RAPID SYNTHESIS OF ^{14}C LABELLED 4(5)-AMINO-5(4)-IMIDAZOLE-CARBOXAMIDE

E. Koltai, D. Bánfi, I. Szatmári*, Maria Hornyák-Hámori*, J. Schawartz* and T. Szüts*

Institute for Drug Research, H-1325 Budapest, POB 82, HUNGARY

SUMMARY

4(5)-Amino-5(4)-imidazole-2-^{14}C-carboxamide was prepared in a two step synthesis. $K^{14}CN$ was converted into ethyl formimidate-^{14}C hydrochloride, which was reacted with 2-amino-2-amidino-acetamide dihydrochloride to give the desired product.

Key Words: Ethyl formimidate-^{14}C hydrochloride, 4(5)-amino-5(4)-imidazole-2-^{14}C carboxamide

INTRODUCTION

4(5)-Amino-5(4)-imidazolecarboxamide (AICA) phosphate is a useful liver protecting agent.[1] It has been investigated biologically since the early fifties.[2] The synthesis of labelled AICA containing ^{14}C in the 4(5) position of the imidazole ring is known[3,4] but the published method leads in a circuitous way to a substance possessing low specific activity and the yield was very poor.** Our synthesis contains only two steps and the

* CHINOIN Pharmaceutical Works Ltd.

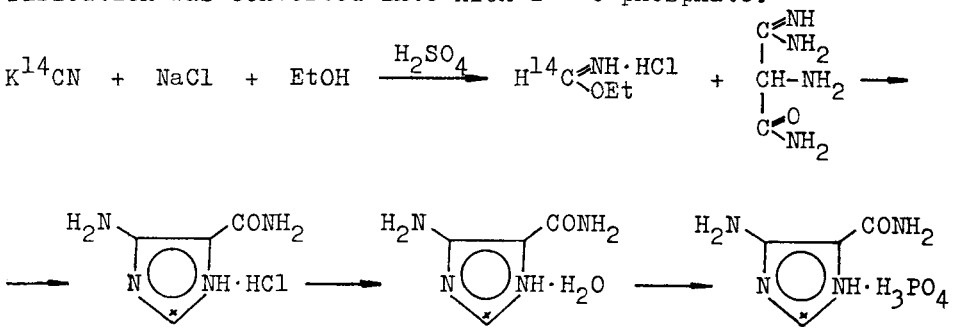
** The ring closure step of the synthesis gave only a 21 % yield.

0362-4803/79/0516-0777$01.00

Received November 8, 1978

compound was prepared in high yield.

First ethyl formimidate-^{14}C hydrochloride was prepared by the modification of Pinner's method.[5] Gaseous H^{14}CN and HCl was generated from a mixture of K^{14}CN and NaCl by conc. H_2SO_4 in a vacuum manifold and this mixture gave ethyl formimidate-^{14}C hydrochloride with ethanol. Then ethyl formimidate-^{14}C hydrochloride was reacted with 2-amino-2-amidino-acetamide dihydrochloride to AICA-2-^{14}C hydrochloride, which after purification was converted into AICA-2-^{14}C phosphate.



EXPERIMENTAL

Melting points are uncorrected. Chromatography was carried out on Kieselgel $PF_{254+366}$ (MERCK) plates. For detection of the radioactive materials autoradiography with FORTE X-ray film and a Berthold LB 2723 scanner were used. Activity was measured by a Packard TRİ-CARB scintillation system.

