SYNTHESIS OF ^{14}C-LABELLED CROTAMITON

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SUMMARY

The synthesis of ^{14}C-labelled crotamiton, which is a fungicide, an insecticide as well as a scabicide is described. Starting from 2-bromonitrobenzene and Cu^{14}CN, o-toluidine, labelled with ^{14}C at the methyl group was prepared by the following sequence of reactions: NO_2-C_6H_4-Br ------> NO_2-C_6H_4-^{14}CN ------> NO_2-C_6H_4-^{14}COOH ------> NO_2-C_6H_4-$^{14}CH_2OH$ ------> NO_2-C_6H_4-$^{14}CH_2Br$ ------> NH_2-C_6H_4-$^{14}CH_3$. Labelled o-toluidine was then heated with crotonic anhydride to give crotonic acid o-toluidide which was then ethylated by treatment with sodium hydride and ethyl iodide to obtain labelled crotamiton.

Key Words: [^{14}C]Crotamiton, [^{14}C]o-Toluidine, [^{14}C]2-Nitrobenzyl bromide, [^{14}C]Crotonic acid-o-toluidide.

INTRODUCTION

Crotamiton (N-ethyl-N-(2-methylphenyl)-2-butenamide) (8) was originally introduced as a fungicide and insecticide (1). Later, it was found to be a good scabicide (2) when massaged as a cream into the skin. To study its disposition and absorption through the skin we have synthesized it labelled with ^{14}C at the methyl group attached to the benzene ring. Details of this synthesis are described in this paper.

METHODS and RESULTS

The synthesis of ^{14}C-labelled crotamiton (8) consists of two parts--synthesis of o-toluidine (6) labelled with ^{14}C at the methyl group, and conversion of o-toluidine (6) into crotamiton (8). The reaction sequence used for the synthesis of labelled o-toluidine (6) starting from 2-bromonitrobenzene (1)

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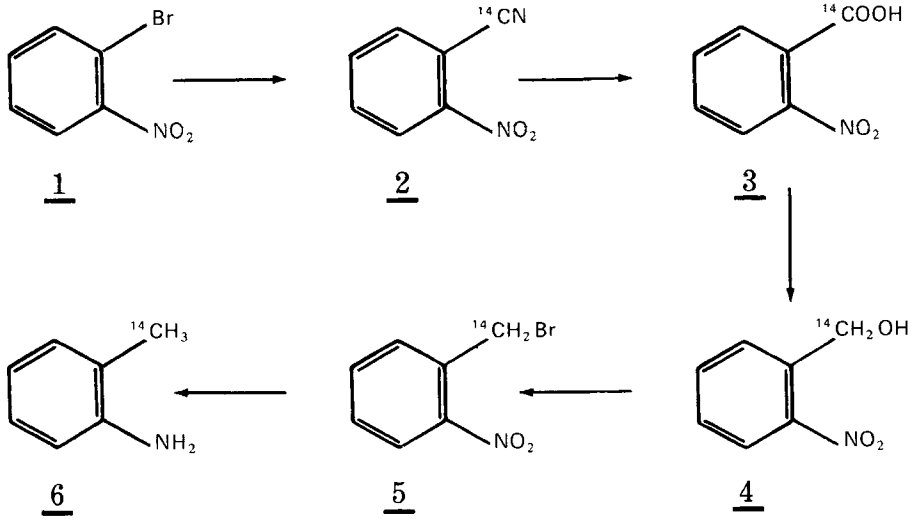
is shown in Scheme 1. o-Toluidine (6) was previously synthesized (3) from

SCHEME 1



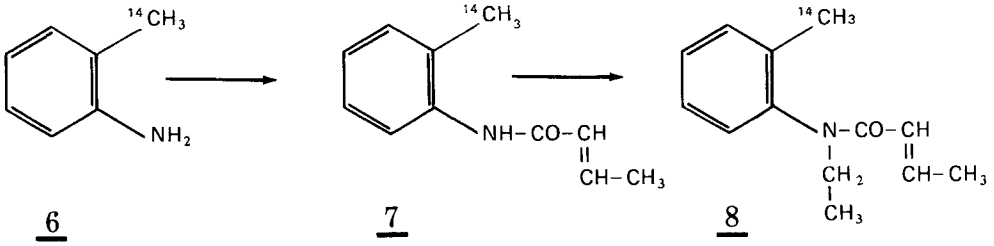
2-bromonitrobenzene (1) via 2-nitrobenzoic acid (3) which was prepared by lithiation of 1 with phenyllithium followed by carboxylation with $^{14}CO_2$. However, 2-nitrobenzoic acid (3) obtained by this method was contaminated with an unidentified impurity (about 12%) and it was not obtained as a crystalline solid. We, therefore, prepared the acid 3 from 1 via the nitrile 2 which was obtained by the reaction of 1 and $Cu^{14}CN$. 2-Nitrobenzoic acid (3) prepared by the hydrolysis of 2 was obtained as a crystalline solid in an overall yield of 66% based on $K^{14}CN$.

