1-CYANO-1-(6-PHENOXY-2-PYRIDINYL-2,6-^{14}C)METHYL 3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-CYCLOPROPANECARBOXYLATE

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SUMMARY

A 15.7 mCi sample of 99% radiochemically pure 1-cyano-1-(6-phenoxy-2-pyridinyl-2,6-^{14}C)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate with a specific activity of 21.3 mCi/mmole was prepared *via* a six step process from 2,6-dichloropyridine-2,6-^{14}C.

Key words: 1-cyano-1-(6-phenoxy-2-pyridinyl-2,6-^{14}C)-methyl 3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate; 2,6-dibromopyridine-2,6-^{14}C; 2-bromo-6-phenoxypyridine-2,6-^{14}C; 6-phenoxypicolinaldehyde-2,6-^{14}C; 1-hydroxy-1-(6-phenoxy-2-pyridine-2,6-^{14}C)acetonitrile

INTRODUCTION

Pyrethroid 1 was a promising new Dow experimental insecticide being considered for use on cotton. A carbon-14 labeled sample was required to initiate the environmental, plant metabolism and pharmacokinetic studies required for registration.

DISCUSSION

Tracer 1 was prepared *via* the six step process depicted in Scheme I.

The reaction conditions were initially determined using non-radioactive reactants (pilot runs). The synthesis of 2,6-dichloropyridine-2,6-^{14}C has previously been reported(1).

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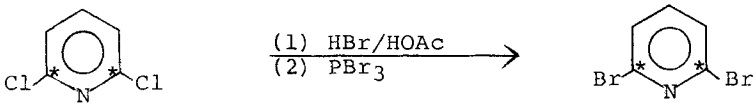
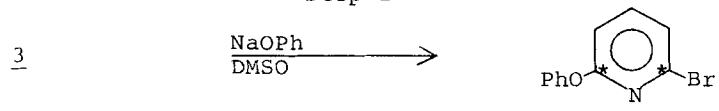
Scheme I

Step 1



2 3

Step 2



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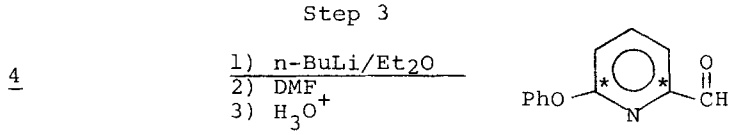
Step 3



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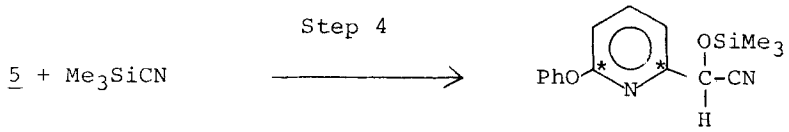
Step 4



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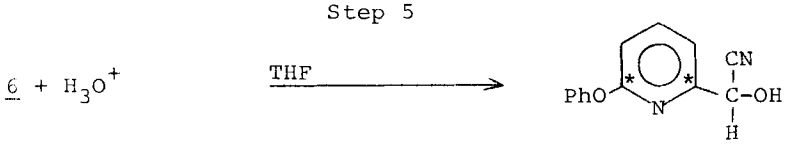
Step 5



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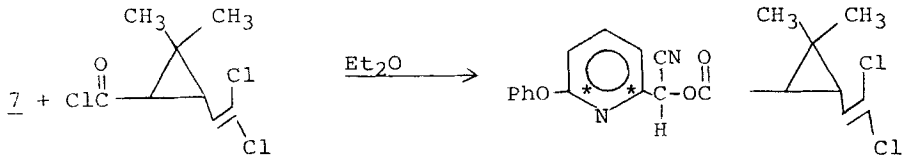
Step 6



(cis/trans mixture)

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The process depicted in Step 1 is a modification of that reported by Mutterer and Weis(2). They converted a series of chlorinated pyridines into the 2,6-dibromo- and, where appropriate, 2,4,6-tribromopyridines by bubbling gaseous HBr through refluxing acetic acid over a 14 hr period. The process as such suffers from the fact that addition of the gaseous HBr on a microscale could cause considerable loss of product. Therefore the reaction was investigated using 48% aqueous HBr. An equilibrium is established consisting of 15 area % 2-bromo-6-chloropyridine and 85 area % 3 by GLC analysis and the ratio is not effected by adding more aqueous HBr. However, >95% conversions are achieved by subsequently adding PBr_3 to the equilibrated solution. In this manner, a 90% yield of 3 was obtained in the pilot run. The yield for this step was not determined in the tracer synthesis.

