SYNTHESIS OF CARBON-14 LABELED 3-PHENYLPROPOXYGUANIDINE CYCLOHEXYLSULFAMATE

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SUMMARY

This report describes the synthesis of carbon-14 labeled 3-phenylpropoxyguanidine cyclohexylsulfamate from barium [^{14}C]-carbonate. The product is labeled at the 3-position of the propyl chain, adjacent to the phenyl ring.

Key Words: Synthesis, Carbon-14, 3-Phenylpropoxyguanadine Cyclohexylsulfamate

DISCUSSION

3-Phenylpropoxyguanidine cyclohexylsulfamate (*4*) is a member of a series of aralkoxyguanidines which exhibit anorexigenic activity in test animals (1). Synthesis of carbon-14 labeled *4* was undertaken to provide a radioactive form of the compound for studying its absorption and metabolic transformations. Because of the likelihood of *in vivo* metabolic degradation of the propyl chain in *4* to produce benzoic acid, a synthetic route was designed, as shown in Scheme 1, to place the carbon-14 label adjacent to the phenyl ring. Phenylmagnesium bromide was treated with carbon-14 dioxide generated from barium [^{14}C]carbonate to give [α-^{14}C]benzoic acid. The acid was reduced with lithium aluminum hydride to [α-^{14}C]benzyl alcohol, which on treatment with thionyl chloride afforded [α-^{14}C]-benzyl chloride. Reaction of the Grignard reagent derived from labeled benzyl chloride with ethylene oxide led to 3-phenyl[3-^{14}]propanol, which was readily converted to 3-phenyl[3-^{14}C]propyl bromide with hydrobromic acid. Alkylation of N-hydroxyphthalimide with the labeled 3-phenylpropyl bromide gave rise to N-(3-phenyl[3-^{14}C]propoxy phthalimide (*1*), which after hydrazinolysis afforded 3-phenyl[3-^{14}C]propoxyamine, isolated as its hydrochloride salt (*2*). Addition of compound *2* to cyanamide according to known procedures (1) produced 3-phenyl[3-^{14}C]propoxyguanidine (*3*), which was converted to its sulfamic acid salt (*4*).

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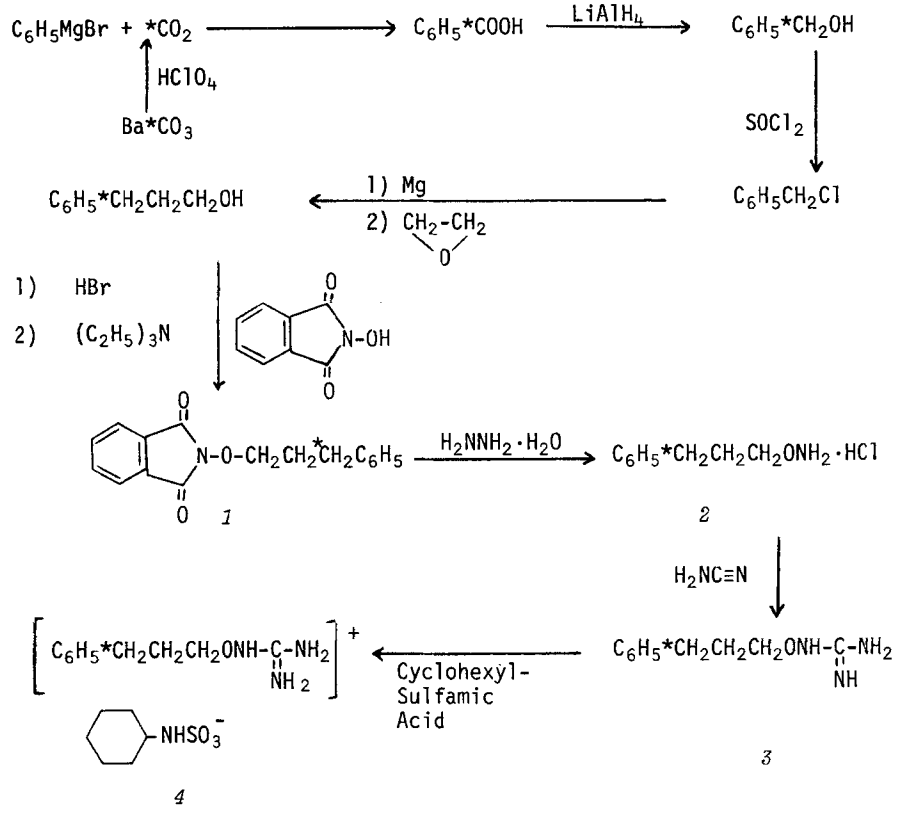
Scheme 1. Synthetic Route for 3-Phenyl[3-^{14}C]propoxyguanidine Cyclohexylsulfamate



