# SYNTHESIS OF 1-(2-ETHOXYETHYL)-2-(4-METHYL-1-HOMOPIPERAZINYL)-[2-$^{14}$C]BENZIMIDAZOLE DIFUMARATE([$^{14}$C]KB-2413)

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SUMMARY

1-(2-Ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)-[2-$^{14}$C]-benzimidazole difumarate([$^{14}$C]KB-2413), a new antihistaminic agent, was prepared from labelled urea.

The synthetic intermediate, 1-(2-ethoxyethyl)benzimidazolone, obtained in good yield by the condensation of N-(2-ethoxyethyl)-o-phenylenediamine with [$^{14}$C]urea, was chlorinated with phosphorus oxychloride and followed by the reaction with N-methylhomopiperazine to give the base of [$^{14}$C]KB-2413. It was then converted to the difumarate, which was obtained in an overall radiochemical yield of 74 % starting from [$^{14}$C]urea.

The specific activity was 54.4 mCi/mmol and its radiochemical purity was 98.0 % in reverse isotope dilution analysis.

Key words : Synthesis, Antihistaminic agent, 1-(2-Ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole difumarate, Carbon-14, Urea

0362-4803/87/030331-08$05.00

Received April 4, 1986

## INTRODUCTION

1-(2-Ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole difumarate (KB-2413) is a new benzimidazole derivative having potent antihistaminic activity and less toxicity in animals compared with other known antiallergic drugs[1-4].

In order to investigate the metabolic fate of KB-2413, it was desired to synthesize labelled compound with carbon-14 at a metabolically stable position.

This paper deals with the synthesis of KB-2413 labelled with carbon-14 at the 2-position of the benzimidazole nucleus of the molecule.

## RESULTS AND DISCUSSION

The synthetic pathway of [$^{14}$C]KB-2413(1) was shown in Fig. 1.

N-(2-Ethoxyethyl)-o-phenylenediamine(4) was prepared just before use, because it was less stable than 1-(2-ethoxyethyl)-amino-2-nitrobenzene(3). Nitro derivative 3 was obtained by the reaction of 2-ethoxyethylamine and o-nitrochlorobenzene(2) which were commercially available.

The condensation reaction of 4 with urea in n-amyl alcohol gave 1-(2-ethoxyethyl)benzimidazolone(5) in satisfactory yield, accounting for 88 % radiochemical yield based on the labelled urea after purification on column chromatography.

When the chlorination of 5 with phosphorus oxychloride was carried out by refluxing in a somewhat similar scale to prepare the labelled compound, 2-chloro-1-(2-ethoxyethyl)-benzimidazole (6) was obtained in poor yield (less than 20 %) and considerable amount of starting meterial 5 and some by-products were found on TLC. Futhermore, attempts to obtain 6 in high yield were

