Synthesis of ^{13}C and ^{14}C Labeled Pirmenol Hydrochloride

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SUMMARY

Pirmenol hydrochloride (cis-(±)-α-[3-(2,6-dimethyl-1-piperidinyl)-propyl]-α-phenyl-2-pyridinemethanol monohydrochloride, CI-845), a new antiarrhythmic drug, was labeled with ^{13}C and ^{14}C. Labeled benzoyl chloride reacted with 2-trimethylsilylpyridine to yield 2-benzoylpyridine. Treatment of the latter with cis-1-(3-chloropropyl)-2,6-dimethylpiperidine gave pirmenol free base, which was subsequently converted to the HCl salt.

Key Words: Pirmenol hydrochloride, ^{13}C, ^{14}C, cis-(±)-α-[3-(2,6-dimethyl-1-piperidinyl)propyl]-α-phenyl-2-pyridinemethanol monohydrochloride, antiarrhythmic, CI-845

INTRODUCTION

Pirmenol hydrochloride (cis-(±)-α-[3-(2,6-dimethyl-1-piperidinyl)-propyl]-α-phenyl-2-pyridinemethanol monohydrochloride, CI-845) is being developed as an orally active, long lasting antiarrhythmic drug for acute and chronic therapy (1,2). ^{14}C and ^{13}C labeled pirmenol hydrochloride were synthesized for metabolism and bioavailability studies.

Unlabeled pirmenol hydrochloride (5) was first synthesized by Fleming (3) by direct coupling of 2-benzoylpyridine with cis-1-(3-lithiopropyl)-2,6-dimethylpiperidine or 2-lithiopyridine with cis-γ-(2,6-dimethylpiperidino)-butyrophenone. In order to incorporate a carbon label into a metabolically

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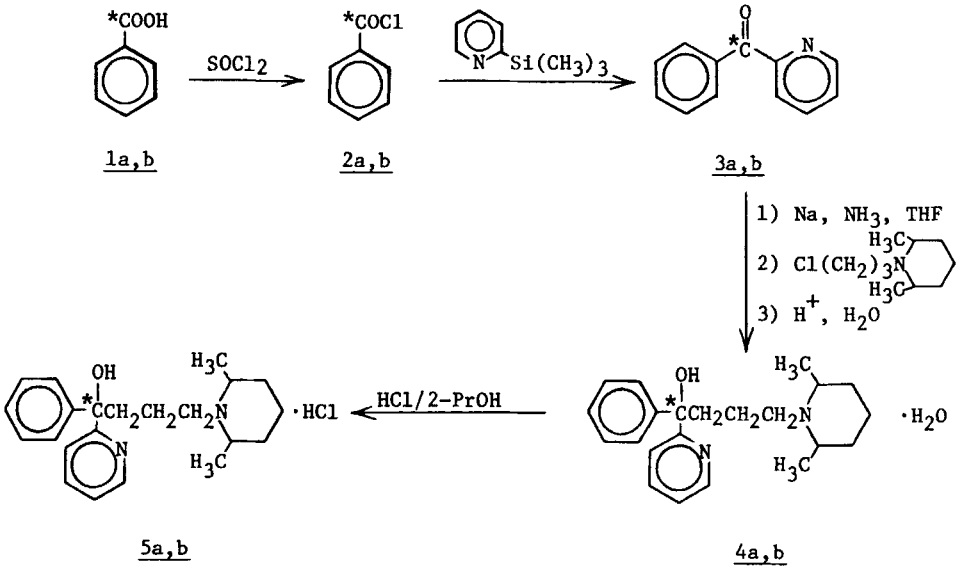
stable position such as the carbinyl carbon, another reaction pathway was necessary. This was accomplished in a five-step synthesis using labeled benzoic acid as the starting material (Scheme 1).



*-indicates location of label
a-^{14}C
b-^{13}C

Scheme 1

RESULTS AND DISCUSSION

The key intermediate in this synthesis of 5 was 2-benzoylpyridine (3). There are numerous literature reports on making unsymmetrical ketones (4,5) and in particular 3 (6-10) using acid chlorides or esters and organometallic reagents. We chose to synthesize labeled 3 utilizing the method of Pinkerton and Thames (11) displacing the trimethylsilyl group from 2-trimethylsilyl-pyridine with labeled benzoyl chloride.

Commercially available labeled benzoic acid was converted to the corresponding acid chloride with excess thionyl chloride. The crude acid chloride was heated with 2-trimethylsilylpyridine to give 3. The reaction was driven to favor product formation by use of excess 2-trimethylsilylpyridine and by distillation of chlorotrimethylsilane during the course of the reaction.

It has been shown that diaryl ketone dianions generated by sodium/ammonia react with alkyl halides to form substituted alcohols (12-14). We utilized the reaction in the synthesis of 4. The dianion of labeled 2-benzoylpyridine was treated with cis-1-(3-chloropropyl)-2,6-dimethylpiperidine in tetrahydrofuran to give 4 according to a modified procedure of Fleming and Hinkley (15). Removal of the liquid ammonia in refluxing tetrahydrofuran was necessary for a better yield. The hydrochloride salt formation was completed with anhydrous HCl in 2-propanol. The overall yield for the four-step synthesis was 28% and 20% for 5a and 5b, respectively.

