SYNTHESIS OF 2-PYRROLIDINONE-5-^{14}C.

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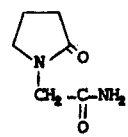
SUMMARY

A convenient synthesis of the pharmacological intermediate 2-pyrrolidinone-5-^{14}C, was developed using potassium cyanide-^{14}C as starting material. Potassium cyanide-^{14}C was converted to 2-pyrrolidinone-5-^{14}C in an overall 56% radiochemical yield.

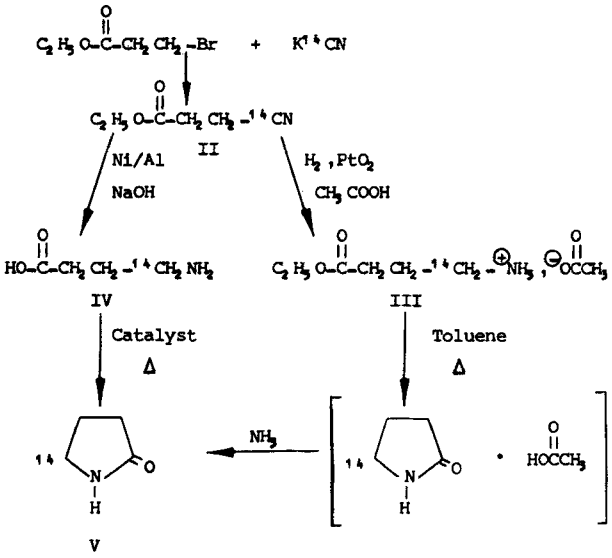
INTRODUCTION

Our work in the preparation of carbon-14 labelled 2-pyrrolidinone ring system was initiated in association with a program of investigation of a possible memory and performance enhancing agent; namely, 2-oxo-1-pyrrolidine acetamide (I).



I

Since a carbon-14 label in the side chain was deemed undesirable, from a standpoint of metabolic stability, our attention was directed to the specific labelling of the pyrrolidine ring. To our knowledge this ring has never been labelled in the 5 position with carbon-14. We wish to report the synthesis of 2-pyrrolidinone-5-^{14}C utilizing the following sequence of reactions.



Potassium cyanide-^{14}C was reacted with ethyl 3-bromopropionate in absolute ethanol to give II.[1] The catalytic hydrogenation of II was effected using platinum oxide catalyst in glacial acetic acid/ethanol. The reduction, a modification of the procedure of Pichat[2], gave exclusively the mono amine III. The use of other catalysts or other reducing agents, such as diborane, 5% rhodium or alumina, nickel/aluminum alloy were either unsuccessful or resulted in hydrolysis of the ester group.

The desirability of maintaining the ester function was enhanced by

the difficulty encountered in the ring closure of 4-aminobutyric acid (IV), the product from the nickel/aluminum alloy reduction.[3] This ring closure[4] necessitated heating the amino acid (IV) in a microdistillation apparatus to temperature exceeding 200°C with a catalyst (Table I), while collecting the distillate (V) as a hydrate.

TABLE I

Cyclization of 4-Aminobutyric Acid (IV)

4-Aminobutyric acid (g)	0.5	0.5	0.5	0.3
Catalyst (g)	None	Li_2CO_3 (0.15)	$MgSO_4$ (0.2)	$MgSO_4$ (0.12)
Yield (%)	27	65	63	80*

*Yield maximized by rinsing distillation condenser with alcohol.

By contrast, the acetate salt of the amino ester (III) produced an excellent yield of 2-pyrrolidinone-5-^{14}C by refluxing in toluene for ten minutes. In our initial development work, the isolation of V was attempted via vacuum distillation. This resulted in considerable loss of product and also produced a 1:1 azeotropic mixture of 2-pyrrolidinone and acetic acid. In the improved synthesis, the reaction mixture was neutralized with anhydrous gaseous ammonia and the product (V) isolated by evaporation of the solvent.