In the previous method (3), the nitro group of 3 was reduced first to the amino group and then the carboxyl group was reduced in two steps via the hydroxymethyl group to the methyl group to obtain o-toluidine (6). In our method, we changed the sequence of reductions because we needed the

intermediate, 2-nitrobenzyl bromide (5) for the synthesis of another compound. The carboxyl group of 3 was first reduced by diborane to give 2-nitrobenzyl alcohol (4) which was then heated with 47% hydrobromic acid to give 2-nitrobenzyl bromide (5). Hydrogenation of 5 in presence of platinum catalyst reduced both the functional groups to give o-toluidine (6).

The preparation of crotamiton (8) from o-toluidine (6) is shown in Scheme 2. o-Toluidine (6) was heated with crotonic anhydride to give the

SCHEME 2



6 7 8

amide 7 which was then alkylated by treatment with sodium hydride followed by heating with ethyl iodide to give crotamiton (8).

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectral data are reported in parts per million (ppm) deshielded with respect to tetramethylsilane. NMR spectra at 90 MHz were recorded on a Varian EM-390 spectrometer and the mass spectra were obtained on an AEI MS-902 instrument. Thin layer chromatography (tlc) was carried out on silica gel 60 F-254 plates of 0.5 mm layer thickness and radio chromatograms were scanned on a Berthold LB 2760 instrument. [^{14}C] Potassium cyanide was obtained from New England Nuclear Corporation of Boston, Massachusetts, U.S.A. and non-radioactive organic chemicals were obtained from Aldrich Chemical Co. of Milwaukee, Wisconsin, U.S.A.

[^{14}C]Cuprous cyanide. To a solution of 3.0 g of cupric sulfate in 10 ml of water at 60^{o} was added a solution of 1.5 g of sodium metabisulfite in 10 ml of water immediately followed by a solution of 0.7812 g of [^{14}C]potassium cyanide (60 mCi of radioactivity) in 4.5 ml of water. The mixture was heated with magnetic stirring at 60^{o} for 15 min. The precipitate of [^{14}C]cuprous cyanide was filtered, washed with water, alcohol and ether. It was then dried at 110^{o}for 24 hours; yield 0.966 g (about 90%).

[^{14}C]2-Nitrobenzonitrile (2). [^{14}C]Cuprous cyanide (966 mg) was added to a solution of 3.0 g of 2-bromonitrobenzene in 30 ml of dimethyl formamide and the mixture was heated with magnetic stirring at 130^{o} for 5 hours. The solvent was removed by distillation under reduced pressure in a rotary evaporator and the residue was treated with a solution of 6.5 g of ferric chloride in water. After stirring for a while, the mixture was extracted with ether three times. The ether solution was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to yield 1.45 g of an oily residue which solidified on standing. Thin layer chromatography on a silica gel plate in toluene showed a major spot identical to that of an authentic sample of 2-nitrobenzonitrile and a minor spot due to the unreacted bromo compound.

[^{14}C]2-Nitrobenzoic acid (3). The above residue, without any further purification, was heated under reflux for 24 hours with a mixture of 16 ml of 47% aqueous hydrobromic acid and 12 ml of acetic acid. The solution was then evaporated under reduced pressure in a rotary evaporator and the residue was treated with aqueous sodium hydroxide solution. The alkaline solution was then extracted with ether to remove any neutral material. The aqueous solution was acidified and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, filtered and concentrated to a small volume.

Toluene was added to the ether solution and ether was removed by boiling. Crystals appeared on cooling. The solid was obtained by filtration m.p. 146-47°. The mother liquor was then chromatographed on a column of silica gel. A yellow colored impurity was eluted with toluene. A yellowish white solid was eluted with ethyl acetate, m.p. 146-47°. Thin layer chromatogram of both of the above solids (total yield 1.32 g) in toluene-ethyl acetate (1:1 by vol) was identical to that of an authentic sample of 2-nitrobenzoic acid, m.p. 147-47.5° (4). The overall yield from $K^{14}CN$ was 66%.

[^{14}C]2-Nitrobenzyl alcohol (4). The above acid (1.32 g) was dissolved in 5 ml of tetrahydrofuran and 30 ml of 1 molar borane solution in tetrahydrofuran was then slowly added to it. The solution was refluxed for two hours. After cooling, 5 ml of conc. hydrochloric acid was added with caution followed by methanol. The solution was then evaporated to dryness in a rotary evaporator. More methanol was added and evaporated again to remove traces of boric acid. The residue (1.1 g) was a white crystalline solid, m.p. 72-74° undepressed on admixture with a sample of authentic 2-nitrobenzyl alcohol (4). Thin layer chromatogram of the labelled alcohol in toluene-ethyl acetate (1:1 by vol) was identical to that of an authentic sample of the unlabelled alcohol.

