Synthesis of ^{14}C-labelled 4-chloro-3-sulfamoyl-N-(3aα,4α,5,6 7α,7aα-hexahydro-4,7-methano-isoindolin-2-yl)-benzamide.

Takaharu Nakamura, Sachiyuki Hamano
and Tohru Horie
Research and Development Division
Eisai Co., Ltd., 4-chome, Koishikawa,
Bunkyo-ku, Tokyo, Japan.

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^{14}C-Labelled compound of antihypertensive 4-chloro-3-sulfamoyl-N-(3aα,4α,5,6,7α,7aα -hexahydro-4,7-methano-isoindolin-2-yl) -benzamide (IV) was synthesized for biotransformation studies in three steps with p-chlorobenzoic acid-carbonyl-^{14}C (I) as the labelled starting material.

Key Words: Antihypertensive drug, 4-Chloro-3-sulfamoylbenzamide derivative, Carbon-14.

INTRODUCTION

4-Chloro-3-sulfamoyl-N-(3aα,4α,5,6,7α,7aα-hexahydro-4,7 -methano-isoindolin-2-yl)-benzamide (IV) has been found to be an effective antihypertensive drug[1]. This paper deals with

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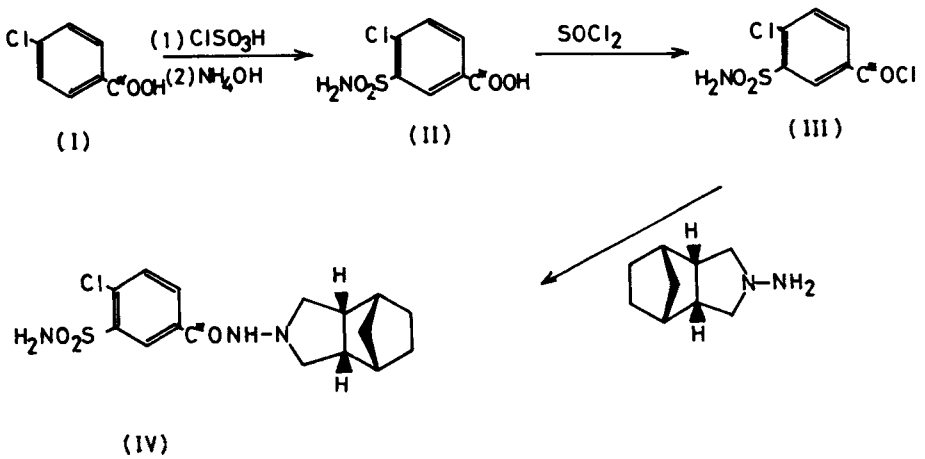
the synthesis of ^{14}C-labelled (IV) in order to study the pharmacological action and biotransformation behaviors of the compound. ^{14}C-Labelled-(IV) was prepared from p-chlorobenzoic acid-carbonyl-^{14}C (I) in three steps and in 13.9 % overall yield according to the method of Sturm et al.[2] and Haele et al.[3] with slight modifications as outlined in Fig. 1.



(I) (II) (III) (IV)

Fig. 1. Outline of synthesis of (IV).

Chlorosulfonation of ^{14}C-(I) with chlorosulfonic acid followed by ammonolysis of the chlorosulfonyl intermediate with 28 % aqueous NH_4OH gave 4-chloro-3-sulfamoylbenzoic acid-carbonyl-^{14}C (II). Treatment of (II) with thionyl chloride afforded the corresponding acid chloride (III), which was then reacted with 2-amino-3aα,4α,5,6,7α,7aα-hexahydro-4,7-methano-isoindoline to give 4-chloro-3-sulfamoyl-N-(3aα,4α,5,6,7α,7aα-hexahydro-4,7-methano-isoindolin-2-yl)-benzamide-carbonyl-^{14}C (IV). The structure of ^{14}C-(IV) was confirmed by comparison (UV spectrum and TLC) with unlabelled authentic specimen of (IV). The ^{14}C-(IV) had a radiochemical purity of 95 % and a specific activity of 31.7 μCi per mg.

EXPERIMENTAL

Measurements of radioactivity were carried out using an Aloka LSC-652 type Liquid Scintillation Counter. The radiochromatograms were recorded using an Aloka Thin Layer Chromatogram Scanner Model TLC-2B and UV spectra on a Hitachi 124 type Spectrophotometer.

4-Chloro-3-sulfamoylbenzoic acid-carbonyl-^{14}C (II)

To p-chlorobenzoic acid-carbonyl-^{14}C (I) (611 mg; 3.90 m moles, 46.8 mCi), chlorosulfonic acid (3 ml) was added and the reaction mixture was heated at 145–150° for 5 hr. The mixture was cooled and treated with ice-water (5 ml) to deposit a colorless solid. The solid was filtered off, washed twice with water (2 ml each) and treated with 28 % NH_4OH (4 ml). A stream of nitrogen was passed through the reaction flask until excess NH_3 was removed. To the solution was added 11.6 N HCl (2 ml) to deposit 4-chloro-3-sulfamoylbenzoic acid-carbonyl-^{14}C (II) as a colorless solid. The compound (II) was filtered off, washed twice with 5 % HCl (2 ml each) and dried over anhydrous $CaCl_2$ *in vacuo*; weighing 489 mg (53 % yield). The radiochemical purity of (II) calculated from the radiochromatogram of the compound (Fig. 2) was 95 %.

