2.46 ($ArC\underline{H}_3$, s), 3.32 ($C\underline{H}_3OCH_2$, s), 3.51 ($OC\underline{H}_2CO$, q, J=16 Hz), 3.78 ($COOC\underline{H}_3$, s), 4.49 ($C\underline{H}CH_3$, q, J=7 Hz), 7.14 ($Ar\underline{H}_3$, m).

Methyl 2-[^{14}C]-N-(2-furoyl)-N-(2,6-xylyl)-DL-alaninate, 6. Freshly distilled 2-furoyl chloride (bp 170°C, 253 mg, 1.93 mmole) was added to 4 (200 mg, 0.96 mmole) and left at room temperature for 2 hr. A saturated solution of $NaHCO_3$ was added to the reaction mixture which was then transfered to a separatory funnel and extracted with methylene chloride (3 x 30 ml). The combined extracts were washed with water (25 ml), dried over Na_2SO_4, filtered and the solvent removed on a rotary evaporator. The crude product was purified on preparative TLC using acetone-hexane (2:3 by vol.). The band with R_f=0.33 was extracted with acetone and crystallized from ethyl ether-hexane (1:1 by vol.) to give 6 (233 mg, 0.77 mmoles, 12.1 uCi/mmole), mp 85°C, lit. mp 70 and 85°C, dimorphic forms (7). Found C 68.4, H 6.1, N 4.5, O 21.0, $C_{17}H_{19}NO_4$ requires C 67.8, H 6.3, N 4.7, O 21.2. IR(KBr) 1750 (ester C=O), 1627 (amide C=O) cm^{-1}. MS 301 (M), 242 ($M-COOCH_3$), 95 ($\overline{[CHCHCHOC]}CO$). NMR(100 MHz) 1.15 ($C\underline{H}_3CH$, d, J=7 Hz), 2.15 ($ArC\underline{H}_3$, s), 2.38 ($ArC\underline{H}_3$, s), 3.78 ($COOC\underline{H}_3$, s), 4.56 ($C\underline{H}CH_3$, q, J=7 Hz), 5.41 ($\overline{[C\underline{H}CHCHOC]}CO$, dd, J=3.5, 1 Hz), 6.09 ($\overline{[CHC\underline{H}CHOC]}CO$, dd, J=3.5, 2 Hz), 7.17 ($Ar\underline{H}_3$, m), 7.30 ($\overline{[CHCHC\underline{H}OC]}CO$, dd, J=1, 2 Hz).

REFERENCES

1. Metalaxyl (Ridomil^R) developed by Ciba-Geigy under code CGA 48988.
2. Furalaxyl (Fongarid^R) developed by Ciba-Geigy under code CGA 38140.

3. Dueck J. and Stone J.R. - Can. J. Plant Science 59: 423(1979).
4. Vogel A.I. - A Textbook of Practical Organic Chemistry. Third Edition, Longmans, Green & Co. Ltd., London, (1962) p. 430.
5. Vogel A.I. - A Textbook of Practical Organic Chemistry. Third Edition, Longmans, Green & Co. Ltd., London, (1962) p. 971.
6. Worthing C.R. - The Pesticide Manual, Sixth Edition, British Crop Protection Council, London (1979) p. 336.
7. Worthing C.R. - The Pesticide Manual, Sixth Edition, British Crop Protection Council, London (1979) p. 289.