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

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SUMMARY

The aliphatic amines, ω-phenylpentylamine and its β-methyl substituted analogue were synthesized from ω-phenylpentanoic acid in 34.7% and 28.5% overall chemical yield respectively. γ-Methyl-ω-phenylpentylamine was prepared from ω-phenylbutyric acid in 39.5% overall chemical yield. Radioiodination of the amines with thallium trifluoroacetate and no-carrier-added [^{131}I]-NaI afforded the corresponding [^{131}I]-labelled amines in 30%, 28% and 36% radiochemical yield respectively and greater than 98% radiochemical purity (calculated specific activity 20 - 40 TBqmmol^{-1}). The position of iodination was established by proton magnetic resonance to be *para* to the alkyl chain.

Key words: radioiodination, pentylamines, thallium, MAO, pulmonary.

INTRODUCTION

Lung injury and diseases can be due to many widely different causative agents resulting in a compromise of its gaseous exchange function. Regardless of the etiology of the disease or injury diagnosis is often delayed until clinical symptoms become apparent, at which time therapeutic measures may well be futile. For this reason, there is a need for diagnostic tests of greater sensitivity that are capable of detecting lung injury at an early stage.

Injury to the lung may reside in the epithelium and/or endothelium. An understanding of the pathogenesis of lung diseases would, therefore, depend on the differentiation between epithelial and endothelial damage. There are about 40 cell types in the lung, of which the most common is the endothelial cells which make up 30 to 40% of the total lung cells. Besides gaseous exchange, the lung is also involved in certain nonrespiratory functions. There is now much conclusive evidence that the lung

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microvascular endothelial cells are the primary site of uptake of numerous endogenous and exogenous compounds including many monoamines[1], a function which is directly related to the endothelial cell number. Acoordingly, pulmonary endothelial cells are prime targets for probes of pulmonary dysfunction at the biochemical level.

Monoamines are known to be metabolized by the monoamine oxidase (E.C. 1.4.3.4, MAO) enzyme system. The enzyme abounds in eukaryotic cells where it is localized in the outer mitochondrial and nuclear membranes. The flavoprotein exists as A and B forms each of which has its own substrate and inhibitor specificities. Metabolism of biogenic amines occurs primarily in the endothelial cells of the microvasculature[2-6]. Different catecholamines are handled differently by the lung. 5-Hydroxytryptamine (5-HT) uptake by the lung is the most studied example of the nonrespiratory functions of the pulmonary system. Greater than 90% of the 5-HT infused into the pulmonary circulation of the dog[7] and rat[8] is removed after the first pass. The uptake of 5-HT from circulation is mediated by an active transport system[3,4,9,10]. It is subsequently degraded by intracellular MAO[8,9]. Similar to 5-HT, norepinephrine is also metabolized by MAO, as well as catechol-O-methyltransferase[10,11]. Its transport is also carrier facilitated, although a different carrier may be involved[3,5]. The transport of phenylethylamine, however, is by simple diffusion[12]. Other biogenic amines such as dopamine and epinephrine undergo little or no metabolic transformation in the pulmonary circulation. Many exogenous amines, for example, chlorpromazine[13], methadone[14], morphine[15], pethidine[16], imipramine[17], chlorcyclizine[18] and amphetamine[19,20] are also concentrated by the lung.

