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NOTE

SYNTHESIS OF 3-METHYL-15-PHENYL-[CARBOXYL-^{14}C]-PENTADECANOIC ACID

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SUMMARY:

β-Methyl-15-phenyl-pentadecanoic acid labelled with carbon-14 was obtained with good yield in two steps from Na^{14}CN, starting from 14-methyl 1-phenyl- tetradecanol methanesulfonate with a specific radioactivity: 108.25 μCi/mg, 1.92 mCi/mmol. and in a radiochemical yield of 50% of the theoretical amount.

INTRODUCTION:

In order to investigate the myocardic metabolism of fatty acids, 3-methyl-15-phenyl-[carboxyl-^{14}C]pentadecanoic acid (MPPA) has been synthesized in good yield from [^{14}C]NaCN. In the mitochondria, the β-oxydation of this fatty acid is stopped by the β-methyl side chain and this allows a longer experimental time in animal study (1-3). The labelled compound **6** was obtained by an original synthesis according to the Scheme 1 (4-9). This most suitable method allowed a reduced cyanide ratio (only 1.3 equivalent with regard to the mesylate compound **6**) without yield falling followed by a simple purification of the[^{14}C]nitrile **7** after the nucleoplilic substitution reaction (10).

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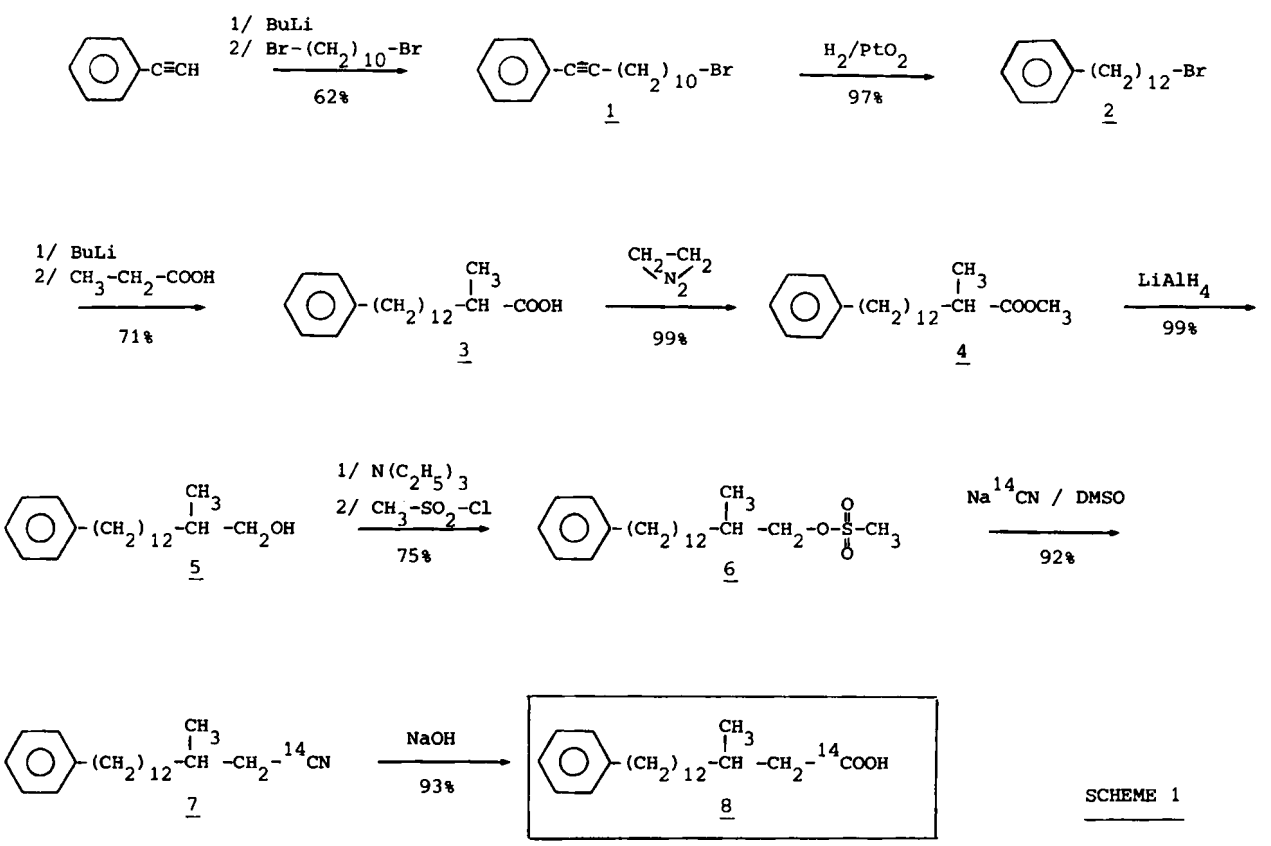
1/ BuLi
2/ Br-(CH2)10-Br
62%
1
H2/PtO2
97%
2
1/ BuLi
2/ CH3-CH2-COOH
71%
3
CH2-CH2
N2
99%
4
LiAlH4
99%
5
1/ N(C2H5)3
2/ CH3-SO2-Cl
75%
6
Na14CN / DMSO
92%
7
NaOH
93%
8

