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RADIOIODINATED ALIPHATIC AMINES AS POTENTIAL PULMONARY IMAGING AGENTS: I. SYNTHESIS OF ω-(4-[^{131}I]-IODOPHENYL)HEXYLAMINE AND ITS β- AND γ-METHYL SUBSTITUTED ANALOGUES.

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SUMMARY

Radioiodinated long chain aliphatic amines which are substrates of pulmonary monoamine oxidase enzyme system are synthesized for evaluation as potential lung imaging agents. ω-Phenylhexylamine (48% overall chemical yield) and its β-methyl substituted analogue (17%) were successfully synthesized from ω-phenylhexanoic acid. γ-Methyl-ω-phenylhexylamine (37%) was prepared from ω-phenylpentanoic acid. Radioiodination of the phenyl moiety of the amines with no-carrier-added [^{131}I]-NaI was achieved *via* a thallium intermediate with 25%, 31% and 36% radiochemical yield respectively in greater than 98% radiochemical purity (calculated specific activity 20 - 40 TBqmmol^{-1}). Thallation of activated aromatic systems proceeded rapidly and in quantitative yields. Isolation of the thallate intermediate was not necessary.

Key words: Radioiodination, aliphatic amines, MAO, thallium, pulmonary.

INTRODUCTION

The functions of the lungs are generally assessed by gaseous exchange and mechanics determination. These measurements, however, may not be informative until the pulmonary system has developed advanced or severe physical and/or pathological changes.[1] For this reason there is a need for more sensitive diagnostic tests capable of detecting pulmonary injury at an early stage. The function of the pulmonary system is dependent on the integrity of its endothelial cells, epithelial type I and type II cells among other cell types. The endothelial cells have been suggested to play a central role in the pathogenesis of many lung injuries and diseases.[1] They are capable of metabolism of many endogenous as well as exogenous compounds entering the pulmonary circulation.[2-6] Consequently, studies of pulmonary metabolism of radioiodinated aliphatic amines which are substrates of the monoamine oxidase

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(amino:oxygen oxidoreductase, EC 1.4.3.4, MAO) system of enzymes of the lung may provide us with useful knowledge of injury to the microcirculation, and will aid in the understanding of the pathogenesis of certain lung diseases. Also, alteration to the chemical structures of these substrates would provide us with an opportunity to evaluate other metabolic pathways of monoamine metabolism and the potential of these radiopharmaceuticals as non-invasive lung imaging agents. These potential metabolic function indicators may well provide the nuclear physician with an early and sensitive index of lung injury and other physiological information heretofore unavailable.