The resulting 2-pyrrolidinone-5-^{14}C (Fig. 1), which was pure enough for subsequent reactions, was converted to I (specific activity 4.1 mCi/mM) by successive reaction with ethyl bromoacetate and methanolic ammonia.[5,6]

EXPERIMENTAL

Radiochromatographic Data

All radioscans were taken on a Berthold Model 6000-10, employing a chart speed of 40"/hr; time const., 10 sec; slit-width, 1 mm. Segmentation was accomplished by liquid scintillation counting of 1/2 cm segments employing hexadecane-^{14}C as the internal standard.

Ethyl 3-cyanopropionate-4-^{14}C (II)[1]

To a stirred suspension of 50 mCi potassium cyanide-^{14}C (0.423 g, 6.5 mM) in 15 ml of absolute ethanol was added, in one portion, 0.905 g (5 mM) of ethyl 3-bromopropionate. The mixture was refluxed for seven hours, and then allowed to stir at room temperature for eighteen hours.

The potassium bromide was filtered and washed with 5 ml of glacial acetic acid. The radiochromatographic purity of the product was determined by thin-layer chromatography on silica GF using a solvent system of cyclohexane/ethyl acetate (60:40). The radiochemical purity was 98% and the product was used directly in the next step. Yields from a number of cold runs were 75-88% from potassium cyanide. The product was routinely 95-98% pure by vapor phase chromatography.

Ethyl 4-aminobutyrate-4-^{14}C, acetate salt (III)

To a prehydrogenated suspension of 0.7 g of platinum oxide catalyst in 50 ml of glacial acetic acid was added the above solution of ethyl 3-cyanopropionate-4-^{14}C, and the resultant mixture hydrogenated in a Paar shaker for five hours at 40 p.s.i. and room temperature.

The catalyst was removed by vacuum filtration through a layer of supercel, and the filtrate evaporated to dryness *in vacuo*. The excess glacial acetic acid was removed azeotropically with n-heptane *in vacuo*. A radiochromatographic purity of 99-100% was confirmed by thin-layer chromatography.

2-Pyrrolidinone-5-^{14}C (V)

The oily residue of ethyl 4-aminobutyrate-4-^{14}C, acetate salt (III) was dissolved in 75 ml of toluene and placed in a 100 ml round bottom flask equipped for downward distillation. The toluene solution was heated to reflux and maintained at this temperature for ten minutes. A distillate of 15 ml was collected. The toluene solution was cooled in a ice/water bath and anhydrous gaseous ammonia bubbled through the solution for

approximately two minutes.

The ammonium acetate was filtered and the filtrate evaporated to dryness in vacuo. The residue was dissolved in ether, dried over magnesium sulfate and filtered. The ether was removed in vacuo and the residual 2-pyrrolidinone-5-^{14}C weighed 0.31 g (28.2 mCi). The overall radiochemical yield was 56% and the product was 95% pure by thin-layer radiochromatography (Fig. 1). Yields from cold runs were in the range of 70-90% from ethyl 3-cyanopropionate. The product was routinely 95% pure by vapor phase chrc ·ography.

