Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIV, No. 1 1

A NINE-STEP SYNTHESIS OF [^{14}C]FLUPIRTINE MALEATE LABELED IN THE PYRIDINE RING‡

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SUMMARY

A nine-step procedure for microscale synthesis of ethyl 2-amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl-2,6-^{14}C carbamate maleate [**10**], [^{14}C]flupirtine maleate, was developed. The synthesis started with the readily available and economical reagents, potassium cyanide-^{14}C and 1,3-dibromopropane making the following intermediates: glutaronitrile-^{14}C [**2**], glutarimide-^{14}C [**3**], 2,6-dichloropyridine-2,6-^{14}C [**4**], 2,6-dichloro-3-nitropyridine-2,6-^{14}C [**5**], 2-amino-3-nitro-6-chloropyridine-2,6-^{14}C [**6**], 2-amino-3-nitro-6-(*p*-fluorobenzylamino)pyridine-2,6-^{14}C [**7**], 2,3-diamino-6-(*p*-fluorobenzylamino)pyridine-2,6-^{14}C [**8**], and ethyl 2-amino-6-{[(4-fluorophenyl)-methyl]amino}-3-pyridinyl-2,6-^{14}C carbamic acid ester hydrochloride [**9**]. The overall yield was 6.3% (5.4 mCi), and the radioactivity was 99.8% as determined by high performance liquid chromatography and liquid scintillation counting.

Key Words: Potassium cyanide-^{14}C, 1,3-Dibromopropane, Preparative Column Chromatography, ethyl 2-amino-6-{[(4-fluorophenyl)-methyl]amino}-3-pyridinyl-2,6-^{14}C carbamate maleate

INTRODUCTION

Flupirtine maleate, ethyl 2-amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl carbamate maleate [**10**], is under development as a novel, centrally-acting analgesic agent (1,2).

The disposition of the drug has been studied in animals (3) and man (4) using the drug labeled with ^{14}C at the benzylic carbon (5). However, because of the significant amount of metabolic cleavage at the benzylic carbon occur-

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‡ A poster presentation on this subject was given at the Second International Symposium on the Synthesis and Applications of Isotopically-Labeled Compounds held in Kansas City, MO, September 1985.

0362-4803/87/010001-14$07.00

Received January 6, 1986
Revised April 8, 1986

ing in all species, additional studies on the disposition of flupirtine maleate are needed with the ^{14}C-label in the pyridine ring.

A nine-step procedure for the preparation of the maleate salt of ethyl 2-amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl-2,6-^{14}C carbamate [**10**] has been developed in our laboratories. This paper describes the details of the labeling procedure starting with the readily available materials, 1,3-dibromopropane [**1**] and potassium cyanide-^{14}C as summarized in Scheme I*.

DISCUSSION

A. Development of Small-Scale Synthesis of Flupirtine Maleate [10] with Unlabeled Material

The preparation of nitriles by the substitution reaction of primary alkyl halides with alkali metal cyanide was described previously (6,7). For example 1,3-dichloropropane readily reacted with the nucleophilic cyanide anion in the presence of the aprotic dipolar solvent dimethylsulfoxide. The similar reaction between 1,3-dibromopropane [**1**] and potassium cyanide was used for the synthesis of glutaronitrile [**2**] in the first step reaction (see scheme I). The reactions were performed with 10 mmol of **1** and 20 mmol of potassium cyanide in aqueous ethanol. The isolated crude product was then purified by column chromatography with a 1:3 mixture of acetone and methylene chloride. The yield was better than 95%.