The overall radiochemical yield of *4* from barium [^{14}C]carbonate was 7.5%

EXPERIMENTAL

Radioactivity determinations were carried out on a Beckmann CPM-100 liquid scintillation spectrometer, by means of the internal standard method. Diotol was used as the counting cocktail. Infrared (IR) spectra were obtained from Nujol mulls with a Perkin-Elmer Model 421 spectrometer. Ultraviolet (UV) spectra were obtained with a Cary Model 14 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian A-60A spectrometer. Melting points were determined in capillary tubes and are uncorrected.

[α-^{14}C]Benzyl Alcohol

[α-^{14}C]Benzoic acid of sp. act. 3.50 mCi/mmol, prepared according to known procedures (2), was reduced with lithium aluminum hydride in dry tetrahydrofuran (THF) according to a modification (3) of the procedure of Nystrom and Brown (4). A solution of 1.306 g of the acid (10.7 mmoles) in 20 ml of THF was added dropwise with stirring over 20 minutes under nitrogen to a suspension of 600 mg of the hydride (15.8 mmoles). The mixture was refluxed with stirring under nitrogen for 2 hours and cooled in an ice bath. To the mixture was added with caution 0.6 ml of water, 0.6 ml of 1N NaOH, and 1.8 ml of water in that order. The mixture was diluted with 20 ml of ether and stirred at room temperature for 20 minutes. The solids were filtered and washed with 150 ml of ether in portions. The combined filtrate and washings were dried over magnesium sulfate and concentrated at reduced pressure to give 1.126 g (97.5% yield) of [α-^{14}C]benzyl alcohol, which was used without further purification in the next step.

3-Phenyl[3-^{14}C]proponal

[α-^{14}C]Benzyl alcohol was converted into 3-phenyl[3-^{14}C]propanol according to previously described procedures (5,6). Treatment of the labeled benzyl alcohol from above with thionyl chloride afforded [α-^{14}C]benzyl chloride. A mixture of 524 mg of labeled benzyl chloride and 963 mg of unlabeled benzyl chloride was dissolved in 20 ml of dry ether. Approximately one-quarter of this solution was added dropwise with stirring to 329 mg (13.5 mmoles) of dry magnesium turnings under 5 ml of dry ether. The reaction was initiated by warming and scratching. The remaining benzyl chloride solution in ether was added dropwise with stirring over 15 minutes so that gentle refluxing was maintained. The mixture was then refluxed for 1 hour, cooled in an ice bath, and a cold solution of 3 ml of ethylene oxide (∿ 70 mmoles) in 10 ml of ether was added dropwise with stirring in 5 minutes. The mixture was allowed to warm to room temperature, and refluxed gently for two hours. The mixture was again chilled in an ice bath, and 6 ml of water was added dropwise with stirring,

followed by 2 ml of 12N hydrochloric acid. The two-phased mixture was stirred for 30 minutes, and the layers were separated. The aqueous phase was extracted with 25 ml of ether and the extract was combined with the organic phase, washed with brine, and dried over magnesium sulfate. Removal of solvent gave 3-phenyl[3-^{14}C]propanol as an oil, which was sufficiently pure for use in the next step.

3-Phenyl[3-^{14}C]propyl Bromide

A mixture of 7 ml of 48% hydrobromic acid and the 3-phenyl[3-^{14}C]propanol from above was refluxed with stirring for 2.5 hours, cooled to room temperature, and extracted with 2x40 ml of ether. The combined extracts were washed with 2x25 ml of water and 2x25 ml of brine, and concentrated at reduced pressure. The residual light brown oil was chromatographed on a column (28 mm ID) of 110 g of silica gel eluted with 900 ml of methylene chloride. The eluate was collected in 18 ml fractions at 3 minutes per fraction. Fractions 11-14 were combined and concentrated to give 1.861 g of 3-phenyl[3-^{14}C]propyl bromide, 80.5% yield (based on 11.7 moles of benzyl chloride used), which was utilized in the next step without further purification.

