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NOTE

SYNTHESIS OF 3-METHYL-15-(p-IODOPHENYL)-PENTADECANOIC ACID LABELLED WITH CARBON-14.

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SUMMARY

Methyl-(p-iodophenyl)-pentadecanoic acid <u>4</u> labelled with carbon-14 in the carboxyl group was obtained in 38% radiochemical yield in five steps from Na^{14}CN at a specific radioactivity of 0.084 mCi/mg, 38.6 mCi/mmol.

Key words: Labelled fatty acid, [^{14}C] fatty acid, B-methyl fatty acid,
Iodinated fatty acid.

INTRODUCTION

Methyl-(p-iodophenyl)-pentadecanoic acid (IMPPA) labelled with carbon-14 has been synthetized in the course of our continuing investigation of the myocardic metabolism of fatty acids (1-3). In the mitochondria, the β-oxidation of this fatty acid is stopped owing to the β-methyl side chain. Further more, a possible β-oxidation will be also stopped by the presence of the phenyl group at the end of the fatty acid chain. This structure allowed us to have some indications on fatty acids uptake and a longer experimental time in the animal study (4, 5).

EXPERIMENTAL

Infrared spectra (IR) were recorded on thin film using Perkin Elmer Spectrometer model 1310. NMR spectra were obtained as $CDCl_3$ solution using a Bruker AC 200 spectrometer. Radioactivity counting was performed on an Intertechnic ABA SL 40 Liquid Beta Scintillation Spectrometer. Thin layer chromatography (TLC) using silicagel 1B2F Baker flex plate and column chromatography was carried out from Merck Kiesegel 60 (ASTM 70-230 Mesh).

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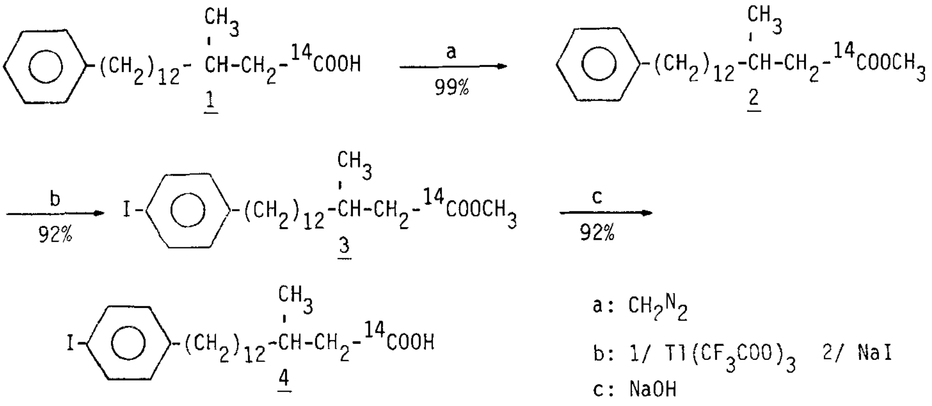
Labelled NaCN (4.3 mCi, 47.7 mCi/mmol) was purchased from CEA (Saclay). Compound 1 was prepared as described previously (6). Specific radioactivity of 1: 108 µCi/mg, 36 mCi/mmol.

SCHEME 1



Methyl 3-Methyl 15-phenyl pentadecanoate[1-^{14}C] 2:

The esterification of 19.3 mg (0.058 mmol) of 1 was realized with an excess of diazomethane, in ether solution, prepared from Diazald (Aldrich Chemie). The solvent was removed in vacuo to give 19.9 mg (0.057 mmol) of the ester 2 (99%) as an colourless oil.

IR (ν **cm^{-1}**): 1740, 645

^{1}H **NMR.** (δ **ppm**): 0.91 (d, 3H, CH_3); 1.00-1.39 (s, 20H, CH_2); 1.45-1.71 (m, 2H, CH_2-CH-CH_2-COOMe); 2.00- 2.4 (m, 2H, -CH_2-COOMe); 2.60 (t, 2H, CH_2-Ar); 3.65 (s, 3H, $COOCH_3$); 7.1-7.55 (m, 5H, arom).

Methyl 3-methyl 15-(p-iodophenyl)-[1-^{14}C]pentadecanoate 3:

To the ester 2, (19.9 mg, 0.058 mmol) in 1.5 ml of trifluoroacetic acid was added 69.4 mg (1.6 equivalent) of thallium trifluoroacetate. The mixture was stirred at room temperature, protected from light, for at least 5 days. The reaction mixture was suspended in 1.5 ml of water and potassium iodide (57.8 mg, 0.35 mmol) was added. The suspension was stirred for 15 min and sodium thiosulphate (47.9 mg, 0.19 mmol) was then added to reduce iodine which had been formed during the reaction. Stirring was continued for 15 min at room temperature. The green mixture turn yellow. The reaction mixture was then acidified with 0.1 HCl solution and diluted with ether (5 ml). The precipitated thallium iodide was removed by filtration. Extraction of the resulting solution with ether and evaporation give 25 mg (0.053 mmol) of 3, yellowish white oil. Yield: 92 % of the theorical amount.

Gas-chromatography: (OV 225, 10%, 3m, 250°C) of an experiment using unlabelled material showed four peaks. The first one corresponding to the starting ester (4%). The second and third peak indicating the existence of a few percent of the o-isomer (3%) and the m-isomer (2%). The aromatic iodide compound was represented by the fourth peak (91%).

NMR ^{1}H (δ ppm): 0.92 (d, 3H, CH_3); 1.00-1.40 (s, 20H, CH_2); 1.45-1.71 (m, 2H, CH_2-CH-CH_2-COOMe); 1.93 (m, 1H, CH-CH_2-COOMe); 2.00-2.40 (m, 2H, CH_2-COOMe); 2.55 (t, 2H, CH_2-Ar); 3.65 (s, 3H, COOMe); 7.00-7.60 (4H, AA'BB', arom.)

3-Methyl-15-(p-iodophenyl)-[1-^{14}C]pentadecanoic acid (IMPPA) 4:
The iodide ester 3 was refluxed in 5 ml of ethanol and 3 ml of 40% NaOH solution. The solution was refluxed until there was no further ammoniac gaz evolution. After cooling, the solution was acidified with 2ml of 10% sulphuric acid and extracted with ether. Evaporation of the ether extract left a light yellow product which was purified by thin layer chromatography with a mixture of hexane/ether/acetic acid (80:50:0.5) to gave 19.1 mg (0.042 mmol) of 4 as white solid. Yield: 92%, m.p.: 50-51°C (litt: 48°-49°C). The radiochemical purity was found to be 99.5% by the radio-TLC method.
Specific radioactivity: 84.2 uCi/mg, 38.6 mCi/mmol
Overall radiochemical yield (1→4): 77%
Overall chemical yield (1→4): 84%
NMR ^{1}H (δ ppm): 0.92 (d, 3H, CH_3); 1.00-1.40 (s, 20H, CH_2); 1.45-1.72 (m, 2H, CH_2-CH-CH_2-COOH); 1.93 (m, 1H, CH-CH_2-COOH); 2.15 (q, 1H, CH_2-COOH); 2.33 (q, 1H, CH_2-COOH); 2.61 (t, 2H, CH_2-Ar); 7.00-7.65 (4H, AA'BB', arom.)

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