SCHEME 1

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) utilized silicagel 1B2F Baker flex plater and column chromatography was carried out from Merck Kiesegel 60 (ASTM 70-230 Mesh). Solvents were redistilled just before utilization from lithium aluminium hydride for tetrahydrofuran (THF) and from calcium hydride for hexamethyl phosphoric triamide (HMPT).[^{14}C]NaCN (4.3 mCi, 47.7 mCi/mmol) was purchased from CEA (Saclay).

1-Bromo-12-phenyl-11-dodecyne 1:

In a dry 100 ml flask equipped with septa and magnetic stirrer, under an argon atmosphere, were placed 12.8g (0.04 mol) of phenylacetylene in 50 ml of dry THF. After cooling to -10°C, 0.04 mol of n-butyllithium (1.6 M in hexane) was added slowly via a syringe. After complete addition, 8 ml of HMPT was added to the yellow solution which turn brown. The solution was stirred at room temperature for 0.5 hr., and transferred to a dropping funnel under argon. The mixture was added to a magnetically stirred solution of 24g (0,08 mol) of 1,10-dibromodecane in 100 ml of dry THF over 3 hr. The temperature was kept between 10°C and 20°C. After 5 hr. of reaction contact the mixture was hydrolyzed by addition of 100 ml of 3N HCl and extracted by pentane (4 x 50 ml). The organic layer was washed with water (2 x 50 ml). After drying over anhydrous sodium sulphate, the solvent was discarded and the yellow residual oil was chromatographed on silicagel using ethylacetate - hexane (2/8) to yield 7.9g (62%) of 1 as a colourless oil.

IR: (ν cm^{-1}): 2220, 645.

^{1}H NMR (δ ppm): 0.95-1.90 (m, 16H, CH_2); 2.41 (t, J = 6.5 Hz, 2H, CH_2-C≡C); 3.40 (t, J = 6.5 Hz, 2H, CH_2Br); 7.07-7.55 (m, 5H, Arom.).

1-Bromo-12-phenyl-decane 2:

The compound 1 (12.8g, 0.04 mol) and 50 mg of platinium oxide in 300 ml of ethylacetate was kept under hydrogen atmosphere with magnetic stirring until the theoretical amount of hydrogen was consumed. Filtration and evaporation of the solvent gave 12.6g of 2 (Yield = 97%) as a colourless oil essentially pure.

IR: (νcm^{-1}): 640.

^{1}H NMR (δ ppm): 0.95-1.92 (m, 20H, CH_2); 2.63 (t, J = 6.5 Hz, CH_2-Ar.); 3.41 (t, J = 6.5 Hz, CH_2Br); 7.07-7.55 (m, 5H, Arom.).

