SYNTHESIS OF CARBON-14 LABELED VIGABATRIN

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Summary

Carbon-14 labeled vigabatrin was synthesized in 5 steps from 5-hydroxymethyl-2-pyrrolidone tosylate and NaCN-[^{14}C]. A key step involved reduction of the resulting nitrile in the presence of excess dimethylamine to give the dimethylamino-ethyl 2-pyrrolidone derivative in one step. This afforded an overall radiochemical yield of 22% and radiochemical purity greater than 98%.

Key Words: Vigabatrin, (*R,S*)-4-Amino-5-hexenoic-6-[^{14}C] acid, NaCN-[^{14}C], Antiepileptic

INTRODUCTION

Vigabatrin, marketed in Europe, is a unique antiepileptic shown to be active when conventional therapies have failed. It was designed as an irreversible inhibitor of *gamma*-aminobutyric acid (GABA) transaminase[1]. A tritiated version was once available from NEN Research Products, but ADME studies required a carbon-14 compound. Although several methods of synthesis of vigabatrin, (*R,S*)-4-amino-5-hexenoic acid (**6**), have been developed[2], the method of Frieben and Gerhart[3] from pyroglutamic acid proved to be the method of choice since cyanide-[^{14}C] could then be used as the source of the label.

RESULTS AND DISCUSSION

Pyroglutamic acid ethyl ester was reduced and converted to tosylate **1** as described by Faber and Wiegrebe,[4] and this material was reacted with carbon-14 labeled NaCN in DMF to give the corresponding nitrile **2** in 87% yield. (In an earlier preparation, it was found that KCN was much less active in this reaction, probably because of decreased

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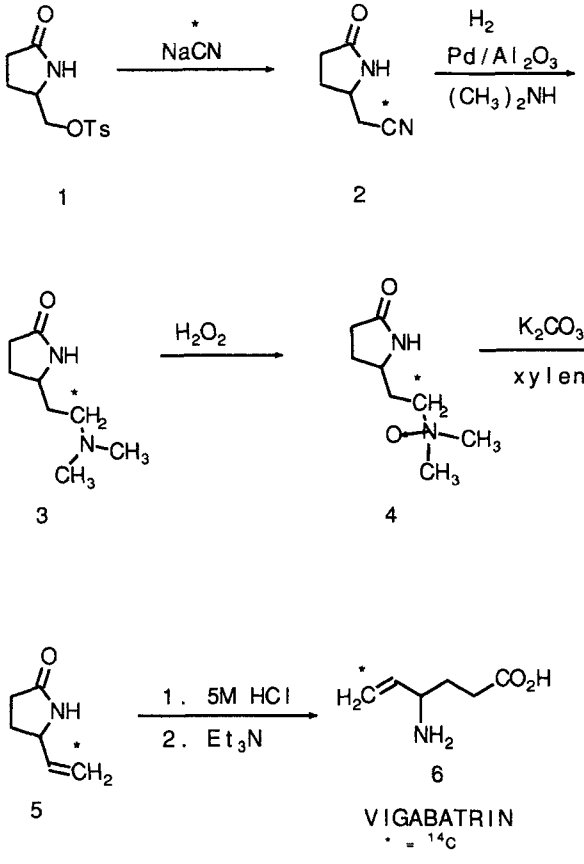
solubility in DMF.) Catalytic reduction of the nitrile in the presence of excess dimethylamine produced *tertiary* amine **3** in 96% yield. Oxidation of the amine with H_2O_2 afforded a 93% yield of *N*-oxide **4**, and elimination of this moiety gave a 64% yield of the vinyl pyrrolidinone **5** after flash chromatography. Acid hydrolysis opened the ring to produce the desired vigabatrin-[^{14}C] **6** in 78% in two lots.

SCHEME



In this preparation, 8.34 mCi, 308 MBq (122 mg) of vigabatrin-[^{14}C] was prepared in the first lot with a specific activity of 8.82 mCi/mmol (68 μCi/mg) and a radiochemical purity of 99.2%. A second lot, diluted with carrier and purified separately, consisted of 5.65 mCi, 209 MBq (257 mg) of vigabatrin-[^{14}C] with a specific activity of 2.89 mCi/mmol (22.4 μCi/mg) and a radiochemical purity of 98.8%.

EXPERIMENTAL

TLC analyses were conducted using EM Silica Gel 60 F_{254} TLC plates. All scintillation counting was conducted using a Packard Minaxi Tri-Carb Liquid Scintillation Counter. The mass spectrum of the product was determined using a Finnigan Model 4500 GC/MS/DS Mass Spectrometer. Sodium cyanide-[^{14}C] was supplied by NEN Research Products, DuPont Merck Pharmaceuticals, Inc., Boston, MA.

