THE SYNTHESIS OF 1-[(1-METHYLETHYL)AMINO]-3-{[(4-METHYLTHIO)-1-NAPHTHALENYL]OXY}-2-PROPANOL HYDROCHLORIDE-NAPHTHALENE-1-^{14}C: 4'-METHYLTHIOPROPRANOLOL

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SUMMARY

The antihypertensive drug, 1-[(1-methylethyl)amino]-3-{[(4-methylthio)-1-naphthalenyl]oxy}-2-propanol hydrochloride has been labeled with carbon-14 in the 1-position of the naphthalene. A total of 18.76 mCi was prepared in five steps starting with 1-naphthol-1-^{14}C. The overall yield for the synthesis was 33.6% following five recrystallizations of the free base. The radiochemical purity of the hydrochloride product was 98.0% by high pressure liquid chromatography (HPLC)/liquid scintillation counting (LSC). The specific activity of the product was found to be 11.68 ∓ 0.45 mCi/mmole. Structural confirmation was done by infrared spectroscopy.

Key words: 4'-Methylthiopropranolol, carbon-14 labeling, β-blocker

INTRODUCTION

During the course of studies on the metabolism of propranolol in man, 4'-methylthiopropranolol (MTP) was identified in urine as a hydrolysis product of an unidentified metabolite of propranolol. Since MTP was found to be more lipophilic than propranolol, it was of interest to investigate how this increase in lipophilicity would affect the cardiovascular actions of the molecule (1). In order to study the metabolism of the drug, we synthesized MTP·HCl labeled with ^{14}C in the 1 position of the naphthalene ring. The details of this synthesis are reported in this paper.

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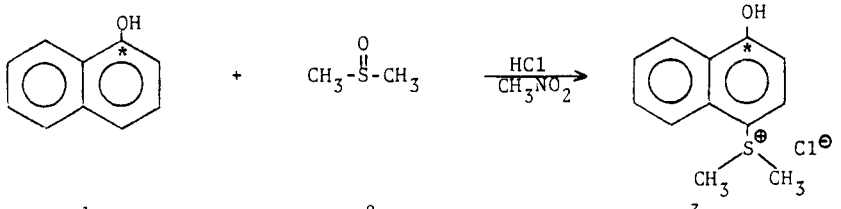
Scheme I

Step 1



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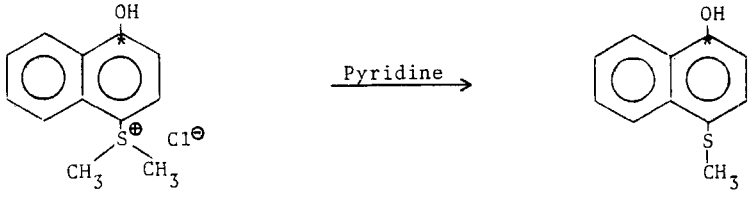
Step 2



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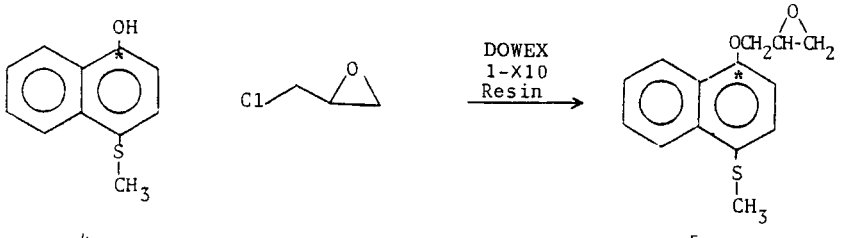

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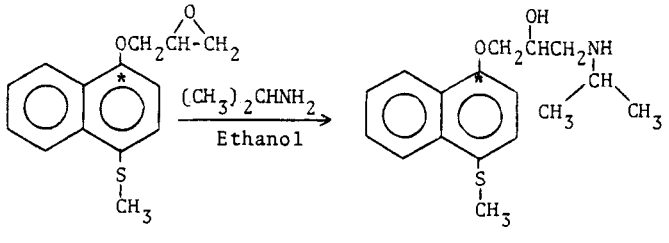
Step 4



