SYNTHESIS OF ^{14}C-LABELLED METOPROLOL

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Summary

The synthesis of ^{14}C-labelled metoprolol, a new antihypertensive drug is described. Starting from p-bromoanisole and $^{14}CO_2$, ^{14}C-labelled p-methoxyphenylethyl alcohol was prepared by the following sequence of reactions: $MeO\text{-}C_6H_4\text{-}Br \longrightarrow MeO\text{-}C_6H_4\text{-}^{14}COOH \longrightarrow MeO\text{-}C_6H_4\text{-}^{14}CH_2OH \longrightarrow MeO\text{-}C_6H_4\text{-}^{14}CH_2Cl \longrightarrow MeO\text{-}C_6H_4\text{-}^{14}CH_2\text{-}CN \longrightarrow MeO\text{-}C_6H_4\text{-}^{14}CH_2\text{-}COOH \longrightarrow MeO\text{-}C_6H_4\text{-}^{14}CH_2\text{-}CH_2OH$. Heating with 47% HBr gave [^{14}C]-p-hydroxyphenylethyl bromide which on treatment with methanol under alkaline condition was converted into [^{14}C]-p-hydroxyphenylethyl methyl ether. Reaction with epichlorhydrin followed by isopropylamine gave [^{14}C]-metoprolol.

KEY WORDS: [^{14}C]-Metoprolol, [^{14}C]-p-Hydroxyphenylethyl bromide, 1,1-Dideutero-2-p-methoxyphenylethyl alcohol.

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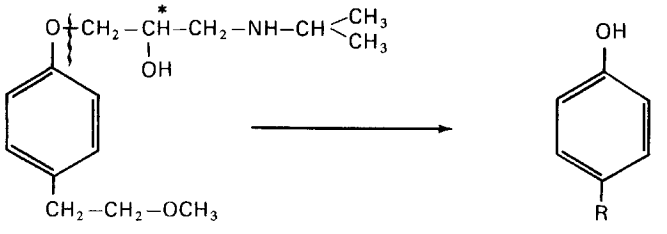
INTRODUCTION

Metoprolol (1) is a new adrenergic β_1-receptor blocking agent (1-3). Unlike propranolol which blocks both β_1 and β_2-receptors, metoprolol preferentially antagonizes the action of sympathomimetic amines on β_1-receptors and is therefore cardioselective. The L (+) tartrate salt of metoprolol has recently been introduced for the treatment of hypertension. The drug is extensively metabolised in man, dog and rat (4-5). These metabolic studies, which were carried out with tritium labelled metoprolol (1) having the label attached to the carbon bearing the hydroxyl group could not show if any metabolism occurred by O-dealkylation as shown in Fig. 1 because the metabolites which would be para-substituted phenolic compounds of type 2 would not be radiolabelled. In order to study this, we synthesized metoprolol labelled with ^{14}C (14) having the label in the methoxyethyl side chain and report the details of the synthesis in this paper.



