RADIOIODINATED ALIPHATIC AMINES AS POTENTIAL PULMONARY IMAGING AGENTS: III. SYNTHESIS OF 6-[^{131}I]-IODOHEXYLAMINE AND ITS β-ALKYL SUBSTITUTED ANALOGUES.

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SUMMARY

The aliphatic amines, 2-methyl- and 2-isopropyl- substituted 6-hydroxy-1-hexylamines were synthesized from ethyl-6-hydroxyhexanoate in 22% and 11% overall chemical yield respectively. 6-hydroxy-1-hexylamine was available commercially. 6-hydroxy-1-hexylamine and its 2-methyl- and 2-isopropyl- substituents were successfully radioiodinated with trimethylsilyl polyphosphate and [^{131}I]-NaI/NaI to afford the corresponding 6-[^{131}I]-labelled amines in 67%, 61% and 55% radiochemical yield respectively and greater than 98% radiochemical purity (specific activity 340 GBq mmol^{-1}).

Key words: radioiodination, iodohexanes, PPSE, MAO, pulmonary, ^{131}I.

INTRODUCTION

Lung injury and diseases due to many widely different causative agents can result in a compromise of gaseous exchange function. Conventional nuclear and non-nuclear diagnostic procedure suffer the drawbacks of a lack of sensitivity and, may be, specificity. For this reason, there is a need for diagnostic tests that are capable of detecting lung injury at an early stage. While the pathogenesis of lung injury remains unclear, damage to the endothelial cells, among other cell types, have been implicated in many cases[1,2]. Besides gaseous exchange, the lung is also involved in certain non-respiratory functions. Compounds as different as peptides, amines, nucleosides and lipids are hydrolyzed, oxidized and/or taken up by the lungs, a function which is directly related to the endothelial cell number[3,4,5,6]. The endothelial cells are the single most common cell type in the lung, representing up to 40% of the total lung cells. If endothelial cell damage is indeed an important initiating event in the pathogenesis of some lung injury, early injury may be reflected in a loss of endothelial cell functions and consequently, an impairment in their barrier and metabolic functions[7,8,9,10,11,12]. Gillis and Catravas[7] have established that the rate of

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extraction or metabolism of several vasoactive substances are altered during lung injury induced by drug, environment or surgery. Moreover, there is ample evidence that impairment of such metabolic functions of the microvasculature can be observed prior to, or in the absence of either morphological or clinical manifestation of injury. Accordingly, pulmonary endothelial cells are the prime targets for probes of pulmonary dysfunction at the biochemical level.

Fowler *et al.*[13] demonstrated a rapid extraction of ^{11}C-*n*-octylamine by the rabbit lung after an intravenous injection of the radiopharmaceutical and proposed[14] the use of ^{11}C-labelled aliphatic amines as potential pulmonary imaging agents. The authors[14] 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 optimum uptake of C-11 labelled aliphatic amines. Among the homologues of aliphatic amines investigated by the authors lung uptake of injected C-11 labelled radiopharmaceuticals ranged from 2.1% for butylamine to 13% for tridecylamine 1 m post injection and lung uptake could be directly correlated with partition coefficient.

In our view, the agent of choice for the study of lung function must be removed from the blood with a near 100% efficiency on the first pass through the pulmonary system. It should be metabolized by the monoamine oxidase (MAO) enzyme system at a rate slow enough to allow sufficient time for data collection by conventional imaging techniques, but should still be cleared from the lung at a fast enough rate to permit the study of dynamic processes to be monitored with a short-lived isotope such as I-122. However, the use of I-122 with a physical half-life of 3.6 m is inconsistent with our reported reaction time of 30 m. Incorporation of I-122 using a halogen exchange reaction is a possibility which has yet to be investigated. Against this expectation is the reality associated with the complexity of the MAO system which makes a coherent and specific analysis of the effect of altering amine structures or their rate of metabolism rather difficult.

The *in vivo* metabolism of monoamines by the lung endothelium is complicated by the presence of a number of enzyme systems. The current thinking is that monoamines are firstly metabolised *via* oxidative deamination to the corresponding aldehydes which may be further metabolized to water soluble products and be excreted in the urine[15,16,17,18]. Those aldehydes formed from the aliphatic amines are then oxidized to the appropriate carboxylic acid by an aldehyde dehydrogenase, followed by complete decarboxylation to carbon dioxide by the fatty acid β-oxidation enzyme system[13]. It is precisely this metabolic sequence that we intend to investigate through the selection of appropriately placed radiolabel and functional groups.

