SYNTHESIS OF THE MUSCLE RELAXANT [^{14}C]L-637,510

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SUMMARY

The synthesis of (E)-3-(9-chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)-benzazepin-11-ylidene)-N,N-dimethyl-1-[3-^{14}C]-propanamine (Z)-2-butenedioate(1:1) (11, [^{14}C]L-637,510), a potential muscle relaxant product for which ^{14}C-labeling was required for metabolism studies, is described. Introduction of the label in the 3-position of the propanamine side chain was accomplished in eight steps from sodium [^{14}C]cyanide with an overall radiochemical yield of 4.8%.

Key Words: (E)-3-(9-Chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)-benzazepin-11-ylidene)-N,N-dimethyl-1-[3-^{14}C]propanamine (Z)-2-butenedioate (1:1), 9-chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)-benzazepin-11-one.

INTRODUCTION

The compound (E)-3-(9-chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)benzazepin-11-ylidene)-N,N-dimethyl-1-propanamine (Z)-2-butenedioate(1:1) (11, L-637,510) exhibits significant muscle relaxant properties.[1] In order to assist in the development process and in particular to investigate both the in vivo distribution and the metabolic fate of this compound in both animals and man, ^{14}C-labeled 11 was required. Since in vivo N-dealkylation of amines is known to occur[2], and because the structurally similar compounds amitriptyline and cyclobenzaprine have been reported to undergo N-demethylation in vivo[3,4], the N-[^{14}C]methyl labeled compound was not considered a reasonable choice for use in tracer studies. Ring labeled material of course would have been an ideal tracer but time constraints did not allow us to undertake this difficult synthesis. Instead we selected the metabolically stable propyl side chain as our choice for label position. Specifically we have synthesized 11 labeled with carbon-14 in the 3-position of the N,N-dimethylamino-1-propyl moiety. This was accomplished using an eight step synthetic route (see SCHEME) from sodium [^{14}C]cyanide as described herein.

DISCUSSION

The reaction of 2-chloroethanol with sodium[^{14}C]cyanide in refluxing ethanol:water(3:1) gave 3-hydroxy[1-^{14}C]propionitrile (1) in 92% yield. Hydrolysis of the nitrile 1 to 3-chloro[1-^{14}C]propionic acid (2) was accomplished

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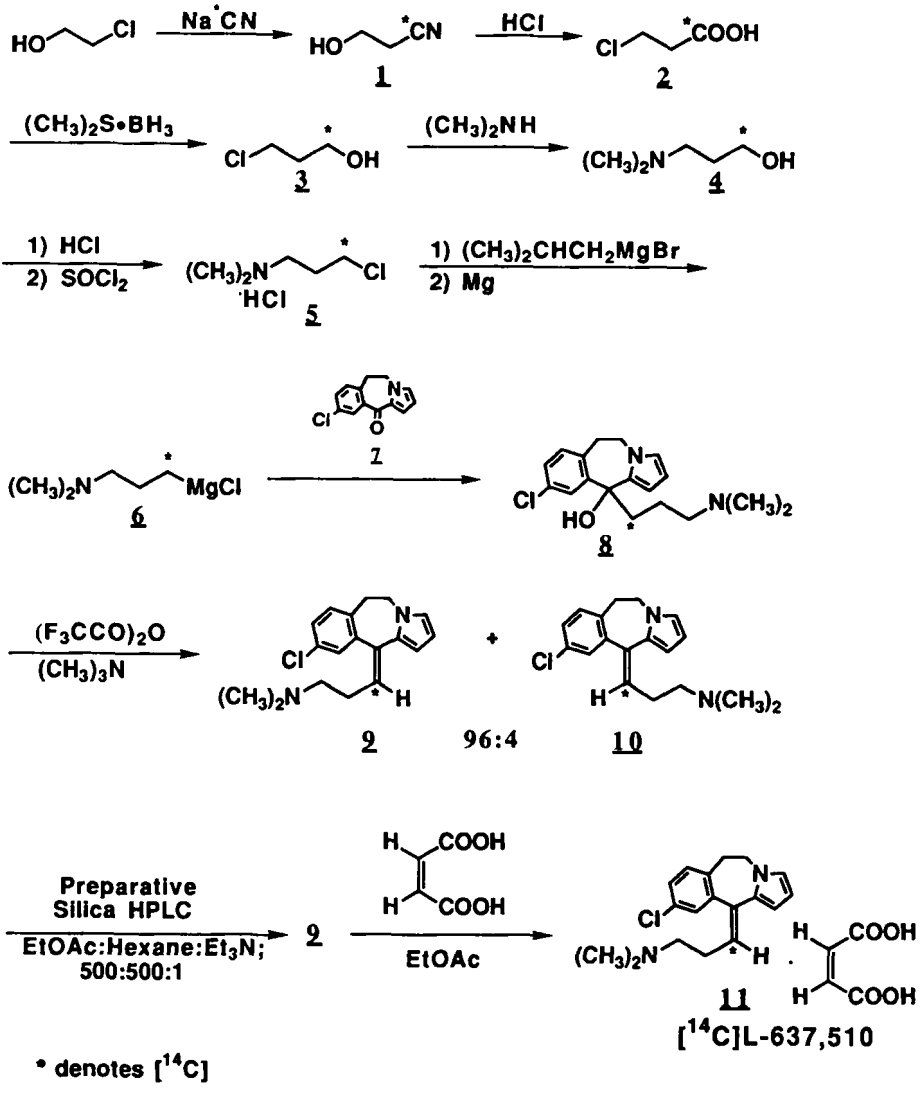
SCHEME