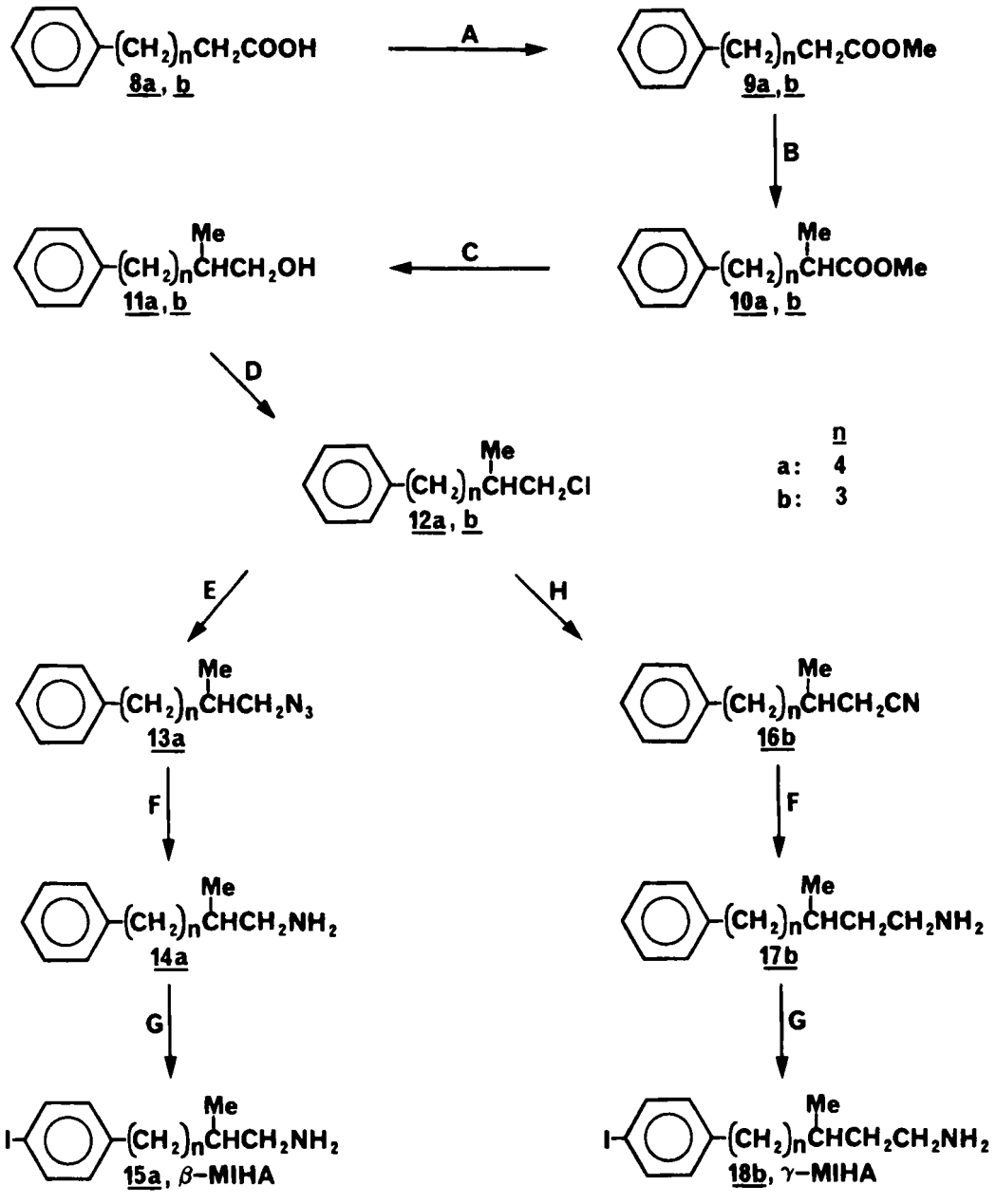
Logical drug design requires that such a design be based on sound physiological, pharmacological or physical principles. A long-chain aliphatic amine targetted for the lung is expected to reach its target organ by either its lipophilicity and/or its affinity for the MAO system. These effects can be studied by varying the length of the aliphatic chains of the amines and the nature and/or position of their substituents.

An intact α-methylene group of the amine is essential for MAO metabolism. Monoamines undergo rapid *in vivo* oxidative deamination and oxidative dehydrogenation to the corresponding carboxylic acids which are then decarboxylated by the β-oxidation system.[2] β-Oxidation of the fatty acids occurs at the β-carbon of the acid (γ-position of the parent amine). Thus, among monoamines with an intact α-methylene group substitution at the β- and γ-position of the amines could alter the substrate-enzyme interaction, the rate of metabolism, and the residence time of the injected radioactivity within the target tissue. The lipophilicity of the amine is also determined by the nature and position of the substituents as well as the length of the alkyl chain. Variation of this property could affect the rate of cellular uptake and subsequent interaction with the target enzyme system.[2]

We now report the synthesis of ω-(4-[^{131}I]-iodophenyl)hexylamine (7, [^{131}I]-IHA), its β-methyl substituted analogue, β-methyl-ω-(4-[^{131}I]-iodophenyl)hexylamine (15a, [^{131}I]-β-MIHA) and its γ-methyl substituted analogue, γ-methyl-ω-(4-[^{131}I]-iodophenyl)hexylamine (18b, [^{131}I]-γ-MIHA). The biological data of these radiopharmaceuticals will be reported elsewhere.

RESULTS AND DISCUSSION

The straight chain ω-(4-iodophenyl)hexylamine (7, IHA) (Scheme 1) and β-methyl-ω-(4-iodophenyl)hexylamine (15a, β-MIHA) (Scheme 2) were synthesized from ω-phenylhexanoic acid. γ-Methyl-ω-(4-iodophenyl)hexylamine (18b, γ-MIHA) was derived from ω-phenylpentanoic acid (Scheme 2).