1 2

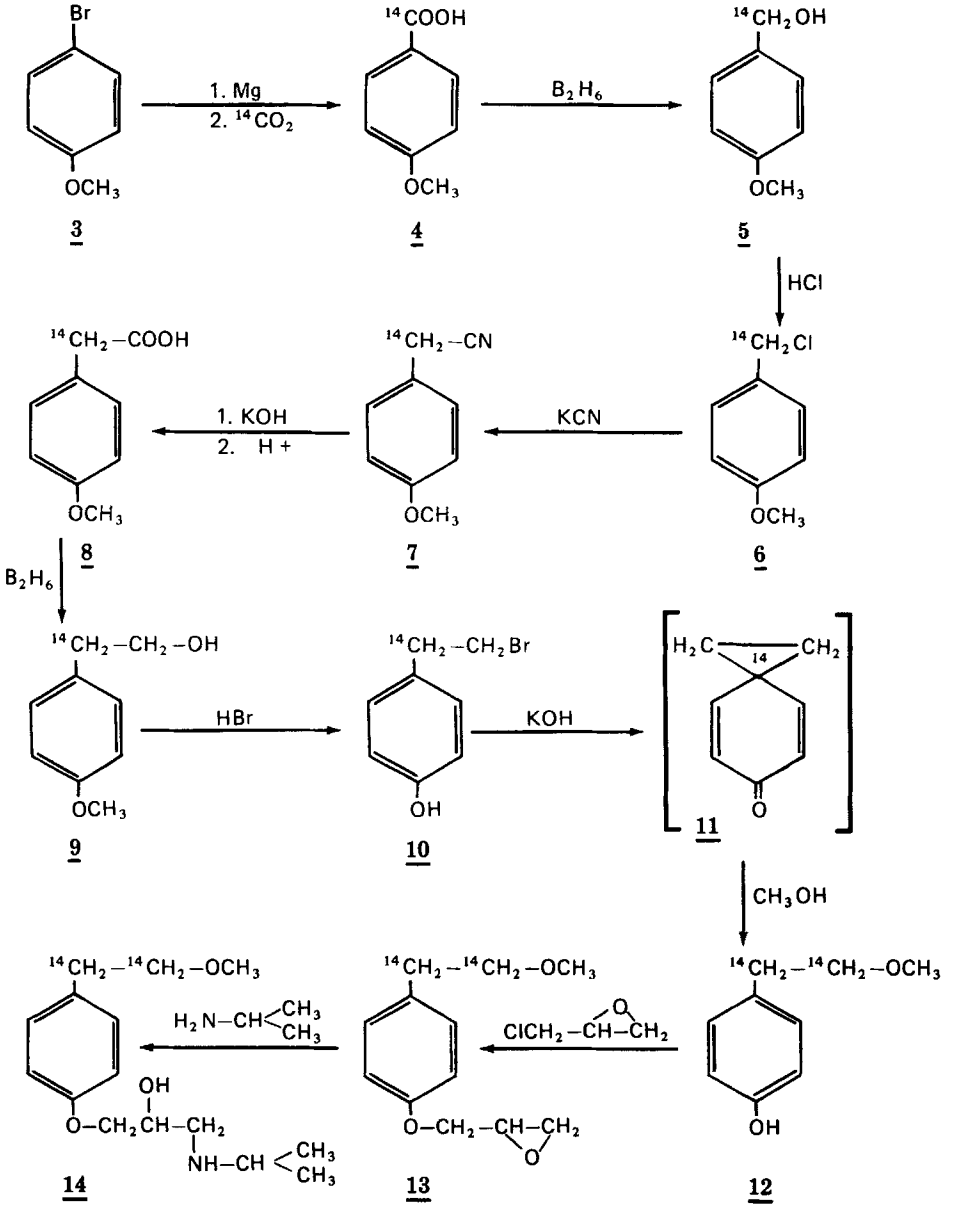
*indicates the position of the label

Fig. 1

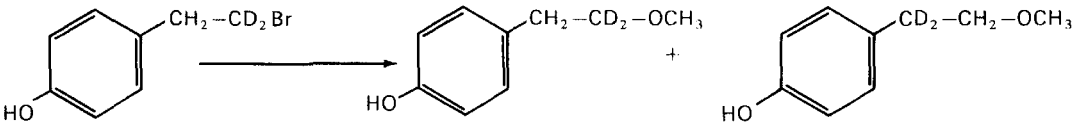
Methods and Results

The reaction sequence used for the synthesis of ^{14}C-labelled metoprolol (14) is shown in Scheme 1.

Scheme 1.



The starting material, p-bromoanisole (3) was converted in a straightforward manner by means of known reactions to ^{14}C-labelled p-methoxyphenylacetic acid (8). The overall yield of 8 in five steps from 3 was 72% based on barium carbonate-^{14}C. Reduction of 8 with borane gave the alcohol 9 which was then heated with 47% hydrobromic acid (6) to give the phenolic bromide 10. The reaction of 10 with methanol under alkaline condition by a known method (7) gave ^{14}C-labelled p-hydroxyphenylethyl methyl ether (12). Since Winstein and Baird (7) have shown that the above reaction proceeds through the intermediate dienone 11, the ^{14}C-label in the side chain would be scrambled and thus both the methylene carbon atoms of the methoxyethyl side chain of 12 would be labelled. To confirm this, we treated the deuterium labelled phenolic bromide 15 with methanol under similar alkaline condition and the product was found by nuclear magnetic resonance spectroscopy to be a mixture of equal amounts of two deuterated compounds 16 and 17. The nuclear magnetic resonance spectrum showed two peaks of equal intensity at 2.7 and 3.5 ppm due to the methylene protons of 16 and 17 respectively.