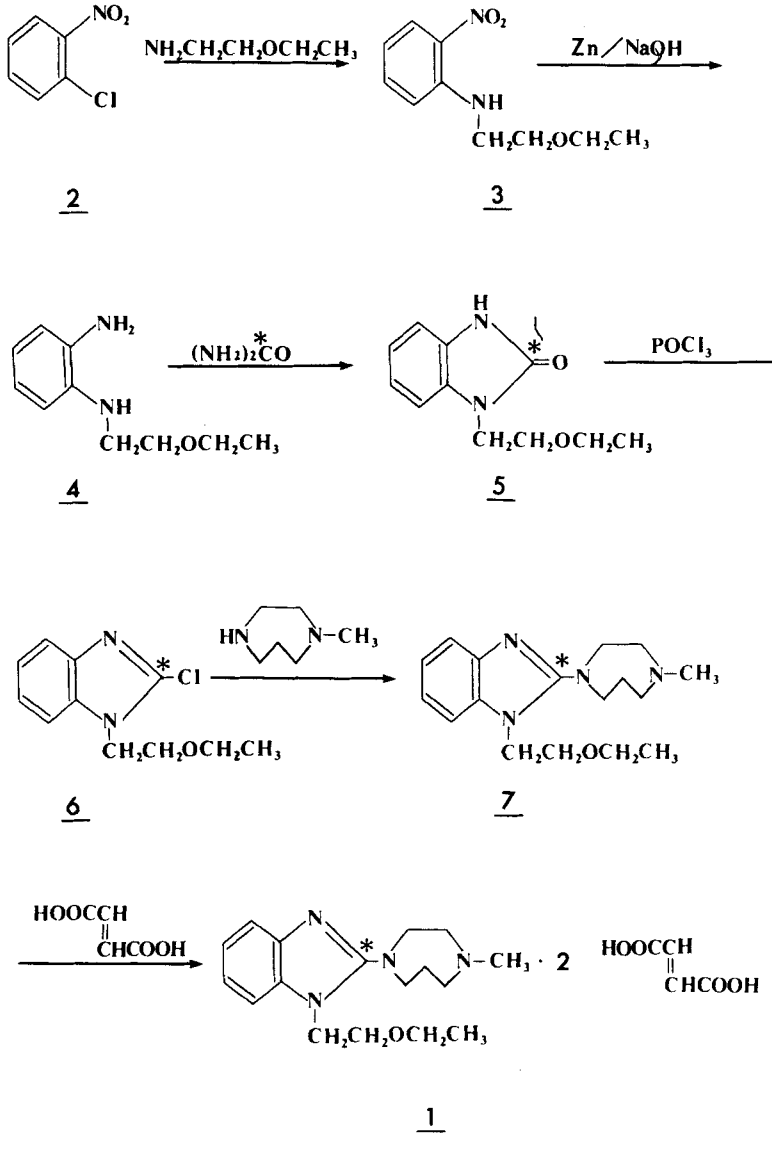


Fig. 1 Scheme for the synthesis of [$^{14}$C]KB-2413

unsuccessful by alterations in the various conditions of reaction, for example, reaction time, temperature and amount of reagents. It suggested that the starting material 5 might be remaining in the case of insufficiency of phosphorus oxycholoride, acting also as a solvent, and that side reactions

such as the fission of ether linkage in side chain of 5 might be occurring to give some by-products in the case of reacting 5 with a large excess of phosphorus oxychloride at a high reaction temperature for long periods.

However we succeeded in preparation of 6 with very high yield and without formation of by-products in the following procedure.

Thus, when 5 and about 3.5 times molar excess of phosphorus oxychroride were placed in a micro vial fitted with a sealing cap and the reaction mixture was stirred at 120 °C for 2 h. Then the resulting product 6 was reacted with N-methyl-homopiperazine to give 7 in the yield of approximately 85 % from 5.

The desired product 1 was prepared in an overall yield of 74 % via four step process from [$^{14}$C]urea.

The radiochemical purity of 1 was 98 % in reverse isotope dilution analysis, and its specific radioactivity was 54.4 mCi/mmol.

## EXPERIMENTAL

### Materials and Methods

[$^{14}$C]Urea was purchased from Amersham International plc.

N-Methylhomopiperazine synthesized by Kohei Chemical Industries, Ltd. was used. All other reagents and solvents of reagent grade were purchased from Wako Pure Chemical Industries, Ltd.

Radioactivity was determined by using a Packard Tri-Carb 3385 scintillation counter after adding scintillator Econofluor (New England Nuclear) to samples. The counting efficiency was

automatically determined by external standardization method.

Thin layer chromatography(TLC) was carried out on Kieselgel 60 $F_{254}$ plate(Merck) and radioactivity on the plates was determined by a packard Model 7201 radiochromatogram scanner.

Column chromatography was performed using a column which was filled with silica gel for chromatography(Wako gel C-200, Wako Pure Chemical Industries, Ltd.).

1-(2-Ethoxyethyl)amino-2-nitrobenzene(3)

A mixture of o-nitrochlorobenzene (2, 45.3 g, 0.287 mol) and 2-ethoxyethylamine(75.0 g, 0.842 mol) was stirred under reflux for 24 h. After cooling, to the solution was added ethyl acetate and the mixture was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave a crude orange oil, which was purified by silica gel corumn chromatography. Elution with n-hexane/ethyl acetate (10:1) gave 3 (35.0 g, 63 %), which showed only one spot on TLC (Rf value ; 0.42, developing solvent ; chloroform).