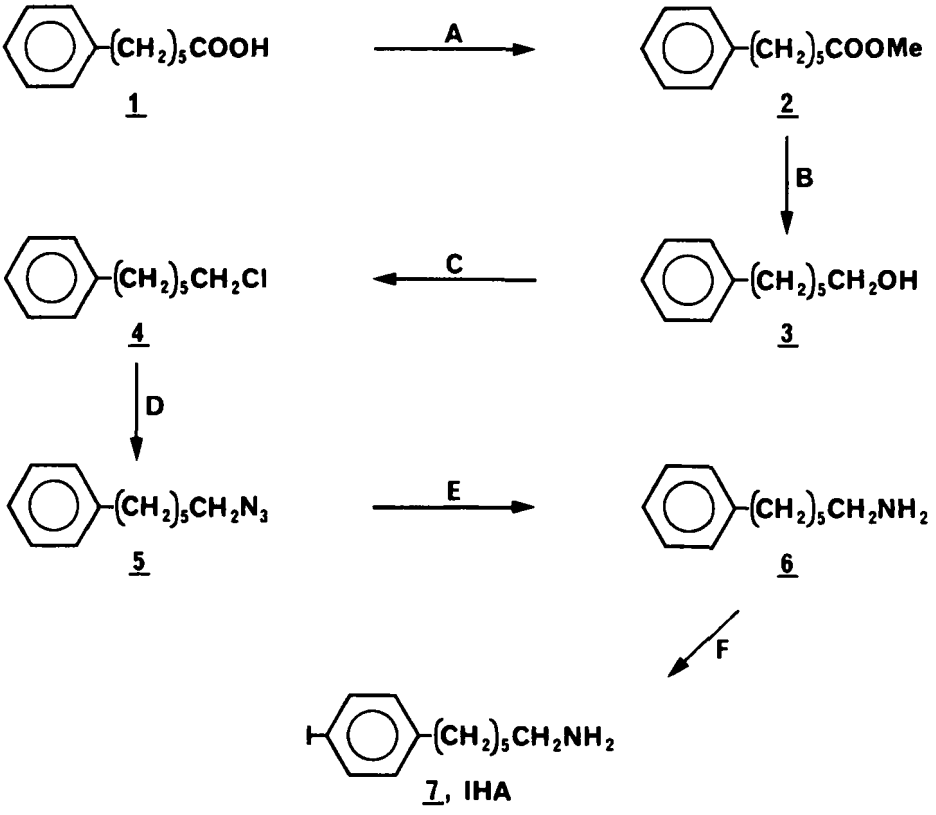


Scheme 1: Synthesis of ω-(4-iodophenyl)hexylamine, IHA. A=CH_3COCl/CH_3OH; B=LAH/Et_2O; C=$SOCl_2$; D=NaN_3/H_2O/Adogen™ 464; E=LAH/THF; F=TTFA/NaI.

Esterification of acids. The esterification of the acids was achieved according to the reported procedure of Everett *et al.*[7] Thus, acetyl chloride (0.75 equivalent) was added slowly to a solution of 1 equivalent of the acid in methanol (50 mL). The solution was refluxed for 1 h and then cooled to room

temperature. An additional 0.75 equivalent of acetyl chloride was then added followed by 2 h of heating at reflux temperature. One-half of the volume of solvent was removed by distillation. The residual solution was diluted with water (40 mL) and extracted with ether (2 x 100 mL). The combined ethereal extracts were washed well with 2N Na_2CO_3 (2 x 50 mL) and water (2 x 50 mL) and dried over anhydrous sodium sulfate (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded the desired ester as a colorless liquid.

Methylation of methyl esters. A solution of lithium diisopropyl amide (LDA) in dry tetrahydrofuran (THF) prepared from 2 equivalents of diisopropylamine (DIA) and 1.5 equivalents of *n*-butyl lithium (*n*-BuLi, 1.6 M solution) at -78°C was treated successively with 2 equivalents of hexamethylphosphoramide (HMPA) and 1 equivalent of the appropriate ester in dry THF. The reaction mixture was stirred at -78°C for 1 h and then at -10°C for 2 h followed by the addition of solid ammonium chloride



Scheme 2: Synthesis of β- and γ-methyl-ω-(4-iodophenyl)hexylamine (β-MIHA, γ-MIHA). A=CH_3COCl/MeOH; B=LDA/THF/MeI; C=LAH/Et_2O; D=$SOCl_2$; E=NaN_3/H_2O/Adogen™ 464; F=LAH/THF; G=TTFA/NaI; H=NaCN/H_2O/Adogen™ 464.