N-(3-Phenyl[3-^{14}C]proxy)phthalimide (*1*)

The procedure used by Martin, *et al.* (1) for preparing N-aralkoxyphthalimides was followed. A solution of 1.846 g of the 3-phenyl[3-^{14}C]propyl bromide (9.26 mmoles) from above, 1.665 g of N-hydroxyphthalimide (10.2 mmoles), and 2.06 g of triethylamine (29.4 mmoles) in 12 ml of dimethylformamide was heated at 100°C with stirring for 3 hours. The mixture was cooled, and 40 g of ice was added in portions with stirring. The mixture was refrigerated and the beige solids were filtered, washed with water and dried. The crude solids, 2.05 g, was chromatographed on a column (28 mm ID) of 110 g of silica gel eluted with 1100 ml of methylene chloride. The eluate was collected in 18 ml fractions at 2.5 minutes per fraction. From the pooled fractions 16-30, there was obtained 1.826 g of crystalline compound *1*, 70% yield, m.p.69-70°C, single

component by thin-layer chromatography (silica gel, 3:1 V/V ethyl acetate: cyclohexane, Rf 0.40) identical to an authentic sample of N-(3-phenylpropoxy)-phthalimide.

3-Phenyl[3-^{14}C]propoxyamine Hydrochloride (*2*)

The hydrazinolysis (7) of compound *1* was carried out by stirring a mixture of 1.826 g of *1* (6.5 mmoles), 0.332 g of hydrazine hydrate (6.6 mmoles), 12 ml of methylene chloride, and 0.45 ml of methanol at room temperature for 17 hours. Solids were removed by filtration and washed with methylene chloride. The combined filtrate and washings were concentrated and the residue was triturated with 30 ml of benzene. Traces of insoluble materials were filtered and the filtrate was concentrated to a pale yellow oil. The oil was again dissolved in benzene, filtered, and treated with a 20% solution of anhydrous hydrogen chloride in isopropanol. The resulting precipitates were filtered, washed with ether, and dried, 0.984 g of *2*, 80.5% yield, m.p. 166-168°C, sp. act. 1.12 mCi/mmol.

3-Phenyl[3-^{14}C]propoxyguanidine Cyclohexylsulfamate (*4*)

A suspension of 0.980 g of *2* (5.22 mmoles) and 0.252 g of cyanamide (6.00 mmoles) in 18 ml of toluene was heated with stirring under nitrogen at 90-95°C for 2 hours. On cooling, the mixture separated into two phases. The top toluene layer was decanted and the heavy syrup containing solids was repeatedly triturated with hexane and ether, which removed the oil. The remaining crystalline residue was dissolved in water, extracted with ether to remove traces of insoluble materials, and the aqueous solution was basified with 6N NaOH. A colorless oil was liberated, which crystallized on cooling. The crystals were collected, washed with ice water, and dried, 0.723 g of 3-phenyl[3-^{14}C]propoxyguanidine (*3*), 72% yield, m.p. 60-61°C, sp. act. 1.13 mCi/mM. A filtered solution of 717 mg of *3* (3.71 mmoles) in 12 ml of acetone was treated with 700 mg of cyclohexylsulfamic acid (3.90 mmoles) in 10 ml of acetone. The mixture was stirred at 0°C for 30 minutes. The resulting crystals were collected, washed with cold acetone and dried, 1.225 g of

3-phenyl[3-^{14}C]propoxyguanidine cyclohexylsulfamate (*4*), 89% yield, m.p. 127-128°C; sp. act. 1.14 mCi/mmol; UV, IR, and NMR spectra identical to those of a standard sample of non-labeled *4*; *anal.*-calculated for $C_{16}H_{28}N_4O_4S$ (mol. wt. 372.48): C, 51.59, H, 7.58, N, 15.04, S. 8.61; found: C, 51.87, H, 7.65, N, 15.39, S, 8.48. This material was found to consist of a single radioactive component by thin-layer chromatography (silica gel, 90:10:1 V/V methylene chloride: methanol: concentrated ammonium hydroxide, Rf 0.48) identical to a standard sample of non-labeled *4*.

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