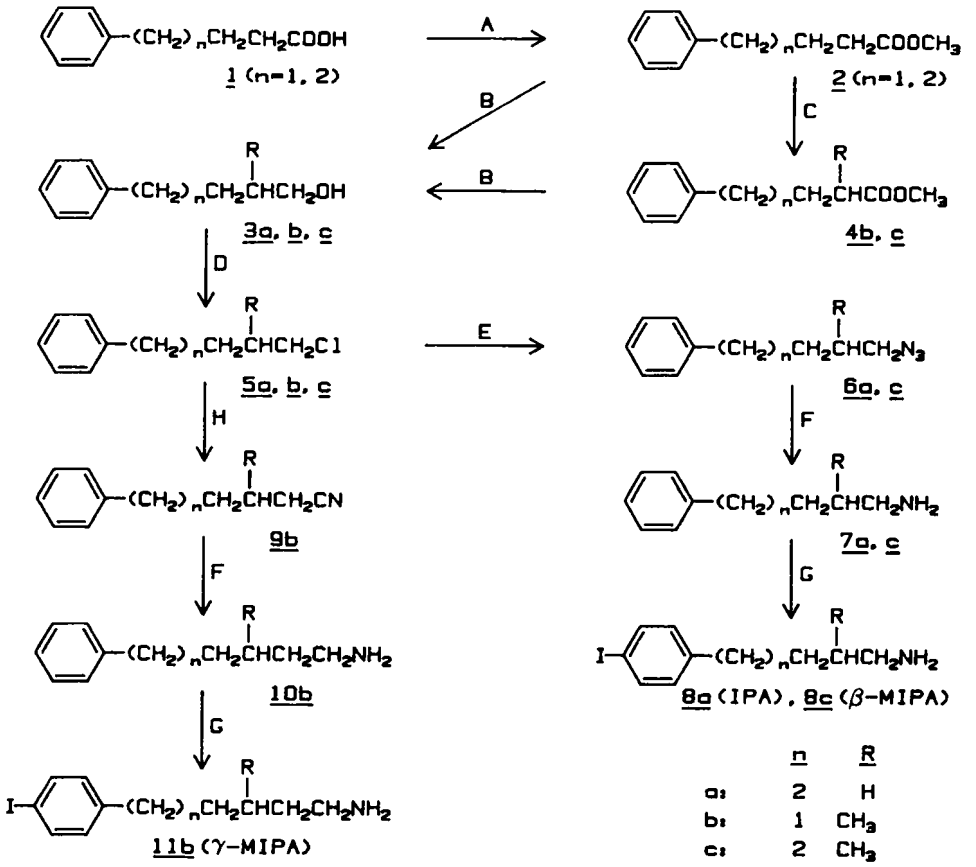
Based on the above, it is apparent that the study of the metabolic function of the pulmonary endothelial cells may provide an index of early lung injury. Also, such a study would be important in understanding the pathogenesis of lung diseases. Fowler *et al.*[21] demonstrated a rapid extraction of ^{11}C-*n*-octylamine by the rabbit lung after an intravenous injection of the radiopharmaceutical and proposed[22] the use of ^{11}C-labelled aliphatic amines as potential pulmonary dynamic imaging agents. The authors[22] demonstrated that an amino group and a relatively lipophilic alkyl group were two of the prerequisites for lung specificity. They have also shown that there is an optimum alkyl chain length, partition coefficient and pKa for optimal pulmonary uptake of carbon-11 labelled aliphatic amines. Among the homologues of aliphatic amines investigated by the authors lung uptake of injected carbon-11 labelled radiopharmaceuticals ranged from 2.18% for butylamine to 13% for tridecylamine 1 m post injection and lung uptake could be directly correlated with partition coefficient. It was also shown by McEwen and Sober[23] that rabbit serum MAO exhibited increasing affinity for *n*-alkylamines with increasing carbon chain length and the maximal velocity (V_{max}) increased with decreasing chain length.

Cyclotron-produced carbon-11 is an ideal radioisotope for dynamic imaging but its accessibility is limited. The user facility needs to be in close proximity to the radionuclide production site. For the researchers with no access to carbon-11 the various radioisotopes of iodine are often employed in radiopharmaceutical labelling. However, an iodine-aliphatic carbon bond is often subjected to bond cleavage because of its relatively low bond strength. This shortcoming could be partially alleviated by the judicious placement of the radioiodine atom or the selection of an alternate radiolabel. Iodine is not a natural component of the endogenous substrates of MAO. The effect of introduction of an iodine atom on the specificity and affinity between the substrate and the enzyme system is not known and can be ascertained only by evaluation in an *in vivo* or *in vitro* system.