5a was found to have a specific activity of 11.1 mCi/mmol. The IR, ^{1}H-NMR, TLC and HPLC were consistent with authentic material. The radiochemical purity was >99% by TLC and HPLC.

The isotopic abundance of 5b was 94.5% as determined by comparing mass spectral peaks at m/e = 324 (M^{+}-CH_3) and 323. The M^{+} peak in the spectrum was too small for quantitation. The decoupled ^{13}C-NMR spectrum showed one very strong peak at δ 77. This corresponded to a peak in the ^{13}C-NMR of unlabeled 5 and was consistent with a shift of a quaternary carbon with a hydroxyl substituent. The IR and ^{1}H-NMR were identical with unlabeled material. The product had >99% chemical purity by HPLC.

EXPERIMENTAL

(α-^{14}C)Benzoic acid, at a specific activity of 10.0 mCi/mmol was purchased from Benchmark Scientific Services. (α-^{13}C)Benzoic acid was obtained from MSD Isotopes with 90 atom-% ^{13}C. 2-Trimethylsilylpyridine was

prepared from 2-lithiopyridine and chlorotrimethylsilane by a modification of the method described by Anderson et al. (16). cis-1-(3-Chloropropyl)-2,6-dimethylpiperidine hydrochloride (3) was supplied by the Chemical Development Group, Warner-Lambert Co., Holland, Michigan. The corresponding free base was obtained by treatment with base.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined on a Varian EM390 spectrometer and ^{13}C-NMR on a Bruker WH90 FT-NMR spectrometer. Chemical shifts were reported in δ (ppm) downfield from tetramethylsilane. Infrared spectra were obtained on a Nicolet MX-1/3600 FT-IR. Mass spectra were collected with a Finnigan Series 4000 G.C.-M.S.

Liquid scintillation counting was done with a Packard 574 liquid scintillation counter using Beckman Ready-Solv MP liquid scintillation cocktail.

Thin layer chromatography (TLC) was done on Analtech silica gel plates (250μ). Sections (5 mm) were scraped and dissolved in methanol and cocktail for liquid scintillation counting. High pressure liquid chromatography (HPLC) was performed using an Altex 110A pump, Du Pont Instruments variable wavelength UV detector at 254 nm, Hewlett-Packard 3390A integrator and United Technologies Packard Tri-Carb RAM 7500 radioactivity monitor. Preparative liquid chromatography was accomplished with an FMI RP-SY pump, EM Lobar size c silica column, and Du Pont Instruments variable wavelength UV detector at 278 nm.

(α-^{14}C)Benzoyl chloride (2a). (α-^{14}C)Benzoic acid (50 mCi, 5.0 mmol, specific activity 10.0 mCi/mmol) was placed in a 10 mL flask and flushed with N_2. Thionyl chloride (2.0 mL, 27 mmol) was added and the solution heated to 80°C for 6.5 h. The excess thionyl chloride was evaporated in vacuo. Toluene was added to aid in removal of the thionyl chloride and

evaporated in vacuo. The light yellow liquid co-chromatographed with an authentic sample of benzoyl chloride. TLC: R_f = 0.89 ($PhCH_3$:AcOH 19:1). The crude sample was used in the next step.

(α-^{13}C)Benzoyl chloride (2b). (α-^{13}C)Benzoic acid (6.91 g, 56.6 mmol) was treated with thionyl chloride (21 mL) as described for 2a. The product was used directly in the next step.

2-(α-^{14}C)Benzoylpyridine (3a). 2-Trimethylsilylpyridine (1.39 g, 10.0 mmol) was added to the benzoyl chloride from the previous step. The flask was fitted with a short-path distillation head and heated to 110°C. A colorless distillate boiling at 50-55°C was collected. After 2.5 h the brown solution was cooled to 50°C. Water (5 mL) was added and the mixture maintained at 50°C for 30 min. The cooled mixture was extracted with ether (2 x 10 mL). The ethereal solution was washed with water and dilute $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated in vacuo to give a yellow oil. After 3 days at 3°C a white solid formed. The oil-solid mixture was triturated with methanol and filtered. The solid was determined to be an unknown side-product by TLC. The methanol was removed in vacuo. The oil was warmed to 50°C under vacuum to remove traces of residual 2-trimethylsilylpyridine, seeded, and cooled to 3°C. A light brown solid was recovered after trituration with hexane. Recovered was 27.7 mCi (55% yield from (α-^{14}C)benzoic acid). TLC: R_f = 0.45 (cyclohexane:EtOAc 4:1) co-chromatographed with authentic 2-benzoylpyridine (Aldrich Chemical Co.).