Of the several synthesis routes investigated (8,9), the most convenient procedure for the synthesis of glutarimide [**3**] was the unimolecular cyclization of **2** (8) in the second step. This procedure requires more than 210°C to cyclize the open chain dinitrile compound in the presence of trifluoroacetic acid as a catalyst. The modified synthetic procedure was successfully applied for the preparation of **3** from **2**. The reactions were studied on a 9-25 mmol scale of the starting material [**2**] in the presence of trifluoroacetic acid in various solvents such as formic, acetic, and propionic acids. As shown in Table 1, formic acid failed to give the desired product. The two

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* The bold-faced arabic numerals are used to designate both labeled and unlabeled structures in Scheme I and the text.

other solvents were significantly better giving a 66% yield of the product. Moreover, the lower yield (18%) under the same conditions, was attributed to a loss of the volatile catalyst, trifluoroacetic acid (bp. 72°C) during the heating of the mixture. To circumvent this problem, an excess amount of 1 mL of acid was utilized leading to a consistent yield of the product (see Table 1). Increased temperature also gave higher yields for the same reaction time. The results are listed in Table 1.

The synthesis of 2,6-dichloropyridine [**4**] by the reaction of **3** with phosphorus pentachloride-phosphorus trichloride was reported (10). However, under the conditions published this reaction gave a mixture of other chlorinated pyridines with the desired product **4**. To optimize the yield of the **4**, the chlorination reactions were carried out on a 4-5 mmol scale of **3** with excess of reagents where the ratio of phosphorus trichloride to phosphorus pentachloride was varied. The optimum yield of **4** was obtained by using the PCl_3/PCl_5 ratio of 6 at room temperature for 70 h.

Compound **4** was nitrated with a mixture of nitric acid and sulfuric acid to give 2,6-dichloro-3-nitropyridine [**5**] as previously described (11). The reaction was performed on a 3-6 mmol scale of the starting material with an excess of the mixture of nitric and sulfuric acid in the ratio of 2.2. The optimal yield was 55-57% under reflux conditions for 3-6 h (see Table 2).

All the synthetic procedures for compounds **6-10** (Scheme I) have been developed by researchers at Homburg Degussa Pharma Gruppe, Germany (5,12,13). The procedures were successfully applied, except for the need of modified work-up procedures in all small-scale steps as described below.

In a small-scale run approximately 1.7-1.9 mmol of **5** was utilized in Step 5. The selective ammonolysis reaction was completed at 22-24°C in 24 h. The purification was carried out by recrystallization from a mixture of ethanol-water. The final yield of **6** was 78-90% (see Table 2).

The amination reaction was carried out in isopropyl alcohol with 1.4 mmol of **6** which readily reacted with p-fluorobenzylamine in the presence of the base, triethylamine. The yield was 100% of the corresponding product, **7** (see Table 2).

A one-pot reaction was carried out for Step 7 and 8 on a 1.4 mmol scale of **7** as the starting material. The reactions included the initial reduction of the 3-nitro group in **7** with Ra-Ni/hydrogen and carbamation by reacting ethyl chloroformate with the 3-amino group in **8** without isolation of the compound. The yield of **9** was 90-98% (see Table 2).

The final step involved the conversion of **9** to **10** by neutralization with ammonium hydroxide and then formation of the maleate salt by addition of maleic acid to the free flupirtine base. The yield of **10** was in the range of 51-56% on the small-scale (1.3 mmol) preparation (see Table 2).

B. Synthesis of Ethyl 2-Amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl-2,6-^{14}C Carbamate Maleate [10]

The radiolabeling procedure was identical to the synthetic procedure of flupirtine maleate [**10**] with unlabeled material described in the Experimental Section, except for the following developed procedures and purification.

a) The stoichiometric reaction of 10 mmol of **1** was performed with 20 mmol of potassium cyanide containing 200 mCi of ^{14}C. After further column purification of the crude product on silica gel with a 10:1 mixture of methylene chloride and acetone as the eluting solvent, the yield was 76% of ^{14}C-labeled **2**. The lower yield of the product, when compared to the procedure with unlabeled KCN, was probably due to radioimpurities in the potassium cyanide-^{14}C.

