

NOTE

SYNTHESIS OF 3-([carbonyl-¹⁴C]p-anisoyl)-1-(2-morpholinoethyl)-2-methylindole maleate

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SUMMARY

A synthetic procedure for producing 3-([carbonyl-¹⁴C]p-anisoyl)-1-(2-morpholinoethyl)-2-methylindole maleate is described. The synthesis is achieved in two steps from 1-(2-morpholinoethyl)-2-methylindole utilising [carbonyl-¹⁴C]p-anisoyl chloride as the source of the radiolabel with an overall chemical yield of 39% and a radiochemical yield of 28%.

Key words: Analgesic, Carbon-14, Synthesis, 3-(p-anisoyl)-1-(2-morpholinoethyl)-2-methylindole maleate

INTRODUCTION

3-([Carbonyl-¹⁴C]p-anisoyl)-1-(2-morpholinoethyl)-2-methylindole maleate is a potent novel analgesic which is currently undergoing evaluation. As part of the development programme a quantity of ¹⁴C-labelled material was required for metabolism and drug disposition studies.

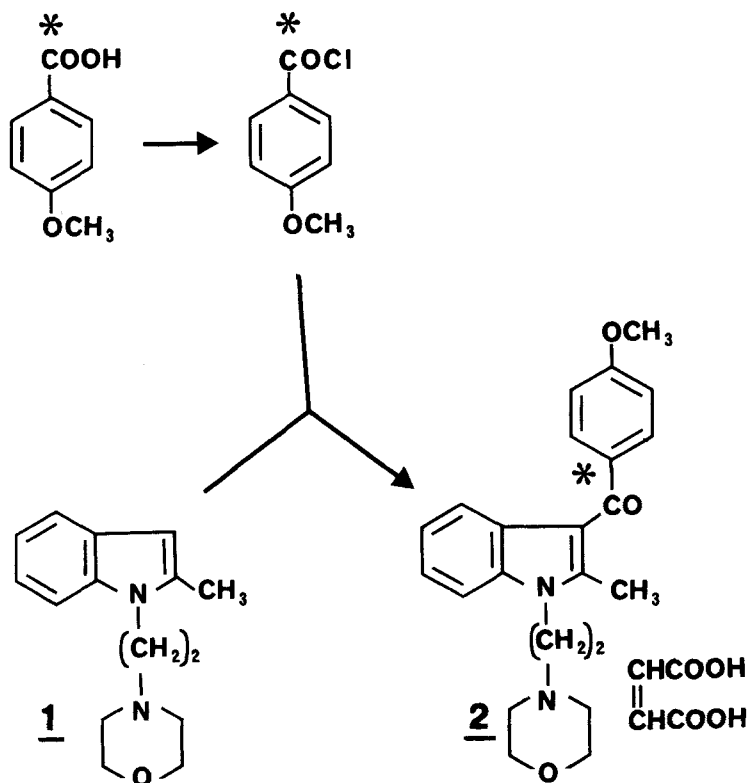
The synthetic procedure used, which is shown in the reaction scheme, began with the preparation of [carbonyl-¹⁴C]p-anisoyl chloride from commercially available [carboxyl-¹⁴C]p-anisic acid. The reaction of the acid chloride with 1-(2-morpholinoethyl)-2-methylindole, 1, in the

presence of aluminium chloride led to the formation of the hydrochloride salt of the required product. This was readily converted to the free base and addition of maleic acid gave the desired product 2.

EXPERIMENTAL

Melting points are uncorrected. Infrared (IR) spectra (KBr dispersions) 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 (Packard) as counting medium.

[Carboxyl- ^{14}C]p-anisic acid was supplied by Physics and Radioisotopes Services, Imperial Chemical Industries, Billingham, Cleveland.



3-((Carboxyl-¹⁴C)p-anisoyl)-1-(2-morpholinoethyl)-2-methylindole hydrochloride

To a 1 ml micro reaction vial were added [carboxyl-¹⁴C]p-anisic acid (8 mCi, 73.5 mg, 0.483 mmol), thionyl chloride (100 μ l, 2.92 mmol) and N,N-dimethylformamide (10 μ l, 0.13 mmol). The resulting brown solution was stirred for 0.5 h at ambient temperature using a calcium chloride tube to protect against moisture. The excess thionyl chloride was removed at 50°C under reduced pressure to yield a dark brown liquid. This liquid was dissolved in dry dichloromethane and transferred to a 5 ml reaction vial containing unlabelled anisoyl chloride (118 mg, 0.69 mmol) and aluminium chloride (156 mg, 1.17 mmol) in dry dichloromethane (1 ml). The resulting black solution was added dropwise to a solution of 1-(2-morpholinoethyl)-2-methylindole, 1, (244 mg, 1.0 mmol) and aluminium chloride (85 mg, 0.63 mmol) in dry dichloromethane (2 ml) in a 10 ml reaction vial. All residual traces of the ¹⁴C-labelled acid chloride were dissolved in dichloromethane (1 ml) and this was also added to the solution of 1. The mixture was stirred for 1.25 h distilled water (2.5 ml) was added dropwise and the resulting slurry was stirred for 1 h. The precipitate was collected by filtration, washed with distilled water (1 ml) and then acetone (2 x 1 ml), before being dried at 60°C under reduced pressure for 12 h. This yielded 218 mg (53%) of crude hydrochloride salt product as a purple crystalline solid which was used without further purification.

3-((Carboxyl-¹⁴C)p-anisoyl)-1-(2-Morpholinoethyl)-2-methylindole maleate, 2,

The crude hydrochloride salt was treated with a mixture of ethyl acetate : 0.88 ammonia (4:1 by vol; 5 ml). The ethyl acetate layer was carefully removed, transferred to a flask and magnesium sulphate (100 mg) and charcoal (20 mg) were added. Following stirring for 10 mins the solution was filtered through a glass fibre filter paper.

The filter paper was washed with ethyl acetate (2 x 5 ml) and the combined filtrates were evaporated to dryness under reduced pressure. The pale pink solid residue was dissolved in ethanol (1 ml) by warming on a water bath to 65°C. To this solution was added a solution of maleic acid (55.5 mg, 0.478 mmol) in ethanol (235 μ l) which had been warmed to 55°C. The solution was seeded with a crystal of 2, and allowed to cool to room temperature with stirring. The solution was further cooled in an ice/acetone bath. The material which crystallised out was collected by filtration, washed with cold ethanol (1 ml) and then dried in a vacuum oven at 65°C under reduced pressure for 48 h. This gave 3-([carbonyl-¹⁴C]p-anisoyl)-1-(2-morpholinoethyl)-2-methyl-indole maleate as pale fawn coloured crystals (190 mg, 0.384 mmol, 5.74 mCi/mmol) with a radiochemical purity of at least 98% by TLC on Merck Silica GF-254 in the following systems:

- i) Ethyl acetate : methanol (96:4), R_f : 0.43
- ii) Chloroform : ethanol : isopropylamine (96:3:1), R_f : 0.36

The TLC, IR and UV properties of the product were shown to be identical to those of an authentic sample of product 2.