Synthesis and radioiodinated labeling of *p*-iodophenyl pentadecanoic acid*

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Abstract A new method for the preparation of *p*-iodophenyl pentadecanoic acid (IPPA) has been developed. The synthesis are described, and physical properties of IPPA are characterized by IR, ^{1}HNMR, elementary analysis and MS. ^{125}I-IPPA can be easily prepared by two methods: direct labeling and solid-phase iodo-exchange labeling, and the yields of labeling are 80% and 65%, respectively. The radiochemical purities are higher than 98% after being extracted with chloroform and hexane.

Keywords *p*-iodophenyl pentadecanoic acid, Fatty acid, Synthesis, ^{125}I-IPPA, ^{125}I-labeling

1 Introduction

Long chain fatty acids are the primary energy source of the normal myocardium. The measurement of regional difference in the uptakes and retention of radiolabelled fatty acids by SPECT techniques could be a valuable diagnostic techniques because the regional fatty acid metabolism may correlate with several types of heart diseases.

In the 1970s Robinson[1] labeled hexadecanoic acid with ^{123}I, and Machulla[2] labeled heptadecanoic acid with ^{123}I. But the release of free iodine following oxidation limited the use of these compounds. To overcome this impediment, substituted long chain iodophenyl pentadecanoic acid (IPPA) and β-methyl iodophenyl pentadecanoic acid(BMIPP)[3] were developed to reduce the background on the image and to decrease the rate at which these compounds were metabolized in an effort to enhance their suitability for tomographic imaging.

The raw materials for the synthesis of IPPA reported by Machulla[4] are expensive and need to be imported. The goal of this study was to develop a synthetic method of IPPA different from Machulla, and to label IPPA with ^{125}I by two methods.

2 Materials and methods

2.1 Reagents

Phenylpropionyl chloride, methyl-11-bromoundecanoate and thallium(Ⅲ) trifluoroacetate were prepared by ourselves. Ethyl acetoacetate, trifluroacetic acid, sodium sulfate, potassium iodide, diethyl glycol, ammonium sulfate, sodium thiosulfate and hydrazine hydrate (85%) were purchased from Shanghai Chemical Co.

2.2 The preparation of IPPA

The preparation procedure of IPPA is presented in Fig.1.

2.2.1 Ethyl phenylpropionyl acetic (I)

Magnesium powder (5 g) was refluxed in 20 ml alcohol containing 1 ml CCl_4. The mixture of ethyl acetoacetate (25 ml, 0.21 mol), alcohol (20 ml) and ether (100 ml) was treated dropwise and kept refluxing for 3 h. The reaction product was cooled to about 0°C, the mixture of phenylpropionyl chloride (34 g, 0.2 mol) and ether (20 ml) was added and kept stirring at 0~5°C for 2 d. The cooled mixture was poured into 200 ml water containing 5 ml of con. H_2SO_4, extracted with ether(3×100 ml), combined the organic layer, dried over anhydrous sodium sulfate and evaporated under vacuum to afford I(32 g, 164~166°C/133.3 Pa, 73%).

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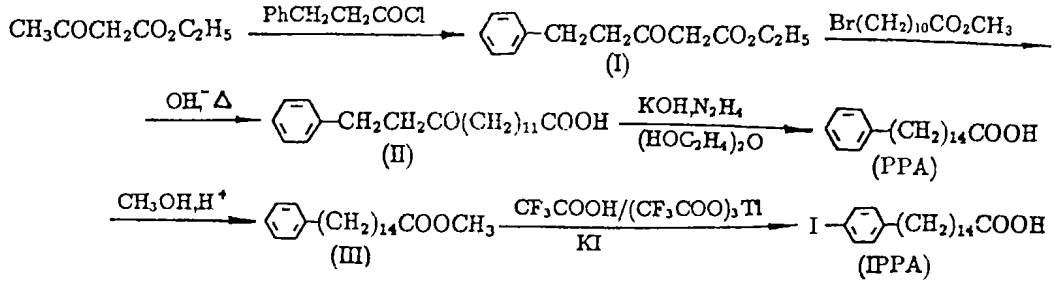