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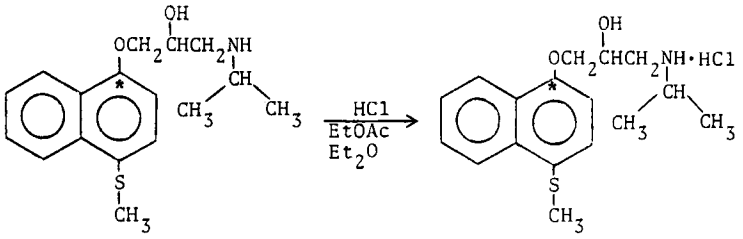
Step 5



6 7

* = carbon-14 label

DISCUSSION

MTP has been synthesized by N. P. Peet (2) of the Dow Chemical Company, Merrell Dow Pharmaceuticals, Inc., Indianapolis, Indiana. The key intermediate in the synthesis of MTP·HCl is 4-(methylthio)-1-naphthol (4). The literature provides a good method (3) for the direct preparation of 4 from 1-naphthol (1) using dimethylsulfoxide and perchloric acid. The potential hazard of handling the perchlorate salt as an intermediate was avoided by development of a new method (4). The new method entailed treating 1-naphthol (1) with dimethylsulfoxide and anhydrous HCl to give the corresponding sulfonium chloride. The chloride salt was then treated with pyridine to give 4.

N. P. Peet describes several synthetic routes to 7. We chose the method which is shown in Scheme I, because of its adaptability to microscale work (2,4).

Treatment of 1-naphthol (1) with one equivalent of dimethylsulfoxide (2) in the presence of anhydrous hydrochloric acid gave (4-hydroxy-1-naphthyl)dimethylsulfonium chloride (3) (86% crude yield). Subsequent treatment of 3 with 8.6 equivalents of pyridine gave 4 at 95% crude yield.

A method described in the literature (5) gave high yields of phenyl glycidyl ether from phenol, epichlorohydrin, and DOWEX* 1-X10. Peet found this method adaptable to 1-naphthol in place of phenol. Using this procedure we treated 4 with a large excess of epichlorohydrin in the presence of DOWEX 1-X10. This method is suspected of producing some epichlorohydrin adduct of the desired glycidyl ether (5). Analysis by HPLC gave two major components for this reaction step. However, no separation was attempted at this point. Reaction of this mixture with an excess of isopropylamine gave 6 at a yield of 86%. Multiple recrystallizations of 6 gave a low yield (32%) of high purity material.

The free base 6 was converted quantitatively to the hydrochloride salt 7 by treatment with ethereal hydrochloric acid in a diluent mixture of ethyl acetate and ethyl ether. The carbon-14 labeled free base was 98.9% radiochemically pure following five sequential recrystallizations of the precursor 6.

The procedure used in synthesizing the carbon-14 labeled product was developed by proceeding through a series of nonlabeled (cold) reactions in which the more troublesome areas were modified until acceptable results were obtained.

EXPERIMENTAL

(4-Hydroxy-1-naphthyl)dimethylsulfonium Chloride-1-^{14}C (3)

The 1-naphthol-1-^{14}C (Pathfinder Laboratories, Lot 800625, 50 mCi, 10.6 mCi/mmole, 4.70 mmole) was transferred through a pouring funnel to a 25 mL pear-shaped flask with a filter frit, and

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rinsed with 3.3 mL of nitromethane. Dimethylsulfoxide, 352 μL (4.96 mmole) was added to the clear solution. The reaction mixture was cooled in an ice bath to ≈0°C, with magnetic stirring. Anhydrous hydrochloric acid was sparged into the cold, stirred solution for 2.0 hours. The resulting slurry of white crystals was allowed to warm to room temperature while the excess HCl was vented to a caustic scrubber. The slurry was further degassed at reduced pressure using a water aspirator. The resulting thick slurry was vacuum dried at 55°C. The crude tan colored product was again cooled to room temperature. It was then extracted with acetone (3 x 1 mL) producing a white precipitate. The residual acetone was stripped off at reduced pressure to yield 1.014 g (87.9%) of the desired intermediate (4-hydroxy-1-naphthyl)dimethylsulfonium chloride-1-^{14}C (3).

