SYNTHESIS OF ^{14}C-LABELED 5-[1-HYDROXY-2-[2-(o-METHOXYPHENOXY)ETHYL-AMINO]ETHYL]-2-METHYLBENZENESULFONAMIDE HYDROCHLORIDE (YM-09538)

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SUMMARY

Preparation of the title compound, a novel antihypertensive agent, is described. The labeled material with a specific activity of 4.76 mCi/mmol was synthesized in a 50.6% radiochemical yield from [U-^{14}C]ethylene oxide *via* a process of six steps.

Keywords: Carbon-14, Phenylethanolamine derivative, Benzenesulfonamide, Antihypertensive agent

INTRODUCTION

It has been reported that 5-[1-hydroxy-2-[2-(o-methoxyphenoxy)ethylamino]ethyl]-2-methylbenzensulfonamide hydrochloride (YM-09538), developed in our laboratory, is a novel α- and β-adrenergic blocking agent and is more potent than labetalol in antihypertensive activity.[1,2] A radiolabeled form of YM-09538 was required for biochemical studies such as metabolism and pharmacokinetics.

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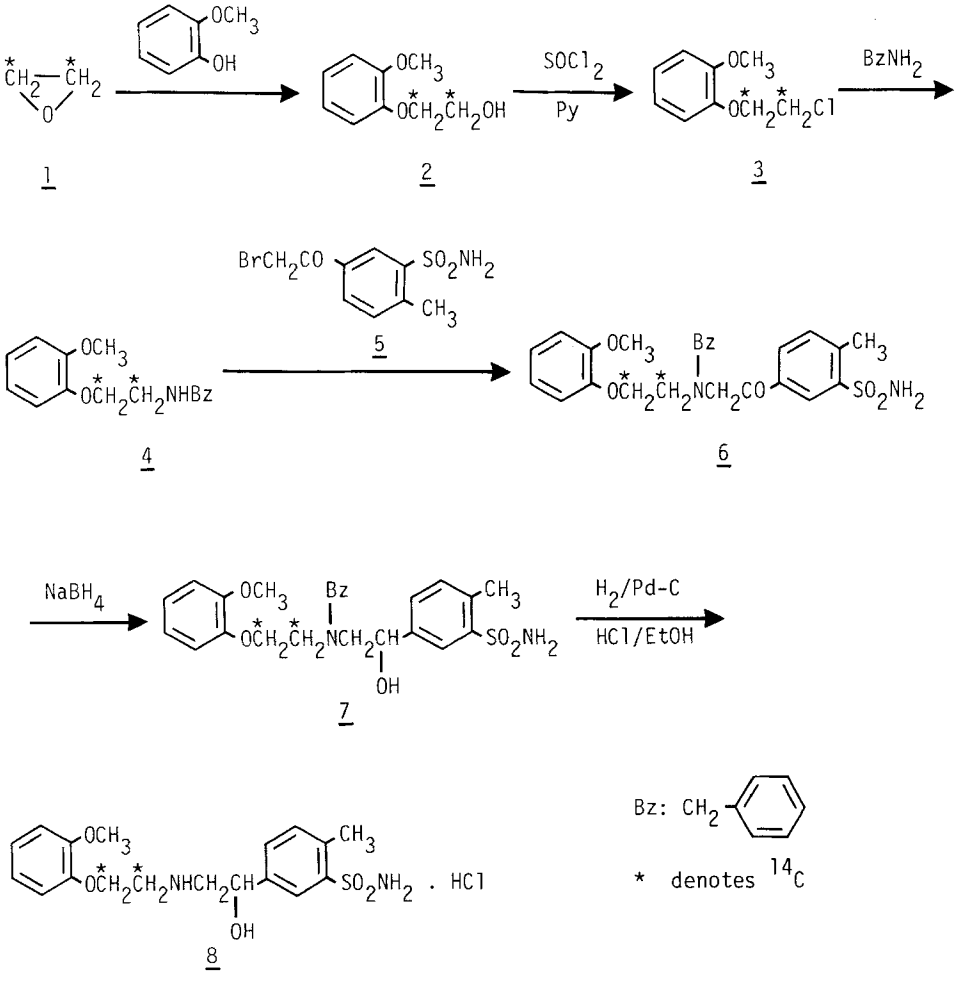
RESULTS AND DISCUSSION

The ethyl moiety of the phenoxyethyl group in YM-09538 seemed a suitable group for labeling with carbon-14 from the viewpoints of the biochemical stability and the synthetic route. Scheme I shows the synthesis of [^{14}C]YM-09538 (8) which was carried out by a modification of the method previously reported.[3)]



