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SYNTHESIS OF THE CARDIOTONIC AGENT ^{14}C-LOPRINONE.

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SUMMARY

^{14}C-Labeled 1,2-dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxo-3-pyridinecarbonitrile hydrochloride monohydrate **6** was synthesized in 5 steps from 6-bromoimidazo[1,2-*a*]pyridine using [2-^{14}C]cyanoacetamide as the source of the radiolabel. The key intermediate, 1-imidazo[1,2-*a*]pyridin-6-yl-2-propanone **3** was prepared by the selective ozonolysis of the propenyl group of 6-(2-methylpropen-3-yl)imidazo[1,2-*a*]pyridine **2** under acidic conditions followed by the reduction with sodium sulfite. The chemical yield of **6** from 4-dimethylamino-3-imidazo-[1,2-*a*]pyridin-6-yl-3-buten-2-one **4** and the radiochemical yield from [2-^{14}C]cyanoacetamide were both 57%. The radiochemical purity and the specific activity of **6** were 98% and 1868.5 MBq/mmol, respectively.

Key words: Loprinone , 1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxo-3-pyridinecarbonitrile hydrochloride monohydrate, Cardiotonic agent, Carbon-14,

INTRODUCTION

1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxo-3-pyridinecarbonitrile hydrochloride monohydrate **6** (loprinone hydrochloride (1)) produced a dose-related positive inotropic response without significant increase in heart rate when administered orally to conscious dogs (2). It is presently under development for the treatment of congestive heart failure. This paper describes the synthesis of ^{14}C-labeled loprinone hydrochloride to enable pharmacokinetic profile studies.

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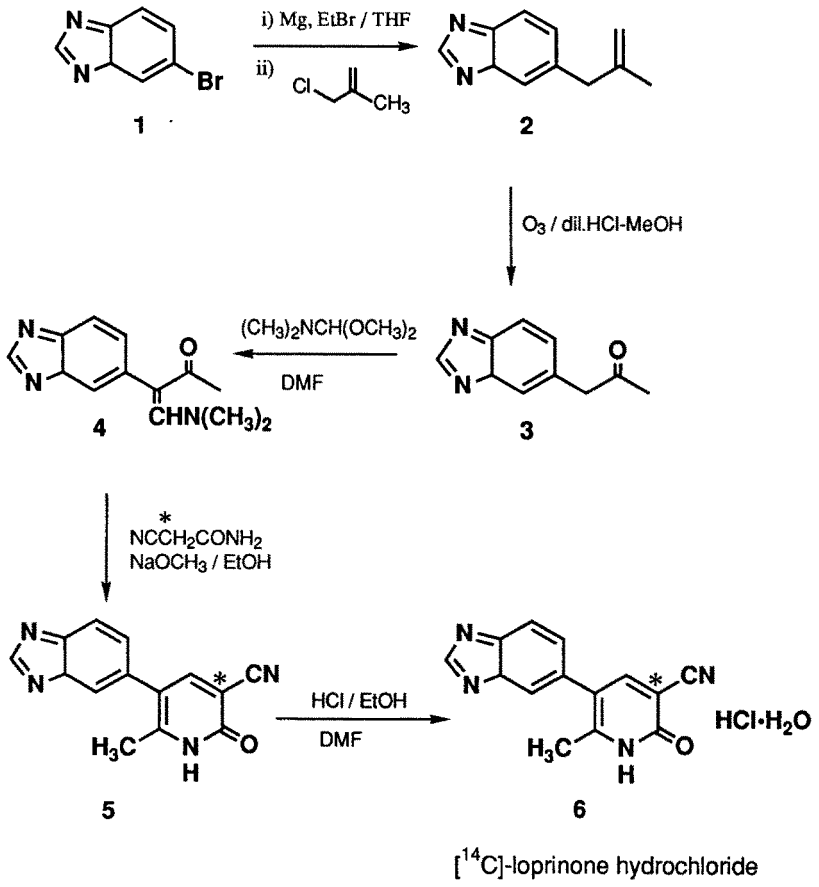
The synthetic procedure, illustrated in Scheme 1, began with the preparation of 6-(2-methylpropen-3-yl)imidazo[1,2-*a*]pyridine **2** derived from the Grignard cross-coupling reaction of 5-bromoimidazo[1,2-*a*]pyridine **1** (3), with 3-chloro-2-methylpropene. Ozonolysis of **2** under acidic conditions followed by reductive degradation with sodium sulfite gave 1-imidazo[1,2-*a*]pyridin-6-yl-2-propanone **3** in 70.5% yield. This route was the most useful among the three examined (4), and the yield of **3** from **1** was 50%. Treatment of **3** with N, N-dimethylformamide dimethylacetal in DMF gave 4-dimethylamino-3-imidazo[1,2-*a*]pyridin-6-yl-3-buten-2-one **4** in



