# A SYNTHESIS OF DL-erythro-2-(4-BENZYLPIPERIDINO)-1-(4-HYDROXYPHENYL)-[1-$^{14}$C]PROPAN-1-OL L-(+)-TARTRATE

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SUMMARY

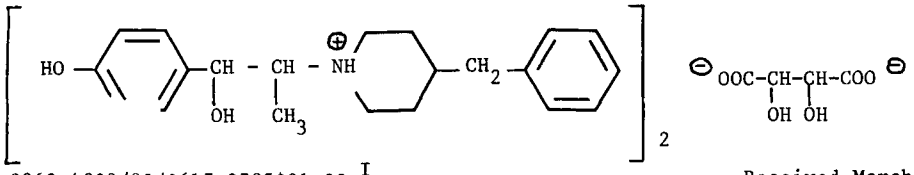
The preparation of DL-erythro-2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-[1-$^{14}$C]propan-1-ol L-(+)-tartrate, Ifenprodil tartrate (Vadilex ®) from barium [$^{14}$C]carbonate is described. The product was obtained in 29.2 % radiochemical yield and at a specific activity of 47.6 mCi/mmol. This was diluted to 2 and 1 mCi/mmol for metabolism and distribution studies in man. The radiochemical purity of the diluted product exceeded 99 %.

Key words : Ifenprodil tartrate, Carbon-14, Synthesis.

## INTRODUCTION

DL-erythro-2-(4-Benzylpiperidino)-1-(4hydroxyphenyl)-propan-1-ol L-(+)-tartrate, Ifenprodil tartrate (Vadilex ®) (I) is used as a potent peripheral and cerebral vasodilator having an α-adrenergic blocking activity, spasmolytic action and antiarrhytmic activity [1]. Several pharmacological studies of this drug have been carried out in animals [1-6] illustrating the above effects.

Ifenprodil tartrate (I) radiolabelled with carbon-14 was required for metabolism and distribution studies in man. This compound was prepared as outlined in the scheme.