N-(2-Ethoxyethyl)-o-phenylenediamine(4)

A solution of 3 (1.70 g, 8.09 mmol) in 10 ml of ethyl alcohol and 10 ml of 2 N sodium hydroxide was stirred under gentle reflux for 30 min, and 5 g of zinc powder was added gradually to the solution with stirring over a period of 1 h. After being stirred under reflux for an additional 1 h, the precipitate was filtered off under heating and washed thoroughly with ethyl acetate. The combined filtrate and washings were extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate. Removal of the solvent under

reduced pressure gave a brown liquid of 4 (1.40 g, 96 %), which was found to be one spot on TLC (Rf value ; 0.13, developing solvent ; chloroform).

A portion of the resulting diamine compound 4 was used for the following reaction without more purification.

1-(2-Ethoxyethyl)benzimidazolone(5)

A mixture of [$^{14}$C]urea (28.5 mg, 0.474 mmol, 26.1 mCi) having the specific activity 55 mCi/mmol, 4 (203 mg, 1.13 mmol) and n-amyl alcohol (1 ml) was heated with stirring at 150 °C for 24 h. After cooling, the solution was mixed with 10 ml of distilled water, extracted three times with each 20 ml of ethyl acetate. The ethyl acetate extracts were washed with 1 N hydrogen chloride and water, dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave a dark-brown solid, which was purified by silica gel column chromatography. Elution with n-hexane/ethyl acetate (2:1) gave a colorless solid of 5 (88.1 mg, 23.0 mCi, 88 %), which showed only one peak on radiochromatogram (Rf value ; 0.16, developing solvent ; n-hezane/ethyl acetate = 1 : 2)

2-Chloro-1-(2-ethoxyethyl)benzimidazole(6)

In a 0.5 ml Micro Product V Vial (Wheaton Scientific) was placed 5 (88.1 mg, 0.427 mmol) and phosphorus oxychloride (225 mg, 1.47 mmol). The container was stoppered with a screw cap which has solid top and Teflon-faced rubber liner, and the mixture was stirred at 120 °C for 2 h.

Excess phosphorus oxychloride was evaporated off under reduced pressure. The residue was mixed with 5 ml of 1 N sodium hydroxide and 5 ml of distilled water, extracted twice with each

10 ml of ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate. Romoval of the solvent under reduced pressure gave a product 6, which showed one spot on TLC (Rf value ; 0.40, developing solvent ; n-hexane/ethyl acetate = 1 : 2), and was used to prepare 7 without purification.

1-(2-Ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole(7)

To the resulting oil of 6, 0.5 ml of N-methylhomopiperazine was added and the atmosphere was displaced with nitrogen gas, followed by heating at 120 °C for 40 h in a closed bottle. After cooling, the solution was mixed with 5 ml of distilled water and 5 ml of 1 N sodium hydroxide, and extracted three times with each 10 ml of benzene. The combined extracts were washed with distilled water and evaporated off under reduced pressure. Furthermore, the residue was dried by the azeotropic distillation with ethyl alcohol, and purified by silica gel column chromatography. Elution with ethyl acetate/methyl alcohol (2:1) gave a pale yellow oil of 5 (107 mg, 19.3 mCi, 84 %), which was found to be pure on a radiochromatogram (Rf value ; 0.43, developing solvent ; triethylamine/methyl alcohol = 1 : 20).

KB-2413(1)

The solution of 7 in ethyl acetate was mixed with exactly twice molar equivalence of fumaric acid and the suspension was stirred sufficiently with sonicater.

The solvent was evaporated off under reduced pressure to afford a colorless crystalline of 1 (190 mg, 19.3 mCi), of which radiochemical purity was 98.0 % in reverse isotope dilution method and specific activity was 54.4 mCi/mmol.

REFFERENCE

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