b) The synthesized product, ^{14}C-labeled **7**, was found to be quite unstable even at room temperature. The product was purified two times by column chromatography with a 1:1 mixture of hexane and tetrahydrofuran as solvent. In spite of two purifications of ^{14}C-labeled **7**, this led to a lower yield of 72% of **9** in steps 7 and 8 (90-100% yields in the "cold-run" experiment).

c) In the ninth step the conversion of the hydrochloride into the maleate of [^{14}C]flupirtine was more successful leading to a higher yield as well as higher purity of the desired maleate. It was carried out by neutralization of the hydrochloride, **9**, by column chromatography on silica gel with a 1:5 mixture of methanol and chloroform, which yielded 90% of the free flupirtine base with a melting point of 113-115°C [Lit. m.p. 115-116°C (5)]. The addition of maleic acid then provided 85% yield of [^{14}C]flupirtine maleate with a melting point of 181-183°C. For comparison the melting point of unlabeled **10** was 179-181°C.

The overall weight yield via nine steps was 6.3%, and the radioyield was 2.7% (5.41 mCi). The specific activity of this sample was determined to be 8.75 mCi/mmol (20.80 µCi/mg). In the summary of the calculation of the loss of the ^{14}C atom, 56-57% of the ^{14}C has been lost based on both the weight yield of the product and the specific activity loss. This was probably due to the impure K^{14}CN and the losses in the reactions including the work-up and purification procedures (see Table 2). Results of HPLC analysis of this substance using scintillation counting of the one-minute eluent fractions showed that radiopurity of the [^{14}C]flupirtine maleate was 99.84%. After 21 days of storage in the refrigerator, the substance was found to be quite stable, giving an unchanged radiopurity of 99.85%.

EXPERIMENTAL

General Methods. Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a JNM-MH-100 NMR spectrometer in chloroform-d_1, acetone-d_6, and dimethylsulfoxide-d_6 with tetramethylsilane as internal standard. Thin-layer chromatography (TLC) was performed on silica gel 60F 254 plates of 0.125 mm thickness (EM Scientific). The radiochemical purity of [^{14}C]flupirtine maleate [**10**] was determined by HPLC (High Performance Liquid Chromatography) followed by scintillation counting (Beckman scintillation spectrometer, Model

LS3801, using Aquasol® scintillator) of the HPLC eluent fractions. All other solvents (THF, dioxane) were freshly distilled over lithium aluminum hydride. Methanol and DMSO were stored over Linde 3-°A molecular sieves. The starting material, potassium cyanide-^{14}C, was purchased from Pathfinder Laboratories (St. Louis, MO).

Procedures

a. Small-Scale Experiments with Unlabeled Material

All reactions were carried out under a nitrogen atmosphere.

Glutaronitrile [2]

The reaction was performed in a 50 mL round bottom flask with a side arm and containing a magnetic stirring bar, reflux condenser, and N_2 outlet connecting tube. At room temperature under N_2 gas 1.3 g (20.0 mmol) of potassium cyanide and 1.60 mL of distilled water were added . Then with vigorous stirring a solution of 1.02 mL (10.0 mmol) of **1** was added to 2.0 mL of absolute ethanol. The cloudy mixture was heated to 110°C for 65 h giving a white precipitate. After the contents of the flask were cooled to room temperature 30 mL of chloroform and 5 mL of water were added. The aqueous layer was saturated with sodium chloride and the organic layer was collected. The combined organic layers were dried over anhydrous magnesium sulfate and charcoal. Filtration and concentration gave a yellowish, oily material in a yield of 1.16 g. The crude product was purified on a column of silica gel using methylene chloride:acetone (3:1). After removing the eluting solvents, 0.89 g (95%) of the colorless oily product was collected. TLC analysis (methylene chloride: acetone/3:1) showed only one spot (R_f = 0.57) corresponding to **2**. H^1-NMR (chloroform-d_1, δ ppm): 2.07 (2H, CH_2, m), 2.64 (4H, $2CH_2$, t).