4-Methylthio-1-naphthol-1-^{14}C (4)

Pyridine, 3 mL (37 mmole) was added to the reactor containing 1.014 g (4.21 mmole) of 3. The resulting mixure was heated to reflux (≈130°C bath temperature) for 1.25 hours. The brown solution was stripped at reduced pressure to 105°C. The residual oil was dissolved in 5 mL of CH_2Cl_2. This solution was extracted first with 5 mL of 10% HCl aqueous solution followed by a 5 mL extraction with deionized water. After stripping off the methylene chloride a 791 mg quantity (86.8% yield) of 4-methylthio-1-naphthol-1-^{14}C (4) was obtained as a dark tan solid.

(((4-Methylthio)-1-naphthalenyl)oxy)methyloxirane-1-^{14}C (5)

DOWEX resin (1-X10), 75 mg, and epichlorohydrin, 5 mL (64 momle) were added to the reactor containing 791 mg (4.157 mmole) of 4. The mixture was heated to reflux (145°C bath temperature) under argon to form a clear brown solution with suspended resin.

After 1.25 hours at reflux, the reactor was cooled slightly before pressure filtering through the side-arm filter. The reactor was rinsed with fresh epichlorohydrin (2 x 1 mL). The washes were combined with the filtrate. The reaction product was concentrated at reduced pressure to a dark red oil, 1.10 g (86.7%) of 5.

1((1-Methylethyl)amino)-3-(((4-methylthio)-1-naphthalenyl)oxy)-2-propanol-naphthalene-1-^{14}C (6)

Absolute ethanol, 6 mL, and isopropylamine, (35 mmole) were added to 1.10 g of crude 5 in the reactor at room temperature under argon. The mixture was refluxed with stirring at 100°C/20 torr. The dark red oil weighed 1.343 g.

The red residue was dissolved in 6 mL of warm ethyl acetate. This solution was extracted with 5 mL of 1 N NaOH. An extraction with 5 mL DI water gave a light amber colored extract with a pH of ≈8. A second extraction with 3 mL of DI water was also amber colored with a pH of ≈7. The crude oil residue was dried for ≈1 hour at 110°C with vacuum. The dry oil was dark red and began to crystallize upon cooling. The dry crude 6 weighed 1.252 g (85.6%).

1st Recrystallization of Free Base (6)

Methyl isobutyl ketone (MIBK), 4.1 mL, was added to the reactor containing 1.252 g of crude 6. When isooctane, 2 mL, was added to the warm solution in MIBK a brown slurry was produced. The slurry was cooled in an ice bath for 0.5 hours before pressure filtering. The wet cake was washed on the filter with an isooctane/MIBK mixture (1:1 v:v) (3 x 1 mL). The first crop was vacuum dried at 80°C/20 torr to yield 582 mg. The filtrate and

washes were combined and concentrated to ≈ one-half the original volume. This solution was allowed to stir overnight. As there were no crystals formed at this point the solution was seeded with a crystal of 6. On cooling a second crop was obtained. This crop was filtered and washed in the same manner as the first crop. The resulting dry crystals weighed 177 mg for a combined yield of 56.8%.

Subsequent Recrystallizations

In a manner similar to that described above, the products of the first recrystallization were recrystallized a total of 5 times. The radiochemical purity of the free base 6 at the end of each recrystallization was determined by HPLC and liquid scintillation counting. The radiochemical purity of 6 was raised from 96.3% after one recrystallization to 98.9% after 5 recrystallizations.