RESULTS AND DISCUSSION

We have reported the radiochemical synthesis of ω-(4-[^{131}I]-iodophenyl)hexylamine and its β- and γ-methyl substituted analogues[24] for evaluation as potential lung imaging agents. The β- and γ-methyl substituents serve as modifiers of the physicochemical and biochemical properties of the radiopharmaceuticals thereby affecting their uptake and metabolism characteristics. In an effort to study the effect of chain length on the biological activity of the aryl substituted aliphatic amines we have synthesized ω-(4-[^{131}I]-iodophenyl)pentylamine and its β- and γ-methyl substituted analogues for evaluation as potential non-invasive pulmonary diagnostic agents. Variation of the alkyl chain length and the introduction of β- or γ-methyl substitution would elucidate the role of chain length, aromaticity, lipophilicity and substitution pattern on their biological disposition and interaction with the pulmonary MAO system. Results of biological evaluation of these radiopharmaceuticals will be reported elsewhere.

ω-(4-Iodophenyl)pentylamine (**8a**, IPA) and its β-methyl substituted analogue (**8c**, β-MIPA) were successfully synthesized from ω-phenylpentanoic acid and γ-methyl-ω-(4-iodophenyl)pentylamine (**11b**, γ-MIPA) was prepared from ω-phenylbutyric acid using established synthetic procedures (**Scheme 1**). Thus, ω-phenylpentanoic acid (**1**, n=2) and ω-phenylbutyric acid (**1**, n=1) were converted to the corresponding methyl esters (**2**, n=1, 2), according to the method of Everett *et al.*[25]. Acetyl chloride (CH_3COCl, 0.75 equivalent) was added slowly with stirring to a solution of 1 equivalent of the acid in methanol (CH_3OH, 50 mL). The solution was maintained at reflux temperature for 1 h and then cooled to room temperature. An additional 0.75 equivalent of CH_3COCl was then added. After 2 h of heating at reflux temperature one-half of the volume of solvent was removed by distillation under reduced pressure. The residual solution was diluted with water (40 mL) and extracted with ether (2 x 100 mL). The combined ether extracts were washed well with 2N Na_2CO_3 (2 x 50 mL) and water (2 x 50 mL) and



Scheme 1: Synthesis of ω-(4-iodophenyl)pentylamine and its β- and γ-methyl substituted analogues (IPA, β-MIPA, γ-MIPA). A = CH_3COCl/CH_3OH; B = LAH/Et_2O; C = $LDA/THF/CH_3I$; D = $SOCl_2$; E = NaN_3/Adogen^{tm} 464; F = LAH/THF; G = TTFA/NaI; H = NaCN/Adogen^{tm} 464.

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 the carbon atom α to the carbonyl function of the esters 2 with methyliodide (CH_3I) and lithium diisopropyl amide (LDA) in THF afforded the compounds **4b** and **4c** respectively. A solution of LDA in dry 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 vigorously at -78°C for 1 h and then at -10°C for 2 h. Solid ammonium chloride was added to the reaction mixture which was allowed to stand overnight, filtered and the solvent removed under reduced pressure. The residue 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.

The methyl esters 2 (n=2), **4b** and **4c** were converted to the corresponding alcohols (**3a**, **3b** and **3c**) by lithium aluminum hydride (LAH) in diethyl ether. A solution of the alcohol in dry ether was added slowly to a suspension of 4 equivalents of LAH in the same solvent at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 2 h, room temperature for 2 h and then at reflux temperature for 1 h. Sufficient ethylacetate was added slowly to the cooled reaction mixture 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 ($MgSO_4$).

The alcohols **3a** - **c** (1 equivalent) were converted to the corresponding alkyl chlorides (**5a** - **c**) by the action of thionyl chloride ($SOCl_2$, 2 equivalents) at reflux temperature for 2 h. Excess thionyl chloride was removed under reduced pressure and the alkyl chlorides were used as such without further purification.

