SYNTHESIS OF ^{14}C-LABELLED 2-(p-CHLORO-α-HYDROXYBENZYL)-BENZIMIDAZOLE (HBBPC)

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SUMMARY

p-Chloro[^{14}C]mandelic acid 2 was prepared from [^{14}C]potassium cyanide and p-chlorobenzaldehyde 1. The condensation of p-chloro[^{14}C] mandelic acid with 1,2-diamino benzene 3 gave the title benzimidazole 4 labelled at the carbon atome 2 of the heterocyclic ring.

Key Words: Benzimidazole, Vasodilatator, Carbon-14.

INTRODUCTION

Benzyl benzimidazole is known as a reference drug in behavioural pharmacology. Since 1974 we found that HBBPC or 2-(p-chloro-α-hydroxybenzyl)-benzimidazole hydrochloride possesses, besides neurotropic properties, an important peripherical vasodilatator activity (1,2,3). Preliminary metabolism study with HBBPC have indicated the necessity of radio-labelled compound for further biochemical studies (4).

Based upon stability relative to metabolic changes (4) and mass spectrometric fragmentation (5) of benzimidazole, the carbon atome 2 of the imidazole ring are chosen for the site of labelling. A convenient route to the p-chloromandelic acid involves the classical treatment of p-chlorobenzaldehyde with potassium cyanide (6). However, using a equimolecular ratio of the starting materials, this reaction (Scheme I) afford a mixture of the intended acid and some by products. Therefore, a study of this reaction on a small scale was undertaken to optimize the production of p-chloromandelic acid with an attendant increase in yield.

Reaction time and temperature both seem to have some influences. A slight excess of potassium cyanide is required. Finally it appears that by adjusting the mole ratio of potassium cyanide and the reaction time, it is possible to control the reaction to favor the acid of choice.

The obtaining of the benzimidazole ring is then realised by condensation between 1,2-diamino benzene and p-chloro[^{14}C]mandelic acid in concentrated hydrochloric acid.

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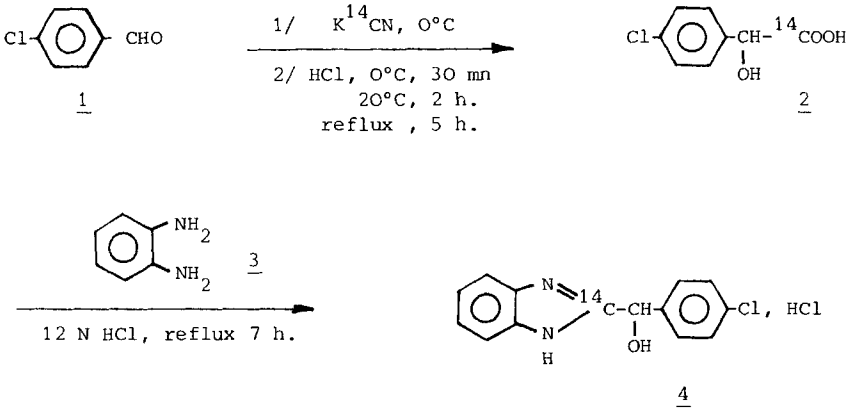

Scheme I

EXPERIMENTAL

All solvents were used dried and distilled. Radioactivity was measured using the Intertechnique ABAC SL 40 liquid beta scintillation spectrometer. For proof of structure, NMR spectra were recorded using a Hitachi Perkin Elmer R.24 A 60 MHz spectrometer, and analytical TLC was carried out on a Vario KS Camag TLC set.

p-Chloro-[^{14}C]mandelic acid 2

To 1 g (7 mmol) of p-chlorobenzaldehyde in ether (1.5 ml), 30 mCi of [^{14}C] potassium cyanide (59.6 mCi/mmol) and 0.78 mg of cold KCN are added. The stirred mixture is cooled in an ice bath. 12N HCl (0.8 ml) is added dropwise. Stirring is continued at 0°C for 30 mn. The solution is then allowed to stand with stirring at the room temperature for 2 hours. The yellow ether solution of the nitrile is isolated and poured in 12N HCl (5ml). The hydrolysis is performed by heating under reflux for 5 hours. After cooling the pH is adjusted to 7 by addition of 30% aqueous NaOH. The aqueous solution is washed with ether (2 x 3 ml) to eliminate traces of unreacted p-chlorobenzaldehyde. Concentrated HCl is added and the white precipitate formed is extracted with ether (3 x 5 ml). Removal of the solvent on the rotary evaporator, in vacuo, yields 0.99 g of 2, (yield: 42 %).

2-p-Chloro-α-hydroxybenzyl)-2 [^{14}C] benzimidazole 4

p-Chloro[^{14}C]mandelic acid 2 (0.99 g), 1,2-diaminobenzene (0.57 g) and 12N HCl (7 ml) are heated under reflux in an oil bath for 7 hours. After cooling , the powderlike precipitate is filtered off from the acid solution, washed successively with ether (2 x 5 ml) and ice (0°C) water (2 x 5 ml) to give 1.55 g of dried benzimidazole 4, (yield: 18 %).

The material show a single spot on TLC over silicagel (Merck F_{254}) plate, (methanol / chloroform, 20 : 80). The radiochemical purity is determined by autoradiography of the above thin layer chromatogram.

Specific activity: 12.09 μCi/mg or 3.57 mCi/mmol.

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