2-(α-^{13}C)Benzoylpyridine (3b). The (α-^{13}C)benzoyl chloride from the previous step was allowed to react with 2-trimethylsilylpyridine (11.8 g, 84.9 mmol) as described for 3a. Recovered was 6.45 g (62% yield) of light brown solid, mp 41-44°C, mp for the unlabeled compound (Aldrich Chemical Co.) 42-44°C. TLC: R_f = 0.41 (cyclohexane;EtOAc 4:1).

cis-(±)-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl--2-pyridine(α-^{14}C)methanol monohydrate (4a). Sodium (0.14 g, 6.1 mmol) was placed in a nitrogen flushed 3-neck flask fitted with a dry-ice condenser, septum, and an ammonia inlet. The flask and condenser were cooled to -78°C and ammonia (15 mL) condensed. The blue solution was stirred for 1 h. 2-(α-^{14}C)Benzoylpyridine (460 mg, 27.7 mCi) in dry tetrahydrofuran (2.5 mL) was added over 10 min. The cooling bath was removed and the solution refluxed for 5 h. The color changed to a dark purple. The flask was once again cooled to -78°C and cis-1-(3-chloropropyl)-2,6-dimethylpiperidine (0.55 g, 2.9 mmol) in tetrahydrofuran (2.0 mL) was added over 5 min. After refluxing for 45 min the ammonia was removed, replacing it with tetrahydrofuran (15 mL). The mixture was heated to reflux for 30 min, the color changing from blue-green to orange. A small amount of methanol was added to destroy any unreacted sodium and the solvent was evaporated in vacuo. To the oily residue was added methanol (10 mL). The mixture was heated to boiling and filtered through Celite rinsing with boiling methanol (2 x 5 mL). Warm water (7 mL) was added. The solution was seeded and cooled. A light yellow solid crystallized. Additional water (3 mL) was added in small portions. The material was collected and dried in vacuo at 40°C. Recrystallization from methanol-water gave 560 mg (15.8 mCi, 57% yield) of 4a. TLC: R_f = 0.54 ($PhCH_3$:Et_3N 19:1), co-chromatographed with an authentic sample of unlabeled 4.

cis-(±)-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl--2-pyridine(α-^{13}C)methanol (4b). In a manner similar to that described for the synthesis of 4a, sodium (1.70 g, 73.9 mmol) in ammonia (45 mL) was treated with 2-(α-^{13}C)benzoylpyridine (6.45 g, 35.1 mmol) in tetrahydrofuran (20 mL). After 5 h of reflux, cis-1-(3-chloropropyl)-2,6-dimethylpiperidine (6.83 g, 36 mmol) was added. The reaction was worked up as described for 4a and 7.52 g of crude 4b was collected in three crops. The

material was purified by preparative liquid chromatography using 5% triethylamine in toluene. Recovered was 5.00 g (42% yield) of anhydrous 4b.

TLC: R_f = 0.35 ($PhCH_3$:Et_3N 19:1).

cis-(±)-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl-2-pyridine(α-^{14}C)methanol hydrochloride (5a). To 4a (0.56 g) was added 2-propanol (0.5 mL) and 1.016 M HCl in 2-propanol (1.54 mL). The mixture was heated to boiling. The solution was cooled to about 35°C and ether (2.1 mL) was added. A precipitate was collected and washed with ether. After drying at 68°C in vacuo, 477 mg (14.1 mCi, specific activity 11.1 mCi/mmol) of off-white solid was recovered (82% yield), mp 171.5-173.0°C (147°C soft). TLC: R_f = 0.45 ($PhCH_3$:Et_3N 19:1); R_f = 0.78 (EtOH:H_2O:NH_4OH 16:3:1); R_f = 0.32 (EtOAc:NH_4OH 99:1). HPLC: Alltech C18, 10μ (4.6 mm ID X 250 mm), 20% CH_3CN in phosphate buffer (0.05 M NaH_2PO_4 with 0.5% Et_3N adjusted to pH 2.60 with H_3PO_4), flow rate 1.0 ml/min, retention time 9.8 min. The radiochemical purity was >99% by TLC and HPLC. ^{1}H-NMR (DMSO-d_6) and IR (KBr) were identical to an unlabeled standard.

cis-(±)-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl-2-pyridine(α-^{13}C)methanol hydrochloride (5b). The hydrochloride salt was generated as described for 5a. Collected was 4.093 g (74% yield) of a colorless crystalline solid, mp 169.0-170.0°C. TLC: R_f = 0.43 ($PhCH_3$:Et_3N 19:1); R_f = 0.22 (EtOAc:NH_4OH 99:1); R_f = 0.79 (EtOH:H_2O:NH_4OH 16:3:1). HPLC: conditions the same as for 5a, retention time 10.13 min, purity >99%. IR(KBr) and ^{1}H-NMR(DMSO-d_6) were identical to an authentic sample. ^{13}C-NMR(DMSO-d_6) δ 77. Mass Spectrum m/e (%I) 339 (M^+, 0.17), 324 (7.11), 227 (25.3), 126 (100), 112 (26). m/e = 324 (M^+-CH_3) and 323 were used to determine an isotopic abundance of 94.5%. Anal. Calc. for $C_{22}H_{30}N_2O \cdot HCl$: C, 70.51; H, 8.27; N, 7.47; Cl, 9.46.

Found: C, 70.76; H, 8.48; N, 7.32; Cl, 9.62.

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