The pentyl chlorides **5a** and **5c** obtained from 1 equivalent of the corresponding alcohols were refluxed overnight with 3 equivalents of sodium azide in water (as a 25% solution) and 0.05 equivalent of the phase-transfer catalyst, Adogen^{tm} 464 (methyltrialkyl(C_8-C_{10})ammonium chloride, Aldrich Chemicals)[26]. 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 azides **6a** and **6c** as a brown viscous liquid which was purified by silica gel column chromatography

(elution solvent 5% ethylacetate in hexane).

Conversion of the azides (**6a** and **6c**) to the amines (**7a** and **7c**) was accomplished by the reductive action of LAH in THF. One equivalent of the substrate to be reduced in dry THF was added slowly to a suspension of 4 equivalents of LAH in dry THF at 0°C under an atmosphere of nitrogen. The reaction mixture was stirred at 0°C for 2 h, room temperature for 0.5 h and then at reflux temperature for 2 h. The reaction mixture was cooled to room temperature and sufficient ethylacetate 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 $MgSO_4$.

To prepare the γ-methyl substituted analogue the butyl chloride **5b** was treated with sodium cyanide (NaCN) and Adogen^{tm} 464. The organic nitrile obtained (**9b**) was then treated with LAH in THF to afford the corresponding amine **10b**.

The amines **7a**, **7c** and **10b** in acetonitrile and an excess of thallium trifluoroacetate (TTFA)[27] were stirred vigorously for 15 m. NaI (4 - 6 equivalents) in a little water was added and stirring was continued for another 15 m. Solid sodium metabisulfite was added until the solution became colorless. The solvent was removed under reduced pressure. Water (0.5 - 1 mL) was added and the pH was adjusted to 12 - 14 with 20% NaOH followed by extraction with ether (3 x 1 mL). Evaporation of the ether under nitrogen afforded the desired iodoamines **8a**, **8c** and **11b** (IPA, β-MIPA and γ-MIPA) which were purified by high pressure liquid chromatography (HPLC) (solvent system 40% methanol in water). Proton magnetic resonance (^{1}H-NMR) spectroscopy of the iodinated products revealed a symmetrical split of the 4 aromatic protons indicating a *para* substitution pattern.

To prepare the radioiodinated amines [^{131}I]-**8a**, [^{131}I]-**8c** and [^{131}I]-**11b** ([^{131}I]-IPA, [^{131}I]-β-MIPA and [^{131}I]-γ-MIPA) a slight excess of the amine was used in the preparation of the thallate which was then treated with no-carrier-added (NCA) [^{131}I]-NaI. The reaction was terminated with solid sodium metabisulfite. The solvent was removed under reduced pressure. Water (0.5 mL) was added and the pH was adjusted to 12 - 14 with 20% NaOH. The ether extracts (3 x 0.5 mL) were evaporated to dryness under a stream of nitrogen after passing through a short column of anhydrous Na_2SO_4. The procedure resulted in the production of NCA radioiodinated amines of high specific activity. Co-chromatography of the radiolabelled amines with authentic "cold" iodinated amines on thin-layer chromatography (TLC) plates in different solvent systems and radio-HPLC indicated that the radiochemical purity was greater than 98%.

Radioiodination *via* thallation is a preferred iodination procedure for many aromatic systems. Thallation of phenyl moieties monosubstituted with alkyl groups occurs almost exclusively at the *para* position of the phenyl ring because of the bulkiness of the incoming thallate group. For the same reason, the use of TTFA also ensures the production of the highly desirable monosubstituted analogue, as multiple iodination of a small molecule would greatly affect its configuration, electronegativity, pKa, partition coefficient, enzyme specificity and affinity, properties that determine its transport characteristics, interaction with receptor site and metabolic fate. We have elected to place the radiolabel in the *para* position of the phenyl ring for reasons of enhanced biological activity, simplicity of synthetic procedure and stability of the label. Winchell *et al.*[28] reported that the order of brain activities of iodophenylalkyl amines was *para* > *meta* > *ortho* as related to the position of the iodo substituent on the phenyl ring. McEwen and Sober[23] also reported that rabbit serum MAO exhibited an increased affintiy for monoamine substrates possessing the electronegative *para* substituents chloro-, hydroxy- and methoxyphenol- which could interact with the polar site of the enzyme. Radioiodination of the phenyl moiety is readily achieved *via* the thallation step and requires no purification of the intermediate. The fact that an iodine-aromatic carbon bond is approximately 16% stronger than an iodine-aliphatic carbon bond[29], *in vivo* deiodination, if occurred, would be to a lesser extent. The eventual metabolic product of the iodinated monoamines is expected to be iodobenzoic acid which could be rapidly removed from circulation as the corresponding hippurate or glucuronate. The last factor also presents other significant advantages. Minimal circulating radioactive iodide and radioiodine-labelled metabolic products could be translated to lower radiation doses to patients and improved scintigraphic resolution.