Fig.1 The scheme of preparing IPPA

2.2.2 13-keto-15-phenylpentadecanoic acid (II)

I(22g, 0.1 mol), sodium(3 g) and anhydrous alcohol(200 ml) were refluxed for 30 min, then methyl-11-bromoundecanoate(29 g, 0.1 mol) was added and kept refluxing for 4 h. After removing the solvent, sodium hydroxide (200 ml, 5%) was added and refluxed to organic layer disappeared. The oil obtained by acidifying the solution with HCl was heated at 140°C for 2 h. After cooling, the residue was recrystallized with petroleum and methanol to give white crystal II (13.3 g, 78~79°C, 40%). IR (cm^{-1}): 1708(-CO-), 1694(-COOH), 1500(-ph); Theo Anal ($C_{21}H_{32}O_3$): C, 75.91%, H, 9.64%. Found: C, 75.64%, H, 9.97%. ^{1}HNMR($CDCl_3$, 10^{-6}): δ, 1.3(s,18H, CH_2), 2.3(m, 4H, phCH_2CH_2), 2.8(m, 4H, CH_2CO), 7.27(m, 5H, Ar-H).

2.2.3 15-Phenylpentadecanoic acid (PPA)

II(11 g 0.033 mol) was refluxed in 50 ml of diethyl glycol containing potassium hydroxide(11 g, 0.2 mol) and hydrazine hydrate(85%, 7 g, 0.1 mol) for 3 h. The product was heating till nitrogen ceased to give off. 100 ml water was added, acidified with HCl and filtered. The crude precipitate was crystallized from methanol to afford white needle crystal PPA(7.2 g, 62~63°C, 68%). IR (cm^{-1}, see Fig.2): 1704(-CO-), 1496(-ph); Theo Anal ($C_{21}H_{34}O_2$): C, 79.25%, H, 10.69%; Found: C, 79.04%, H, 10.98%. ^{1}HNMR($CDCl_3$, 10^{-6}, see Fig.3): δ, 1.3(s, 24H, CH_2), 2.6(t, 2H, phCH_2), 2.34(t, 2H, CH_2CO), 7.25(m, 5H, Ar-H). MS (M/Z, see Fig.4): 318(M^+, 56.9), 300(M^+-H_2O, 74.6), 92(M^+-CH $(CH_2)_{12}COOH$, 100).