The generation of 2-bromo-6-phenoxypyridine 4 (Step 2) proceeded well in either DMF or DMSO to afford a ca. 85% yield of purified product in both the pilot and tracer syntheses.

The procedure used for the preparation of aldehyde 5 in Step 3 is similar to that reported by J. E. Parks, B. E. Wagner and R. H. Holm(3) for the synthesis of 6-bromopyridine-2-aldehyde, except that slightly higher temperatures were required to initiate the various reactions. The pilot run afforded a 65% yield of aldehyde whereas a 75% yield was achieved in the tracer synthesis.

Steps 2 and 3 of the above reaction sequence were applied directly to 2,6-dichloropyridine in an attempt to eliminate Step 1. Step 2 proceeded smoothly affording 2-chloro-6-phenoxypyridine in a 75% yield. However, Step 3 could not be accomplished. Products other than aldehyde 5 were produced.

The reaction of aldehydes and ketones with timethylsilylcyanide to afford the corresponding trimethylsilyl ethers of the resultant cyanohydrins (Step 4) is a well known reaction affording product in high yield even in those cases in which the usual cyanohydrin reactions do not occur(4). When applied to aldehyde 5, a quantitative yield of 6 was obtained.

Subsequent conversion of 6 to 7 had been accomplished prior to the publication of P. G. Gassman and J. J. Talley(5). As in their studies, a high yield (100%) of cyanohydrin was obtained. Subsequent reaction of cyanohydrin 7 with 2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropanecarboxylic acid chloride afforded the desired product 1 in >90% yields.

Using the above sequence, a 60% overall yield of 99% radiochemically pure 1-^{14}C with a specific activity of 21.3 mCi/mmole was obtained.

EXPERIMENTAL

The GLC analyses were conducted on a Hewlett Packard 5830A instrument using a 2' x 4 mm glass column containing 10% SE30 on 80/100 Chromosorb WHP. The following conditions were used unless otherwise stated: Temp 1: 100°C, Time 1: 2.0 min; Temp 2: 250°C, Time 2: 5.0 min, Rate: 20°/min, Inj. Temp: 275°C, FID Temp: 300°C, N_2 Flow: 60 ml/min.

2,6-Dibromopyridine-2,6-^{14}C(3)

To a 50-ml round-bottomed flask equipped with a stirring bar and condenser was added 182.0 mg of 2,6-dichloropyridine-2,6-^{14}C (1.230 mmole, 31.4 mCi, 25.5 mCi/mmole), 10 ml of glacial HOAc and 2.0 ml of 48% aqueous HBr. The solution was heated at 128-130°C for 6.5 hours (oil bath) and 2.7 ml of PBr_3 added dropwise over a 0.75 hour period. Heating was continued for 16 hours. The red solution was cooled in an ice bath, diluted with 20 ml of n-pentane and 40 ml of H_2O and the phases mixed. The mixture was extracted continuously with 20 ml of n-pentane over a 4 hour period. The resultant solution was analyzed by GLC (Temp 1: 50°C): 6.37 min (0.12 area %), 7.14 min (0.12%), 7.51 min (3.94%, 2-bromo-6-chloropyridine) 7.92 min (95.8%, 3). The solvent was removed at 100 mm and 24°C affording 3 as a white crystalline product.