EXPERIMENTAL

Infrared (IR) spectroscopy was performed on the "neat" compounds with a Nicolet FT-IR Spectrometer Model 5DX. ^{1}H-NMR spectra were recorded on a Varian EM390 90 MHz 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 systems 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^{tm} (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 **1** (n=2) and ω-phenylbutyric acid **1** (n=1) are commercial products of Aldrich Chemicals. Reagent grade solvents were used in chemical synthesis 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-Phenylmethylpentanoate (**2**, n=2). The titled compound was synthesized from ω-phenylpentanoic acid **1** (n=2) (14.24 g, 80 mmol), acetyl chloride (2 x 4.71 g, 2 x 60 mmol) and methanol (50 mL) 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); 2.4 (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).

ω-Phenylmethylbutanoate (**2**, n=1). The titled compound was synthesized from ω-phenylbutyric acid **1** (n=1) (13.12 g, 80 mmol), acetyl chloride (2 x 4.71 g, 2 x 60 mmol) and methanol (50 mL) in 85.9% yield (12.24 g): IR: ν max 1745 cm^{-1} (ester C=O); ^{1}H-NMR: δ 1.8 - 2.1 (m, 2H, H-3); 2.3 (t, 2H, H-2); 2.6 (t, 2H, H-4); 3.6 (s, 3H, -OCH_3-1); 7.2 - 7.4 (m, 5H, -C_6H_5-4).

ω-Phenylpentanol (**3a**). Reaction of compound **2** (n=2) (1.92 g, 10 mmol) with LAH (1.51 g, 40 mmol) afforded the titled compound as a colorless liquid (1.42 g, 86.5%). IR: ν max 3320 cm^{-1} (-OH); ^{1}H-NMR: δ 1.2 - 1.9 (m, 7H, H-2, H-3, H-4, -OH-1); 2.7 (t, 2H, H-5); 3.7 (t, 2H, H-1); 7.1 - 7.5 (m, 5H, -C_6H_5-5).

α-Methyl-ω-phenylmethylpentanoate (**4c**). Reaction of **2** (n=2) (1.92 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 (1.70 g, 12 mmol) and dry THF (50 mL) afforded the methylated ester in 89% yield (1.84 g). IR: ν max 1737 cm^{-1} (ester C=O); ^{1}H-NMR: δ 1.2 (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); 3.6 (s, 3H, -OCH_3-1); 7.1 - 7.4 (m, 5H, -C_6H_5-5).

β-Methyl-ω-phenylpentanol (**3c**). Reaction of compound **4c** (1.03 g, 5 mmol) with LAH in ether (0.76 g, 20 mmol) afforded the titled compound as a colorless liquid (0.81 g, 91%). 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).

α-Methyl-ω-phenylmethylbutanoate (**4b**). Reaction of **2** (n=1) (1.78 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 (1.70 g, 12 mmol) and dry

THF (50 mL) afforded the methylated ester in 81.8% yield (1.57 g). IR: ν max 1737 cm^{-1} (ester C=O); ^{1}H-NMR: δ 1.2 (d, 3H, $-CH_3$-2); 1.4 - 2.1 (m, 2H, H-3); 2.3 (m, 1H, H-2); 2.6 (t, 2H, H-4); 3.7 (s, 3H, $-OCH_3$-1); 7.1 - 7.4 (m, 5H, $-C_6H_5$-4).