(*R,S*)-5-(Cyano-[^{14}C]-methyl)-2-pyrrolidinone, (2) A mixture of 673 mg (2.5 mmol) of (*R,S*)-5(((4-methylbenzenesulfonyl)oxy)methyl)-2-pyrrolidinone (**1**), 123 mg of NaCN-[^{14}C] (2.5 mmol, 50 mCi, 20 mCi/mmol) and 10 mL of dry DMF was heated at 85°C for 18 h under argon. The reaction mixture was cooled to room temperature and CH_2Cl_2 (60 mL) was added. The resultant mixture was filtered through a pad of Celite. The filtrate was concentrated under a stream of N_2 with heating to 70°C. The residue was dried *in vacuo* for 1.5 h and finally purified by flash chromatography (SiO_2, 20% EtOH in CH_2Cl_2) to give 270 mg of labeled nitrile **2.**

(*R,S*)-5-(2'-*N,N*-Dimethylamino-2'-[^{14}C]-ethyl)-2-pyrrolidinone, (3) To a solution of 270 mg (2.18 mmol) of labeled nitrile **2** and 270 mg (2.18 mmol) of unlabeled **2** in dry EtOH (6 mL) was added 2 mL of 4.4 M Me_2NH in EtOH and 450 mg of 5% Pd/Al_2O_3 (Engelhard). The slurry was stirred under H_2 (1 atm) for 64 h at room temperature, then filtered through a 0.45 μm nylon filter to remove the catalyst. The EtOH was evaporated with a stream of N_2 to give 651 mg of **3** (96%).

(*R,S*)-5-(2'-*N,N*-Dimethylamino-2'-[^{14}C]-ethyl)-2-pyrrolidinone, *N*-oxide, (4) To a stirred solution of 651 mg (4.17 mmol) of **3** in H_2O (3 mL) at room temperature, 0.5 mL of 30% H_2O_2 was added. After 2 h another 0.5 mL of H_2O_2 was added followed at 20 h by 0.35 mL of H_2O_2. The reaction was stirred for 4 h longer and then the excess H_2O_2 was decomposed with 4 mg of Pt black. After 18 h, the mixture was filtered through a 0.45 μm nylon filter and the filtrate extracted with CH_2Cl_2 (2 X 1 mL) to remove neutral impurities. The aqueous layer was concentrated by evaporation of added MeCN (4 X 15 mL). The resulting crystalline residue was dried *in vacuo* to yield 670 mg of *N*-oxide **4** (93%).

(*R,S*)-5-Vinyl-2'-[^{14}C]-2-pyrrolidinone, (5) A mixture of *N*-oxide **4** (670 mg, 3.9 mmol) and powdered K_2CO_3 (670 mg, 4.85 mmol) in 10 mL of xylene was heated at reflux for 4 h. After cooling to room temperature, the mixture was filtered through a bed of Celite

and the xylene was evaporated. The crude product was purified by flash chromatography (100 g SiO_2 eluted with 10% MeOH in CH_2Cl_2) to afford 278 mg of vinyl pyrrolidinone **5** in 64% yield.

(*R,S*)-4-Amino-5-hexenoic-6-[^{14}C] acid, Vigabatrin-[^{14}C], (6) Vinyl pyrrolidinone **5** (278 mg, 2.5 mmol) was heated with 5 M HCl (5 mL) at 95°C in an oil bath for 4 h. The oil bath temperature was lowered to 65°C and the solvent was evaporated with a stream of N_2. Additional H_2O (2 mL) and MeCN (20 mL) were added and evaporated in a similar manner. The resulting solid was dissolved in EtOH (3 mL) and iPrOH (2 mL), the solution was neutralized by adding Et_3N (0.38 mL), and then stirred overnight at -5°C. The crystallized product was collected on a filter and dried to afford 122 mg (38% yield) of vigabatrin-[^{14}C] (**6**) with a specific activity of 8.8 mCi/mmol (68 μCi/mg): CIMS (CH_4) m/z 130 (M+1).

A second crop of **6** (130 mg, 40% yield) was isolated from the filtrate. Dilution of this sample with unlabeled **6** produced 257 mg of vigabatrin-[^{14}C] with a specific activity of 2.9 mCi/mmol (22 μCi/mg): CIMS (CH_4) m/z 130 (M+1).

ANALYSES

PURITY Samples of both products were analyzed by HPLC using a 5 μm Spherisorb C-6 column (250 X 4.6 mm) in series with a 10 μm Partisil SCX column (250 X 4.6 mm) with a mobile phase consisting of 1.5 g of Na_2PO_4 H_2O and 1.0 g of H_3PO_4 dissolved in MeCN (25 mL)/H_2O (975 mL), UV detection λ = 210 nm, and a flow rate of 1.0 mL/min. The chemical purity was determined to be 99.5% for the first product and 98.8% for the second. The HPLC eluant was collected in 30 sec fractions and these were counted by liquid scintillation using BioSafe II™ Scintillation Cocktail. By this method, the radiochemical purity was determined to be 99.2% for the first product (**6**, 122 mg) and 98.8% for the second product (**6**, 257 mg).

SPECIFIC ACTIVITY Samples of each of these two products were weighed, diluted to volume, and aliquots of each were counted by liquid scintillation to give specific activities of 8.82 mCi/mmol and 2.89 mCi/mmol, respectively.

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