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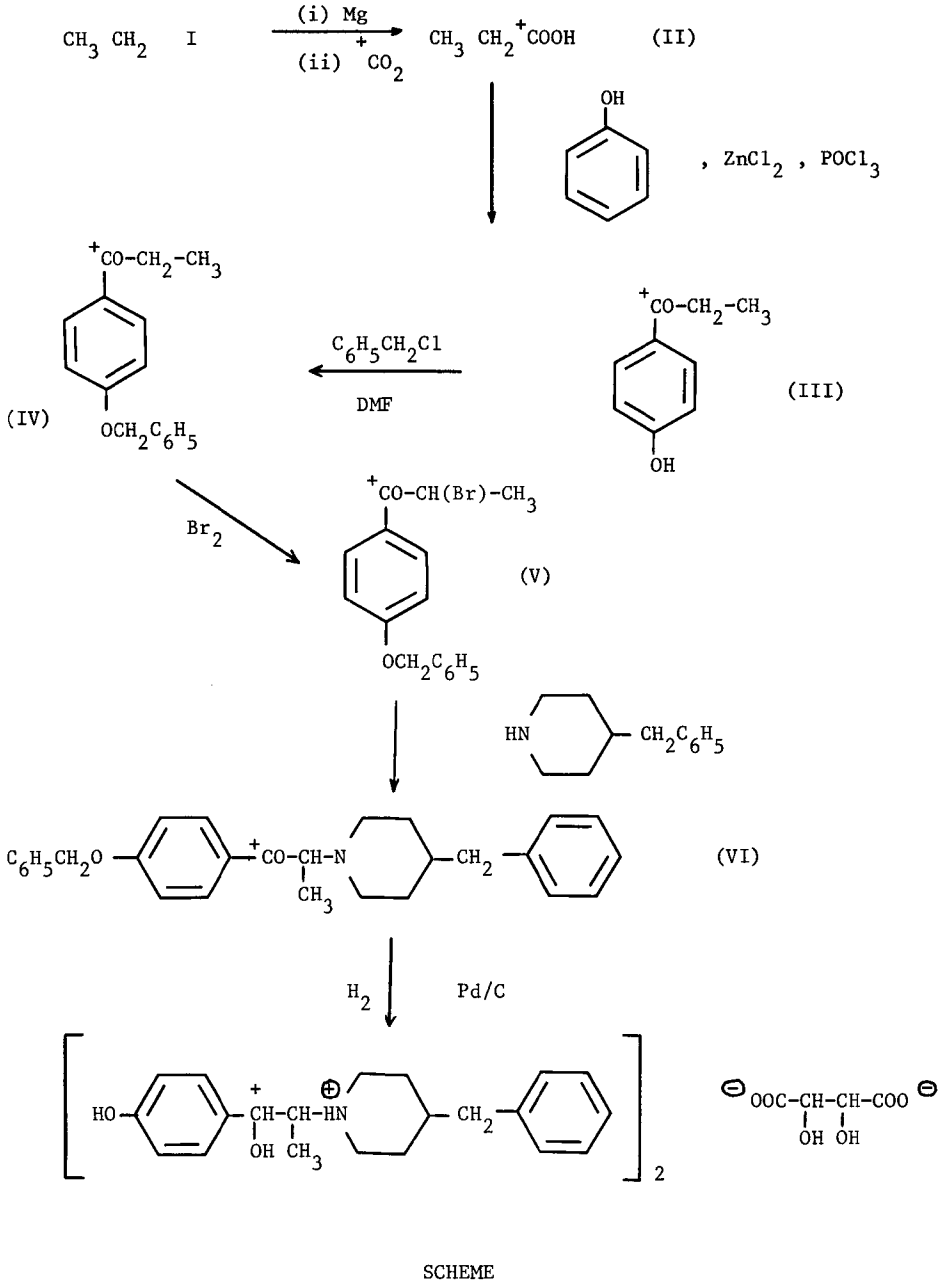
CH3 CH2 I
(i) Mg
(ii) CO2
CH3 CH2 COOH
(II)
OH
, ZnCl2 , POCl3
CO-CH2-CH3
C6H5CH2Cl
DMF
(III)
(IV)
OCH2C6H5
Br2
CO-CH(Br)-CH3
(V)
HN
CH2C6H5
C6H5CH2O
CO-CH-N
CH3
CH2
(VI)
H2
Pd/C
HO
CH-CH-HN
OH CH3
OOC-CH-CH-COO
OH OH
2

SCHEME

## D I S C U S S I O N

Initial experiments carried out on cold material showed that highest yields of the intermediate 4-hydroxypropiophenone (III) are obtained from barium carbonate via the Friedel-Crafts reaction of propionic acid with phenol. An alternative route via 4-benzyloxybenzoic acid prepared by carbonation of the Grignard reagent from 4-benzyloxybromobenzene and subsequent treatment of the corresponding acid chloride with dialkylcadmium gave inferior yields.

[1-$^{14}$C] Propionic acid was prepared from barium [$^{14}$C]carbonate in a similar manner to the previously described method [7]. This was then reacted with phenol in the presence of zinc chloride and phosphorus oxychloride to afford 4-hydroxy-[1-$^{14}$C]propiophenone (III) which was purified by preparative layer chromatography. Treatment with benzyl chloride in DMF (110°/1 hour) afforded the benzyl ether (IV) in quantitative yield, which on bromination in acetic acid gave the 2-bromoketone (V). Subsequent condensation with 4-benzylpiperidine in ethanol under reflux for 2 hours afforded 4-benzyloxy-2-(4-benzylpiperidino)-[1-$^{14}$C]propiophenone (VI) which was purified by column chromatography on silica.

