# SYNTHESIS OF [$^{14}$C]2-PIPECOLINYL-5-AMINO-4'-CHLORO-BENZOPHENONE (LF.1695)

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## SUMMARY

Two synthetic routes lead to [$^{14}$C] LF.1695. The first one starts with labelled triphenyl methyl phosphonium iodide. This Wittig reagent reacts with benzyl piperidinone to afford benzylmethylidene piperidine 3 . The reduction of 3 gives labelled pipecoline 4 which is condensed with an adduct affording an intermediate nitro compound 5 . LF.1695 6 labelled at the methyl group is then obtained by catalytic reduction.

The second route uses labelled chloro-nitro benzoic acid as starting material. The treatment of the corresponding acid chloride by Friedel-Crafts reaction gives the chloro-nitro-chloro-benzophenone 9 in good yield. Condensation of 9 with pipecoline according to the method described above gives an intermediate nitro compound 10 which is reduced to afford LF.1695 11 labelled at the carbonyl group.

Key Words: LF.1695 $^{14}$C, Immunomodulator.

## INTRODUCTION

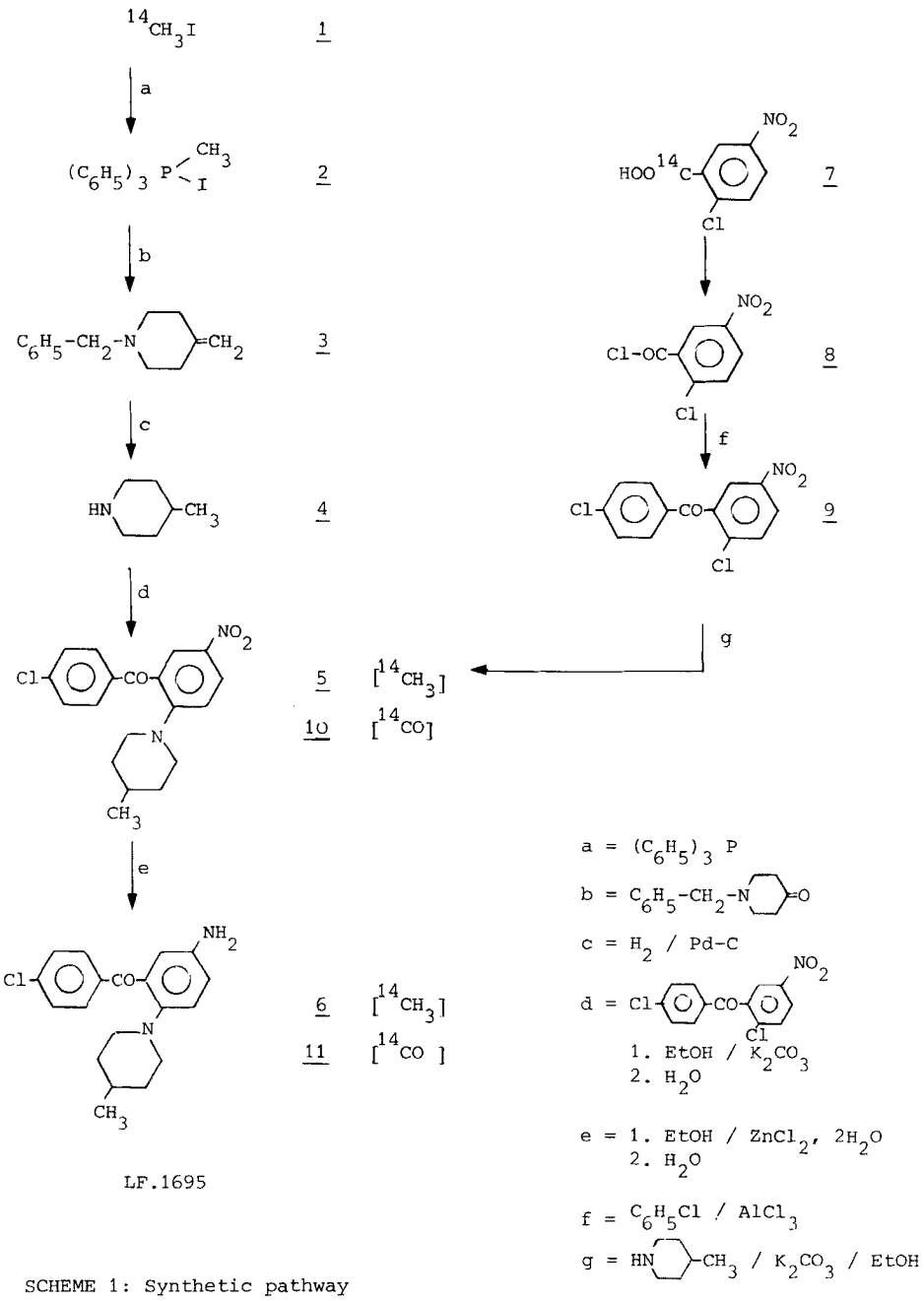
LF.1695 is a new immunomodulator which has been selected among a series of benzoyl-phenylpiperidines for clinical evaluation. We describe here the synthesis of two molecules of LF.1695 labelled at different centers which were required in order to study the distribution and the metabolism of this compounds in rats and monkeys.

## EXPERIMENTAL

All solvents used were dried and distilled. All radioactivity counting was performed with a Intertechnique ABAC SL 40 Liquid Beta Scintillation Spectrometer. For proof of structure, nmr spectra were recorded using a Hitachi Perkin Elmer R.24 A 60 MHz Spectrometer. The final product was purified by flash chromatography (1).