in 83% yield by heating 1 in concentrated hydrochloric acid at 110°C in a sealed tube. Reduction of the acid 2 with borane•methyl sulfide in ether gave 3-chloro-[1-^{14}C]propanol (3) in 93% yield. Treatment of 3 with aqueous dimethylamine at 100°C in a sealed tube resulted in the formation of 3-N,N-dimethylamino-[1-^{14}C]propanol (4) in 71% yield. Acidification of 4 with gaseous hydrogen chloride in toluene followed by the addition of thionyl chloride and heating to reflux provided a 75% yield of the key radioactive intermediate, 3-N,N-dimethylamino-[1-^{14}C]propyl chloride hydrochloride (5). The hydrochloride salt 5 was suspended

in dry tetrahydrofuran and in a novel neutralization was converted to its free base using an equivalent amount of isobutylmagnesium bromide. The addition of magnesium metal and a subsequent two hour reflux period provided Grignard reagent 6. This procedure allowed us to by-pass the more traditional and lower yielding neutralization using aqueous caustic followed by extraction, isolation, and dissolution of the formed free base in tetrahydrofuran prior to Grignard formation. Addition of 9-chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)-benzazepin-11-one (7) to the solution of Grignard reagent 6 provided carbinol adduct 8 in 33% yield. The use of one equivalent of oxalic acid in refluxing ethanol converted 8 to a 1:1 mixture of E- and Z-olefins 9 and 10, respectively. However, when the dehydration of 8 was carried out in methylene chloride at -60°C using trifluoroacetic anhydride and trimethylamine the ratio of the desired E-isomer 9 to the unwanted Z-isomer 10 was 96:4. Isomer separation and purification of this mixture by preparative HPLC gave a 63% yield of pure 9 from carbinol 8. Crystallization of 9 from ethyl acetate as the malcate salt gave the final product 11 in 63% yield. The overall yield for the eight steps was 4.8%.

EXPERIMENTAL

Radioactivity determinations were carried out with a Packard Tri-Carb Model 3320 liquid scintillation counter using 0.42% Omnifluor™ in toluene:ethanol (7:3) as scintillation medium. The GC (HP 5710A) analysis conditions were: OV-101 or OV-17 (1/4" x 6'), injection temp. 250°C, carrier gas 5% carbon dioxide/argon at 30 ml/min, FID. Analytical TLC was performed using silica gel 60 F-254 (E. Merck glass plates, 5 x 20 cm) with radioactivity measurements made with a Berthold Model LB2760 scanner. The HPLC system used for analysis consisted of a 4.6 mm x 25 cm Whatman Partisil column, two Beckman Model 100A pumps, a Beckman Model 421 controller, and an LDC Spectromonitor II UV detector. HPLC radioactivity measurements were done using a Berthold LB504 Radioactivity Monitor with Hewlett Packard HP3388A computer integration. Preparative HPLC was accomplished using a Whatman M20 (22.1 mm x 50 cm) Partisil column.