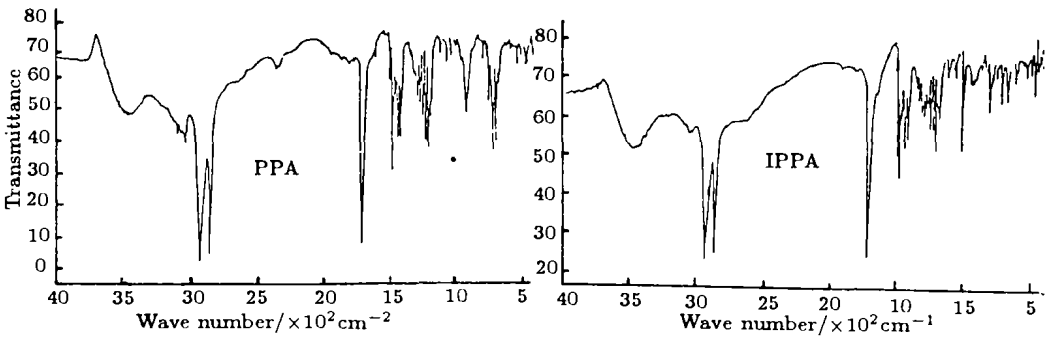

Fig.2 IR spectrum of PPA and IPPA

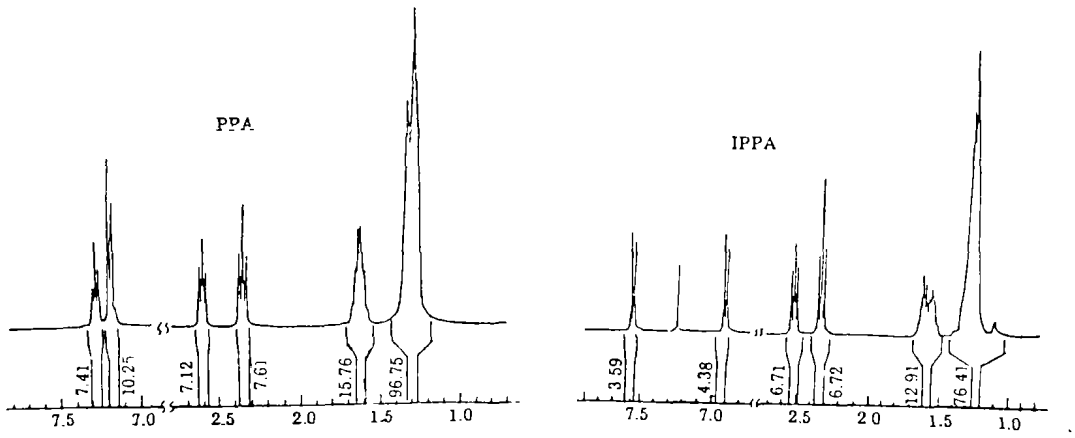

Fig.3 ^{1}HNMR spectrum of PPA and IPPA ($CDCl_3$)

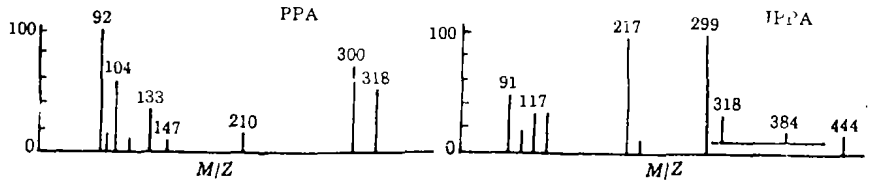

Fig.4 Mass spectrum of PPA and IPPA

2.2.4 Methyl 15-phenyl pentadecanoate (III)

PPA (2g, 0.006mol) was refluxed in 20ml methanol containing 0.2ml con. H_2SO_4 for 2h. After cooling, white scale crystal III(1.4g, 38~39°C, 70%). IR (cm^{-1}): 1704(-CO-), 1496(-ph); Theo Anal($C_{22}H_{36}O_2$): C, 79.52%, H, 10.84%. Found: C, 79.48%, H, 10.54%. ^{1}HNMR($CDCl_3$, ppm): δ, 1.3(s, 24H, CH_2), 2.6(t, 2H, phCH_2), 2.34(t, 2H, CH_2CO), 3.76(s, 3H, OCH_3), 7.25(m, 5H, Ar-H).

2.2.5 15-(*p*-iodophenyl) pentadecanoic acid (IPPA)

III(0.66 g, 0.002 mol) and thallium trifluoroacetate (1.63g, 0.003 mol) in 60 ml of trifluoroacetic acid were stirred under red light at room temperature for 5 d. Potassium iodide (1.33g) in 10 ml water was added, and the resulting mixture was stirred for 15 min. Followed by the addition of sodium thiosulfate (1g), the mixture was refluxed for another 15 min. Poured into 100ml water and filtered. The crude precipitate was crystallized from methanol to give yellow needle crystal IPPA(0.4g, 93~95°C, 45%). IR (cm^{-1}, see Fig.2): 1700(-CO-), 1500(-ph); Theo Anal ($C_{21}H_{33}O_2I$): C, 56.76%, H, 7.43%. Found: C, 56.60%, H, 7.64%. ^{1}HNMR($CDCl_3$, 10^{-6}, see Fig.3): δ, 1.3(s, 24H, CH_2), 2.57(t, 2H, phCH_2), 2.3(t, 2H, CH_2CO), 7.27(m, 5H, Ar-H). MS (M/Z, see Fig.4): 444(M^+, 14.1), 299(M^+-I, H_2O, 100), 217(M^+-I, $CH(CH_2)_3COOH$, 99.0), 91(M^+-I, $CH(CH_2)_{12}COOH$, 44.5).

