

SYNTHESIS OF THE FUNGICIDE [ $^{14}\text{C}$ ]TRIADIMEFON

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## SUMMARY

The synthesis of the fungicide [ $^{14}\text{C}$ ]triadimefon is described. Bromine transformed pinacolone into  $\alpha$ -bromopinacolone; this reacted with 4-chloro-[ $\text{U-}^{14}\text{C}$ ]phenol yielding 1-(4-chloro [ $\text{U-}^{14}\text{C}$ ]phenoxy)-3,3-dimethyl-2-butanone; this was transformed by bromine into 1-(4-chloro [ $\text{U-}^{14}\text{C}$ ]phenoxy)-1-bromo-3,3-dimethyl-2-butanone; this last compound reacted with 1,2,4-triazole to yield [ $^{14}\text{C}$ ]triadimefon, i.e., 1-(4-chloro [ $\text{U-}^{14}\text{C}$ ]phenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone. [ $^{14}\text{C}$ ]Triadimefon, having the specific activity 0.88 mCi/mmol, was obtained in 58% overall yield from 4-chloro [ $\text{U-}^{14}\text{C}$ ]phenol.

Key words: [ $^{14}\text{C}$ ]Triadimefon, Fungicide, Carbon-14

## INTRODUCTION

Triadimefon [1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone], 3, is a recent systemic fungicide widely used for the protection of cereals against mildews and rusts (1). Little is known and published about the metabolism of triadimefon in the cereals, on account of the lack of the labelled fungicide (2). For that reason, we synthesized [ $^{14}\text{C}$ ]triadimefon in order to study its metabolism in cereals. For the metabolism studies,  $^{14}\text{C}$  is more appropriate than tritium; for toxicological interests, we labelled the 4-chlorophenyl ring.

There is no clear published experimental method for the synthesis of unlabelled triadimefon, the patents giving often contradictory informations (3,4); there is no description at all

about the synthesis of [ $^{14}\text{C}$ ]triadimefon. We thus first developed a method for the synthesis of triadimefon which used 4-chlorophenol, the last compound being available as uniformly labelled in the ring with  $^{14}\text{C}$ .

### EXPERIMENTAL

4-Chloro [ $^{14}\text{C}$ ]phenol (uniformly labelled in the ring; 99% purity) was purchased from the Radiochemical Centre, Amersham, Great-Britain. The solvents were of analytical grade from Merck; before use, acetone was dried with potassium carbonate and distilled, whereas diethyl ether was distilled from  $\text{LiAlH}_4$ . The reactions were protected from humidity by means of calcium chloride tubes. The radioactivities were measured in solution by means of the Packard Tri-Carb 2425 scintillation counter. The bands and spots of the plates of thin-layer chromatography were measured with the Berthold radioscanner II (LB2723). The analytical (t.l.c.) and preparative (p.t.l.c.) thin-layer chromatographies were made with plates from Merck (Kieselgel 60 F254, 20x20 cm) whose thickness respectively were 0.25 and 2 mm.

TABLE 1

T.l.c. of the main reactants and products

T.l.c. solvent	4-chloro-phenol	<u>2</u>	1,2,4-Tri-azole	<u>3</u>
	$R_F$			
Chloroform	0.67	0.79	0.23	0.50
Ethyl acetate	0.93	0.91	0.43	0.85
Methanol	0.86	0.87	0.72	0.89
Toluene	0.48	0.59	0	0.28
Benzene, dioxane, acetic acid, 90/25/4	0.78	0.91	0.14	0.78

The infra red (IR) and mass spectra (MS) were respectively obtained with the Perkin-Elmer 297 and Varian-MAT 311 (70 eV) spectrometers.

α -Bromopinacolone, 1

A solution of 33.6 g of bromine (0.21 mol) and 0.5 g of zinc (II) chloride in 90 ml of chloroform was added dropwise (during about 1 hr) to a stirred solution of 25 g of pinacolone (0.25 mol) in 350 ml of chloroform maintained at 0°. In order to start the reaction (discoloration), sometimes it was necessary to bring for a short time the solution of pinacolone to 10°. The discolored solution was washed with an aqueous solution of sodium carbonate (0.1 M, 70 ml), dried with sodium sulfate, the chloroform was evaporated under vacuum in a rotavapor, and the fractional distillation of the residue gave the compound 1 (b.p. 71-73°, 10 mm; 34 g, 0.19 mol, 76% relatively to the pinacolone). IR (thin film, cm<sup>-1</sup>): 2980, 2880 (C-H); 1725 (C=O); 1480; 1395, 1370 [C-H in C(CH<sub>3</sub>)<sub>3</sub>]; 1282, 1227, 1154, 1060, 1005, 937, 870, 835; 755 (C-Br). MS [m/e(relative intensity)]: 180(35), 178(33), M<sup>+</sup>; 137(5), 135(5), M<sup>+</sup>-HC(CH<sub>3</sub>)<sub>2</sub>; 123(12), 121(10), M<sup>+</sup>-C(CH<sub>3</sub>)<sub>3</sub>; 95(26), 93(30), [CH<sub>2</sub>Br]<sup>+</sup>; 85(82), [CO-C(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>; 57(100), [C(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>.