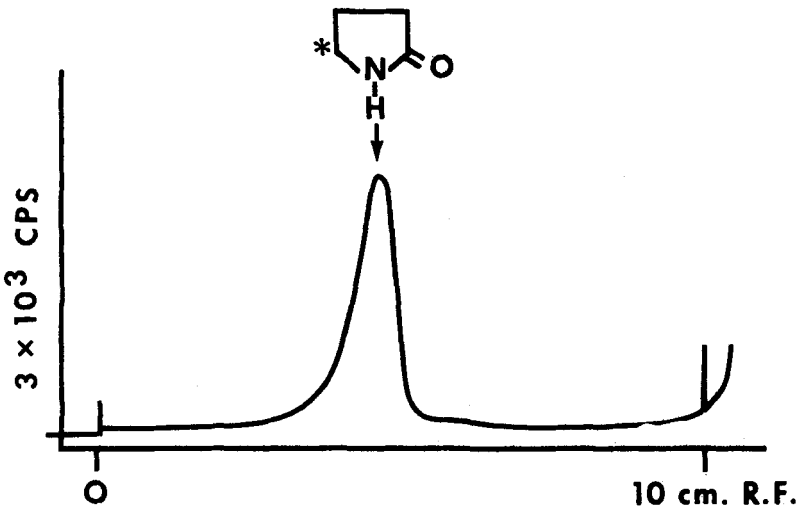


Fig. 1. Radiochromatogram of V.----Silica GF.
Solvent: Chloroform/methanol (90:10)

2-Oxo-1-pyrrolidine acetamide-5-^{14}C (I)

The 28.2 mCi of V was converted into 8 mCi of crude I (28.5% radiochemical yield) by successive reaction with ethyl bromoacetate and methanolic ammonia utilizing literature procedures.[5,6] This material was subsequently diluted and purified to give a first crop of I (3.1 mCi)

which melted at 150.5-152.5°C. The specific activity was 4.1 mCi/mM (0.029 mCi/mg).

The radiochromatographic purity of the product was determined by thin-layer chromatography (Fig. 2). A radiochemical purity of 99.5% was confirmed by segmentation.

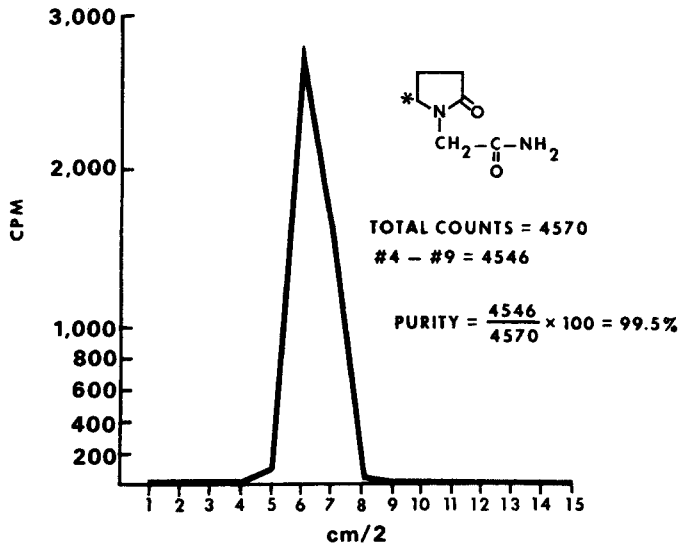


Fig. 2. Radiochromatogram of I.----Silica GF.
Solvent: chloroform/methanol/formic acid (50:50:3)

4-Aminobutyric acid (IV)

To a stirred solution of 0.46 g of ethyl 3-cyanopropionate (3.5 mM) in 9 ml of ethanol and 9 ml of 2 N sodium hydroxide (18 mM) at room temperature was added 1.5 g of nickel/aluminum alloy in one portion. The reaction exothermed to 50°C and stirring was continued for 1 1/2 hours. The catalyst was filtered off and washed with dilute sodium hydroxide and warm ethanol. The filtrate was concentrated to a small volume in vacuo, and adjusted to pH 7 with 10% hydrochloric acid. The inorganics were

removed by passing the solution through 50-100 mesh AG 50 WX 8 (15 ml bed volume) ion exchange column. The column was eluted with 1 N ammonium hydroxide and the eluates combined and lyophilized to give 0.28 g (78%) of product.

2-Pyrrolidinone (V) from 4-aminobutyric acid

To 0.3 g of 4-aminobutyric acid (2.8 mM) was added 0.12 g of magnesium sulfate catalyst and the finely dispersed reaction mixture placed in a microdistillation apparatus. The reaction flask was slowly heated (oil bath) to 210-230°C, and distilled to dryness. The product weighed 0.24 g (80%) and was found to contain one equivalent of water of hydration. The product was 98% pure by vapor phase chromatography.

ACKNOWLEDGEMENTS

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