2-Bromo-6-phenoxypyridine-2,6-^{14}C(4)

To the 50-ml flask containing 3 was added 134.1 mg (1.425 mmole) of phenol and 5 ml of DMSO (previously dried over molecular

sieves). The resultant stirred solution was purged with N_2 and 100.5 mg of 50% NaH in mineral oil (2.094 mmole) gradually added. The mixture was stirred at 24°C for 0.25 hours and at 80°C for 0.5 hours. The mixture was cooled, diluted with 30 ml of 5% NaOH and extracted continuously with 20 ml of Et_2O over a 5.5 hour period. The Et_2O extract was dried ($MgSO_4$), filtered and the filtrate analyzed by GLC to contain 44.7 area % 3 (Rt = 4.64 min), and 50.5 area % 4 (Rt = 7.31 min). The solvent was removed *in vacuo* and the residue treated as above with 88.0 mg (0.935 mmole) of phenol, 5 ml of DMSO and gradually with 69.0 mg (1.44 mmole) of 50% NaH. After 1.17 hours at 80° the mixture was cooled and the product isolated as described above to afford by GLC analysis 82.6 area % 4 and 7.1% 2,6-diphenoxypyridine with no 3 observed. The repetition of the NaH treatment was not necessary in the corresponding pilot run.

The solution was concentrated to 2 ml and the residue chromatographed on 100 g of Brinkman silica gel G60 using $CHCl_3$ for elution. The tracer was isolated in 150 ml of solution. GLC analysis afforded 92.9 area % pure product (Rt = 7.29 min) containing 2.20 area % 2-chloro-6-phenoxypyridine-2,6-^{14}C (Rt = 6.85 min) and 3.9 area % 2,6-diphenoxypyridine-2,6-^{14}C (Rt = 9.19 min). Solvent removal afforded 277.6 mg of 4 as a white crystalline solid.

6-Phenoxypicolinaldehyde-2,6-^{14}C(5)

The radiolabeled 4 (∿1.031 mmole) was transferred with 10 ml of Et_2O to a 50-ml round-bottomed flask containing a side arm and stirring bar. The flask was purged with N_2 and the 24/40 joint stoppered with a stopper equipped with a Teflon sleeve. The side arm was stoppered with a serum cap through which was attached a N_2 filled balloon *via* a syringe needle. The solution was cooled to -78°C (dry ice-acetone bath) causing precipitation. N-Butyl lithium (1.15 ml of 1.6M solution in n-hexane, 1.94 mmole) was added and the mixture stirred 5 minutes and allowed to warm until complete dissolution results (*ca*-30°C). The solution was placed in a -10°C ice-acetone bath for 5 minutes and the resultant orange solution again cooled to -78°C. Dimethyl formamide, 0.15 ml (1.94 mmole, previously dried over

molecular sieves) was added and the solution stirred at -78°C for 0.5 hour. The solution was allowed to warm for 10 minutes, placed in an ice bath and stirred for 0.5 hour. The hazy yellow solution was treated with 5 ml of 6N HCl and the phases mixed for 0.25 hour. The mixture was diluted with 5 ml H_2O, saturated with NaCl, and extracted continuously with 15 ml of Et_2O over a 5 hour period. The solvent was removed *in vacuo* and the yellow oily residue chromatographed through 100 g of silica gel G60 with $CHCl_3$. The tracer was isolated in 250 ml of solution (GLC: 6.94 min, 99.1 area % 5). Solvent removal afforded 155.4 mg (0.7731 mmole) of 5 as a light yellow oil.

1-Hydroxy-1-(6-phenoxy-2-pyridine-2,6-^{14}C)acetonitrile (7)

To the 50-ml round bottomed flask containing radiolabeled 5 (0.7731 mmole) was added 7.6 mg of KCN, 5 ml Et_2O, 28.8 mg of dicyclohexyl-18-crown-6 and 150 µl (1.201 mmole) of trimethylsilyl cyanide. The solution was stirred 1.0 hour and the solvent removed under a N_2 atmosphere. The residue was dissolved in 5 ml of THF and 1 ml of 1N HCl added. The solution was stirred 5 minutes after which time GLC (Rt 6 = 8.79 min, Rt 7 = 6.93 min) and TLC (1" x 4" silica gel plate, $CHCl_3$) analyses indicated complete reaction. The solvent was removed at 24°C and 60 mm and the residue chromatographed through 100 g of Brinkman Silica Gel G60 with 2:3 (v/v) acetone:*n*-hexane. Product was isolated in 200 ml of solution. The solvent was removed *in vacuo* and the residue dissolved in Et_2O and filtered into a tared flask. The filtrate was analyzed by GLC: Rt 7 = 6.92 min (99.7 area %).