(2 g). The reaction mixture was allowed to stand overnight and filtered. The residue left after the solvent

had been removed under reduced pressure was extracted with ether (3 x 25 mL) which was washed successively with water (2 x 25 mL) and saturated NaCl solution (2 x 25 mL) and then dried over anhydrous Na_2SO_4. The viscous liquid obtained after removal of the solvent was passed through a silica gel column (elution solvent system 20% ethylacetate in hexane). In all cases the methylated esters were obtained as a pale yellow viscous liquid with no optical rotation indicating a racemic mixture.

Reduction with lithium aluminum hydride (LAH). One equivalent of the substrate to be reduced in dry ether (or dry THF) was added slowly to a suspension of 4 equivalents of LAH in the same solvent at 0°C under an atmosphere of nitrogen. The reaction mixture was stirred at 0°C for 2 h, room temperature for 2 h in ether (0.5 h in THF) and then at reflux temperature for 1 h in ether (2 h in THF). The reaction mixture was cooled to room temperature and ethylacetate (15 mL) was added dropwise to destroy the excess LAH. The resultant solution was filtered and the solvent removed under reduced pressure. The residue was extracted with ether (2 x 50 mL). The combined ether extracts were washed well with water (2 x 25 mL) and dried over anhydrous magnesium sulfate ($MgSO_4$).

Synthesis of alkyl chlorides from alcohols. The alkyl chlorides were prepared by refluxing 1 equivalent of the appropriate alcohol and 2 equivalents of thionyl chloride for 2 h. Excess thionyl chloride was removed under reduced pressure and the alkyl chloride was used as such without further purification.

Synthesis of alkyl azides from alkyl chlorides.[8] The chloride obtained from 1 equivalent of alcohol was refluxed overnight with 3 equivalents of sodium azide in water (as a 25% solution) and a catalytic amount (0.05 equivalent) of the phase-transfer catalyst, Adogen™ 464 (methyltrialkyl(C_1-C_{10})-ammonium chloride, Aldrich Chemicals). The ether extracts (2 x 50 mL) of the cooled reaction mixture were washed with cold water (2 x 25 mL) and dried over anhydrous Na_2SO_4. Removal of the ether under reduced pressure afforded the azide as a brown viscous liquid which was purified by silica gel column chromatography (elution solvent 5% ethylacetate in hexane).

Synthesis of alkyl amines from alkyl azides. The reduction of alkyl azides to the corresponding amines by LAH in THF was performed as described above. Removal of the solvent under reduced pressure afforded a viscous liquid which was dissolved in 25 mL ether and extracted with 2N HCl (2 x 25 mL). The acidic aqueous layer was neutralized with 20% aqueous NaOH. The required amines separated as an oily layer which was extracted again with ether (2 x 25 mL) and dried over anhydrous Na_2SO_4. Removal of the ether yielded the required amine as a pale yellow liquid which was characterized by infrared (IR) and proton magnetic resonance (^{1}H-NMR) spectroscopy.

Iodination with thallium trifluoroacetate and sodium iodide.[9] Iodination of the phenyl moiety of the

amines was achieved with thallium trifluoroacetate (TTFA) and sodium iodide (NaI) without the isolation of the thallate intermediate. Treatment of the amines with a slight excess of TTFA in acetonitrile (0.5 - 1 mL) for 15 m afforded the thallates which were used in the subsequent iodination reaction without further purification. A solution (0.2 mL) of NaI (3 - 5 equivalents) was added to the thallate with vigorous stirring for 15 m. Solid sodium meta-bisufite was added with continuous stirring until a colorless solution was obtained. The pH of the solution was then adjusted to 12 - 14 by the addition of 20% NaOH. The solvents were removed under reduced pressure. Water (0.5 - 1 mL) was added to the residue to effect dissolution followed by extraction with ether (3 x 0.5 mL). The combined ether extracts were dried by passage through a short column of anhydrous Na_2SO_4. Evaporation of the ether under a stream of nitrogen afforded the desired iodoamine which was purified by high-pressure-liquid chromatography (HPLC) (solvent system 40% methanol in water). ^{1}H-NMR spectroscopy of the iodinated products revealed a symmetrical split of the 4 aromatic protons indicating a *para* substitution pattern. Iodination *via* thallation introduces only a single iodine atom into the phenyl ring. A monoiodo compound is often desirable for the preservation of physicochemical properties of the substrate especially those of small molecular weight. Thallation specifically fulfills this requirement as the bulky thallate group precludes the possibility of multiple substitution as confirmed by our experience in the laboratory.