Scheme I

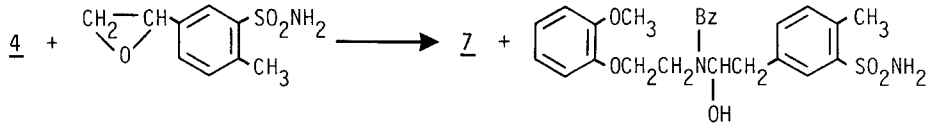
In the large-scale preparation,[4] phenoxyethanol (2) was derived by the reaction of guaiacol with 1.6 mole equivalents of ethylene chlorohydrin in a good yield based on guaiacol. Alkylations of guaiacol with equimolar ethylene bromohydrin and 1,2-dibromoethane resulted in low conversion of alkylating agents to the desired product. In the radiosynthesis it is necessary to maximise the yield based on the radiolabeled precursor. Since ethylene oxide reacted quantitatively with guaiacol according to the method of Boyd and Marle[5] [U-^{14}C]ethylene oxide (1) was selected as a starting material for the radiosynthesis. A small excess of guaiacol was heated with radiolabeled 1 in ethanolic sodium ethoxide to afford 2 in 92% yield.

In the presence of a catalytic amount of pyridine, 2 was chlorinated using an excess of thionyl chloride under reflux in benzene to provide the chloride (3, 98.5%). Addition of the catalyst was essential to complete the chlorination. In the reaction of 3 with benzylamine, it was necessary to suppress formation of by-products one of which was the tertiary amine $(o\text{-}CH_3OC_6H_4OCH_2CH_2)_2NCH_2C_6H_5$. Yield of the desired secondary amine (4) was strongly dependent on the reaction temperature and the molar ratio of 3 and benzylamine. Optimum conditions were as follows; heating 3 with a large excess (about 10 mole equivalents) of benzylamine at 100°C for 4 hr gave the labeled 4 in 96.6% yield accompanied with a negligible amount of by-products after purification by column chromatography.

The literature[3] described that bromoketone (5)[3,6] was converted to aminoketone (6) by use of an excess (2.2 mole equivalents) of 4, which played a role of scavenger of hydrogen

bromide formed, under the condition of reflux in 2-butanone. The reaction conditions were modified to improve the radiochemical yield. A mixture of labeled 4 and a small excess of 5 in dimethylformamide was allowed to warm at 50°C in the presence of anhydrous potassium carbonate, whereupon the reaction was completed within 30 min. The reaction mixture was subjected to quick purification by column chromatography because of the lability of 6 in solution. The desired product 6 was isolated as a crystalline solid in 92.7% yield. Reduction of 6 with sodium borohydride followed by column chromatography gave a 96% yield of aminoalcohol (7).

An alternative preparation of 7 by the reaction of 4 and epoxide (9)[3] was investigated. In this case, unfortunately, the



9 10

isomeric aminoalcohols (7 and 10) could not be readily separated and no improvement in the isomer ratio was obtained under various conditions.

Removal of the benzyl group of 7 by hydrogenolysis with palladium catalyst in the presence of equimolar hydrogen chloride, followed by recrystallization, furnished the desired [^{14}C]YM-09538 (8). The overall radiochemical yield from [^{14}C]ethylene oxide was 50.6%.

EXPERIMENTAL

[U-^{14}C]ethylene oxide was purchased from Amersham International plc, Amersham, England. The labeled products were characterized by co-chromatography (TLC) with non-radioactive standards. TLC analyses were conducted on precoated plates of Merck Silica Gel 60F_{254}. For column chromatography, silica gel (Wakogel C-200) was used. All evaporations were carried out under reduced pressure. Radioactivity measurement was made with a Packard Tri Carb Liquid Scintillation Spectrometer, Model 3255. Radiochemical purity was determined by thin layer chromatography with a Radio-TLC Scanner LB 2723 (Berthold).

2-(o-Methoxyphenoxy)[1,2-^{14}C]ethanol (2)

Guaiacol (501.6 mg), NaOEt (13.6 mg), and ethanol (2 ml) were placed in a sealed tube (A*). A break-seal ampoule (B*) containing 20 mCi (25.7 mg) of [U-^{14}C]ethylene oxide (1), a vessel (C*) containing non-radioactive ethylene oxide (1, 135.5mg) and A* were attatched to a manifold. After A* and B* were cooled in liquid nitrogen and evacuated, the break-seal of B* was broken and the labeled 1 distilled into A*. In a similar manner non-radioactive 1 was transferred from C* to A*. The tube was then removed from the manifold and sealed with a gas burner, keeping the contents cool with dry ice. The tube was immersed in an oil bath at 70°C for 20 hr. The dark-violet colored reaction mixture obtained was concentrated and the residue, dissolved in benzene (2 ml x 5), was applied to a column of silica gel (16 g). The column was eluted successively with benzene-ethyl acetate (9:1 v/v) and (1:1 v/v).