Glutarimide [3]

To a predried reaction tube containing a small stirring bar was added 0.89 g (9.46 mmol) of **2**, 8.0 mL of glacial acetic acid and 1.0 mL of trifluoroacetic acid. The reaction tube was fitted with a vacuum-tight screw type valve. The contents of the tube was cooled to dry ice temperature causing the solution to freeze solid. By using a water aspirator pump, the reaction tube was put under 33 mm Hg pressure and the valve screwed tightly closed to hold the vacuum. After warming to room temperature, the reaction tube was slowly heated to 210°C by an oil bath for 7 h. The acetic acid was removed under reduced pressure to give a yellow, oily material. To the contents 20 mL of a solution of 80% aqueous methanol was added and refluxed at 85°C for 16 h. After removal of the methanol-water under reduced pressure, the resulting oily material was dissolved in 50 mL of methylene chloride and dried over anhydrous magnesium sulfate and charcoal. Filtration and concentration under reduced pressure gave a partially solidified material. It was dissolved in 5 mL of methylene chloride and precipitated out with hexane:ether (1:1) to yield 0.62 g of a white crystalline solid . The solid was further purified on a column of silica gel using methylene chloride: acetone (3:1). After removing the eluting solvents, 0.60 g (56%) white crystalline solid, m.p. 153°-155°C, was collected. TLC analysis (methylene chloride: acetone/3:1) showed one spot (R_f = 0.42) corresponding to **3**. H^1-NMR (chloroform-d_1, δ ppm): 2.00 (2H, CH_2, m), 2.58 (4H, $2CH_2$, t).

2,6-Dichloropyridine [4]

To a predried 100 mL round bottom flask with a side arm, 0.63 g (5.57 mmol) of **3**, 3.95 g (18.97 mmol) of phosphorus pentachloride, and 9.79 mL (11.22 mmol) of phosphorus trichloride were added under N_2. The heterogenous mixture was vigorously stirred at room temperature for 72 h giving a homogenous solution. The reaction mixture was transferred into 250 mL of petroleum ether and cooled to 0°C. Then 175 mL of distilled water was slowly added and stirred for 30 min at 0°C. The two layers were separated, and the aqueous layer was re-extracted two times with petroleum ether. The collected organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to get a white crystalline solid. After drying in a vacuum desiccator for 1 h, 0.63 g (76%) of white crystalline product, m.p. 82°-85°C, was collected. TLC analysis (toluene:hexane/1:1) showed only one spot (R_f = 0.41) corresponding to **4**. H^1-NMR (chloroform-d_1, δ ppm): 7.32 (2H, aromatic, d), 7.68 (1H, aromatic, t).

2,6-Dichloro-3-nitropyridine [5]

To the reaction flask, under N_2, was added 0.45 g (3.04 mmol) of **4** and a solution of 3.50 mL (39.13 mmol) of nitric acid and 9.10 mL (89.18 mmol) of sulfuric acid. The reaction mixture was heated to 108°C for 6 h observing the evolution of a brown gas. After the reaction mixture was cooled to room temperature, a mixture of 90 mL of water and ice was slowly poured into it at 0°C. The solid was filtered and washed with excess water to remove all traces of acid. The solid was dried overnight in a vacuum desiccator to yield 0.32 g (55%) of yellow solid, m.p. 56-60°C. TLC analysis (toluene: hexane/1:1) showed one spot (R_f = 0.36) corresponding to **5**. H^1-NMR (DMSO-d_6, δ ppm): 7.94 (1H, aromatic, d), 8.70 (1H, aromatic, d).