The identities of each of the labeled intermediates, as well as of the final product (11), were established by co-elution via GC, HPLC, or TLC of the radiolabeled substance with authentic unlabeled compounds obtained from either Aldrich Chemical Co., Inc. (Milwaukee, Wis.) or from Merck & Co., Inc. (Rahway, N.J.).[1]

3-Hydroxy-[1-^{14}C]propionitrile (1)

To 189 mg (3.70 mmol, 54.0 mCi/mmol, 200 mCi) of sodium [^{14}C]cyanide was added 4 ml water and 1 ml ethanol. The resulting solution was partially concentrated to ~1 ml by warming (60°C bath) while under a stream of nitrogen. Sodium cyanide (188 mg, 3.84 mmol) was added followed by a solution of 729 mg (9.06 mmol) 2-chloroethanol in 2.8 ml of ethanol. The mixture was refluxed for 24

hours, then cooled and carefully concentrated under reduced pressure. Distillation of the residue at 0.1 mm yielded 499 mg of the nitrile 1 (92%, bp 55°C).

3-Chloro-[1-^{14}C]propionic acid (2)

A mixture of 1 (499 mg, 6.93 mmol) and 7 ml of 12 N hydrochloric acid was heated for 42 hours at 110°C in a sealed tube. The reaction vessel was cooled to room temperature and opened. Sodium chloride (5 g) was added and the product partitioned into ether. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield 841 mg (152 mCi, 83%) of crude 2 as an oily residue. This material was used directly in the next step without purification

3-Chloro-[1-^{14}C]propanol (3)

The crude isolate (841 mg, 5.74 mmol, 152.0 mCi) of 2 from above was dissolved in 7 ml of anhydrous ether. A solution of 0.9 ml (9.0 mmol) of 10 M borane•methyl sulfide in 3 ml of anhydrous ether was added over 15 minutes. After 4 hours, analysis by GC (OV-17, 80°C) indicated complete conversion of starting material 2 (Rt = 4.1 min) to pure product 3 (Rt = 2.9 min, the same as reference material). Ether (10 ml, 0°C) was added to the reaction mixture followed by 3 ml of cold water. Addition of sufficient anhydrous potassium carbonate to completely absorb the water and subsequent decantation from the resulting solid residue gave an ether solution which upon concentration yielded 1033 mg (142.0 mCi, 93%) of the alcohol 3.

3-(N,N-Dimethylamino)-[1-^{14}C]propanol (4)

A solution of crude 3 (1033 mg, 5.36 mmol, 142.0 mCi) in 2.5 ml of water and 6.86 g of aqueous dimethylamine (27% by weight in H_2O) was heated at 100°C for 5 hours in a sealed container. The contents were removed and extracted with ether. The extract was dried over anhydrous magnesium sulfate and filtered. The filtrate contained 101.3 mCi (3.82 mmol, 71%) of radioactive material which by GC analysis (OV-101, 90°C, Rt = 2.7 min) was essentially pure 4. Toluene (5 ml) was added and the ether was removed by atmospheric distillation. A portion of the toluene solution of 4 was used directly in the next reaction.

3-N,N-Dimethylamino-[1-^{14}C]propyl chloride hydrochloride (5)

Gaseous hydrogen chloride was added above the surface of a cold (0°C) solution of 4 (3.69 mmol, 97.9 mCi) in dry toluene (5 ml) for 10 minutes. To the resulting slurry of amine hydrochloride was added 1723 mg (14.5 mmol) of thionyl chloride. The mixture was warmed to reflux and kept at reflux for 2 hours. After cooling, solvent was removed in vacuo to give 805 mg of solid residue. Crystallization from ethanol:ether (1:15) yielded 436 mg (2.76 mmol, 73.1 mCi, 75%) of pure 5

as determined by radioscan of a silica TLC plate developed with chloroform:methanol (7:3).