The fractions which contained a single component corresponding to 2 on TLC (benzene-ethyl acetate 5:2 v/v) were concentrated to dryness to give pure 2 as an oil. No radioactive impurity was detected by TLC. Yield: 566.3 mg (92.0%).

2-(o-Methoxyphenoxy)[1,2-^{14}C]ethylchloride (3)

A mixture of 2 (566.3 mg), benzene (6 ml), pyridine (10 µl) and thionyl chloride (350 µl) was heated under reflux for 5 hr. After cooling the mixture was washed successively with water, saturated aq. $NaHCO_3$ and saturated aq. NaCl. The organic layer was dried ($MgSO_4$) and evaporated to afford 3 as a crystalline solid. The product was used in the next step without further purification (TLC; benzene-ethyl acetate 5:2 v/v). Yield: 618.6 mg (98.5%).

N-Benzyl-2-(o-methoxyphenoxy)[1,2-^{14}C]ethylamine (4)

A mixture of 3 (618.6 mg) and benzylamine (3.6 ml) was heated at 100°C for 4.5 hr. The cooled reaction mixture was diluted with water (8 ml) and extracted twice with benzene (12 ml, 8 ml). The combined organic extracts were washed with water and dried (K_2CO_3). After removal of the solvent the residue was subjected to column chromatography (SiO_2, 34 g). Mixtures of benzene and ethyl acetate as eluents were used in successive ratio of 15%, 30% and 50% of ethyl acetate. The fractions were analyzed by TLC and those containing the desired product were combined and evaporated to give 4 as an oil. Yield: 823.5 mg (96.6%). The radiochemical

purity was greater than 99% by TLC analysis (benzene-ethyl acetate-methanol 10:3:1 v/v).

5-[N-Benzyl-N-[2-(o-methoxyphenoxy)[1,2-^{14}C]ethyl]aminoacetyl]-2-methylbenzenesulfonamide (6)

To a solution of 4 (823.5 mg) in dimethylformamide (16 ml) were added anhydrous K_2CO_3 (883 mg) and 5-bromoacetyl-2-methylbenzenesulfonamide (5, 1.028 g).[6] The mixture was stirred at 35°C for 30 min. After removal of the solvent, ethyl acetate (15 ml) and water (15 ml) were added to the residue. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (15 ml). The combined organic layers were washed with saturated aq. NaCl, dried ($MgSO_4$) and evaporated. The residue was rapidly applied to a silica gel column (55 g) and eluted with benzene-ethyl acetate (4:1 v/v) to obtain pure crystals of 6. Yield: 1.39 g (92.7%). The product was radiochemically pure by TLC analysis (benzene-ethyl acetate-methanol 10:3:1 v/v).

5-[1-Hydroxy-2-[N-benzyl-N-[2-(o-methoxyphenoxy)[1,2-^{14}C]ethyl]-amino]ethyl]-2-methylbenzenesulfonamide (7)

To a cooled solution of 6 (1.39 g) in methanol (30 ml) at 0°C was added by portions 200 mg of $NaBH_4$. The mixture was stirred for 4.5 hr at 0°C. After completion of the reaction the solvent was evaporated and the residue was diluted with water (20 ml). The

mixture was extracted twice with ethyl acetate (20 ml, 10 ml), and the combined extracts were washed with saturated aq. NaCl, dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography (SiO_2, 27 g). The column was eluted first with benzene, then with a mixture of benzene and ethyl acetate (4:1 v/v) to afford 7 (1.27 g, 96.0%) as an amorphous solid with a radiochemical purity of approximately 96% by TLC analysis (benzene-ethyl acetate-methanol 10:3:1 v/v). The product was contaminated by small amounts of impurities which could be removed in the subsequent stage by recrystallization.

5-[1-Hydroxy-2-[2-(o-methoxyphenoxy)[1,2-^{14}C]ethylamino]ethyl]-2-methylbenzenesulfonamide hydrochloride (8)

To a solution of 7 (1.27 g) in methanol (40 ml) were added 4.8N ethanolic hydrogen chloride (620 µl) and 10% palladium on charcoal (200 mg). The mixture was subjected to hydrogenation at room temperature until the uptake of hydrogen had ceased (3 hr). The reaction mixture was filtered and the filtrate was evaporated. To the residue was added ethanol (4 ml) and the resulting solution was stirred at 0°C overnight to complete crystallization. The crystals were filtered off and washed with isopropanol followed by recrystallization from ethanol (7 ml) to obtain pure 8. Yield: 862.2 mg (76.7%, 10.1 mCi). Specific activity: 4.76 mCi/mmol; radiochemical purity: greater than 99 % by TLC analysis (1,2-dichloroethane-isopropanol-conc.NH_4OH 40:15:2 v/v).

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