Radioiodination of amines. Thallation was carried out with a slight excess of the amines. Substitution of "cold" NaI with no-carrier-added (NCA) [^{131}I]-NaI afforded the [^{131}I]-labelled amines which were purified by radio-HPLC (solvent system 40% methanol in water). Radio-HPLC and co-chromatography of the radiolabelled amines with authentic "cold" iodinated amines on TLC plates in different solvent systems indicated that the radiochemical purity was 98-99%.

Many methods of radioiodination are available in a nuclear medicine laboratory. Some of these procedures involve carrier iodine, while others require lengthy and elaborate techniques unsuitable for routine production of iodinated radiopharmaceuticals. Thallation, as an intermediate step in iodination, was advocated by McKillip *et al.*[9] The procedure, however, is not fully utilized in nuclear medicine. We have successfully adapted this procedure in the radioiodination of many aromatic functions in our laboratory. Our experience suggests that iodination *via* thallation has many merits:

1. production of a monoiodo compound,
2. thallation is simple and fast. Thallation of the reported amines is complete in 5 to 10 m,
3. isolation and purification of the arylthallium intermediate is not required. However, it can be easily isolated in high chemical purity, if the need arises,
4. solutions of arythallium compounds are usually very stable,

5. NCA iodination is easily achieved, opening up several opportunities with high specific activity radiolabelled compounds:
    a. the study of receptors,
    b. the study of zero order kinetics,
    c. reduced toxicity, and
    d. minimize solubility problem.
6. in the case of our reported amines the iodination kinetics is very fast. This makes possible the use of ^{123}I (a positron emitter) as a radiolabel.

EXPERIMENTAL

Infrared spectroscopy was performed on the "neat" compounds with a Nicolet FT-IR Spectrometer Model 5DX. ^1H-NMR spectra were recorded on a Varian EM390 90MHz NMR Spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) separation was carried out on Whatman MK6F Silica Gel Microslides (solvent systems: chloroform:methanol:NH_4OH 16:8:1 volume by volume (v/v); toluene:methanol:NH_4OH 20:10:1 v/v; chloroform:methanol:triethylamine 20:2:5 v/v) and Whatman $MKC_{18}F$ Reversed Phase TLC Plates (solvent system: upper phase of ethylacetate:*n*-propanol:water, 4:1:2 v/v, diluted with ethylacetate, 8:1 v/v). Visualization of developed plates was effected using short wavelength ultraviolet light and 4% ninhydrin in *n*-butanol (weight by volume). Analysis of radioactivity on TLC plates was performed with a Berthold LB2821 Proportional Counter and a Canberra Series 40 Multi-channel Analyser. HPLC and radio-HPLC equipment consist of a Tracor 981 HPLC Controller equipped with a Tracor 955 LC Pump, Tracor 950 Chromatographic Pump, Tracor 970A Variable Wavelength Detector (operating at 264 nm), 10 μ C_{18} μ-Bondapak™ (Walters Assoc.) reverse phase column (3.9 mm i.d. x 30 cm length), Ortec 402M Power Supply, Ortec 456 High Voltage Power Supply, Ortec 490 Amp & SCA, Canberra Lin/Log Ratemeter Model 1481L, and a 2 in x 2 in Na(Tl) crystal. All solvents used in HPLC analysis were of HPLC grade and were degassed before use. ω-Phenylpentanoic acid **8b** is a commercial product of Aldrich Chemicals. Reagent grade solvents were used in chemical sysnthesis and chromatography and were fractionally distilled and dried before use. [^{131}I]-NaI was purchased from Edmonton Radiopharmaceutical Center, Edmonton, Alta. (specific activity approximately 300 GBq mg^{-1} iodide).