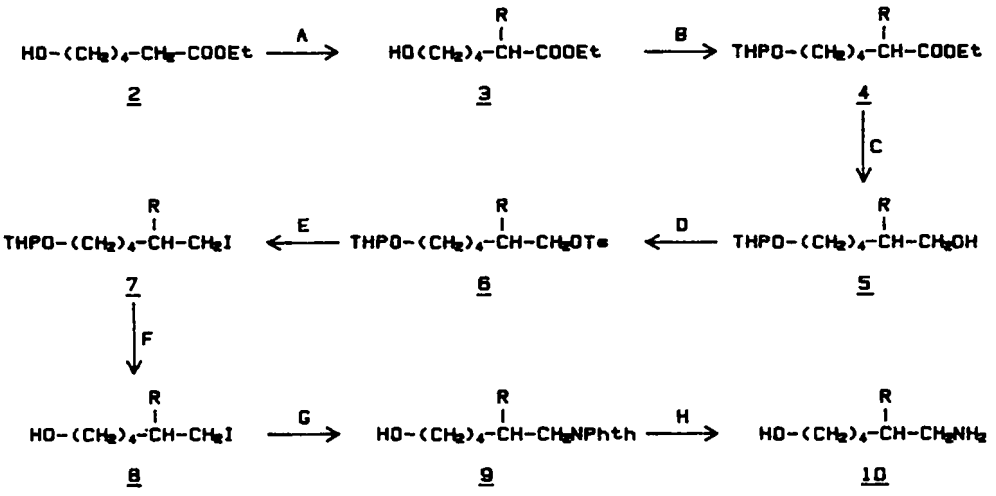
The rationale behind our approach in the selection of compounds is based on our understanding of the structure-activity relationship of the MAO system. We have synthesized a series of radiolabelled β- and γ-monosubstituted branched chain hexylamine[19,20] and pentylamine[21] derivatives for evaluation of their pulmonary uptake and clearance. These compounds were selected because they represent an almost constant pKa (9.5) which is the optimum range for lung uptake. While the α-methylene remains unsubstituted, thus allowing for metabolism by the monoamine oxidase (MAO) system, the β-methylene was monosubstituted with alkyl groups which vary both in size and lipophilic character. This may alter the orientation of the substrate on the active site of the MAO system sufficiently to affect the rate of metabolism of these compounds and thus provides us with an ideal radiopharmaceutical useful for tomographic lung function studies. This approach is extremely important in the design of labelled compounds for use by both positron emission tomography (PET) and single photon tomography (SPECT).

RESULTS AND DISCUSSION

We have synthesized a number of ω-[^{131}I]-labelled straight chain and β-monosubstituted aliphatic amines for evaluation as potential lung imaging agents. The α-position is open to permit MAO enzymatic reactions. The β-position is monosubstituted with various alkyl groups to alter the orientation and interaction between the substrates and the MAO enzyme system.

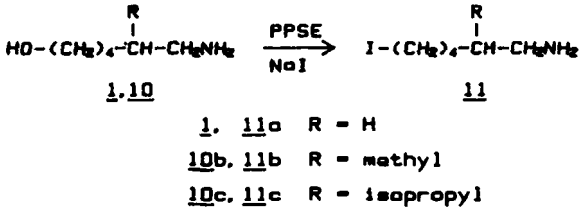
2-methyl- and 2-isopropyl-6-hydroxy-1-hexylamines **10b** and **10c** were synthesized from ω-caprolactone using established synthetic procedures (Scheme 1). Thus, ethyl-6-hydroxy-hexanoate **2** was synthesized in 90% yield by the conventional acid catalyzed ring opening of ω-caprolactone with dry ethanol.