1((1-Methylethyl)amino)-3-(((4-methylthio)-1-naphthalenyl)oxy)-2-propanol hydrochloride-naphthalene-1-^{14}C (7)

The purified free base 6, 498 mg (1.63 mmole) was dissolved in 4 mL of warm ethyl acetate which formed a clear solution after cooling to ≈22°C. This solution was further diluted with 7 mL of dry ethyl ether. Saturated anhydrous ethereal HCl, 2 mL, was added dropwise to the solution of 6. The hydrochloride salt of 6 precipitated as fine white crystals. After stirring the slurry for 1 hour an additional 1 mL of the ethereal HCl solution was added and stirring at ≈22°C was continued for ≈60 hours. The white slurry was pressure filtered, washed with 2 mL of dry ethyl ether. The fine white crystals (7) were vacuum dried at 25°C/20 torr to a constant weight of 549.5 mg (1.607 mmole, 98.6% yield, 33.6% overall yield).

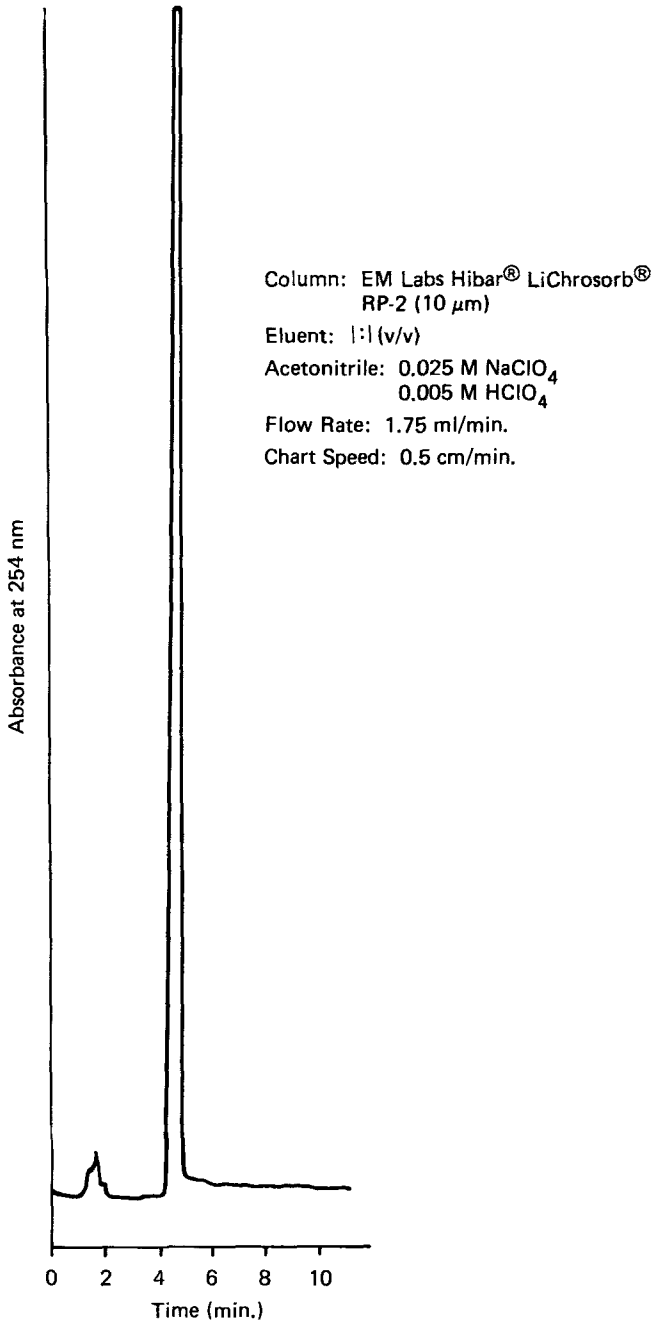

Figure 1. HPLC Chromatogram of the Final Product, ^{14}C-Labeled 4'-Methylthiopropranolol Hydrochloride

ANALYSIS

High Pressure Liquid Chromatography (HPLC) Analysis

An analytical HPLC system was used to monitor the course of the reaction and to determine the purity of the final product. The system employed an EM Labs, Hibar® II LiChrosorb® RP-2 (10 μm) column with an isocratic elution solvent of 1:1 (v/v) acetonitrile: aqueous 0.025 M $NaClO_4$ and 0.005 M $HClO_4$. The flow was 1.75 mL/min and detection was by UV absorption at 254 nm. The retention time of 7 was compared to a sample of unlabeled MTP·HCl and found to be identical. To determine the radiochemical purity of the final product, fractions (15 sec.) of the HPLC eluent were collected in glass scintillation vials and assayed by liquid scintillation counting. Figure 1 shows an HPLC chromatogram of the carbon-14 labeled MTP·HCl final product. It is identical to an HPLC chromatogram of an unlabeled MTP·HCl. Results of the liquid scintillation analysis of fractions showed the hydrochloride product to be 98% radiochemically pure.