ω-Phenylhexanoic acid **1**, **8a**. Compound **1** was prepared according to the method of Papa *et al.*[10] in 60% yield starting from adipic acid monoethyl ester.

ω-Phenylmethylhexanoate **2**, **9a**. The titled compound was synthesized from the acid **1** (15.36 g, 80 mmol), acetyl chloride (2 x 4.71 g, 2 x 60 mmol) and methanol (50 mL) in 89% yield (14.6 g): IR: ν max 1745 cm^{-1} (ester C=O); ^{1}H-NMR: δ 1.3-1.9 (m, 6H, H-3, H-4, H-5); 2.3 (t, 2H, H-2); 2.6 (t, 2H, H-6); 3.7 (s, 3H, -OCH_3-1); 7.3-7.5 (m, 5H, -C_6H_5-6).

ω-Phenylhexanol **3**. Reaction of compound **2** (2.06 g, 10 mmol) with LAH (1.51 g, 40 mmol) afforded the titled compound as a colorless liquid (1.5 g, 84.2%). IR: ν max 3320 cm^{-1} (-OH); ^{1}H-NMR: δ 1.1-1.9 (m, 9H, H-2, H-3, H-4, H-5, -OH-1); 2.6 (t, 2H, H-6); 3.6 (t, 2H, H-1); 7.3-7.5 (m, 5H, -C_6H_5-6).

ω-Phenylhexyl chloride **4**. Treatment of **3** (4.0 g, 22 mmol) with thionyl chloride (5.34 g, 45 mmol) at reflux temperature for 2 h afforded compound **4** .

ω-Phenylhexyl azide **5**. The alkyl chloride **4** (4.37 g, 22 mmol) was treated with sodium azide (4.38 g, 67 mmol) and Adogen™ 464 (0.52 g, 1 mmol) overnight at reflux temperature. The azide was obtained after column chromatography as a brown viscous liquid (3.4 g, 74.5%). IR: ν max 2098 cm^{-1} (-N_3); ^{1}H-NMR: δ 1.5-2.0 (m, 8H, H-2, H-3, H-4, H-5); 2.7 (t, 2H, H-6); 3.3 (t, 2H, H-1); 7.3-7.5 (m, 5H, -C_6H_5-6).

ω-Phenylhexylamine **6**. Reduction of the azide **5** (1.6 g, 7.8 mmol) by LAH (1.196 g, 31.5 mmol) in dry THF afforded the desired alkyl amine as a pale yellow liquid (1.2 g, 86.3%). IR: ν max 3361 cm^{-1} (-NH_2); ^{1}H-NMR: δ 0.9-1.8 (m, 8H, H-2, H-3, H-4, H-5); 2.1 (m, 2H, -NH_2-1); 2.3-2.9 (m, 4H, H-1, H-6); 7.3-7.5 (m, 5H, -C_6H_5-6).

ω-Iodophenylhexylamine (**7**, **IHA**). Reaction of the alkyl amine **6** (25 mg, 0.14 mmol) with TTFA (87.8 mg, 0.16 mmol) and NaI (63 mg, 0.42 mmol) afforded **IHA** (39.2 mg, 92%). IR: ν max 3361 cm^{-1} (-NH_2); ^{1}H-NMR: δ 1.2-1.8 (8H, H-2, H-3; H-4; H-5); 2.1 (m, 2H -NH_2-1); 2.5-2.8 (m, 4H, H-1, H-6); 7.2 (d, 2H, H-2', H-6'); 7.3 (d, 2H, H-3', H-5').

ω-[^{131}I]-Iodophenylhexylamine ([^{131}I]-**7**, [^{131}I]-**IHA**). Reaction of **7** (1 mg, 0.006 mmol) with TTFA (2.2 mg, 0.004 mmol) and NCA [^{131}I]-NaI (120 GBq) afforded [^{131}I]-**IHA** in 25% radiochemical yield (30 GBq). Radio-HPLC and co-chromatography with authentic unlabelled compounds on TLC plates indicated a radiochemical purity of greater than 98%. Specific activity was calculated to be 20 - 40 $TBqmmol^{-1}$.

