Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIV, No. 2

SYNTHESIS OF ^{14}C-LABELLED 2-AMINOPYRIDINE

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SUMMARY

2-Aminopyridine is a versatile building block in the preparation of certain heterocycles such as imidazo[1,2-a]-pyridines, pyrido[1,2-a]-pyrimidin-ones and substituted derivatives thereof. ^{14}C-labelled 2-aminopyridine was synthesized as follows: potassium-[^{14}C]cyanide (I) was reacted with epichlorohydrin (II) to give 3-hydroxy-[1,5-$^{14}C_2$]glutaronitrile (III). The latter was cyclized to 2-amino-6-bromo-[2,6-$^{14}C_2$]pyridine (IV) which was then reductively dehalogenated to the 2,6-$^{14}C_2$-labelled title compound (V) in 36 % overall chemical and radiochemical yield, based upon I. The product was radiochemically pure (99.1 %) according to high-performance liquid chromatography and thin-layer chromatography, and had a specific activity of 9.06 mCi/mmol.

Key words: 2-amino-6-bromo-[2,6-$^{14}C_2$]pyridine, 2-amino-[2,6-$^{14}C_2$]pyridine

INTRODUCTION

Ongoing research in our laboratories was concerned with the synthesis of compounds containing such heterocycles as 2H-pyrido[1,2-a]-pyrimidin-2-ones,

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0362-4803/87/020119-05$05.00

Received February 10, 1986
Revised May 28, 1986

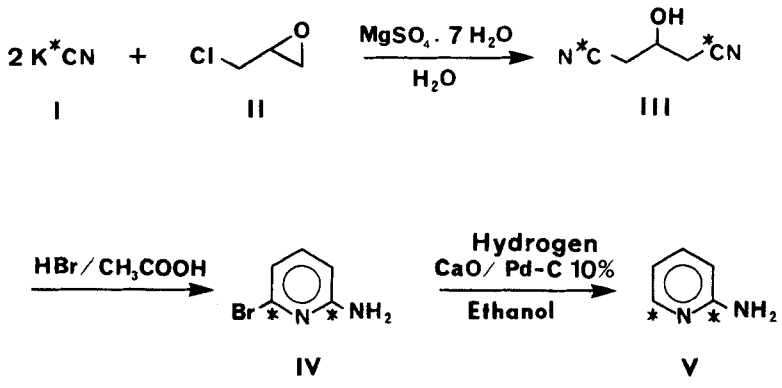
4H-pyrido[1,2-a]-pyrimidin-4-ones and substituted versions thereof. Since all of these compounds can be obtained by simply reacting 2-amino-pyridine with α-halo-carbonyl intermediates (1), α-bromoacrylic acids (2), ethylethoxy methylene malonate (2, 3), ß-keto esters (3), diethylmalonate in polyphosphoric acid (PPA) (3), diketene (4) or α-acetyl-γ-butyrolactone in PPA (5), the ^{14}C-labelled 2-aminopyridine might well be the synthon of choice for the specific introduction of a label in any of these heterocycles. This might facilitate studies of the metabolic fate of drugs containing these moieties in animals and man.

To our knowledge, the synthesis of labelled 2-aminopyridine had not previously been published. Noël et al. (6) lined out the preparation of [2,6-$^{14}C_2$] pyridine in a 5-step reaction sequence starting from sodium-[^{14}C]cyanide and 1,3-dibromopropane in a 27 % overall yield. The amination of pyridine via standard methods (7) is indicated and should afford the title product in 67 % yield.

In 1962, Johnston (8) described the preparation of 3-hydroxy glutaronitriles which were converted in a one-step procedure to 2-amino-6-bromopyridines (9). Reductive bromination of some of these compounds and derivatization with phenylisocyanate gave unspecified amounts of the dehalogenated phenylurethanes of the resulting aminopicolines.

As the latter method promised to furnish 2-aminopyridine in a high yield via a short and elegant route, and as the intermediate 2-amino-6-bromo-[2,6-$^{14}C_2$]pyridine in itself is a useful compound, we attempted to synthesize the 2-amino-[2,6-$^{14}C_2$]pyridine following this lead.