Specific Activity Determination of ^{14}C-Labeled MTP·HCl

The specific activity was determined by weighing five-3 mg samples of the final product into separate 10 mL volumetric flasks. Using distilled water, the flasks were diluted to volume and one milliliter samples were taken and placed in five other 10 mL volumetrics. Each of these five flasks were filled to volume and triplicate (30 μL) aliquots of each were assayed by liquid scintillation counting using a representative standards method. Results of the counting showed the specific activity to be 11.68 ∓ .45 mCi/mmole.

Structural Confirmation of the Product

Infrared spectroscopy was used to verify the structure of the final product. Less than 1 mg of product was used to prepare a

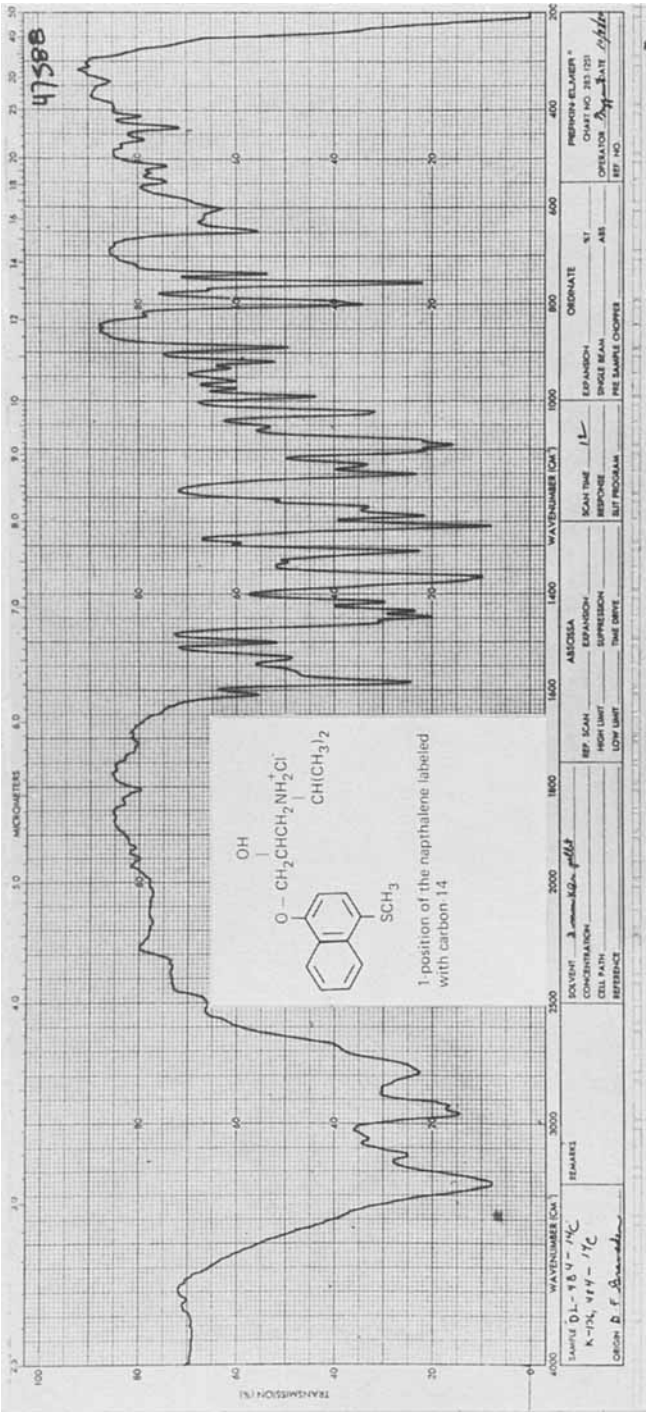

Figure 2. IR Scan of the Final Product, ^{14}C-Labeled 4'-Methylthiopropranolol Hydrochloride