9-Chloro-6,11-dihydro-11-(3-N,N-dimethylamino-[1-^{14}C]propyl)-5H-pyrrolo(2,1-b)(3)benzazepine-11-ol (8)

To a cooled (0°C) suspension of 436 mg (2.76 mmol, 73.1 mCi) of 5 in 4 ml of dry tetrahydrofuran was added 1.5 ml (3.24 mmol) of 2.16 M isobutylmagnesium bromide in tetrahydrofuran. The resulting solution was warmed to room temperature, then 94 mg (3.86 mmol) of magnesium and 193 mg (1.03 mmol) of ethylene dibromide were added. The reaction was heated to reflux and after 2 hours all of the magnesium had completely reacted. To the resulting, cooled (0°C) Grignard solution was added a solution of 757 mg (3.27 mmol) of the ketone 7[5] in 3 ml of dry tetrahydrofuran. The temperature of the reaction mixture was raised to 25°C and the mixture was stirred overnight. Quench of the reaction mixture with 2 ml of 5 N sodium hydroxide, followed by ether extraction and concentration of the ether extract gave crude product. Preparative HPLC (Partisil, chloroform:methanol:ammonium hydroxide; 1000:20:1) provided the pure alcohol 8 (24.0 mCi, 33% from 5). Analysis by silica TLC (methanol:ammonium hydroxide;100:1) and radioscan indicated pure (99+%) product. In vacuo solvent removal followed by the addition of 15 ml of dry methylene chloride provided a solution which was used directly in the next reaction.

(E)-3-(9-Chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)benzazepin-11-ylidene-N,N-dimethyl-1-[3-^{14}C]propanamine (9)

To a cooled (-45°C), vigorously stirred solution of the alcohol 8 (0.91 mmol, 24.0 mCi) in 15 ml dry methylene chloride was applied gaseous trimethylamine above the surface for 10 minutes. The mixture was cooled to -78°C and a solution of 570 mg (2.71 mmol) of trifluoroacetic anhydride in 4 ml dry methylene chloride was added. The reaction mixture was warmed to -60°C and after 1/2 hour quenched at that temperature with 2.0 ml of 2.5 N sodium hydroxide. After warming to room temperature, the organic layer was removed and the aqueous layer was extracted with methylene chloride (3 x 10 ml). The combined extracts, after drying and concentration, gave 377 mg of crude product. Radiochemical analysis by HPLC (Partisil, ethyl acetate:hexane:triethylamine; 65:35:1) indicated this material to be 76% compound 9 (Rt 9.0 mins.) and 3% compound 10 (Rt 10.5 mins). Preparative HPLC (Partisil, ethyl acetate:hexane:triethylamine; 500:500:1) of the crude gave 199 mg (0.57 mmol, 15.2 mCi, 63%) of the desired E-isomer 9.

(E)-3-(9-Chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)benzazepin-11-ylidene)-N,N-dimethyl-1-[3-^{14}C]propanamine (Z)-2-butenedioate (1:1) (11, [^{14}C]L-637,510)

To a solution of 199 mg (0.57 mmol, 15.2 mCi) of the free base 9 in 6 ml warm (40°C) ethyl acetate was added 60 mg (0.69 mmol) of maleic acid. The solution was concentrated under a stream of nitrogen to ~4 ml. The resulting slurry was kept

at 0°C for 18 hours then filtered to give 149 mg (0.36 mmol, 9.6 mCi, 63%, 4.8% overall) of crystalline (E)-3-(9-chloro-5,6-dihydro-11H-pyrrolo(2,1-b)(3)benzazepin-11-ylidene)-N,N-dimethyl-1-[3-^{14}]propanamine (Z)-2-butenedioate (1:1). This material co-eluted with authentic (unlabeled) product 11 on silica TLC (methanol:ammonium hydroxide; 100:1) and a radioscan of the plate indicated a radiochemical purity of 98.8%.

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