[^{14}C]2-Nitrobenzyl bromide (5). The labelled alcohol (1.1 g) was heated with 5 ml of 47% aqueous hydrobromic acid at 95-100° for 7 hours. After cooling, the reaction mixture was extracted with ether. The ether solution was washed with sodium carbonate followed by saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether solution was evaporated to dryness to give 1.1 g of an oily residue which solidified on standing. Thin layer chromatogram in toluene was identical to that of authentic 2-nitrobenzyl bromide.

[^{14}C]o-Toluidine (6). The above bromide was dissolved in 20 ml of acetic acid and 0.3 g platinum oxide catalyst was added to it and the mixture was shaken in an atmosphere of H_2 in a Paar hydrogenation apparatus at 40 p.s.i. for 2 hours. The solution was filtered and acetic acid was removed by distillation under reduced pressure in a rotary evaporator. The residue was treated with an aqueous solution of sodium hydroxide. The basic solution was then extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give 0.5 g of a yellow oil (39% overall yield from K^{14}CN). Thin layer chromatogram in ethyl acetate-toluene (1:1 by vol) was identical to that of an authentic sample of o-toluidine.

[^{14}C]o-Crotonotoluidide (7). The labelled o-toluidine (0.5 g) was mixed with 0.5 g of unlabeled o-toluidine and dissolved in 10 ml anhydrous ether. Crotonic anhydride (1.75 g) was added to this solution which was then refluxed for 2 hours. After cooling, the crystalline solid was removed by filtration, yield 0.808 g. Further amount (0.130 g) of the amide was isolated from the mother liquor by the following treatment. The mother liquor was stirred with an aqueous solution of sodium bicarbonate and the ether layer separated. After drying over anhydrous magnesium sulfate, the ether solution was concentrated to a small volume. Petroleum ether was added to the ether solution and the amide crystallized as fine needles. The total yield was 0.939 g, m.p. 128-29^{o}, undepressed on admixture with a non-radioactive sample of o-crotonotoluidide, m.p. 128-29^{o} (1).

[^{14}C]Crotamiton (8). A solution of the labelled o-crotonotoluidide (930 mg) in 5 ml of tetrahydrofuran was dropwise added to a magnetically stirred slurry of 550 mg of sodium hydride (50% dispersion in mineral oil) in 15 ml of tetrahydrofuran. The mixture was stirred for 15 min. at 45-50^{o}. Ethyl iodide (3.15 g) dissolved in 2 ml of tetrahydrofuran was then

added to the above mixture and refluxed for 3 hours. After cooling, a few drops of water were added to the reaction mixture which was then evaporated to dryness in a rotary evaporator. The residue was extracted with ether. The ether solution was washed with aqueous solution of sodium sulfite followed by saturated solution of sodium chloride. After drying over anhydrous magnesium sulfate, the ether solution was evaporated to dryness to give a yellow oil which was purified by chromatography on a column of silica gel. The material was eluted from the column with toluene, 2% ethyl acetate in toluene and finally 5% ethyl acetate in toluene. The fraction eluted with 5% ethyl acetate in toluene on evaporation gave 473 mg (10% yield based on $K^{14}CN$) of pure [^{14}C]crotamiton as a yellow oil, spec. radioactivity 9.13 uCi/mg.

Infrared bands: 1665 cm^{-1}(C=O), 1630 cm^{-1}(C=C) and 967 cm^{-1}(trans C-H).

NMR ($CDCl_3$) peaks; 1.1 (t, $C\underline{H}_3CH_2$-), 1.6 (d, $C\underline{H}_3$-CH=), 2.2 (s, $C\underline{H}_3$-Ar), 3-4.3 (m, $C\underline{H}_2$-CH_3), 5.4 (d, CO-$C\underline{H}$ =C), 6.5-7.0 (m, CH_3-$C\underline{H}$=CH-CO), 7.0-7.4 (m, aromatics).

Mass spectrum; m/e 203 (M^+), 188 (M-CH_3), 135 (M-C_4H_4O), 120 (135-CH_3). The chemical purity of 8 was determined by thin layer chromatography in toluene-ethyl acetate (8:2 by vol) and in chloroform-acetone (9.5:0.5 by vol) followed by visualization in ultraviolet light when only one spot due to crotamiton was observed. The radiochemical purity of 8 was checked by scanning the above tlc plates for radioactivity. It was found to be at least 99% pure.

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