2-Amino-3-nitro-6-chloropyridine [6]

To a predried 100 mL round bottom flask with a side arm outlet tube was added 0.36 g (1.86 mmol) of **5** and 30 mL of anhydrous isopropanol. Using a water bath, the reaction flask was kept at 24°C while anhydrous ammonia gas was bubbled into the homogenous reaction solution for 22 h. The isopropanol was then removed under reduced pressure to yield a yellow solid. To the contents was added 100 mL of THF:ether (1:1) and 20 mL of water to dissolve the solid. At 0°C the aqueous layer was made basic (pH ~9) with a 10% sodium hydroxide solution. The aqueous layer was then saturated with sodium hydroxide pellets. The yellow organic layers were dried over anhydrous magnesium sulfate and charcoal, filtered, and concentrated to give a yellow solid. The crude product was dissolved in 10 mL of hot anhydrous ethanol and then cooled to room temperature. The precipitated solid was filtered and then dried in a vacuum desiccator for three days at room temperature, yielding 0.25 g (78%) of a yellow solid, m.p. 188-191°C. TLC analysis (THF: hexane/1:1) showed only one spot (R_f = 0.61) corresponding to **6**. H^1-NMR (DMSO-d_6, δ ppm): 6.93 (1H, aromatic, d), 8.41 (2H, NH_2, s), 8.59 (1H, aromatic, d).

2-Amino-3-nitro-6-(p-fluorobenzylamino)pyridine [7]

Under N_2 gas 0.25 g (1.44 mmol) of **6**, 7.0 ml of anhydrous isopropanol, 0.33 mL (2.88 mmol) of p-fluorobenzylamine, and 0.50 mL (3.60 mmol) of triethylamine were added. The resulting heterogenous mixture was refluxed at

90°C for 18 h becoming yellow and homogenous. The volume of isopropanol was reduced to half under reduced pressure. The contents of the flask was cooled to 0°C and then 60 mL of water was added to cause precipitation of a yellow solid. After 1.5 h at 0°C the solid was filtered and washed well with excess water. The solid was then dried in a vacuum desiccator overnight to yield 0.38 g (100%) of yellow solid, m.p. 171- 174°C. TLC analysis (THF:hexane/-1:1) showed only one spot (R_f = 0.47) corresponding to **7**. H^1-NMR (DMSO-d_6, δ ppm): 4.52 (2H, CH_2, d), 5.98 (1H, aromatic, d), 7.08 (2H, aromatic, m), 7.36 (2H, aromatic, m), 7.95 (1H, aromatic, d), 7.95 (2H, NH_2, s), 8.30 (1H, NH, t).

Ethyl 2-Amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl carbamic acid ester hydrochloride [9]

To a predried 300 mL reaction beaker, under N_2, 0.38 g (1.44 mmol) of **7**, 0.28 g of anhydrous magnesium sulfate, 7.6 mL of dry dioxane and a small amount of pure Raney-nickel as a catalyst were added. Under N_2 atmosphere the beaker was sealed inside a Parr hydrogenation bomb, which was flushed out with N_2. Hydrogen gas (99.99% purity) was introduced into the bomb to 600 psi at a constant temperature water bath (80°C) using a circulating pump. The bomb was internally heated through a heating coil and a shaker machine was used to stir the bomb back and forth for 21 h. Using a predried airless filter funnel with a sintered glass filter connected to a 100 mL round bottom flask under N_2, the contents of the beaker in the bomb were transferred to the funnel to filter off the mixture under a pressure of N_2. To the resulting purple solution was added 0.23 mL (2.38 mmol) of ethyl chloroformate under N_2. The reaction flask was covered with aluminum foil to shield the contents from light. After stirring 1 h at room temperature, a green precipitate was formed which was allowed to stir overnight while protected from light. The solid was filtered and then washed with a mixture of dioxane: ether (1:1) and then with pure ether. After drying, 0.44 g (90%) of a green solid, m.p. 213-215°C, was collected. TLC analysis (chloroform:methanol/4:1) showed one spot (R_f = 0.63) corresponding to **9**. H^1-NMR (DMSO-d_6, δ ppm): 1.18 (3H, CH_3, t), 3.95 (2H, CH_2, q), 4.47 (2H, CH_2, bs), 5.92 (1H, aromatic, d), 7.12 (2H, aromatic, d), 7.02 (1H, NH, s), 7.40 (4H, aromatic, m), 7.40 (1H, NH, s), 8.40 (2H, NH_2, s).

