NOTES

PREPARATION OF 5-Amino-3,4'-Bipyridin-6(1H)-one-5^{14}C A NEW CARDIOTONIC AGENT

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ABSTRACT

Inocor^{TM} brand of amrinone[1] (5-amino-3,4'-bipyridin-6(1H)-one-5^{14}C) a new positive inotropic agent was obtained [^{14}C] labelled at Carbon 5 in 55% overall yield.

Key Words: Inocor^{TM}, Cardiotonic Agent, Carbon-14, Synthesis

INTRODUCTION

Inocor^{TM}, a brand of the generic drug amrinone, is a new, potent, non-toxic cardiotonic drug undergoing extensive clinical evaluation as a candidate to replace digitalis in the treatment of congestive heart-failure.[2a,b] A description of the procedure for providing [^{14}C] labelled amrinone for metabolic and drug distribution studies is the subject of this communication.

The procedure[3] (scheme I) began with the preparation of α-[(dimethylamino)-methylene]-4-pyridineacetaldehyde 1 derived from the Vilsmeier-Haack formylation of 4-methylpyridine, as reported by Arnold.[4] condensation of the iminoaldehyde 1 with cyanoacetamide-2-^{14}C 2, gave intermediate nitrile 3 which was hydrolyzed directly to the amide 4. Hofmann rearrangement of the amide 4 gave the desired 3-aminopyridylpyridone 5.

EXPERIMENTAL

Cyanoacetamide-2-^{14}C (2) was custom synthesized by the New England Nuclear Corporation. The specific activity was reported to be 3.58 mC/mmol. Its purity was checked on a TLC plate (E. Merck silica gel 60 F-254) eluted with CH_3CN:CH_3OH:i-$PrNH_2$ (88:10:2). The material obtained was pure as indicated by a single symmetrical peak on the radioscan of the TLC plate-Rf=0.7. Sodium methylate was purchased from the Matheson, Coleman and Bell Company.

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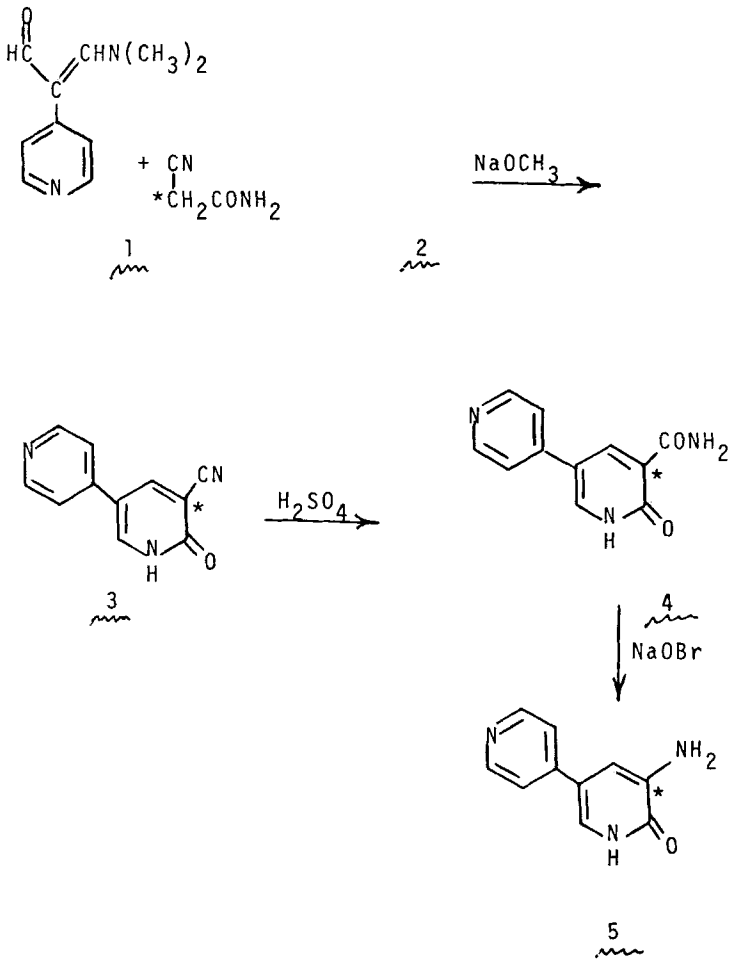
Scheme I