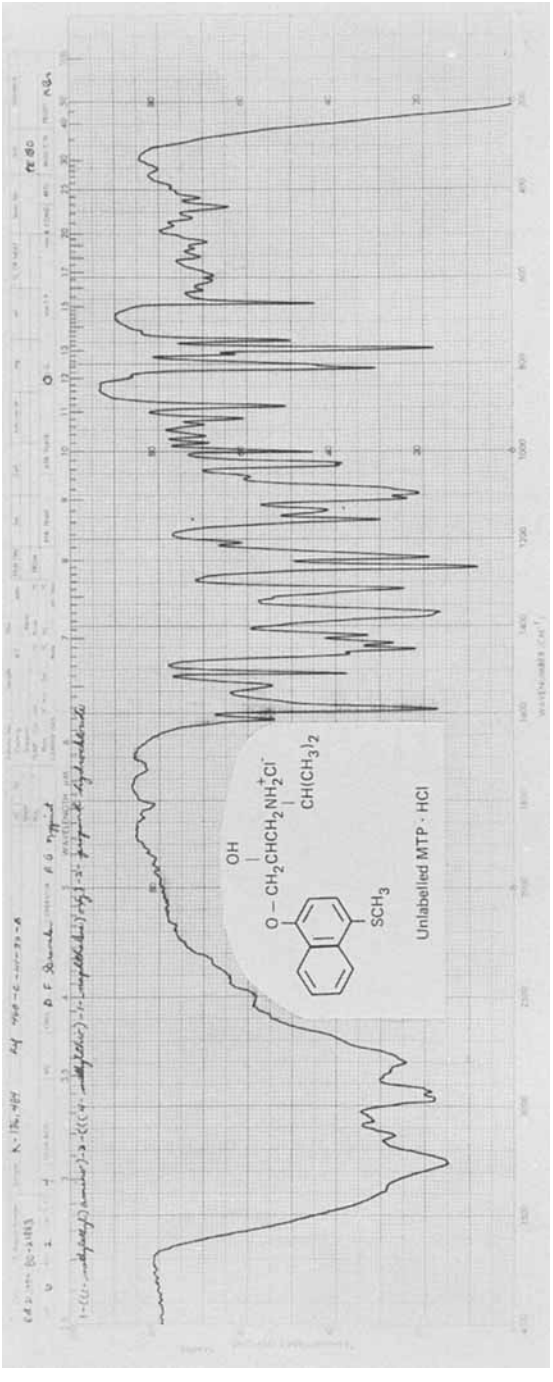

Figure 3. IR Scan of Unlabelled 4'-Methylthiopropranolol Hydrochloride

3 mm KBr pellet. The IR spectra were recorded using a Perkin-Elmer 180 spectrometer. Figure 2 is an IR scan of the labeled product. This scan supports the structure of 7 (5). The IR scan of an unlabelled MTP•HCl sample is shown in Figure 3 as a comparison. It is essentially identical to the IR spectrum obtained for the labelled products.

RESULTS

A total of 18.76 mCi of 1-((1-methylethyl)amino)-3-(((4-methylthio)-1-naphthalenyl)oxy)-2-propranol hydrochloride-naphthalene-1-^{14}C was prepared in five steps starting with 1-naphthol-1-^{14}C. The overall yield for the synthesis was 33.6% following five recrystallizations of the free base. The radiochemical purity of the hydrochloride product was 98% by HPLC/LSC indicating that 98.0% of the radioactivity was eluted in a fraction with the same retention time as an unlabeled MTP•HCl sample.

The specific activity of the product was found to be 11.68 ∓ .45 mCi/mmole.

Structural confirmation was done by infrared spectroscopy. The IR spectral features of the carbon-14 labeled sample support the proposed structure.

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