0362-4803/84/100899-05$01.00

Received April 25, 1984
Revised May 24, 1984




SCHEME 1: Synthetic pathway

Triphenyl [$^{14}$C]methyl phosphonium iodide 2 (2). To a solution of 2g (10.5 mM) of purified triphenyl phosphine in 12 ml of anhydrous ether contained in a flask fitted with a dropping funnel and a reflux condenser surmounted with a calcium chloride tube, are added 244 mg of [$^{14}$C]methyl iodide 1 (1.72 mM, 58 mCi/mmol) in ether. After 15 mn, 836 mg (5.9 mM) of unlabelled methyl iodide in ether are added and the mixture is allowed to stand for four days at room temperature under stirring. After evaporation of the solvent, the residue is recrystallized from cold diisopropyl ether to yield 2.62 g of the phosphonium salt 2 (84.6 %).

N-Benzyl-4-[$^{14}$C]methylidene piperidine 3 . A suspension of 426 mg of sodium hydride in 5 ml of DMSO is stirred for 30 mn under nitrogen atmosphere. The Wittig reagent 2 (2.62 g) in 5 ml of DMSO is then added. After 4 hours of stirring at room temperature, a yellow mixture is formed. Freshly distilled benzylpiperidinone (1.21 g, 6.4 mM) in 2 ml of DMSO is added dropwise and the resulting mixture stirred for about 15 additional hours. The mixture is hydrolyzed on crushed ice, and the product extracted with pentane (3 x 10 ml). The solvent is evaporated and the residue recrystallized from cold pentane to yield 1.05 g of 3 (87 %).

p-[$^{14}$C]Methylpiperidine hydrochloride 4 . To a solution of 1.05 g of 3 in ether is added slowly a solution of ether saturated with hydrochloric acid. After 1 hour of stirring, acetic acid (10 ml) and a small amount of 10 % of Pd on charcoal are then added together with hydrogen (1 atmosphere). Stirring is continued for about 1 day at 118°C. After removal of the catalyst by filtration and evaporation of the solvent, the residue is treated with benzene to remove all trace of acetic acid. The pipecoline hydrochloride 4 is dried over phosphoric anhydride yielding 0.74 g (97.5 %) of compound which is used in the next step without further purification.

2-(p-[$^{14}$C]Methylpiperidinyl)-5-nitro-4'-chloro-benzophenone 5 . A solution of 0.74 g (7.5 mM) of pipecoline hydrochloride 4 , 1.63 g (5.5 mM) of 2-chloro-5-nitro-4'-chloro-benzophenone and 0.94 g of potassium carbonate in 3 ml of absolute ethanol are refluxed during four hours under nitrogen atmosphere. The mixture is hydrolyzed by cold water, and the product is extracted with toluene (3 x 15 ml) giving 1.85 g (94.4 %) of a yellow nitro intermediate.

2-(p-[$^{14}$C]Methylpiperidinyl)-5-amino-4'-chloro-benzophenone 6 (LF.1695). To 1.85 g (5.2 mM) of the nitro compound 5 in 11 ml of absolute ethanol, 11.2 g (82 mM) of zinc chloride dihydrate are added and the mixture is refluxed for about 30 mn at 80°C. After cooling, it is hydrolyzed by crushed ice and the product is extracted with ethyl acetate (3 x 5 ml). The organic layer is washed with 40% aqueous sodium hydroxide and evaporated to dryness, affording 1.35 g (87 %) of the crude product which is purified by flash chromatography (Silicagel 60 (Merck n° 9385) 400-230 mesh; eluant: toluene / ethyl acetate (6:1); flow rate : 5 cm/mn. The chemical yield of the pure product is 0.92 g (54.3 %). The specific radioactivity is 27 μCi/mg (8.87 mCi/mmol).

2-Chloro-5-nitro-[carbonyl-$^{14}$C]benzoyl chloride 8 . To 610 mg (3mM) of 2-chloro-5-nitro-benzoic acid 7 (35 mCi/mmol) and 1.424 g of the unlabelled acid (7 mM) in 5 ml of chlorobenzene, are added dropwise 2.3 g (11 mM) of phosphorus pentachloride and stirring is continued for about four hours at 7&0°C. Evaporation of the solvent under reduced pressure gives 2.2 g of 8 (100 %).

2,4'-Dichloro-5-nitro-[carbonyl-$^{14}$C]benzophenone 9 . A solution of 2.2 g (10 mM) of 8 , 5ml (49 mM) of chlorobenzene and 2 g (15 mM) of aluminium chloride is allowed to stand overnight at room temperature. The hydrolysis is

carried out with a solution of hydrochloric acid and crushed ice. The light yellow solution is extracted by 3 x 10 ml of ethyl acetate. The organic layer is washed with an aqueous sodium hydroxide solution and evaporated under reduced pressure to yield 2.66 g of 9 (90 %).

2-(p-Methylpiperidinyl)-5-nitro-4'-chloro-[carbonyl-$^{14}$C]benzophenone 10 . This condensation is obtained from 2.66 g of 9 , 1.26 ml of pipecoline hydrochloride, 1.76 g of potassium carbonate in 6 ml of absolute ethanol according to the procedure described above (compound 5 ). The yield is 3.20 g (99.4 %).

2-(p-Methylpiperidinyl)-5-amino-4'-chloro-[carbonyl-$^{14}$C]benzophenone 11 . This reduction is carried out starting with 3.20 g of 10 , 20 g of zinc chloride dihydrate in 25 ml of ethanol as described above for compound 6 . Crude product (2.54 g, 87 % of the theoretical amount) was obtained leading to 1.98 g of pure product (Chemical yield: 68.75 %) after flash chromatography. Specific radioactivity: 34.4 µCi/mg (11.09 mCi/mmol).

## REFERENCES

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