SYNTHESIS OF 2-AMINO-7-ISOPROPYL-5-OXO-5H-[1]BENZOPYRANO-[2,3-b][2-^{14}C]PYRIDINE-3-CARBOXYLIC ACID (AA-673-^{14}C)

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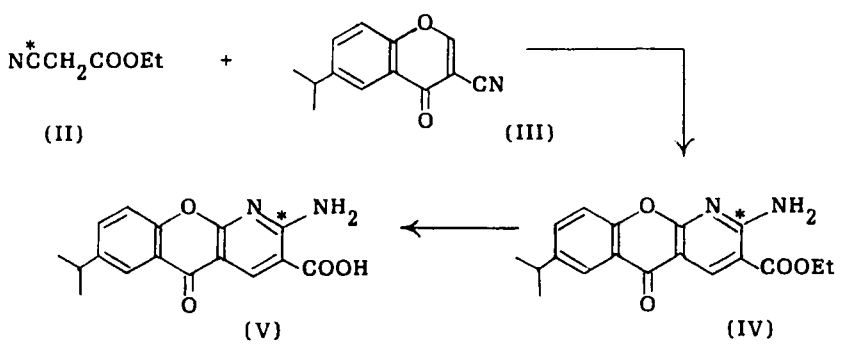
2-Amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylic acid (AA-673) was found in these laboratories during the course of the studies on antiallergic agents. It exhibited an inhibiting activity against both the passive cutaneous anaphylaxis reaction in rats and the Arthus type allergy upon oral and intravenous administrations.[1]

This paper deals with the synthesis of 2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b][2-^{14}C]pyridine-3-carboxylic acid (V) for the study of the metabolic fate in animals. According to the procedure reported by Mandel and Brown,[2] the reaction of K^{14}CN (I) with chloroacetic acid gave [^{14}C]cyanoacetic acid, which was esterified with ethanol in the presence of conc H_2SO_4 to afford ethyl [^{14}C]cyanoacetate (II) in 67 % yield based on I.



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6-Isopropyl-4-oxo-4H-1-benzopyran-3-carbonitrile (III) was reacted with II in the presence of piperidine to give ethyl 2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b][2-^{14}C]pyridine-3-carboxylate (IV) in 84 % yield based on II. Hydrolysis of IV in a mixture of acetic acid and 50 % H_2SO_4 gave V having a specific activity of 913.16 MBq/mmol. The overall radiochemical yield of V was 44 % based on I.

EXPERIMENTAL

Ethyl [^{14}C]cyanoacetate (II)

A mixture of chloroacetic acid (95 mg) in 1N K_2CO_3 (1 ml) and 925 MBq (64.9 mg) of K^{14}CN was stirred at room temperature for 40 min, and the mixture was then heated to 80-90° c for 50 min. The mixture was acidified with 2N HCl (0.5 ml) and evaporated in vacuo. The residue was dissolved in EtOH (20 ml) and insoluble potassium chloride was removed by filtration. The filtrate was evaporated in vacuo to give a residue, which was dissolved in a mixture of dried EtOH (5 ml) and conc H_2SO_4 (0.06 ml). The solution was refluxed for 2 h and neutralized with 2N K_2CO_3 under cooling in an ice-water bath. Evaporation of the solution in vacuo left a residue, which was extracted with ether (3 x 10 ml). The extract was dried and concentrated to give 76 mg (67 % yield) of II.

Ethyl 2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b][2-^{14}C]pyridine-3-carboxylate (IV)

A mixture of II (76 mg), piperidine (60 mg) and 6-isopropyl-4-oxo-4H-1-benzopyran-3-carbonitrile (143 mg) in 2 ml of EtOH was refluxed for 1.5 h and then allowed to stand at room temperature overnight. After the mixture was cooled in an ice bath, the crystals which precipitated were filtered off, washed with EtOH and dried in vacuo. IV was obtained in 84 % yield (184 mg) based on II.

2-Amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b][2-^{14}C]pyridine-3-carboxylic acid (V)

A mixture of IV (184 mg) in acetic acid (1.2 ml) and 50% H_2SO_4 (1.2 ml) was heated at 130° c for 5 h with stirring and allowed to stand at room temperature overnight. The mixture was diluted with 20 ml of ice water to afford white crystals, which were dissolved in water (50 ml) containing triethanolamine (200 mg). The solution was extracted with ethyl acetate (25 ml). The aqueous layer was acidified with conc HCl and extracted with ethyl acetate. The combined extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from EtOH to yield V (135 mg) having a specific activity of 913.16 MBq/mmol. Identity of V was confirmed by its Rf-value (0.53) on TLC and the retention time of HPLC (8.25 min) with that of an authentic sample. The radiochemical yield was 44% based on I at a radiochemical purity greater than 99.5%.

Analytical procedure of V

TLC plates were 20 cm glass plate precoated with silica gel 60 (Merck) and developed in a mixture of chloroform, acetone and formic acid (20:10:1, v/v). The radioactivity on the TLC was measured with an Aloka JTC-203 radioscanner system. The HPLC system equipped with an UV detector (254 nm) and a 0.4 x 15 cm column packed with Nucleosil 5C18 was operated as follows: pressure 100 Kg/cm^2; flow rate 1.2 ml/min; temperature 22° c; mobile phase, a mixture of phosphate buffer (pH 8.0) and acetonitrile (35:10, v/v). The radiochemical purity was determined by counting the radioactivity in each effluent (0.25 ml collection) of the HPLC using an Aloka LSC-671 liquid scintillation spectrometer.

REFERENCES

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