ω-Phenylmethylpentanoate **9b**. Reaction of **8b** (14.24 g, 80 mmol) with acetyl chloride (2 x 4.71 g, 2 x 60 mmol) and methanol (50 mL) afforded compound **9b** in 88.5% yield (13.6 g). IR: ν max 1745 cm^{-1}

(ester C=O); ^{1}H-NMR: δ 1.4-1.9 (m, 4H, H-3, H-4); 2.35 (t, 2H, H-2); 2.7 (t, 2H, H-5); 3.7 (s, 3H, -OCH_3-1); 7.1-7.5 (m, 5H, -C_6H_5-5).

α-Methyl-ω-phenylmethylhexanoate **10a**. Reaction of **9a** (2.06 g, 10 mmol) with DIA (2.02 g, 20 mmol), HMPA (3.58 g, 20 mmol), *n*-BuLi (0.96 g, 15 mmol), methyl iodide (1.70g, 12 mmol) and dry THF (50 mL) afforded the methylated ester in 59.1% yield (1.3 g). IR: ν max 1738 cm^{-1} (ester C=O); ^{1}H-NMR: δ 1.1 (d, 3H, -CH_3-2); 1.2-1.9 (m, 6H, H-3, H-4, H-5); 2.3 (m, 1H, H-2); 2.6 (t, 2H, H-6); 3.6 (s, 3H, -OCH_3-1); 7.1-7.5 (m, 5H, -C_6H_5-6).

α-Methyl-ω-phenylmethylpentanoate **10b**. The synthesis of compound **10b** from **9b** (1.92 g, 10 mmol) was similar to that of **10a** with yield of 1.84 g (89%). IR: ν max 1737 cm^{-1} (ester C=O); ^{1}H-NMR: δ 1.15 (d, 3H, -CH_3-2); 1.3-2.0 (m, 4H, H-3, H-4); 2.3 (m, 1H, H-2); 2.6 (t, 2H, H-5); 3.65 (s, 3H, -OCH_3-1); 7.1-7.4 (m, 5H, -C_6H_5-5).

β-Methyl-ω-phenylhexanol **11a**. Reduction of the methyl ester **10a** (1.1 g, 5 mmol) by LAH (0.76 g, 20 mmol) in dry ether afforded the alcohol **11a** (0.945 g, 98%). IR: ν max 3345 cm^{-1} (-OH); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-2); 1.1-1.9 (m, 8H, H-2, H-3, H-4, H-5, -OH-1); 2.6 (t, 2H, H-6); 3.5 (m, 2H, H-1); 7.1-7.5 (m, 5H, C_6H_5-6).

β-Methyl-ω-phenylpentanol **11b**. Compound **11b** was obtained from the methyl ester **10b** (1.03 g, 5 mmol) in 91% yield (0.81 g). IR: ν max 3328 cm^{-1} (-OH); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-2); 1.1-1.9 (m, 6H, H-2, H-3, H-4, -OH-1); 2.6 (t, 2H, H-5); 3.5 (m, 2H, H-1); 7.1-7.5 (m, 5H, -C_6H_5-5).

β-Methyl-ω-phenylhexylazide **13a**. Reaction of the crude alkyl chloride **12a** (1.05 g, 5 mmol) with sodium azide (0.098 g, 15 mmol) and Adogen™ 464 (0.116 g, 0.25 mmol) afforded the titled compound **13a** in 64.5% yield (0.70 g). IR: ν max 2098 cm^{-1} (-N_3); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-2); 1.1-1.9 (m, 7H, H-2, H-3, H-4, H-5); 2.6 (t, 2H, H-6); 3.2 (d, 2H, H-1); 7.1-7.5 (m, 5H, -C_6H_5-6).

β-Methyl-ω-phenylhexylamine **14a**. Reduction of the azide **13a** (0.325 g, 1.5 mmol) with LAH (0.227 g, 5 mmol) and 30 mL dry ether afforded the methylated hexylamine in 52.4% yield (0.15 g). IR: ν max 3304 cm^{-1} (-NH_2); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-2); 1-1.9 (m, 7H, H-2, H-3, H-4, H-5); 2.1 (m, 2H, -NH_2-1); 2.3-2.8 (m, 4H, H-1, H-6); 7.1-7.4 (m, 5H, -C_6H_5-6).