Alkylation of the carbon atom α to the carbonyl function of the ester **2** with methyliodide (MeI) or isopropyliodide (Me_2CHI) and lithium diisopropyl amide (LDA) in tetrahydrofuran (THF) afforded the compounds **3b** or **3c** 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, 1.5 M solution) at -78°C was treated successively with 2 equivalents of hexamethylphosphoramide (HMPA) and 1 equivalent of the ester in dry THF. The reaction mixture was stirred at -78°C for 2 h. Then 1.2 equivalents of an appropriate alkyliodide was added in one portion and stirring was continued at -78°C for 1 h and then the temperature was slowly raised to -10°C. 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 50 mL) which was washed successively with water (2 x 50 mL) and



A=LDA/THF/RI; B=DHP/CH_2Cl_2/TsOH; C=LAH/Et_2O;
D=TsCl/pyridine; E=NaI/acetone; F=TsOH/MeOH;
G=potassium phthalimide/DMF; H=hydrazine/MeOH.

Scheme 1: Synthesis of 2-Alkyl-6-hydroxy-1-hexylamines



Scheme 2: Synthesis of 6-Iodo-1-hexylamines

saturated NaCl solution (2 x 50 mL) and then dried over anhydrous sodium sulphate (Na_2SO_4). Removal of the solvent left a pale yellow oil which was distilled under reduced pressure to yield the corresponding alkylated esters as colorless oils. In all cases the alkylated esters showed no optical rotation indicating a racemic mixture.

The ω-hydroxyl groups of the esters 3b and 3c were protected as the tetrahydropyranyl ethers 4b and 4c respectively by treatment with dihydropyran and *p*-toluenesulfonic acid prior to reduction of the esters to the alcohols 5b and 5c. One equivalent of ester 3 and a catalytic amount of *p*-toluenesulfonic

acid were added to a magnetically stirred solution of 2 equivalents of dihydropyran in methylene chloride at 0°C. Stirring was continued at 0°C for 2 h and the reaction mixture was successively washed with saturated sodium bicarbonate solution (3 x 50 mL), water (2 x 50 mL) and saturated sodium chloride solution (3 x 50 mL) and dried over anhydrous magnesium sulphate ($MgSO_4$). Removal of the solvent yielded a yellow liquid which was purified either by distillation under reduced pressure in the case of compound **4b** or by silica gel column chromatography (elution solvent 10% ethylacetate in hexane) in the case of compound **4c** to yield the tetrahydropyranyl ethers as colourless oils.

The ethyl esters **4b** and **4c** were reduced to the corresponding alcohols **5b** and **5c** by lithium aluminum hydride (LAH) in diethyl ether. A solution of the ester **4b** or **4c** in dry ether was added slowly to a suspension of 6 equivalents of LAH in the same solvent at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 1 h, room temperature for 2 h and then at reflux temperature for 2 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 $MgSO_4$. Removal of ether yielded the alcohols **5b** or **5c** as colorless liquids which were used as such for further reactions.

The primary alcoholic groups of **5b** and **5c** were then derivatized with *p*-toluenesulfonyl chloride in pyridine to yield the tosylates **6b** and **6c** respectively. A mixture of alcohol **5b** or **5c** in pyridine and 1.5 equivalents of *p*-toluenesulfonyl chloride was stirred at 0°C for 1 h. The reaction mixture was refrigerated overnight and then poured onto ice (5 g) and extracted with methylene chloride (2 x 50 mL). The combined organic extracts were washed well with water (5 x 50 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent yielded the tosylates **6b** or **6c** as viscous liquid in quantitative yield.

The tosylates **6b** and **6c** were converted to the iodides **7b** and **7c** respectively by treatment with sodium iodide (NaI) in acetone. A solution of the tosylate **6b** or **6c** in acetone was refluxed overnight with NaI (4 equivalents). The cooled reaction mixture was filtered and the solvent removed under reduced pressure. The residue was extracted with methylene chloride (2 x 50 mL). The combined methylene chloride extracts were washed well with water (2 x 25 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent yielded the iodide **7b** or **7c** as a pale yellow liquid which was used as such for further reactions.

The ω-hydroxyl groups were then deprotected by treatment with *p*-toluenesulfonic acid. A methanolic solution of the tetrahydropyranyl ether **7b** or **7c** was stirred at room temperature for 4 h with

a catalytic amount of *p*-toluenesulfonic acid. Methanol was removed by distillation and the residue left behind was extracted with methylene chloride (2 x 50 mL). The organic layer was washed successively with saturated sodium bicarbonate solution (2 x 50 mL) and water (2 x 50 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded **8b** or **8c** as a pale yellow viscous liquid.