15 16 17

The phenolic ether 12 was condensed with epichlorhydrin to give the epoxy compound 13 which was then reacted with isopropylamine to obtain ^{14}C-labelled metoprolol (14). The L (+)-tartrate salt, prepared according to the published procedure (5) was 98% radiochemically pure and the overall yield from barium carbonate-^{14}C was about 16.8%.

Experimental

Melting points are uncorrected. Nuclear magnetic resonance (nmr) spectral data are reported in ppm deshielded with respect to tetramethyl silane. Thin layer chromatography (tlc) was carried out on silic gel 60 F-254 plates of 0.5 mm layer thickness. $Ba^{14}CO_3$ was purchased from New England Nuclear Corporation of Boston, Massachusetts, USA.

[^{14}C]-p-Methoxybenzoic acid (4). A solution of p-methoxyphenyl magnesium bromide was prepared by heating 2.8 g of p-methoxybromobenzene and 0.36 g of magnesium in 15 mL of tetrahydrofuran. The solution was then diluted with 15 mL of ether and the reaction flask was connected to a high vacuum line and carbonated by standard procedure with $^{14}CO_2$ generated from 1.58 g of $Ba^{14}CO_3$ (40 mCi). After standard work up, 1.10 g of the acid (91% yield) was obtained as a crystalline solid, m.p. 181-83°, undepressed on admixture with an authentic sample of cold material.

[^{14}C]-p-Methoxybenzyl alcohol (5). To a solution of 1.1 g of 4 in 10 mL of tetrahydrofuran was added 35 mL of 1 molar solution of borane in tetrahydrofuran and the mixture was heated under reflux for one hour. The solution was then treated with 3 mL of water followed by 4 mL of $NaHCO_3$ solution and evaporated to dryness in a rotary evaporator under reduced pressure. The residue was treated with 3 mL of NaCl solution and extracted with ether. After drying with $MgSO_4$ the ether solution was evaporated to dryness to give 0.9 g of 5 (90% yield) as a colorless oil which on tlc in ethyl acetate showed only spot identical to that of an authentic sample of p-methoxybenzyl alcohol.

[^{14}C]-p-Methoxyphenylacetic acid (8). The above oil (0.9 g) was stirred at room temperature with 20 mL of conc. HCl solution for four hours. After diluting with water, the reaction mixture was extracted with ether. The product obtained after removal of ether was dissolved in 25 mL of

acetone and 0.78 g of potassium cyanide and 0.1 g of potassium iodide were added to the acetone solution which was then refluxed for 20 hours. The residue obtained after removal of acetone was treated with water and extracted with ether and the product obtained after removal of ether was dissolved in a mixture of 10 mL of ethanol and 10 mL of 50% KOH solution was added to it. The mixture was heated under reflux for 18 hours. Ethanol was removed by evaporation and the residue dissolved in water. The aqueous solution was acidified by addition of conc. HCl soln and the acidic material extracted with ether. After drying with $MgSO_4$, the ether solution was evaporated to dryness to give 0.96 g (89% yield) of a white solid, m.p. 85-86°, undepressed on admixture with an authentic sample of p-methoxyphenylacetic acid.

[^{14}C]-2-p-Methoxyphenylethyl alcohol (9). The above acid (0.96 g) was dissolved in 5 mL of tetrahydrofuran and 15 mL of 1 molar solution of borane in tetrahydrofuran was added to it. The solution was then heated under reflux for 3 hours. After cooling, the solution was treated with 1 mL of conc. HCl solution and evaporated to dryness. The residue was treated with 5 mL of NaCl solution and extracted with ether. After drying with $MgSO_4$, the ether solution was evaporated to dryness to give 0.82 g (93% of yield) of an oil. The nmr spectrum showed a singlet at 3.6 ppm ($-O\underline{CH}_3$), a triplet at 3.75 ppm ($-CH_2-\underline{CH}_2-OH$) and another triplet at 2.65 ppm ($-\underline{CH}_2CH_2-OH$) in the aliphatic region.