Ethyl 2-Amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl carbamate maleate [10]

To a 250 mL erlenmeyer flask with a magnetic stirring bar 0.44 g (1.30 mmol) of **9** was added to 150 mL of a THF:ether (1:1) solution. After cooling to 0°C, 10 mL water was added to completely dissolve the solid. Ammonium hydroxide (28.5% NH_3) was dropwise added to the solution until a pH ~ 9 was reached. The mixture was stirred for 20 min at 0°C with excess ammonium hydroxide, then the two layers were separated and the organic layer collected. After addition of 100 mL of THF:ether (1:1), the aqueous layer was saturated with sodium hydroxide pellets at 0°. The resulting two layers were separated and the organic layer collected. The combined organic layers (purple color) were dried over anhydrous magnesium sulfate and charcoal. Filtration and concentration gave a brown oily material. The oily material was dissolved in 20 mL of THF: ether (1:1) and then a solution of 0.21 g (1.81 mmol) of maleic acid was added at 0°C in 3.0 mL of THF: ether (1:1). A green precipitate formed immediately and then an excess of THF: ether (1:1) was added and cooled at 0°C for 1 h. The resulting solid was filtered and washed with excess THF:ether (1:1) and dried. Collected 0.28 g (51%) of slightly green product, m.p. 179-181°C corresponding to **10**. H^1-NMR (DMSO-d_6, δ ppm): 1.20 (3H, CH_3, t), 4.06 (2H, CH_2, q), 4.38 (2H, CH_2, s), 5.78 (1H, aromatic, d), 6.12 (2H, 2CH, s), 7.28 (5H, aromatic, m), 7.28 (2H, 2NH, m), 8.26 (2H, NH_2, s).

b. <u>^{14}C-Labeling Experiment</u>

[^{14}C]Glutaronitrile [2]

The procedure was similar to Step 1 in the cold experiment section with the exceptions that 0.744 g (11.5 mmol - 200 mCi) of potassium cyanide-^{14}C and 0.556 g (8.5 mmol) of unlabeled potassium cyanide was used and that the product was purified on a column of silica gel using methylene chloride: hexane (10:1). The yield was 0.71 g (76%) of colorless oily product.

2,6-^{14}C-Glutarimide [3]

The procedure was similar to Step 2 in the cold experiment section with the exceptions that 0.71 g (7.6 mmol) of [^{14}C]labeled **2** was used and that the product was purified on a column of silica gel using methylene chloride: acetone (3:1) and then recrystallized from ether:hexane (1:1). The yield was 0.52 g (61%) of white crystalline solid, m.p. 153°-155°C.

2,6-Dichloropyridine-2,6-^{14}C [4]

The procedure was similar to Step 3 in the cold experiment section with the exceptions that 0.52 g (4.6 mmol) of [^{14}C]labeled **3** was used and that the product was purified on a column of silica gel using toluene:hexane (1:1). Yield was 0.51 g (75%) of white crystalline solid, m.p. 84°-85°C.

2,6-Dichloro-3-nitropyridine-2,6-^{14}C [5]

The procedure was similar to Step 4 in the cold experiment section with the exception that 0.51 g (3.5 mmol) [^{14}C]labeled **4** was used. Yield was 0.33 g (50%) of yellow solid, m.p. 55°-57°C.

2-Amino-3-nitro-6-chloropyridine-2,6-^{14}C [6]

The procedure was similar to Step 5 in the cold experiment section with the exceptions that 0.33 g (1.7 mmol) of [^{14}C]labeled **5** was used and that the product was purified on a column of silica gel using THF: hexane (1:1). Yield was 0.22 g (74%) of yellow solid, m.p. 190°- 192°C.