The iodides **8b** and **8c** were then converted to the phthalimido derivatives **9b** and **9c** by treatment with potassium phthalimide in dry dimethylformamide (DMF). A mixture of the iodides **8b** or **8c** in dry DMF and potassium phthalimide (1.5 equivalents) was heated to 120°C for 8 h with stirring. DMF was removed by distillation under reduced pressure and the residue obtained was poured onto ice (5 g) and extracted with methylene chloride (2 x 50 mL). The combined organic extracts were washed well with water (2 x 50 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent yielded the phthalimides **9b** or **9c** as brown viscous oils which were purified by silica gel column chromatography (elution solvent 20% ethylacetate in hexane).

Hydrazinolysis of **9b** and **9c** afforded the ω-hydroxyamines **10b** and **10c** respectively. The phthalimido derivatives **9b** or **9c** (1 equivalent) in dry methanol was treated with 1.5 equivalents of hydrazine hydrate under reflux for 4 h. On cooling the resultant solution to 0°C, the phthalazide separated out as a white powder which was removed by filtration. The residue obtained after the removal of methanol from the filtrate was purified by silica gel column chromatography (elution solvent chloroform:methanol:triethylamine 65:35:5). The hydroxyamines **10b** or **10c** was obtained as a colorless oil.

6-hydroxy-1-hexylamine **1** was available commercially. The hydroxyamines **1**, **10b** and **10c** were converted to the corresponding iodoamines **11a** - **c** using trimethylsilyl polyphosphate (PPSE)[22] and NaI (Scheme 2). PPSE is easily produced in quantitative yield provided care has been taken to dry the reagents beforehand and that the reaction is conducted under dry nitrogen. The use of toluene was found unsatisfactory in spotting TLC plates without the use of a diluting solvent such as methanol. Methylethyl ketone (MEK) was determined to be an equally acceptable solvent for the iodination process and consequently replaced toluene in the iodination reaction step. Radioiodination was carried out in a similar fashion using [^{131}I]-NaI/NaI. The "cold" and "hot" iodinated alkylamines are chemically unstable. The loss of radioiodine occurred readily and was most extensive with 6-iodohexylamine (20% in less than 30 min). Dehalogenation of the 2-methyl substituted analogue proceeded at about the same rate. The isopropyl analogue was relatively more stable with 18% deiodination in 30 min. The low iodine-aliphatic carbon bond strength certainly contributes to their instability which is also compounded by the ease of formation of a ring system as a result of a displacement reaction between the iodine and nitrogen atom. The slightly greater stability of the iso-propyl derivative is probably due to the steric interference of the

isopropyl group. The implication of this finding is that care must be exercised in the interpretation of biodistribution data.

The spectral data of the compounds reported here are in accordance with their respective structures.

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. Mass spectra (MS) were determined with a Hewlett Packard 5995A Gas Chromatograph/Mass Spectrometer. 6-hydroxy-1-hexylamine is a commercial product 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) and was diluted with carrier NaI before use (final specific activity approximately 340 GBq mmol^{-1}).

Ethyl-6-hydroxy-2-methylhexanoate **3b**. The titled compound was synthesized from ethyl-6-hydroxyhexanoate **2** (2.0 g, 12.5 mmol), DIA (2.53 g, 25 mmol), HMPA (4.48 g, 25 mmol), *n*-BuLi (1.6 g, 25 mmol), methyl iodide (2.13 g, 15 mmol) and dry THF (50 mL) in 78% yield (1.7 g). b.p.: 76-78°C/0.25 mm; IR: ν max 3510 cm^{-1} (-OH); 1745 cm^{-1} (-C=O); ^{1}H-NMR: δ 1.1 (d, 3H, J

= 6Hz, -CH_3-2); 1.3 (t, 3H, J = 6Hz, -CH_2-CH_3-1); 1.3 - 2.0 (m, 7H, H-3, H-4, H-5, -OH-6); 2.4 (m, 1H, H-2); 3.6 (t, 2H, J = 6Hz, H-6); 4.2 (q, 2H, J = 7Hz, -CH_2-CH_3-1); MS: (m/e) 174.