TLC analysis (5 x 20 cm Merck Silica Gel 60-F 254 plate, 2:3 (v/v) n-hexane:acetone) affords product of 98.1% radiochemical purity.

The solvent was removed *in vacuo* to afford 185.7 mg (0.805 mmole at 98.1% purity, ∿100% yield) of 7 as a viscous yellow oil.

1-Cyano-1-(6-phenoxy-2-pyridinyl-2,6-^{14}C)methyl 3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (1)

To the 50-ml pear-shaped flask containing radiolabeled 7 was added 7 ml of Et_2O. The 3-(2,2-dichloroethenyl)-2,2-dimethyl-

cyclopropanecarboxylic acid chloride was distilled and 207.0 mg (0.9099 mmole) of the center cut (bp 60-64° at 0.1 mm, 97.0 GLC area % pure) was added to the flask. To the stirred solution was added 140 µl (1.00 mmole) of Et_3N causing immediate precipitation. After 5 minutes a 0.4 µl aliquot of the mother liquor was analysed by GLC: Rt = 5.07 min (7.06 area %, unreacted acid chloride), Rt = 6.97 min (1.0%, 7) Rt = 13.01 min (86.5%, 1). The mixture was stirred 0.5 hr, filtered through a scintered glass filter and the solvent removed *in vacuo*. The viscous oily residue was chromatographed through 100 g of Brinkman silica gel G60 with $CHCl_3$. Product was isolated in 250 ml of solution. The solvent was removed *in vacuo* to afford 308.3 mg (0.7388 mmole, 60.0% overall yield) of radiolabeled 1 as a colorless oil.

The tracer was dissolved in 10 ml of benzene solution (Volumetric flask, Solution I) and a 0.5 ml portion of Solution I diluted to 50 ml (Solution II). A 1.0 ml aliquot of Solution II was diluted to 100 ml (Solution III). The radiometric analyses of these solutions affords 15.74 mCi of 99% radiochemically pure 1-pyridine-2,6-^{14}C with a specific activity of 21.31 mCi/mmole.

RADIOMETRIC DETERMINATION

The radioactivity was determined in a Packard Tricarb Liquid Scintillation Spectrometer using a New England Nuclear Aquasol®. Triplicate assays of Solution III were taken.

The radiochemical purity was determined by spotting 4 µl aliquots of Solution II along with standard samples of 1, cyanohydrin 7 and aldehyde 5 on five Merck 5 x 20 cm Silica Gel 60-F 254 plates and developing the plates in the following solvent systems: (A) CH_2Cl_2 (B) $CHCl_3$ (C) 3:7 (v/v) n-hexane; acetone (D) 1:1 (v/v) n-hexane:acetone (E) 7:2:1 (v/v/v) n-hexane:EtOAc:HOAc. The plates were scanned on a Vanguard auto scanner connected to a Hewlett Packard 5830A integrator affording product of 99+% radiochemical purity.

The plates were exposed to a Kodak X-Ray film NS-5T for 19.5 hours. Plates A and B show minor impurities at R_f = 0.3 versus

1 at R_f = 0.46 and 0.50 for Plate A (cis/trans isomers) and 0.46 for Plate B.

A second plate containing 1 µl of Solution I and 2 µl of Solution II was developed in $CHCl_3$ and scraped into 5 mm sections. The sections were diluted with 3 ml of 50% aqueous MeOH and 12 ml of NEN Aquasol, counted and a histogram obtained on the data affording product of 99.8% radiochemical purity.

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