β-Methyl-ω-phenylbutanol (**3b**). Reaction of **4b** (1.92 g, 10 mmol) with LAH (1.51 g, 40 mmol) in dry ether afforded **3b** in 97% chemical yield (1.59 g). IR: ν max 3323 (-OH); ^{1}H-NMR: δ 0.9 (d, 3H, $-CH_3$-2); 1.2 - 1.9 (m, 4H, H-2, H-3, -OH-1); 2.6 (t, 2H, H-4); 3.5 (m, 2H, H-1); 7.1 - 7.4 (m, 5H, $-C_6H_5$-4).

ω-Phenylpentyl azide (**6a**). The alkyl chloride **5a** (0.91 g, 5 mmol) was treated with sodium azide (0.098 g, 15 mmol) and Adogen^{tm} 464 (0.116 g, 0.25 mmol) overnight at reflux temperature. The azide was obtained after column chromatography as a brown viscous liquid (0.70 g, 69.8%). IR: ν max 2100 cm^{-1} ($-N_3$); ^{1}H-NMR: δ 1.4 - 2.0 (m, 6H, H-2, H-3, H-4); 2.7 (t, 2H, H-5); 3.3 (t, 2H, H-1); 7.2 - 7.5 (m, 5H, $-C_6H_5$-5).

β-Methyl-ω-phenylpentylazide (**6c**). Reaction of the crude alkyl chloride **5c** (0.98 g, 5 mmol) with sodium azide (0.098 g, 15 mmol) and Adogen^{tm} 464 (0.116 g, 0.25 mmol) afforded the titled compound **6c** in 78.8% yield (0.80 g). IR: ν max 2098 cm^{-1} ($-N_3$); ^{1}H-NMR: δ 0.9 (d, 3H, $-CH_3$-2); 1.2 - 2.0 (m, 5H, H-2, H-3, H-4); 2.6 (t, 2H, H-5); 3.2 (d, 2H, H-1); 7.1 - 7.4 (m, 5H, $-C_6H_5$-5).

ω-Phenylpentylamine (**7a**). Reduction of the azide **6a** (0.737 g, 3.9 mmol) by LAH (0.592 g, 15.6 mmol) in dry THF afforded the desired alkyl amine as a pale yellow liquid (0.41 g, 65.0%). IR: ν max 3360 cm^{-1} ($-NH_2$); ^{1}H-NMR: δ 0.9 - 1.8 (m, 6H, H-2, H-3, H-4); 2.1 (m, 2H, $-NH_2$-1); 2.3 - 2.9 (m, 4H, H-1, H-5); 7.2 - 7.5 (m, 5H, $-C_6H_5$-5).

β-Methyl-ω-phenylpentylamine (**7c**). Reduction of the azide **6c** (0.304 g, 1.5 mmol) with LAH (0.227 g, 6 mmol) in dry THF afforded the methylated pentylamine in 50.5% yield (0.134 g). IR: ν max 3296 cm^{-1} ($-NH_2$); ^{1}H-NMR: δ 0.9 (d, 3H, $-CH_3$-2); 1.1 - 1.9 (m, 5H, H-2, H-3, H-4); 2.0 (m, 2H, $-NH_2$-1); 2.3 -2.8 (m, 4H, H-1, H-5); 7.1 - 7.5 (m, 5H, $-C_6H_5$-5).

ω-(4-Iodophenyl)pentylamine (**8a**, **IPA**). Reaction of the alkyl amine **7a** (22 mg, 0.14 mmol) with TTFA (87.8 mg, 0.16 mmol) and NaI (63 mg, 0.42 mmol) afforded **IPA** (35.1 mg, 90%). IR: ν max 3360 cm^{-1} ($-NH_2$); ^{1}H-NMR: δ 1.1 - 1.8 (6H, H-2, H-3; H-4); 2.1 (m, 2H $-NH_2$-1); 2.5 - 2.8 (m, 4H, H-1, H-5); 7.2 (d, 2H, H-2', H-6'); 7.3 (d, 2H, H-3', H-5').