Ethyl formimidate-^{14}C-hydrochloride

A reaction flask containing 0.58 ml (460 mg, 10 mmoles) of abs. ethanol was connected to a vacuum manifold. After its freezing with liquid nitrogen a mixture of H^{14}CN and HCl liberated from 652 mg (10.0 mmoles, 76.34 mCi) of K^{14}CN and 590 mg (10.2 mmoles) of NaCl, respectively, was introduced. Then the manifold was allowed to attain normal pressure and the reaction flask was warmed to 0^{o}C and kept at this temperature for 24 hrs. Crystallization began at the second hour and the following day it was complete. The yield was 1.10 g (nearly

quantitative), 76.3 mCi.*

4(5)-Amino-5(4)-imidazole-2-^{14}C-carboxamide hydrochloride

Methanol (10 ml) was added into the reaction flask containing the above ethyl formimidate-^{14}C hydrochloride (1.10 g, 10 mmoles) and the mixture was stirred at room temperature for 15 minutes. Ethyl formimidate dissolved slowly, then white crystals separated. Then urea (0.66 g, 11 mmoles) and 2-amino-2-amidino-acetamide dihydrochloride** (1.89 g, 10 mmoles) were added and the mixture was stirred and refluxed for 2.5 hours, then the stirring was continued at room temperature for 2 hours and the mixture was kept at 0°C overnight. The next day the mixture was filtered off and the crystals were washed with cold ethanol (5 ml); 1.485 g (9.1 mmoles, 91 %) AICA hydrochloride was obtained. The material contained urea and other impurities.

4(5)-Amino-5(4)-imidazole-2-^{14}C-carboxamide phosphate

The crude AICA-2-^{14}C hydrochloride was dissolved in water (3 ml) and solid $NaHCO_3$ (0.84 g, 10 mmoles) was added in small portions.*** After the addition crystallization began. The mixture was kept at 0°C for 2 hours, filtered off and the crystals**** were washed with 1 ml of ice water.***** The crystals were dissolved in hot ethanol (5 ml) and a mixture of 85 % phosphoric acid (0.3 ml) and ethanol (1.2 ml) was added. The separated crystals were recrystallized from 50 % ethanol (5 ml), treated with

* The material obtained in this way was identical with the material prepared by the Ohme's method.[6]

** Prepared by Smith's and Yates's method.[7]

*** If the solution is bubbling after the last portion, more $NaHCO_3$ (10-20 mg) was added.

**** The crystals of AICA-2-^{14}C monohydrate showed only one spot upon TLC (toluene-xylene-dioxan-isopropanol-conc. NH_4OH 1:1:3:3:1)

***** By adding inactive AICA monohydrate to the mother liquor a second crop was obtained with low specific activity.

charcoal and 0.510 g (2.27 mmoles) of AICA-2-^{14}C phosphate were obtained. M. p.: 193-196°C (lit.[8]: 190°C). Measured activity: 15.19 mCi. Radiochemical yield: 19.9 %. The material showed only one spot on a TLC plate (tetrahydrofuran-isopropanol-conc. NH_4OH 5:3:2).

ACKNOWLEDGEMENTS

The authors wish to thank Mrs. Maria Kaizler and Z. Sebesi-Sütő for technical assistance.

REFERENCES

1. K. Szepesházi, K. Lapis, A. Jeney, B. Szende, J. Schawartz, E. Ujhelyi, J. Takács, I. Kovalszky and A. Tompa: Kisérletes Orvostudomány (Experimental Medicine) 30, 195 (1978).
2. M.P. Schulman, J.M. Buchanan and C.S. Miller: Fed. Proc. 9, 225 (1950).
3. C.S. Miller, S. Gurin and D.W. Wilson: Science 112, 654 (1950).
4. C.S. Miller, S. Gurin and D.W. Wilson: J. Am. Chem. Soc. 74, 2892 (1952).
5. D.G. Neilson: Imidates Including Cyclic Imidates p. 385, in "The Chemistry of Functional Groups" (S. Patai editor), Wiley, 1975, New York.
6. R. Ohme and E. Schmitz: Angew. Chem. 79, 531 (1967).
7. L.H. Smith and P. Yates: J. Am. Chem. Soc. 76, 6080 (1954).
8. J. Schawartz and Maria Hornyák-Hámori: Hung. Pat. 164 397 (1971).