1-(4-Chloro[U-<sup>14</sup>C]phenoxy)-3,3-dimethyl-2-butanone, 2

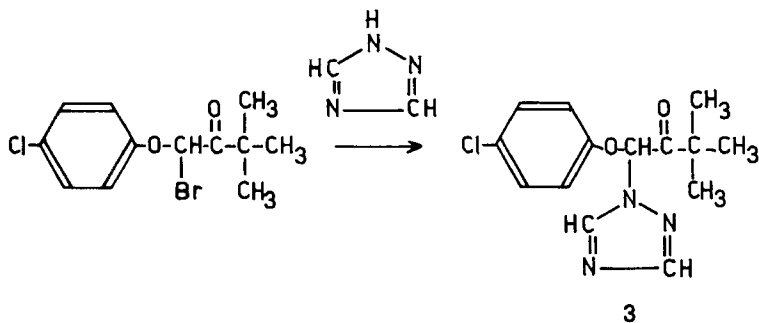
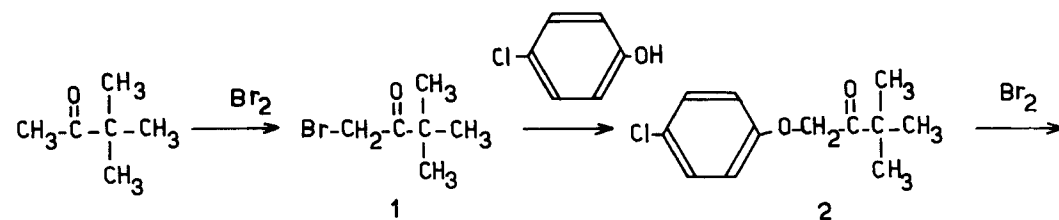
A mixture of 140 mg of 4-chlorophenol (1.09 mmol), 6.3 mg of 4-chloro[U-<sup>14</sup>C]phenol (0.049 mmol, 1 mCi), 204 mg of α-bromopinacolone (1.14 mmol) and 157 mg of potassium carbonate (1.14 mmol) in 25 ml of acetone was refluxed with stirring during 20 hrs. Acetone was evaporated under vacuum in a rotavapor, the residue was mixed with 20 ml of water and 50 ml of chloroform, the chloroform layer was separated, and the aqueous layer was extracted two times with 2x50 ml of chloroform. The chloroform solutions were gathered, the chloroform was evaporated under vacuum in a rotavapor, the residue was dissolved in some chloroform and applied as a band on a p.t.l.c. plate. Elution with ethyl acetate gave one radioactive band (R<sub>F</sub>=0.91) which corresponded to compound 2. That band was scraped off, extracted with ethyl acetate, ethyl acetate was evaporated under vacuum in a rotavapor, and the residue corresponded to 221 mg of compound 2 (0.98 mmol, 0.86 mCi, 86%) which crystallized; it was both chemically and radiochemically pure (> 99%) as shown by comparison with the standard of

compound 2. T.l.c. (Table 1). IR (KBr,  $\text{cm}^{-1}$ ): 2970, 2870 (C-H); 1720 (C=O); 1595, 1580, 1490 (C-H in the aromatic cycle); 1435; 1366 [C-H in  $\text{C}(\text{CH}_3)_3$ ]; 1285, 1245 (C-O, ether); 1165, 1105; 1050 (C-O, ether); 992; 820, 800 (C-H in the aromatic cycle); 770 (C-Cl). MS [m/e(relative intensity)]: 228(12), 226(35),  $\text{M}^+$ ; 143(3), 141(8),  $[\text{C}_{10}\text{H}_{14}\text{OCH}_2]^+$ ; 130(2), 128(8),  $[\text{C}_{10}\text{H}_{14}\text{OH}]^+$ ; 113(10), 111(32),  $[\text{C}_{10}\text{H}_{14}]^+$ ; 99(8),  $[\text{CH}_2\text{COC}(\text{CH}_3)_3]^+$ ; 85(19),  $[\text{COC}(\text{CH}_3)_3]^+$ ; 57(100),  $[\text{C}(\text{CH}_3)_3]^+$ .