β-Methyl-ω-(4-iodophenyl)pentylamine (**8c**, **β-MIPA**). Treatment of **7c** (8.8 mg, 0.05 mmol) with TTFA (38 mg, 0.07 mmol) and NaI (42 mg, 0.28 mmol) afforded the iodoamine in 89.6% yield (13.5

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, 5H, H-2, H-3, H-4); 2.0 (m, 2H, -NH_2-1); 2.3 - 2.8 (m, 4H, H-1, H-5); 7.2 (d, 2H, H-2', H-6'); 7.3 (d, 2H, H-3', H-5').

ω-(4-[^{131}I]-Iodophenyl)pentylamine ([^{131}I]-**8a**, [^{131}I]-**IPA**). Reaction of **7a** (1 mg, 0.006 mmol) with TTFA (2.1 mg, 0.004 mmol) and NCA [^{131}I]-NaI (120 GBq) afforded [^{131}I]-**IPA** in 30% radiochemical yield (36 GBq, calculated specific activity 20 - 40 TBqmmol^{-1}). Radio-HPLC and co-chromatography with authentic unlabelled compounds on TLC plates indicated a radiochemical purity of greater than 98%.

β-Methyl-ω-(4-[^{131}I]-iodophenyl)pentylamine ([^{131}I]-**8c**, [^{131}I]-**β-MIPA**). Reaction of **7c** (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 28% radiochemical yield (34 GBq, calculated specific activity 20 - 40 TBqmmol^{-1}). Analysis by radio-HPLC and TLC indicated a radiochemical purity of greater than 98%.

β-Methyl-ω-phenylbutyl nitrile (**9b**). The alkyl chloride **5b** (2.19 g, 12 mmol) was refluxed overnight with sodium cyanide (2.90 g, 60 mmol, as a 33% aqueous solution) and Adogen^{tm} 464 (0.06 g, 0.13 mmol). 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 (1.5 g, 72.4%). IR: ν max 2254 cm^{-1} (-CN); ^{1}H-NMR: δ 1.15 (d, 3H, -CH_3-2); 1.5 - 2.1 (m, 3H, H-2, H-3); 2.3 (d, 2H, H-1); 2.7 (t, 2H, H-4); 7.1 - 7.5 (m, 5H, -C_6H_5-4).

γ-Methyl-ω-phenylpentylamine (**10b**). A solution of **9b** (1.038 g, 6 mmol) in dry THF (20 mL) was reduced by LAH (0.91 g, 24 mmol) in dry THF (80 mL) as previously described. The mixture was filtered and the filtrate was evaporated to dryness 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 **10b** as a pale yellow viscous liquid (0.849 g, 80%). IR: ν max 3279 cm^{-1} (-NH_2); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-3); 1.1 - 1.8 (m, 5H, H-2, H-3, H-4); 2.1 (m, 2H, -NH_2-1, exchangeable with D_2O); 2.4 - 2.8 (m, 4H, H-1, H-5); 7.1 - 7.5 (m, 5H, -C_6H_5-5).

γ-Methyl-ω-(4-iodophenyl)pentylamine (**11b**, **γ-MIPA**). Treatment of **10b** (4.7 mg, 0.027 mmol) with a slight excess of TTFA (16 mg, 0.03 mmol) and NaI (19 mg, 0.13 mmol) afforded **11b** (7.4 mg, 92%). IR: ν max 3275 cm^{-1} (-NH_2); ^{1}H-NMR: δ 0.9 (d, 3H, -CH_3-3); 1.1 -1.8 (m, 5H, H-2, H-3, H-4); 2.1

(m, 2H, -NH_2-1); 2.4 - 2.8 (m, 4H, H-1, H-5); 7.2 (d, 2H, H-2', H-6'); 7.3 (d, 2H, H-3', H-5').

γ-Methyl-ω-(4-[^{131}I]-iodophenyl)pentylamine ([^{131}I]-**11b**, [^{131}I]-γ-MIPA). The titled compound was prepared from **10b** (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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