SYNTHESIS OF 1-BENZYL-4-[(5,6-DIMETHOXY[2-^{14}C]-1-INDANON)-2-YL]-METHYLPIPERIDINE HYDROCHLORIDE (E2020-^{14}C)

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SUMMARY

1-Benzyl-4-[(5,6-dimethoxy[2-^{14}C]-1-indanon)-2-yl]-methylpiperidine hydrochloride (1) (E2020-^{14}C), an acetylcholinesterase inhibitor for studying the pharmacokinetic profiles of E2020, was synthesized from 5,6-dimethoxy[2-^{14}C]-1-indanone (2) as the labelled starting material.

Key words: acetylcholinesterase inhibitor, E2020, 5,6-dimethoxy-[2-^{14}C]-1-indanone, 1-benzyl-4-formylpiperidine, 1-benzyl-4-[(5,6-dimethoxy[2-^{14}C]-1-indanon)-2-yl]methyl-piperidine

INTRODUCTION

Acetylcholinesterase (AChE) inhibitors are proper candidates for drug treatment of patients with Alzheimer's disease based on the "cholinergic hypothesis".

We found that novel piperidine derivatives potently inhibit AChE activity[1]. 1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methyl-piperidine hydrochloride (E2020) is one of the most potent AChE inhibitors[1].

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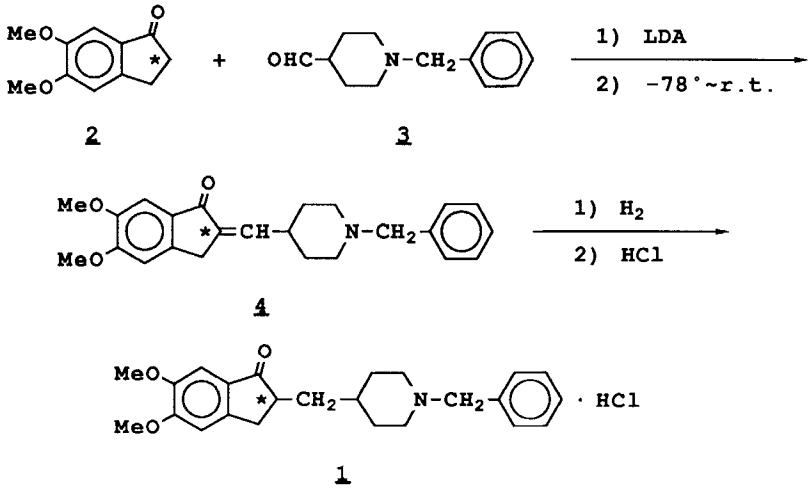
This paper describes the synthesis of ^{14}C-labelled E2020 (1) in order to study the pharmacokinetic profile of E2020. ^{14}C-labelled E2020 was prepared from 5,6-dimethoxy[2-^{14}C]-1-indanone (2) and 1-benzyl-4-formylpiperidine (3)[2] (Scheme 1). Aldol reaction of 2 and 3 followed by dehydration gave the enone (4) which was purified by recrystallization. Compound (4) was hydrogenated to afford a saturated ketone. This ketone was purified by column chromatography and converted to the hydrochloride by the usual method. After recrystallization of the hydrochloride, ^{14}C-labelled E2020 (1) was obtained in 30 % yield based on 2. The structure of ^{14}C-labelled E2020 was confirmed by comparison (TLC) with unlabelled authentic specimen of 1. ^{14}C-labelled E2020 (1) had a radiochemical purity of 99.0 % and a specific activity of 44.6 mCi per mmol.

Scheme 1. Synthesis of ^{14}C-labelled E2020



EXPERIMENTAL

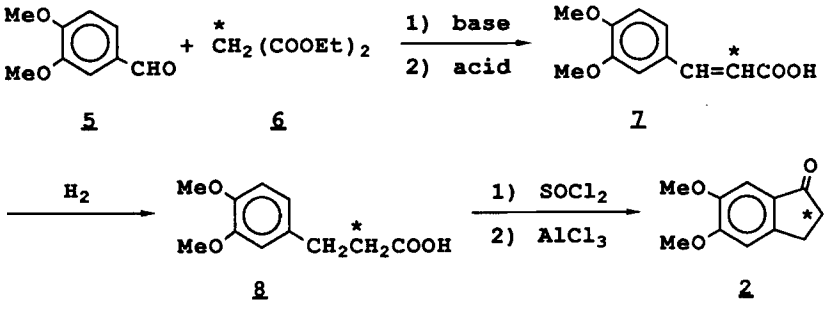
Thin-layer chromatography was developed using Kieselgel 60F_{254} plate (Merck). Wakogel C-200 (Wako Pure Chemical Industries Ltd) was used for silica gel column chromatography.