2.3 The preparation of ^{125}I-IPPA

^{125}I-IPPA can be prepared by two methods: One is to radioiodinate PPA directly[5], and the other is to radioionate IPPA with solid-phase iodo-exchange labeling.[6]

2.3.1 Direct labeling

PPA (1.0 mg) was dissolved in 1ml thallium trifluoroacetate and allowed to stand at room temperature for 1 h. $Na^{125}I$(18.5 MBq) was added to the in situ parathallium complex and sealed to react for 1h at 60°C to yield ^{125}I-IPPA, and extracted by chloroform or hexane

(3× 1 ml) to purify.

2.3.2 Solid-phase iodo-exchange labeling

IPPA (0.5 mg) and ammonium sulfate (1.5 mg) were dissolved in ethanol (0.5 ml). After the addition of $Na^{125}I$(18.5 MBq), the solution was dried under a steam of nitrogen and allowed to react for 2 h at 170°C to form ^{125}I-IPPA. Cooled to room temperature and extracted by chloroform or hexane to purify.

2.4 Radiochemical purity (RCP)

2.4.1 TLC:

For silica gel sheets with the solvent of 5% ethanol in ether, R_f value for ^{125}I-IPPA and $^{125}I^-$ were 1.0 and 0.0 (see Fig.5a), respectively.

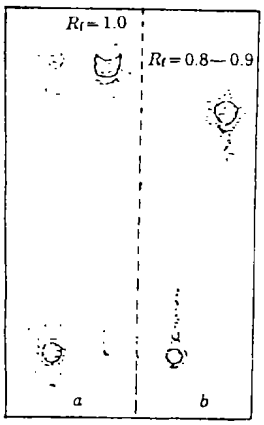

Fig.5 TLC autoradiogram of ^{125}I-IPPA

For silica gel plates (soaked in HSA) with the solvent of 2.5% methanol in methylene chloride, R_f value for ^{125}I-IPPA and $^{125}I^-$ were 0.8~0.9 and 0.0(see Fig.5b), respectively.

After drying all chromatographic strips mentioned above, TLC autoradiogram of ^{125}I-IPPA were carried out by exposing them in GS250 Phosphor Molecular Image for 2 h.

2.4.2 HPLC

C-18 PRP reverse-phase column(ϕ4 mm× 300 mm) was eluted with 95% methyl alcohol at a flow rate of 1.0 ml/min. The retention time of ^{125}I-IPPA and $^{125}I^-$ were 5.1 min and 2.04 min(25°C), respectively.

RCP of ^{125}I-IPPA was over 98% determined by TLC and HPLC.

3 Results and discussions

3.1 We have developed the synthetic route of IPPA different from that of Machulla. All the intermediate products are characterized. The yield of II is about 40%, which is obviously higher than 20% of Ref.[4]. All data of IR, ^{1}HNMR and MS of the terminal products PPA and IPPA are in accordance with those of Ref.[4].

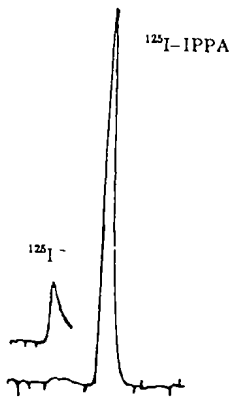

Fig.6 HPLC of ^{125}I-IPPA

3.2 Compared to routine iodo-labeling methods, direct labeling of PPA using an organic thallium intermediate has the advantages of low temperature, shortage of reaction time and high labeling efficiency. From the Fig.6 of HPLC, one can see that there are no any other

iodo-labeling products by using thallium trifluoroacetate.

3.3 Solid-phase iodo-exchange labeling of IPPA was similar to routine iodo-exchange labeling. RLY (radiolabelling yield) were 65% and RCP were over 98% after purification. In order to overcome the harsh reaction conditions and low yield in iodo-labeling, we use copper(I) as catalyst and excessive reducing agent.[7] A RLY of 95% can be obtained, and the method is simple and rapid. A detailed study is proceeding.

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