SYNTHESIS OF [CARBONYL-^{14}C]HEXOPAL

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SUMMARY

A synthetic procedure for producing [carbonyl-^{14}C]Hexopal (meso-inositol [carbonyl-^{14}C]nicotinate) is described. The synthesis is achieved in two steps using [carbonyl-^{14}C]nicotinic acid as the source of the radiolabel with an overall chemical yield of 75% and a radiochemical yield of 67%.

Key words: Peripheral vasodilator, Carbon-14, Synthesis, Hexopal, meso-inositol nicotinate.

Introduction

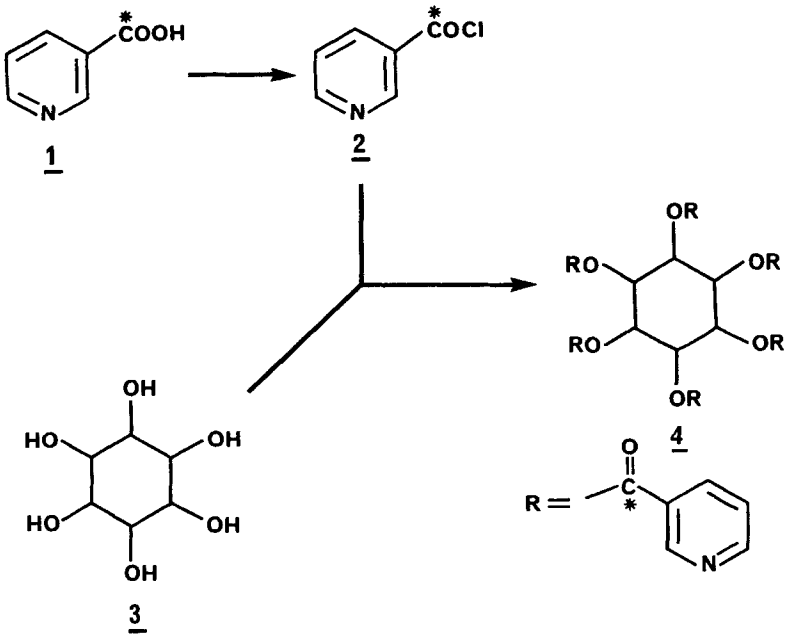
Hexopal[1] (meso-inositol nicotinate)[2] is well established in the treatment of circulatory and peripheral vascular disorders[3]. As part of our ongoing studies on this compound a quantity of ^{14}C labelled material was required for metabolism and drug disposition studies. Studies using radiolabelled meso-inositol nicotinate have been previously reported, however, the synthetic and analytical data were not comprehensively detailed[4].

Results and Discussion

The synthetic procedure used, which is shown in the reaction scheme, began with the preparation of [carbonyl-^{14}C]nicotinoyl chloride by treating commercially available [carboxyl-^{14}C]nicotinic acid with phosphorus oxychloride in pyridine.

0362–4803/89/010103–04$05.00

Received May 13, 1988
Revised June 28, 1988



Scheme

During a series of optimisation experiments it was confirmed, as noted previously[1], that the yield of the desired product was maximised by using an excess of phosphorus oxychloride during the first stage of the reaction. However, though the yields were better, the quality of the material obtained was adversely affected by the use of a significant excess, with the melting point being depressed by 2-3 °C, and the impurity level being increased by approximately 2%. Accordingly, a half molar equivalent excess of phosphorus oxychloride was used in the generation of the nicotinoyl chloride(2). The meso-inositol(3) was added to a solution of the acid chloride in a stepwise fashion and the crude product was precipitated from the hot solution on the addition of water. Subsequent purification by preparative thin layer chromatography gave the desired product, 4.

Experimental

Melting points are uncorrected. Infrared (IR) spectra (KBr dispersion) were recorded with a Perkin Elmer 177 spectrophotometer. Ultraviolet (UV) spectra were recorded on a Beckmann spectrophotometer. Radioactivity measurements were performed on a Packard TRICARB 300C counter using Instagel as the counting medium.

[Carboxyl-^{14}C]nicotinic acid was supplied by Amersham International plc with a *nominal* activity of 56 mCi/mmol.

[Carbonyl-^{14}C]Hexopal

Nicotinic acid (495 mg, 4.02 mmol) and [carboxyl-^{14}C]nicotinic acid (2 mCi, 56 mCi/mmol) were suspended in dry Aristar pyridine (1.33 ml) under nitrogen atmosphere and phosphorus oxychloride (186 ul, 2.03 mmol) was added dropwise via a syringe and septum to the stirred mixture. The temperature of the mixture rose to 60°C and was maintained at this temperature for one hour. meso-Inositol (122.5 mg, 0.68 mmol) was added gradually so that the temperature did not exceed 50°C. The reactants were maintained at this temperature for three hours and then distilled water (2.5 ml) was added slowly with stirring. After thirty minutes the precipitated solid was collected by filtration, washed with water (10 x 2.0 ml) and acetone (3 x 2.0 ml) and dried under vacuum for twelve hours to give crude [carbonyl-^{14}C]Hexopal as a white solid (439 mg, 80%).

Purification of [carbonyl-^{14}C]Hexopal

The crude product (80 mg) was dissolved in a mixture of chloroform and methanol (90:10 v/v, 2 ml) and applied onto the preabsorbent area of a Whatman Type PLK5F preparative TLC plate. The plate was developed for a distance of 16.5 cm in an unsaturated TLC tank using chloroform : methanol (90:10 v/v). The plate was removed from the tank and allowed to dry without heating. The band containing [carbonyl-^{14}C]Hexopal was collected and was slurried with chloroform : methanol (90:10 v/v, 40 ml) for thirty minutes. The silica was removed by filtration and the filtrate was retained. The TLC procedure was repeated until all of the crude product had been processed and the combined filtrates were evaporated to dryness under reduced pressure to 4 as a white crystalline solid (413 mg, 0.51 mmol, 2.88 mCi/mmol) with a radiochemical purity of at least 99% by TLC on Merck Silica GF 254 in the following systems.

1. Chloroform : methanol (90:10), Rf : 0.35
2. Ethyl acetate : methanol : acetic acid : water (50:5:5:5), Rf 0.23

The TLC, IR, UV and melting point properties of the product were shown to be identical to those of an authentic sample of 4.

References

1. British Patent 1,053,689

2. C.O. Badgett and C.F. Woodward, J. Amer. Chem. Soc., 1947, 69, 2907

3. B. Goldstein, J.G. Burnet-Merlin, A.I. Herszkiowiez, E.B. Fernandez, and J.C. Galeano, La Semana Medica, 1966, 128, 502

4. R. Brattsand and L. Harthon, Arzneimittel-Forsch, 1971, 21, 1335.