2-Methyl-14-phenyl tetradecanoic acid 3:

In a dry 500 ml flask equipped with septa and magnetic stirrer, under atmosphere of argon, were placed 11.7g (0.037 mol) of diisopropylamine redistilled in 250 ml of dry THF. After cooling to -15°C, 0.037 mol of n-butyllithium (1.6 M in hexane) was introduced slowly via a syringe and the solution was stirred in a bath ice-aceton during 1hr. 1.25g (0.017 mol) of propionic acid was added very slowly to the previous solution. After complete addition, 14.6 ml of HMPT was added and the stirrer was started at room temperature for 0.5 hr. 5.5g (0.017 mol) of 12-bromo-1-phenyl decane 2 in 25 ml of dry THF was added for two hours. The temperature was kept between 40° and 50°C overnight to a magnetically stirring. The mixture was hydrolyzed by the addition of 500 ml of a satured solution of ammonium chloride and extracted with pentane (3 x 100 ml). The extract was dried over anhydrous sodium sulphate, and the solvent was discarded giving a yellow solid which was chromatographed on silica gel using ethylacetate-hexane (2/8) to yield 3.8g (71%) of 3 as a white solid melted at 47°C.

IR (ν cm^{-1}): 3200-2800, 1760, 645.

^{1}**H NMR** (δ ppm): 1.10 (d, 3H, CH_3); 1.00-1.42 (s, 20H, CH_2); 1.45-1.78 (m, 2H, CH_2-CH-COOH); 2.61 (t, J = 6,5 Hz, 2H, CH_2-Ar); 7.10-7.55 (m, 5H, Arom.).

Methyl 2-methyl-14-phenyl-tetradecanoate 4:

The esterification of 1.1g (0.035 mol) of 3 was realized with an excess of diazomethane, in ether solution, prepared from Diazald (Aldrich Chimie). The solvent was removed in vacuo to give 1.15g of the ester 4 (99%) as a colourless oil.

IR (ν cm^{-1}): 1740, 645.

^{1}**HNMR** (δ ppm): 1.10 (d, 3H, CH_3); 1.12-1.45 (s, 20H, CH_2); 1.45-1.78 (m, 2H, CH_2-CH-COOMe); 2.46 (m, 1H, CH-COOMe); 2.61 (t, J = 6,5 Hz, 2H, CH_2-Ar); 3.65 (s, 3H, $COOCH_3$); 7.1-7.55 (m, 5H, Arom).

2-Methyl-14-phenyl-tetradecanol 5:

A solution of 6 mmol of lithium aluminium hydride in 40 ml of anhydrous ether was placed in a 250 ml three-necked flask equipped with a reflux condenser, a dropping funnel and a mechanical stirrer. The reaction vessel was protected from moisture by calcium chloride. Through the dropping funnel, 1.10 g of ester (0.033 mol) was introduced at a rate such as to produce gentle reflux and the stirring was kept during 30 minutes after the later addition portion. The excess hydride was decomposed with precaution by addition of water. Then the mixture was poured into 200 ml of ice water, and 30 ml of 10% sulfuric acid was added. After separation of the ether layer, the aqueous

layer was extracted with two further 100 ml portions of ether. The product obtained after evaporation of the ether extracts was a white solid (0.97g). Yield: 99% of the theoretical amount. Melting point: 30°C.

IR (νcm^{-1}): 3500, 645.

^{1}H NMR (δ ppm): 0.90 (d, 3H, CH_3); 1.00-1.45 (s, 20H, CH_2); 1.48-1.72 (m, 2H, CH_2-CH-CH_2OH); 2.60 (t, 2H, CH_2-Ar); 3.31-3.62 (m, 2H, CH_2OH); 7.10-7.55 (m, 5H, Ar).

2-Methyl-14-phenyl tetradecanol methanesulfonate 6:

In a 250 ml three-necked flask equipped with a magnetical stirrer, inlet and outlet tubes for purified nitrogen, and a dropping funnel (connected with the nitrogen inlet tube), 9.7g (0.032 mol) of 5 was dissolved in 70 ml of toluene redistilled. Triethylamine redistilled (0.045 mol) was added dropwise to the further solution which was chilled in an ice bath and 0.042 mol of methane sulfonyl chloride in 20 ml of toluene was introduced dropwise during 1 hr. The ice bath was removed and the stirring was continued for another two hr. at room temperature. After filtration and drying over anhydrous sodium sulphate, evaporation of the solvent gave 0.92g (75%) of 6 as a white solid. Melting point: 24°C.

IR (ν cm^{-1}): 1360, 1180, 960, 645.