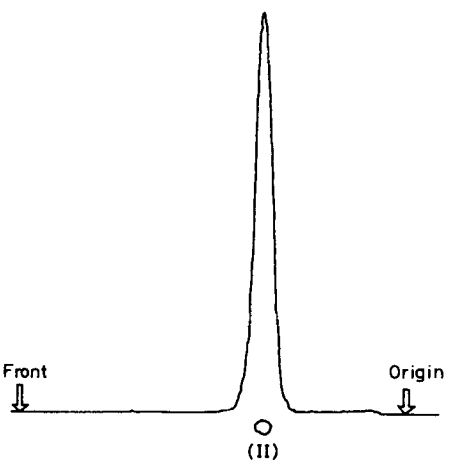


Fig. 2. Radioscans of (II) on TLC developed with benzene/methanol/acetic acid (16 : 4 : 1).

4-Chloro-3-sulfamoylbenzoyl chloride-carbonyl-^{14}C (III)

To (II) (489 mg), thionyl chloride (5 ml) was added and the mixture was heated under reflux for 2 hr. Evaporation of the reaction mixture under reduced pressure afforded 4-chloro-3-sulfamoylbenzoyl chloride-carbonyl-^{14}C (III) as a colorless solid.

4-Chloro-3-sulfamoyl-N-(3aα,4α,5,6,7α,7aα-hexahydro-4,7-methano-isoindolin-2-yl)-benzamide-carbonyl-^{14}C (IV)

To a suspension of (III) in dioxane (2 ml), a mixture of 2-amino-3aα,4α,5,6,7α,7aα-hexahydro-4,7-methano-isoindoline (300 mg; 1.98 m moles) and triethylamine (0.2 ml) in dioxane (2 ml) was added. The reaction mixture was heated at 50° for 10 min. and allowed to stand at room temperature for 2 days. The precipitated solid was filtered off, washed twice with 50 % aqueous methanol (2 ml each) and recrystallized from 50 % aqueous methanol to give ^{14}C-(IV) as colorless needles (206 mg, 13.90 % yield from (I); specific activity 31.7 μCi per mg, λ_{max}^{MeOH} nm (ε) : 278 (2830), 287 (2450).

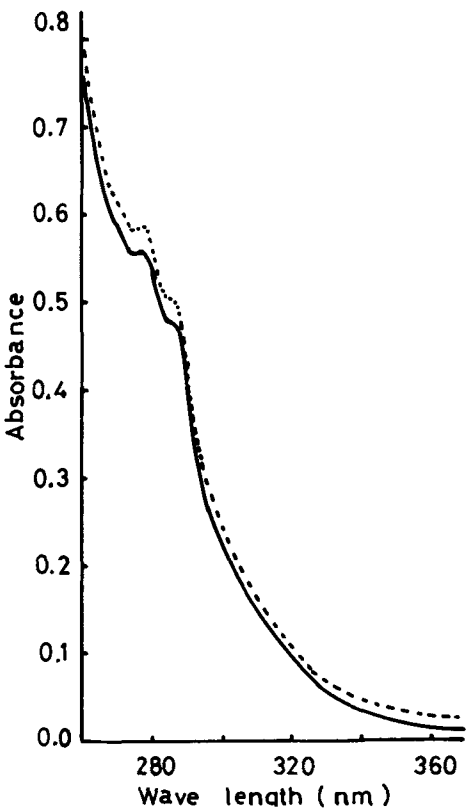


Fig. 3. UV spectra of (IV) and unlabelled authentic (IV).
——— : unlabelled (IV)
----- : (IV)

(Fig. 3); Rf on TLC (Kieselgel GF_{254} (Merk)) developed with benzene/acetone (1 : 1, v/v) : 0.75. On TLC of ^{14}C-(IV), a single radioactive peak appeared at Rf coincident with that of a fluorescent spot due to unlabelled authentic specimen of (IV) detected under UV lamp (Fig. 4).

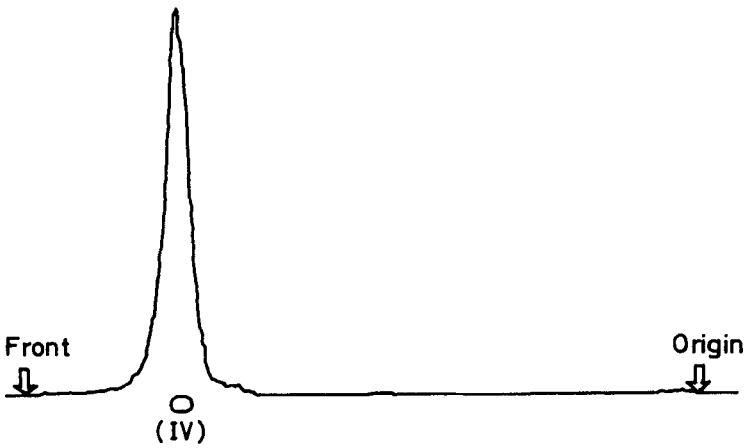


Fig. 4. Radioscans of (IV) on TLC developed with benzene/acetone (1 : 1).

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