[^{14}C]-2-p-Hydroxyphenylethyl bromide (10). The above oil (0.82 g) was refluxed with 25 mL of 47% HBr solution for 12 hours. After cooling, the reaction mixture was diluted with water and extracted with ether. The ether extract was washed with $NaHCO_3$ solution, dried with $MgSO_4$ and evaporated to dryness to give 0.9 g (83% yield) of an orange oil which on tlc in chloroform showed only one spot identical to that of an authentic sample of p-hydroxyphenylethyl bromide.

1,1-Dideutero-2-p-hydroxyphenylethyl bromide (15). To a solution of 3 g of p-methoxyphenylacetic acid in 15 mL of tetrahydrofuran was added 50 mL of 1 M solution of deuterated borane in tetrahydrofuran. The solution was then refluxed for 3 hours and then worked up as described above for the preparation of 9 to get 2.4 g of 1,1-dideutero-2-p-methoxyphenylethyl alcohol. The nmr spectrum showed a singlet at 3.65 ppm ($-OCH_3$) and a singlet at 2.65 ppm ($-\underline{CH_2}-CD_2-OH$). The alcohol was then heated with 40 ml of 47% HBr solution and worked up as described above for the preparation of 10 to get 2.5 g of 15 as an orange oil. The nmr spectrum showed a singlet at 3.1 ppm ($-\underline{CH_2}-CD_2-Br$).

Reaction of 1,1-dideutero-2-p-hydroxyphenylethyl bromide with methanol and sodium hydroxide. A solution of 1 g of 15 in 5 mL of methanol was added to a solution of 4 g of sodium hydroxide in 40 mL of methanol and the solution was refluxed for 3 hours. Methanol was removed by evaporation and water was added to the residue which was then extracted with ether and the ether extract discarded. The aqueous solution was then acidified with conc. HCl solution and extracted with ether. The ether solution was dried with $MgSO_4$ and evaporated to dryness to give 0.5 g of a light yellow oil. The nmr spectrum showed three singlets in the aliphatic region at 2.7 ($-\underline{CH_2}-CD_2-OCH_3$), 3.5 ($-CD_2-\underline{CH_2}-OCH_3$) and 3.3 ppm ($-O\underline{CH_3}$).

[^{14}C]-2-p-Hydroxyphenylethyl methyl ether (12). A solution of 0.9 g of the bromo compound 10 in 5 mL of methanol was added to a solution of 3 g of sodium hydroxide in 30 mL of methanol and the solution was refluxed for 3 hours. After working up in the same way as described above for the deuterium compound 0.465 g (68% yield) of a light yellow oil was obtained which on tlc in chloroform showed only spot identical to that of a cold sample of 2-p-hydroxyphenylethyl methyl ether.

[^{14}C]-3-(p-2-Methoxyethylphenoxy)-1,2-epoxypropane (13). A mixture of 0.465 g of the above oil, 0.83 g of potassium carbonate and 1 mL of epichlorhydrin in 20 mL of acetone was refluxed for 18 hours. The mixture was then evaporated to dryness and the residue treated with water. The organic matter was extracted with ether. The ether extract was dried with $MgSO_4$ and then evaporated to dryness to give 0.568 g (89% yield) of a yellow oil which on tlc in chloroform/toluene (1:1 by vol) showed only spot.

[^{14}C]-1-Isopropylamino-3-(p-2-methoxyethylphenoxy)-propanol-2 (14). The above oil was dissolved in 20 mL of isopropanol and 1 mL of isopropylamine was added to the solution which was then heated under reflux for 3 hours. The reaction mixture was then evaporated to dryness and the residue chromatographed on a column of silica gel using ethyl acetate as eluant. After the impurities were eluted with ethyl acetate, the product was eluted with ethyl acetate-methanol (1/1 by vol). Evaporation of the solvent gave 370 mg (51%) of a light yellow oil which on thin layer chromatography in ethyl acetate-methanol (1/1 by vol) showed only one spot identical with that of an authentic sample of cold material.

[^{14}C]-Metoprolol tartrate. The above oil (370 mg) was dissolved in 10 mL of acetone and treated at 50° with 100 mg of L(+)-tartaric acid and allowed to crystallize at room temperature overnight. The solid (466 mg) was obtained by filtration and dried in vacuo. The nmr and mass spectra conformed to those of an authentic sample of cold metoprolol tartrate. The radiochemical purity was checked by thin layer chromatography followed by radioscanning of the tlc plate and autoradiography. The compound was found to be at least 98% radiochemically pure.

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