Potassium-[^{14}C]cyanide I was reacted with epichlorohydrin II (scheme I) in an aqueous solution buffered with magnesium sulphate at 5-10° C to furnish 3-hydroxy-[1,5-$^{14}C_2$]glutaronitrile III in 71 % yield. The crude material was cyclized in acetic acid saturated with hydrogen bromide at room temperature and 2-amino-6-bromo-[2,6-$^{14}C_2$]pyridine IV with a 97.5 % HPLC purity was isolated in 67 % yield. Hydrogenation gave 2-amino-[2,6-$^{14}C_2$]pyridine in 76 % yield of 99.1 % purity by HPLC.



Scheme I

EXPERIMENTAL

Methods and Materials

Radioactivity measurements, determination of the radiochemical purity (elution took place with a linear gradient running from 100 % of water:diisopropylamine 100:0.2 by volume to 100 % of acetonitrile:diisopropylamine 100:0.2, by volume) and thin layer chromatography (eluants: chloroform:methanol 90:10) were performed as described earlier (10).

Potassium-[^{14}C]cyanide (54 mCi) was obtained from ICI, Billingham, Cleveland (U.K.) at a specific activity of 53.4 mCi/mmol. It was diluted with unlabelled KCN to a specific activity of 5.4 mCi/mmol.

3-Hydroxy-[1,5-$^{14}C_2$]glutaronitrile III

A solution of $MgSO_4$.7 H_2O (2.24 g, 9.08 mmol) in water (1 ml) was cooled to 5-10° C. To it was slowly added a solution of potassium-[^{14}C]cyanide (649 mg, 9.98 mmol, 54 mCi) in water (2.75 ml). The mixture was stirred for 45 minutes at 5-10° C. Epichlorohydrin (392 µl, 5 mmol) was slowly introduced and the mixture was stirred for 72 hours at room temperature. Thorough extraction with ethyl acetate (30 ml) and solvent evaporation left a crude oil, which was used for the next reaction step without purification. It contained 38.3 mCi of radioactivity (71 % based upon [^{14}C]KCN).

2-Amino-6-bromo-[2,6-$^{14}C_2$]pyridine IV

A saturated solution of hydrogen bromide in acetic acid (5 ml) was cooled to 5° C. Crude III was slowly added onto the stirred solvent. After 15 min-

utes a precipitate was formed. At that time, the vessel containing the crude starting material was rinsed with acetic acid (3 x 0.4 ml) which was added to the mixture. After stirring for 1.5 h, the reaction mixture was cooled on an ice bath and made alkaline (pH 10) with 20 % sodium hydroxide. A precipitate formed and the reaction mixture was stirred for another 0.5 h at room temperature. It was then extracted with diethyl ether (5 x 25 ml). The combined organic layers were washed with water (20 ml), dried on magnesium sulphate, and evaporated at aspirator pressure on a water bath at 30° C. The residue contained IV (500 mg, 48 % based upon [^{14}C]KCN). The product had a specific activity of 51 µCi/mg or 9.04 mCi/mmol and was 97.5 % radiochemically pure (HPLC).

2-Amino-[2,6-$^{14}C_2$]pyridine V

To a solution of IV (500 mg, 2.88 mmol) in ethanol (40 ml) was added powdered calcium oxide (270 mg, 4.83 mmol) and 10 % Pd on charcoal (200 mg). Debromination took place under hydrogen atmosphere and was complete within 1 hour. The reaction mixture was then filtered over dicalite and evaporated. The residue was dissolved, with cooling, in water (10 ml) and the solution was thoroughly extracted with chloroform (30 ml). The organic layer was dried on magnesium sulphate, filtered over dicalite and evaporated at 40° C under vacuum to leave V (215 mg, 2.19 mmol) in 76 % yield. The specific activity was 92.3 µCi/mg (9.06 mCi/mmol). The 2-amino-[2,6-$^{14}C_2$]pyridine was shown to be 99.2 % radiochemically pure by HPLC and showed only one spot by TLC.

ACKNOWLEDGEMENT

The authors gratefully acknowledge W. Verluyten for HPLC analyses and B. Wouters for typing the manuscript.

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