2-Amino-3-nitro-6-(p-fluorobenzylamino)pyridine-2,6-^{14}C [7]

The procedure was similar to Step 6 in the cold experiment section with the exceptions that 0.22 g (1.27 mmol) of [^{14}C]labeled **6** was used and that the product was purified on a column of silica gel using THF:hexane (1:1). Yield was 0.30 g (90%) of yellow solid, m.p. 168°- 171°C.

Ethyl 2-Amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl-2,6-^{14}C carbamic acid ester hydrochloride [9]

The procedure was similar to Steps 7 and 8 in the cold experiment section with the exception that 0.30 g (1.14 mmol) of [^{14}C]labeled **7** was used. Yield was 0.28 g (72%) of green solid, m.p. 211-213°C.

Ethyl 2-Amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl-2,6-^{14}C carbamate maleate [10]

The 0.28 g (0.82 mmol) of [^{14}C]labeled **9** was neutralized by chromatographing the solid on a column of silica gel using methanol:chloroform (1:5). After removing the solvents under reduced pressure, the resulting solid was dissolved in a solution of ether:THF (4:1) to which was added a solution of 0.12 g (1.03 mmol) of maleic acid in 5 mL of ether:THF (4:1). A white precipitate immediately formed to which was added excess ether:THF (4:1) and cooled at 0°C for 30 min. The solid was filtered and washed with excess ether. After drying, the yield was 0.26 g (76%) of white solid **10**, m.p. 181°-183°C, radioyield 2.7% (5.4 mCi).

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TABLE 1: SYNTHESIS OF GLUTARIMIDE [3] FROM GLUTARONITRILE [2][a]

Solvent (R-COOH)	TFAA[c] (mL)	Time/Temp (h) (°C)	Yield[b] (%)
H	0.1	16/160	0
CH_3	0.1	18/210	66
CH_3CH_2	0.1	18/210	66
CH_3	0.1	18/210	18
CH_3	1.0	6/160	16
CH_3	1.0	6/185	51
CH_3	1.0	6/210	65
CH_3	1.0	7/210	56[d]

[a] Starting material, 9-25 mmol of 2 was used.
[b] Isolated yield
[c] TFAA represents Trifluoroacetic acid.
[d] The yield obtained from the synthesized compound 2.

TABLE 2: SYNTHESIS OF [^{14}C]FLUPIRTINE MALEATE [10] FROM 1,3-DIBROMOPROPANE [1] AND POTASSIUM CYANIDE-^{14}C VIA A NINE STEP EXPERIMENT