Scheme I

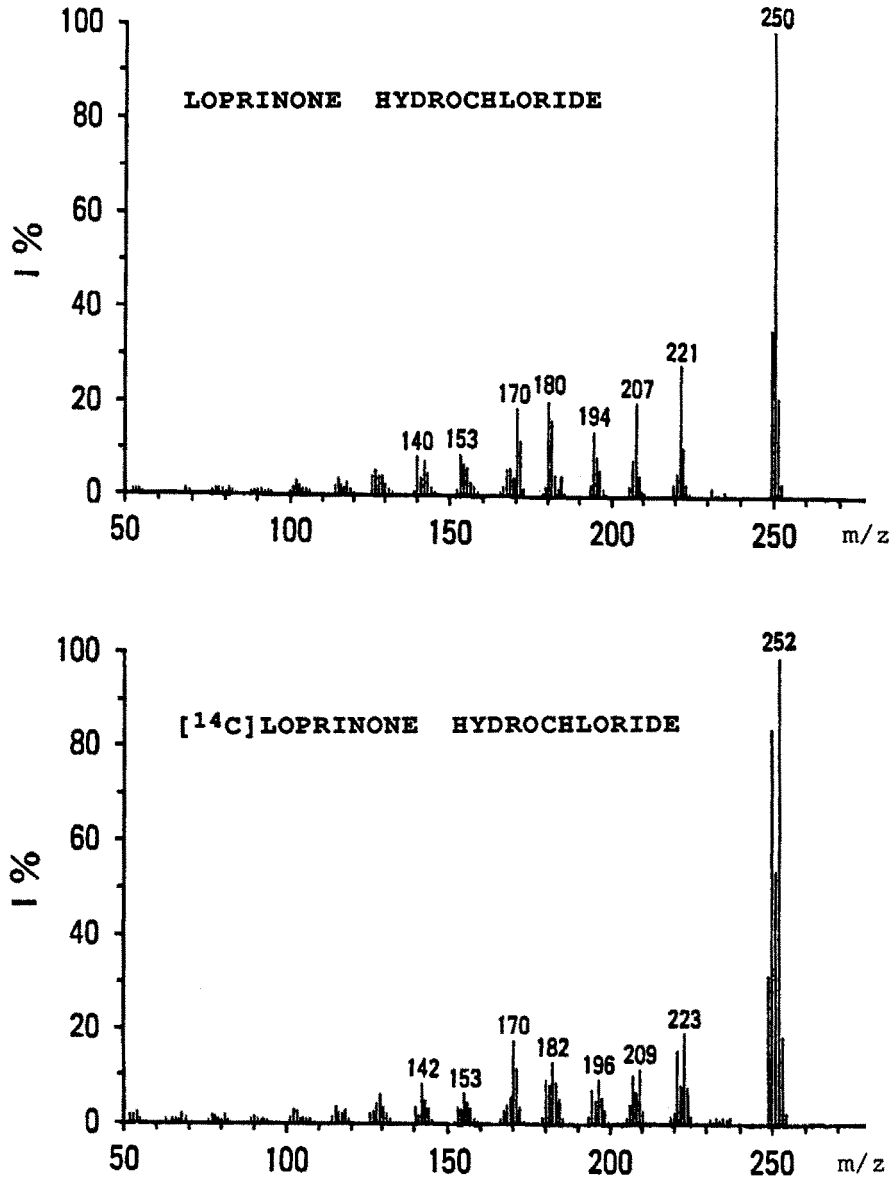


Fig 1. Mass spectra of loprinone hydrochloride and [^{14}C]loprinone hydrochloride.