^{1}H NMR (δ ppm): 0.90 (d, 3H, CH_3); 1.10-1.48 (s, 20H, CH_2); 1.50-1.71 (m, 2H, CH_2-CH-CH_2SO_3Me); 1.85 (m, 1H, CH-CH_2SO_3Me); 2.60 (t, J = 6.5 Hz, 2H, CH_2-Ar.); 2.95 (s,3H, SO_3-CH_3); 3.90-4.15 (m, 2H, CH_2-SO_3Me); 7.10-7.55 (m, 5H, Arom)

2-Methyl-14-phenyl-tetradeca [^{14}C]nitrile 7 :

[^{14}C]sodium cyanide (4.44 mg, 0.09 mmol, 1.3 eq, 4.3 mCi, 47.7 mCi/mmol) was placed in a 10 ml two-necked flask fitted with a condenser, inlet and outlet tubes for dried nitrogen and a stirrer. A solution of 26.6 mg (0.07 mmol) of 6 in 2 ml of anhydrous dimethylsulfoxyde was added. The mixture was stirred vigourously and heated in a oil bath at 85°C for 8 hr. Air-free water (3 ml) and then 2 ml of diethyl oxyde were added slowly to the cold reaction mixture. The organic layer was washed with water (2 x 2 ml). Evaporation of solvent and drying over vacuo gave a yellow oil. A further purification by ethylacetate-hexane (2/8) thin layer chromatography gave 20.8 mg (92%) of 7 as a white powder.

IR (ν cm^{-1}): 2200, 645.

Stable compound:

^{1}H NMR (δppm): 1.05 (d, 3H, CH_3); 1.05-1.45 (s, 20H, CH_2); 1.51-1.68 (m, 2H, CH_2-CH-CH_2CN); 1.84 (m, 1H, CH-CH_2-CN); 2.12-2.47 (m, 2H, CH_2CN); 2.60 (t, 2H, CH_2-Arom); 7.10-7.55 (m, 5H, Arom.).

3-Methyl-15-phenyl-[carboxyl-^{14}C]pentadecanoic acid 8

Into a 10 ml flask, fitted with a condenser, was placed a solution of labelled nitrile (20.8 mg) in 2 ml of methanol and 1.5 ml of 40% NaOH. The solution was refluxed until there was no further ammoniac evolution. After cooling and acidification by addition of 12N HCl, the resulting mixture was washed, dried and concentred to give 19.3 mg of 8 (93%) of a white solid, (Chemical yield 6 → 8 83%; radiochemical yield 50%) at a specific activity of 108.3 µCi/mg, 1.92 mCi/mmol). The radiochemical purity was found to be 99,5% by the radio-TLC method.

Stable compound:

IR (ν cm^{-1}): 3300-2800, 1720. **^{1}HNMR** (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_2COOH); 1.93 (m, 1H, CH-CH_2COOH); 2.15 (q, 1H, CH_2COOH); 2.33 (q, 1H, -CH_2COOH); 2.61 (t, 2H, CH_2-Ar.); 7.09-7.55 (m, 5H, Arom).

References

(1) Elmaleh D.R., Livni E., Levy S., J. Nucl. Med., 1982, 23 , 103-104.
(2) Elmaleh D.R.., Livni E., Levy S., Varnum D., Strauss H.W., Brownel. G., Int. J. Nucl. Med. Biol., 1983, 10 , 181-187.
(3) Mahadevan V., Phillips F., Lundberg W.O., Lipids, 1966, 1 , (3), 185.
(4) Pfeiffer P.E., Silbert L.S., J. Org. Chem., 1970, 85 , 1, 262-264.
(5) Ahmad K., Strong F.M. J. Am. Chem. Soc., 1948a, 70 , 1699-1700.
(6) Ahmad k., Bompus F.M., Strong F.M. J. Am. Chem. Soc. 1948b, 70 , 3391-3394.
(7) Nystrom R.F., Brown J.W. J. Am. Chem. Soc., 1947, 69 , 1197-1199.
(8) Boyer J., Corriu R.J.P., Pey R., Poirier M., Reye C. Synthesis, 1986, 8 , 646.
(9) Baldwin J.J., Raab A.W., Menslerkarison B.H. et Mac Clure D.E. J. Org. Chem., 1978, 43 , 4876.
(10) Baumann W.J. and Mangold. H.K., J. Lipid Research, 1968, 9 , 287.