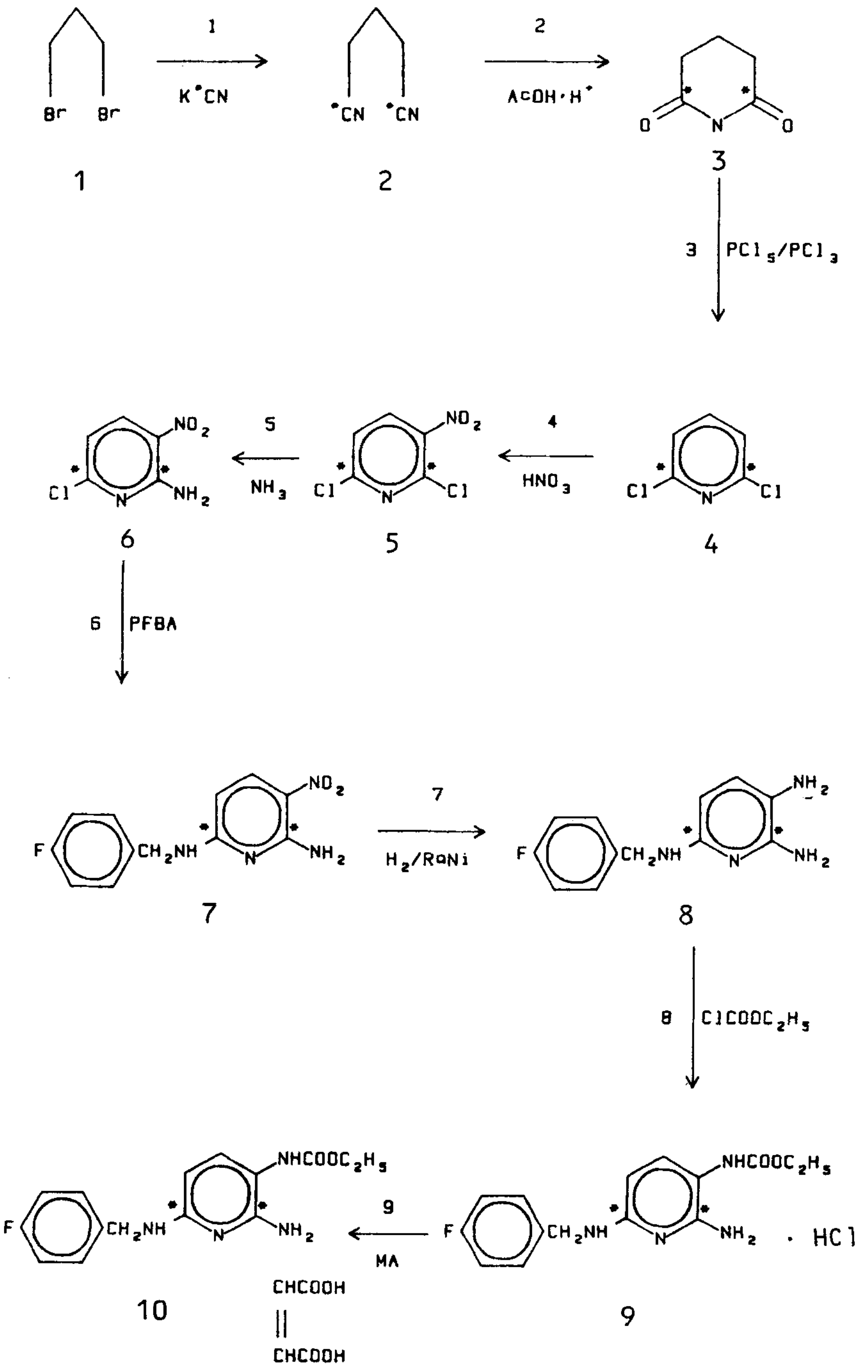
Step (#)	Product (#)	Lit. MP (°C)	Cold Exp.[a] % (g) MP(°C)	Labeled Exp.[b] % (g) MP (°C)
1	**2**	101-102 (7)[c]	95 (0.60) --	76 (0.71) --
2	**3**	152-154 (14)	58 (0.60) 153-155	61 (0.52) 153-155
3	**4**	86-88 (15)	76 (0.63) 82-85	75 (0.51) 82-84
4	**5**	55-60 (11)	55 (0.32) 56-60	50 (0.33) 55-57
5	**6**	195-196 (13)	78 (0.25) 188-191	74 (0.22) 190-192
6	**7**	172-174 (12)	100 (0.38) 171-174	90 (0.30) 168-171
7 & 8	**9**	209-211 (5)	90 (0.44) 213-215	72 (0.28) 211-213
9	**10**	183-185 (5)	51 (0.28) 179-181	76 (0.26) 181-183

[a] Starting materials, 10.0 mmol of **1** and 20.0 mmol of potassium cyanide were used.

[b] Starting materials, 10.0 mmol of **1** and 20.0 mmol of potassium cyanide [11.5 mmol (200 mCi), $K^{14}CN$, and 8.5 mmol, KCN] were used.

[c] The temperature listed under "Lit. MP" is a boiling point at 1.5 torr.

SCHEME I : SYNTHESIS OF ^{14}C-FLUPIRTINE MALEATE



*C = ^{14}C PFBA = P-FLUOROBENZYLAMINE MA = MALEIC ACID