β-Methyl-ω-(4-iodophenyl)hexylamine (**15a**, β-MIHA). Treatment of **14a** (9.5 mg, 0.05 mmol) with TTFA (38 mg, 0.07 mmol) and NaI (42 mg, 0.28 mmol) afforded the iodoamine in 90% yield (14 mg). IR: ν max 3304 cm^{-1} (-NH_2); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-2); 1.1-1.9 (m, 7H, H-2, H-3, H-4, H-5); 2.1 (m, 2H, -NH_2-1); 2.3-2.8 (m, 4H, H-1, H-6); 7.2 (d, 2H, -H-2', H-6'); 7.3 (d, 2H, -H-3', H-5').

β-Methyl-ω-(4-[^{131}I]-iodophenyl)hexylamine ([^{131}I]-**15a**, [^{131}I]-β-MIHA). Reaction of **14a** (1 mg, 0.005 mmol) with TTFA (2.1 mg, 0.004 mmol) and NCA [^{131}I]-NaI (120 GBq) afforded the titled compound in 31% radiochemical yield (37 GBq). Analysis by radio-HPLC and TLC indicated a radiochemical purity of greater than 99% (calculated specific activity 20 - 40 TBqmmol^{-1}).

β-Methyl-ω-phenylpentyl nitrile **16b**. The alkyl chloride **12b** (2.33 g, 12 mmol) was refluxed overnight with sodium cyanide (2.90 g, 60 mmol, as a 33% aqueous solution) and Adogen™ 464 (0.06 g). Ethereal extracts (3 x 25 mL) of the cooled reaction mixture were washed with cold water (2 x 25 mL) and dried over anhydrous Na_2SO_4. Removal of the ether followed by silica gel column chromatography (elution solvent system 20% ethylacetate in hexane) afforded the nitrile as a brown viscous liquid (1.84 g, 83.2%). IR: ν max 2246 cm^{-1} (-CN); ^{1}H-NMR: δ 1.05 (d, 3H, -CH_3-2); 1.1-2.0 (m, 5H, H-2, H-3, H-4); 2.2 (d, 2H, H-1); 2.6 (t, 2H, H-5); 7.1-7.5 (m, 5H, -C_6H_5-5).

γ-Methyl-ω-phenylhexylamine **17b**. A solution of **16b** (1.12 g, 6 mmol) in dry THF (20 mL) was reduced by LAH (0.91 g, 24 mmol) in dry THF (80 mL) as previously dscribed. The mixture was filtered and the filtrate was evaporated to dyness under reduced pressure. The residual viscous liquid was taken up in ether (25 mL) and extracted with 2N HCl (3 x 25 mL). The aqueous layer was neutralized with 20% NaOH. The required amine separated as an oily layer which was extracted with ether (3 x 25 mL) and dried over anhydrous Na_2SO_4. Removal of the ether under reduced pressure afforded compound **17b** as a pale yellow viscous liquid (0.71 g, 62%). IR: ν max 3222 cm^{-1} (-NH_2); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-3); 1.1-1.9 (m, 7H, H-2, H-3, H-4, H-5); 2.1 (m, 2H, -NH_2-1, exchangeable with D_2O); 2.3-2.9 (m, 4H, H-1, H-6); 7.1-7.5 (m, 5H, C_6H_5-6).

γ-Methyl-ω-(4-iodophenyl)hexylamine (**18b**, γ-MIHA). Treatment of **17b** (5 mg, 0.027 mmol) with a slight excess of TTFA (16 mg, 0.03 mmol) and NaI (19 mg, 0.13 mmol) afforded **18b** (7.6 mg, 92%). ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-3); 1.1-2.0 (m, 7H, H-2, H-3, H-4, H-5); 2.1 (m, 2H, -NH_2-1); 2.3-3.0 (m, 4H, H-1, H-6); 7.2 (d, 2H, H-2', H-6'); 7.3 (d, 2H, H-3', H-5').

γ-Methyl-ω-(4-[^{131}I]-iodophenyl)hexylamine ([^{131}I]-**18b**, [^{131}I]-γ-MIHA). The titled compound was prepared from **17b** (1 mg, 0.005 mmol) by the action of TTFA (2.1 mg, 0.004 mmol) and NCA [^{131}I]-NaI (120 GBq) in 36% radiochemical yield (43 GBq, calculated specific activity 20 - 40 TBqmmol^{-1}). Radio-HPLC and TLC analysis indicated a radiochemical purity of greater than 98%.

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