74.5% (4). Condensation of **4** with [2-^{14}C]cyanoacetamide and followed by conversion to the hydrochloride provided ^{14}C-loprinone hydrochloride **6** in 57% chemical and radiochemical yield. The structure of the compound was confirmed by comparison with unlabeled authentic sample. The radiochemical purity of this material was 98% and the specific activity was 1868.5 MBq/mmol.

EXPERIMENTAL

A Berthold Linear Analyzer LB 2832 and Aloka TLC Scanner JTC 203 were used to detect radioactivity. Liquid scintillation counting was performed on an Aloka Scintillation Counter LSC 903. Uv spectra were recorded from Shimadzu double-beam spectrophotometer UV-300. Mass spectra were run using a JMS-DX300 spectrometer. [2-^{14}C]Cyanoacetamide was purchased from Amersham International plc. The specific activity was reported to be 1887 MBq/mmol and the radiochemical purity by TLC 97%.

The syntheses of 6-(2-methyl-propen-3-yl)imidazo-[1,2-*a*]pyridine **2**, 1-imidazo[1,2-*a*]pyridin-6-yl-2-propanone **3** and 4-dimethylamino-3-imidazo[1,2-*a*]pyridin-6-yl-3-buten-2-one **4** were reported in our preceding paper (4).

1,2-Dihydro-5-imidazo[1,2-a]pyridin-6-yl-6-methyl-2-oxo-[3-^{14}C]-3-pyridinecarbonitrile **5**

151 mg (2.79 mmol) of sodium methoxide was added portionwise to a solution of 1480 MBq of [2-^{14}C]cyanoacetamide and 183 mg (0.798 mmol) of **4** in 5 mL of ethanol and the mixture was refluxed with stirring for 2 h. After removal of solvent, 4 mL of water was added to the residue and 10% AcOH was added until the solution became slightly acidic. After cooling in an ice-water bath, the precipitate was collected by filtration and washed with cold water. The crude product was dissolved in 100 mL of methanol and treated with 150 mg of charcoal at 80°C. The charcoal was filtered and the filtrate was concentrated to about 10 mL. The solution was cooled in

an ice bath and the solid were collected by filtration and washed with 5 mL of ethanol to give 138 mg (68.5%) of **5**.

1,2-Dihydro-5-imidazo[1,2-a]pyridin-6-yl-6-methyl-2-oxo-[3-^{14}C]-3-pyridinecarbonitrile hydrochloride monohydrate **6** (**^{14}C-loprinone hydrochloride**)

To a solution of 138 mg of **5** in 10 mL of DMF was added a solution of 5.5 mL of 10% ethanolic HCl followed by 47 mL of AcOEt. The precipitate was collected by filtration, washed with Et_2O and dried to afford 139 mg (57% from **4**) of **6** with specific activity of 1868.5 MBq/mmol (57% from [2-^{14}C]cyanoacetamide) and a radiochemical purity of 98% by TLC (acetone /H_2O/NH_4OH; 90: 10: 1, R_f = 0.61 and $CHCl_3$/MeOH; 4:1, Rf = 0.65). λ_{max} in H_2O nm (ε): 210 (29110), 254 (18440), 342 (8830). Identification of **6** was confirmed by comparison of its R_f values on TLC, uv spectrum and mass spectrum (Fig 1) with those of the unlabeled authentic compound [mp >300°C. Anal. Calcd for $C_{14}H_{10}N_4O \cdot HCl \cdot H_2O$: C, 55.16; H, 4.30; N, 18.39. Found: C, 55.26; H, 4.40; N, 18.44].

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