Measurements of radioactivity were carried out using an Aloka LSC-9000 type Liquid Scintillation Spectrometer. Thin-layer radiochromatography was performed using a Berthold LB-2842 Automatic TLC Linear Analyzer.

5,6-Dimethoxy[2-^{14}C]-1-indanone (2)

The labelled starting material (2), which was prepared from 3,4-dimethoxybenzaldehyde (5) and diethyl[2-^{14}C]malonate (6) according to the method outlined in Scheme 2, was purchased from Amersham International Ltd.

Scheme 2. Synthesis of 5,6-dimethoxy[2-^{14}C]-1-indanone



1-Benzyl-4-[(5,6-dimethoxy[2-^{14}C]-1-indanon)-2-ylidenyl]methyl-piperidine (4)

n-Butyllithium (1.6 M in hexane, 1.39 ml; 2.22 mmol) was added to a solution of diisopropylamine (0.312 ml; 2.22 mmol) in tetrahydrofuran (THF) (4 ml) at 0 °C. The mixture was stirred at 0 °C for 10 min and then cooled to -78 °C, and a solution of 5,6-dimethoxy[2-^{14}C]-1-indanone (2) (432 mg; 2.22 mmol, 100 mCi) in THF (6 ml) and hexamethylphosphoric triamide (0.389 ml; 2.22 mmol) were added to the mixture. After the mixture was stirred at -78 °C for 15 min, a solution of 1-benzyl-4-formylpiperidine (3) (475 mg; 2.34 mmol) in THF (4 ml) was added.

The temperature of the mixture was gradually raised to room temperature, followed by stirring for 2 h. An aqueous 1 % ammonium chloride solution was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo to give a solid, which was recrystallized from dichloromethane - diisopropyl ether (IPE) to afford the title compound (4) as a white crystal. Identification of 4 was confirmed by comparison of its RF-value with an unlabelled authentic sample on TLC. RF-value of the compound (4) was 0.60 in dichloromethane / methanol (10:1, v/v).

1-Benzyl-4-[(5,6-dimethoxy[2-^{14}C]-1-indanon)-2-yl]methyl-piperidine hydrochloride (1)

The above compound (4) was dissolved in THF (15 ml), followed by an addition of 10 % palladium-carbon (50 mg). The mixture was hydrogenated at room temperature under atmospheric pressure for 3 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane / methanol, 100:1). The elutent was concentrated in vacuo, and the residue was dissolved in dichloromethane. Hydrogen chloride - ethyl acetate was added to the resulting solution, followed by concentration in vacuo to give crystals, which were recrystallized from dichloromethane - IPE to afford the title compound (1) (280 mg, 30 % yield from 2; specific activity, 44.6 mCi/mmol, radiochemical purity, 99.0 %) as a white crystal. Identification of 1 was confirmed by comparison of its RF-values with those of an unlabelled authentic sample on TLC developed by three different solvent systems. RF-values of the compound (1) were 0.58 in chloroform / methanol (10:1, v/v)

(Fig.), 0.09 in dioxane / acetonitrile / acetic acid (70:30:1), and 0.63 in chloroform / methanol / diethylamine (100:10:1).

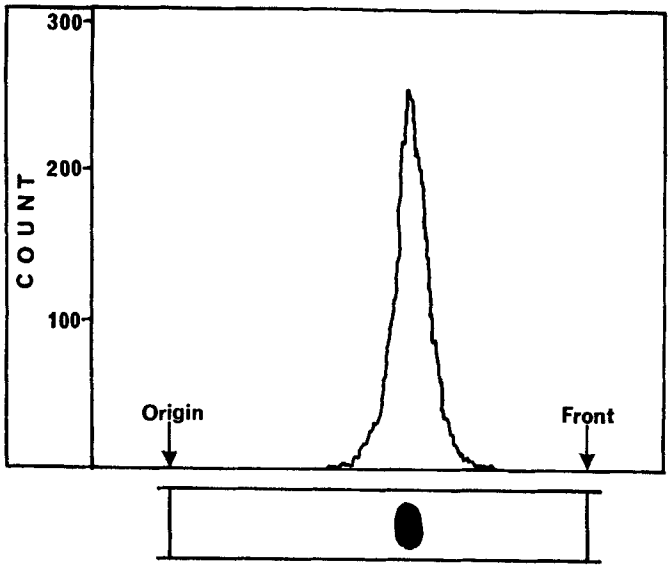


Fig. Radioscans of ^{14}C-labelled E2020 (1) on TLC developed with chloroform / methanol (10:1)

REFERENCE

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