SYNTHESIS OF ^{14}C-LABELLED MILRINONE

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SUMMARY

A synthetic procedure for producing ^{14}C-labelled milrinone is described. The synthesis was achieved in two steps from 1-(4-pyridyl)propan-2-one utilising [2-^{14}C]cyanoacetamide as the source of the radiolabel. The overall chemical yield was 46% and the radiochemical yield 35%.

Key words: Milrinone, Cardiotonic agent, Carbon-14, Synthesis.

INTRODUCTION

Milrinone[1], 3, (1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile), is a potent new cardiotonic agent related to amrinone[1], which is currently undergoing clinical evaluation[2]. As part of the development programme a quantity of ^{14}C-labelled milrinone was required for metabolism and drug disposition studies.

The synthetic procedure used, which is shown in Scheme 1, began with the preparation of 4-(dimethylamino)-3-(4'-pyridyl)but-3-en-2-one, 2, derived from the condensation of N,N-dimethylformamide dimethyl acetal with 1-(4-pyridyl)propan-2-one, 1. Condensation of the intermediate, 2, with [2-^{14}C]cyanoacetamide gave the desired product, 3.

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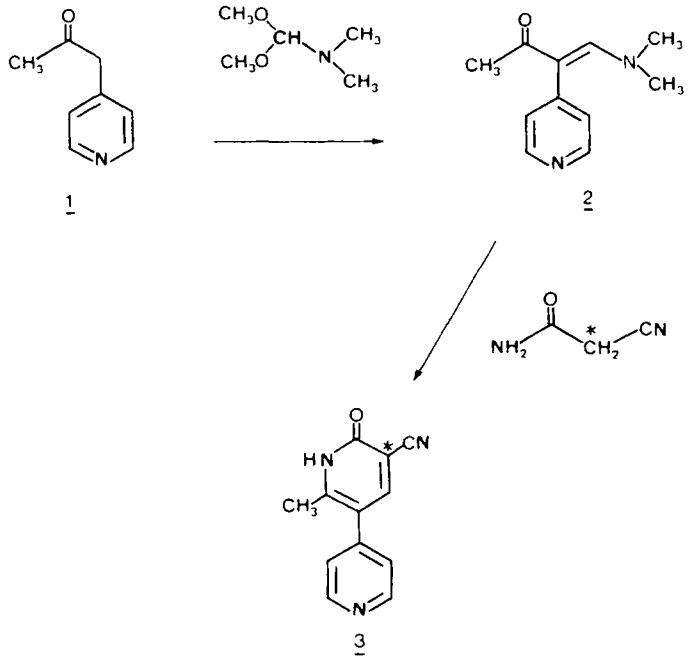
SCHEME 1



EXPERIMENTAL

Melting points are uncorrected. Infra red (IR) spectra (KBr dispersions) were recorded with a Perkin Elmer 177 spectrophotometer. Nuclear magnetic resonance (NMR) spectral data were measured in $CDCl_3$ using a Varian (EM 360) 60 MHz spectrometer and reported in δ units relative to tetramethylsilane. Mass spectra (MS) were obtained on a AEI MS9 mass spectrometer. Differential scanning calorimetry (DSC) was carried out on a Mettler TA3000 thermal analysis system. Radioactivity measurements were performed on a Packard TRICARB 300C counter using Instagel (Packard) as counting medium. Thin layer chromatography (TLC) was carried out on 0.25 mm G-60 F_{254} silica gel plates (Merck) in the following system:

(i) Chloroform: methanol: isopropylamine (70:20:10)

Plates were scanned on a Panax scanner.

[2-^{14}C]Cyanoacetamide was supplied by Physics and Radioisotopes Services, Imperial Chemical Industries, Billingham, Cleveland. The specific activity was reported to be 27.4 mCi/mmol and the radiochemical purity by TLC greater than 97%.

1-(4-Pyridyl)propan-2-one, 1

This compound was obtained from Reilly Tar Chemical Corporation, Indianapolis, Indiana, U.S.A.: IR: 1720 cm^{-1} (carbonyl); NMR: 8.6 (d) and 7.2 (d) (four 4-substituted pyridyl protons), 3.8 (s) (two methylene protons linked to a carbonyl and pyridyl), 2.2 (s) (three methyl protons linked to a carbonyl); MS: m/e 135 (M).

4-(Dimethylamino-3-(4'-pyridyl)but-3-en-2-one, 2

A mixture of 1-(4-pyridyl)propan-2-one, 1 (3.64 g, 26.9 mmoles) and N,N-dimethylformamide dimethyl acetal (3.6 g, 30.2 mmoles) in N,N-dimethylformamide (DMF) (30 ml) was stirred under nitrogen at ambient temperature for 5 h. The solution was concentrated under reduced pressure to a thick oil which solidified on standing overnight. Recrystallisation from isopropyl acetate (30 ml) and work up yielded 5.3 g (67%) of 2 as pale yellow crystals. mp 118.5-122.0°C. IR : 1565 cm^{-1} (conjugated carbonyl); NMR : 8.6 (d) and 7.2 (d) (four 4-substituted pyridyl protons), 7.6 (s) (one olefinic proton), 2.8 (s) (six N,N dimethyl protons), 2.0 (s) (three methyl protons); MS : m/e 190 (M).

1,6-Dihydro-2-methyl-6-oxo[[5-^{14}C]3,4'-bipyridine]-5-carbonitrile, 3

A sodium methoxide solution prepared by dissolving sodium (300 mg, 13.05 mmoles) in methanol (10 ml) was added dropwise to a solution of [2-^{14}C]cyanoacetamide (2mCi), unlabelled cyanoacetamide (575 mg, 6.84 mmoles) and 2 (1.00 g, 5.26 mmoles) in methanol (5 ml) under a nitrogen atmosphere. When the addition was

complete the reaction mixture was stirred for 1 h at room temperature and heated under reflux for 2.5 h before being allowed to cool to room temperature over 30 min. The cooled mixture was diluted with distilled water (5 ml), concentrated under reduced pressure and glacial acetic acid was added until the solution was slightly acidic to pH test paper. After further cooling to 5^{o}C for 4 h the resulting solid was collected by filtration, dried and recrystallised from DMF (8 ml). This gave [^{14}C]milrinone (510 mg, 2.42 mmoles, 0.29 mCi/mmol) with a radiochemical purity of 99% as determined by TLC. The TLC, IR and DSC properties of the product were shown to be identical to those of an authentic sample of milrinone.

REFERENCES

1. Milrinone and amrinone are United States adopted names.

2. Pastelin, G., Mendez, R., Kabela, E. and Farah, A. - Life Sciences 33: 1787 (1983) and references therein.