Cleavage of the benzyl ether and concomitant reduction of the ketone function by hydrogenation at room temperature and atmospheric pressure in methanol in the presence of 0.5 mole equivalent of L-(+)-tartaric acid afforded DL-<u>erythro</u>-2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-[1-$^{14}$C]propan-1-ol L-(+)-tartrate (29.2 mCi) at a specific activity of 49.7 mCi/mmol and a radiochemical purity of 97 %. A portion of this was then diluted with inactive carrier to 2 and 1 mCi/mmol for use in clinical studies. Recrystallisation of the diluted material then gave the desired compound with a radiochemical purity greater than 99 %.

The product was identical to an authentic sample of Ifenprodil tartrate.

## EXPERIMENTAL

Ether, which refers to diethyl ether, and DMF, when required dry, were stored over 4A molecular sieves. All reagents used were of analytical quality. Zinc chloride was freshly ground and dried in a vacuum desiccator over calcium chloride for 2 hours prior to use. Merck silica gel 60 (70-230 mesh) was used for column chromatography. The plates used for thin and preparative layer chromatography were Merck precoated silica gel GF 254, 0.25 mm for the former and 2.0 mm for the latter.

Barium [$^{14}$C]carbonate was purchased from CEN-Saclay, Gif-sur-Yvette, France. Samples were counted on a Searle Mark III counter using Instagel (Packard) as counting medium. The photographic film used for autoradiography was Kodak "Kodirex" X-ray film.

The solvent systems used for chromatography were as follows :

a) benzene : ethyl acetate (80:20)

b) petroleum ether (b.p. 60-80) : chloroform : acetone (15:60:25)

c) benzene : acetic acid : methanol (45:4:8)

d) methanol : 0.88 ammonia (100:1.5)

### [1-$^{14}$C]Propionic Acid (II)

The Grignard reagent was prepared from magnesium (0.51 g, 21 mmole) in 15 ml of dry ether to which was slowly added redistilled ethyl iodide (1.6 ml, 20 mmole) in 15 ml of dry ether. The reaction mixture was allowed to reflux for 30 minutes.

[$^{14}$C]Carbon dioxide (100 mCi, 1.9 mmole) was generated from barium [$^{14}$C]carbonate in the usual way [8] on a vacuum manifold and was dried over phosphorus pentoxide.

The Grignard solution (3.8 ml, 2.3 mmole) [9] was transferred by syringe to the reaction vessel which was immediately attached to the manifold and the reaction mixture frozen with liquid nitrogen. The [$^{14}$C]carbon dioxide (100 mCi) was vacuum transferred to the reaction vessel and the reaction

mixture stirred at -20°C for 1 hour. Nitrogen was bled into the manifold and water (1.4 ml) followed by 10 % sulphuric acid (2.8 ml) was added to the product which was then stirred for 15 minutes.

The product was extracted with ether (4 x 10 ml) and the combined ether layers were washed with a dilute solution (1 %) of sodium dithionite. The dithionite solution was then back extracted with three portions of ether which were combined with the main ether fraction. The solution was dried, filtered and the ether evaporated under a gentle stream of $N_2$. This was then used directly for the next stage.

4-Hydroxy [1-$^{14}$C]propiophenone (III)

To the [1-$^{14}$C]propionic acid from the previous stage was added phenol (0.2 g, 2.12 mmole), redistilled phosphorus oxychloride (0.53 ml, 5.78 mmole) and zinc chloride (0.84 g, 6.16 mmole) and the reaction mixture heated at 59-60°C for three hours. The product was poured into ice water containing a little sodium dithionite (10 mg) and was extracted with four aliquots (4 x 10 ml) of ether, which were combined, washed with water and dried ($Na_2SO_4$). The solution was filtered, and the solvent then evaporated in vacuo. The residue was then purified by preparative layer chromatography in solvent system (a). The desired band was located under U.V. 254 nm, and the product eluted with ether to yield 4-hydroxy-[1-$^{14}$C]propiophenone (III) (160 mg, 1.05 mmole) which was dissolved in ethanol and counted (46.5 mCi). The radiochemical yield from barium [$^{14}$C]carbonate was 46.5 %.