### $[^{14}\text{C}]$ Triadimefon, 3

A solution of 206 mg of compound 2 (0.91 mmol, 0.80 mCi) in a mixture of 5 ml of chloroform and 25 ml of diethyl ether was stirred, maintained at 35-40°, and treated dropwise with a solution of 146 mg of bromine (0.91 mmol) in 10 ml of chloroform. After discoloration, the solvent was evaporated under vacuum in a rotavapor. The residue was dissolved in 30 ml of acetone, 189 mg of 1,2,4-triazole (2.73 mmol) were added, the stirred mixture was refluxed during 15 hrs, acetone was evaporated under vacuum in a rotavapor, the residue was mixed with 20 ml of water and 50 ml of chloroform, the chloroform layer was separated, and the aqueous layer was extracted two times with 2x50 ml of chloroform. The chloroform solutions were gathered, the chloroform was evaporated under vacuum in a rotavapor, the residue was dissolved in some chloroform and applied as a band on a p.t.l.c. plate. Elution with ethyl acetate gave one radioactive band ( $R_F=0.85$ ) which corresponded to compound 3. That band was scraped off, extracted with ethyl acetate, ethyl acetate was evaporated under vacuum in a rotavapor, and the residue corresponded to 193 mg of compound 3 (0.66 mmol, 0.58 mCi, 72%) which crystallized; it was both chemically and radiochemically pure (> 99%), as shown by comparison with the standard of compound 3. T.l.c. (Table 1). IR (KBr,  $\text{cm}^{-1}$ ): 3000 (C-H); 1730 (C=O); 1590, 1505, 1495 (C-H of the aromatic cycles); 1385 [C-H in  $\text{C}(\text{CH}_3)_3$ ]; 1280, 1222 (C-O, ether); 1195, 1180, 1135, 1100; 1075, 1050, 1015 (C-O, ether); 995, 960, 910; 870, 830 (C-H of the aromatic cycles); 775 (C-Cl). MS [m/e(relative intensity)]: 295(1), 293(3),  $\text{M}^+$ ; 281(1), 279(3),  $\text{M}^+-\text{N}$ ; 269(1), 267(3),  $\text{M}^+-\text{CN}$ ; 258(2),  $\text{M}^+-\text{Cl}$ ;

238(1), 236(2), M<sup>+</sup>-C(CH<sub>3</sub>)<sub>3</sub>; 210(5), 208(16),  
 [C<sub>1</sub>C<sub>6</sub>H<sub>4</sub>OCHN=CHN=CH]<sup>+</sup>; 181(7), [N=CHN=CHNCOCOC(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>; 154(4),  
 181-HCN; 130(5), 128(13), [C<sub>1</sub>C<sub>6</sub>H<sub>4</sub>OH]<sup>+</sup>; 113(1), 111(4), [C<sub>1</sub>C<sub>6</sub>H<sub>4</sub>]<sup>+</sup>;  
 99(5), [CH<sub>2</sub>COC(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>; 85(15), [COC(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>; 69(10),  
 [NHN=CHN=CH]<sup>+</sup>; 57(100), [C(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>.



## RESULTS AND DISCUSSION

[<sup>14</sup>C]Triadimefon was prepared from 4-chloro[U-<sup>14</sup>C] - phenol by the sequence of reactions shown in Scheme 1. Bromination of pinacolone was carried out by modifications of the method reported by Widman and Wahlberg (5). Compound 2 was obtained by modifications of the method of Bisagni and Rivalle (6). The synthesis of [<sup>14</sup>C]triadimefon 3 from compound 2 was carried out by a new sequence of reactions not published up to the present time, nor for the synthesis of the unlabelled triadimefon, nor for the synthesis of the labelled one.

[<sup>14</sup>C]Triadimefon was both chemically and radiochemically pure (> 99%) as shown by comparison with the standard of triadimefon at the t.l.c., IR, and MS. [<sup>14</sup>C]Triadimefon, having the specific activity 0.88 mCi/mmol, was obtained in 58% overall yield from 4-chloro [U-<sup>14</sup>C]phenol.

## ACKNOWLEDGEMENTS

This work was supported by Grant n° 2035A from the Institut pour l' Encouragement de la Recherche Scientifique dans l' Industrie et l' Agriculture (IRSIA, Belgium).

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