Compound 4. 1,6-Dihydro-6-oxo-[3,4'-Bipyridine]-5-Carboxamide-5^{14}C. Iminoaldehyde 1, 896 mg (5.1 mmol) was mixed, stirred and refluxed in 25 mL of CH_3OH solution with 550 mg (10.2 mmol) of $NaOCH_3$ and 470 mg (5.6 mmol) of cyanoacetamide-2^{14}C (2). After 25 min considerable solid nitrile 3 had separated. The hot reaction mixture was diluted with 25 mL i-PrOH, refluxed for 15 min, and the resulting thick slurry cooled in ice.

The yellow nitrile (3) was collected on a glass frit funnel, washed with cold i-PrOH and Et_2O, and air dried with suction. The light yellow cake was dampened on the funnel with concentrated H_2SO_4 and transferred in chunks to a 125 mL Erhlenmeyer filter flask. A total of four milliliters of H_2SO_4 was dripped onto the solid and used to wash the remaining compound from the funnel into the flask. The resulting dark brown solution was heated on the steam bath for 10 min then cooled in ice, and pieces of ice and concentrated NH_4OH introduced until a 50 mL volume was reached, and the solution was strongly alkaline to test paper. Precipitation of the desired amide 4 was complete within a few minutes. The amide was filtered onto a tared fritted glass funnel washed with cold H_2O, acetone, and Et_2O to give after drying 789.4 mg (72%) of cream colored product.

Compound 5. 5-amino-3,4'-Bipyridin-6(1H)-one-5-^{14}C. A solution of 880 mg (22 mmol) of NaOH in 20 mL H_2O was used to wet down the solid cake of amide in the funnel. The dampened solid was lifted and transferred to a 50 mL Erhlenmeyer filter flask. The funnel was washed down with the remainder of the NaOH solution and suction applied to clear the funnel and plate. The suspended solid was warmed on the steam bath until complete solution of the sodium salt of 4 was achieved. The solution was then cooled with stirring to -15°C bringing down heavy precipitation of the sodium salt. Stirring of the thick suspension was continued as 645 mg (4.0 mmol) of Br_2 was dripped into the slurry. Each drop of Br_2 instantaneously decolorized and caused partial dissolution of the suspended sodium salt. The final clear amber solution was heated for one hour on the steam bath, charcoaled (Darco G60), filtered hot and the bright yellow filtrate cautiously treated with 6N HCl until CO_2 evolution had ceased. The yellow crystalline amine 5 was collected, washed with acetone, Et_2O and dried to give 678 mg (98%) of crude product. The amine was dissolved in 50 mL of hot water containing 10% DMF. The solution was charcoaled and filtered to give a transparent yellow filtrate. Seeding the filtrate with cold product produced

long, clear, yellow needles of amrinone 5. A second crop was obtained by evaporation of the filtrate to 1/2 of its volume and seeding with amrinone.

The total weight of product obtained by this method was 528 mg (77%). Specific activity = 2.1 mC/mmol. Chemical purity was confirmed by TLC on silica gel plates in two solvent systems, and by comparison of the UV absorbance of the product to that of authentic amrinone. Radiochemical purity was determined by radioscans of the TLC plates.

TLC: EtOAC: CH_3OH:HCOOH (50:48:2) Rf=0.35
$CHCl_3$: CH_3OH:ACOH (70:20:10) Rf=0.5

UV:	MAXIMUM	MINIMUM
Amrinone	253	277
Amrinone-^{14}C	253	277

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REFERENCES

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