4-Benzyloxy-[1-$^{14}$C]propiophenone (IV)

4-Hydroxy-[1-$^{14}$C]propiophenone (46.5 mCi, 160 mg) was dissolved in dry DMF (9 ml) and anhydrous potassium carbonate (159 mg, 1.15 mmole) followed by benzyl chloride (0.14 ml, 1.22 mmole) were added and the reaction mixture heated with stirring at 110°C for 1 hour.

The product was poured into water and extracted with three aliquots

of ether (3 x 15 ml). These were combined, washed with water and dried ($Na_2SO_4$). The solution was filtered and the ether evaporated in vacuo to afford 4-benzyloxy-[1-$^{14}$C]propiophenone (IV) (274 mg).

4-Benzyloxy-2-bromo-[1-$^{14}$C]propiophenone (V)

Glacial acetic acid (2.7 ml) and 27.3 mg of freshly ground aluminium chloride were added to 4-benzyloxy-[1-$^{14}$C]propiophenone (274 mg) and the mixture heated at 45° for 30 minutes. The temperature was lowered to 38°C and a solution of bromine (0.063 ml) in glacial acetic acid (0.45 ml) was added by syringe over a period of 15 minutes. The reaction mixture was left stirring at 38°C for 1 hour.

The product was transferred to iced water and was extracted with ether (4 x 10 ml). The ether layers were combined, washed with water and dried ($Na_2SO_4$). Evaporation of the ether in vacuo afforded the product which was dried in a vacuum desiccator over calcium chloride to constant weight (396 mg). This was used for the following stage without further purification.

4-Benzyloxy-2-(4-benzylpiperidino)-[1-$^{14}$C]propiophenone (VI)

4-Benzyloxy-2-bromo [1-$^{14}$C] propiophenone (396 mg) in ethanol (3.70 ml) was treated with 4-benzylpiperidine (0.45 ml) and the mixture heated under reflux for 2 hours. The product was diluted with water and extracted with ether (4 x 10 ml). The combined ether layers were washed with water, dried ($Na_2SO_4$) and evaporated to yield the product (41.1 mCi, 584 mg). Purification of the product was achieved by preparative layer chromatography in solvent system (b), the desired band located under U.V. 254 nm, and the product subsequently eluted with ether, followed by evaporation in vacuo. T.l.c. [solvent system (b)] indicated a radiochemical purity of 98 %.

A persistent slight yellow colouration was removed by passage

in benzene through a florisil column (15 x 1 cm, 60-100 mesh).

The solvent was evaporated in vacuo to afford the desired product (30.0 mCi, 269 mg) at 46.7 mCi/mmol in a radiochemical yield of 30 % from barium [$^{14}C$]carbonate.

DL-erythro-2-(4-Benzylpiperidino)-1-(4-hydroxyphenyl)-[1-$^{14}C$]propan-1-ol L-(+)-tartrate (I)

4-Benzyloxy-2-(4-benzylpiperidino)-[1-$^{14}C$]propiophenone (30.0 mCi, 269.4 mg) was dissolved in methanol (100 ml) and L-(+)-tartaric acid (49.2 mg) added, the mixture stirred until the solution was homogeneous and 10 % Pd/C (100 mg) was added. The mixture was then hydrogenated at atmospheric pressure and room temperature. After 15 hours a further 50 mg of Pd/C was added and the reaction continued for another 45 hours.

The reaction mixture was filtered through a 5 micron millipore filter to afford the desired product (29.2 mCi). This was analysed by tlc in systems (c) and (d) and found to have a radiochemical purity of 97 %. The radiochemical yield was 29.2 % from barium [$^{14}C$]carbonate and at a specific activity at 46.7 mCi/mmol.

A portion of the product (3.67 mCi) was removed and diluted with inactive carrier (700 mg) to 2 mCi/mmol. This was recrystallised from methanol to yield the product with a radiochemical purity greater than 99 %. A further dilution was undertaken on 200 mgs of this product to 1 mCi/mmol and these two diluted samples at 1 and 2 mCi/mmol were used for metabolic and clinical distribution studies.

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