Ethyl-6-hydroxy-2-isopropylhexanoate **3c**. The titled compound was synthesized from ethyl-6-hydroxyhexanoate **2** (2.0 g, 12.5 mmol), DIA (2.53 g, 25 mmol), HMPA (4.48 g, 25 mmol), *n*-BuLi (1.6 g, 25 mmol), isopropyl iodide (2.25 g, 15 mmol) and dry THF (50 mL) in 58% yield (1.47 g). b.p.: 80-82°C/0.25 mm; IR: ν max 3510 cm^{-1} (-OH); 1745 cm^{-1} (-C=O); ^{1}H-NMR: δ 0.9 (d, 3H, J = 6Hz, -CH-CH_3-2); 1.3 (t, 6H, J = 6Hz, -CH_2-CH_3-1, -CH-CH_3-2); 1.4 - 2.2 (m, 8H, H-3, H-4, H-5, -OH-6, -$CH(CH_3)_2$-2); 2.4 (m, 1H, H-2); 3.6 (t, 2H, J = 6Hz, H-6); 4.2 (q, 2H, J = 7Hz, -CH_2-CH_3-1); MS: (m/e) 202.

Ethyl-2-methyl-6-tetrahydropyranyloxyhexanoate **4b**. Reaction of compound **3b** (4.35 g, 25 mmol) with dihydropyran (4.2 g, 50 mmol) in methylene chloride (100 mL) in the presence of catalytic amount of *p*-toluenesulfonic acid afforded the titled compound as a colorless liquid in 91.4% yield (5.9 g). b.p.: 92-95°C/0.25 mm; IR: ν max 1745 cm^{-1} (-C=O); ^{1}H-NMR: δ 1.1 (d, 3H, J = 6Hz, -CH_3-2); 1.3 (t, 3H, J = 6Hz, -CH_2-CH_3-1); 1.3 - 2 (m, 12H, H-3, H-4, H-5, H-2', H-3', H-4'); 2.5 (m, 1H, H-2); 3.3 - 3.8 (m, 4H, H-6, H-5'); 4.2 (q, 2H, J = 7Hz, -CH_2-CH_3-1); 4.6 (m, 1H, H-1'); MS: (m/e) 258.

Ethyl-2-isopropyl-6-tetrahydropyranyloxyhexanoate **4c**. Reaction of compound **3c** (2.5 g, 12.37 mmol) with dihydropyran (2.1 g, 25 mmol) in methylene chloride (50 mL) in the presence of a catalytic amount of *p*-toluenesulfonic acid yielded **4c** as a yellow viscous liquid which was purified by silica gel column chromatography (elution solvent 10% ethylacetate in hexane) to obtain the titled compound as a colorless liquid in 90.4% yield (3.2 g). IR: ν max 1737 cm^{-1} (-C=O); ^{1}H-NMR: δ 0.9 (d, 3H, J = 6Hz, -CH-CH_3-2); 1.3 (m, 6H, -CH_2-CH_3-1, -CH-CH_3-2); 1.4 - 2.1 (m, 13H, H-3, H-4, H-5, H-2', H-3', H-4', -$CH(CH_3)_2$-2); 2.35 (m, 1H, H-2); 3.3 - 3.8 (m, 4H, H-6, H-5'); 4.2 (q, 2H, J = 7Hz, -CH_2-CH_3-1); 4.5 (m, 1H, H-1'); MS: (m/e) 286.

2-Methyl-6-tetrahydropyranyloxy-1-hexanol **5b**. Reaction of compound **4b** (3.87 g, 15 mmol) with LAH (3.41 g, 90 mmol) in ether (100 mL) afforded the titled compound as a colorless liquid (2.61 g, 80%). IR: ν max 3410 cm^{-1} (-OH); ^{1}H-NMR: δ 0.9 (d, 3H, J = 6Hz, -CH_3-2); 1.3 - 1.9 (m, 14H, H-2, H-3, H-4, H-5, H-2', H-3', H-4', -OH-1); 3.3 - 3.8 (m, 6H, H-1, H-6, H-5'); 4.6 (m, 1H, H-1').

2-Isopropyl-6-tetrahydropyranyloxy-1-hexanol **5c**. Reaction of compound **4c** (3.2 g, 11.2 mmol) with LAH (2.55 g, 67.2 mmol) in ether (75 mL) afforded the titled compound as a colorless liquid (2.48 g, 91%). IR: ν max 3727 cm^{-1} (-OH); ^{1}H-NMR: δ 0.9 (d, 6H, J = 6Hz, -$CH(CH_3)_2$-2); 1.1 - 2.0 (m,

15H, H-2, H-3, H-4, H-5, -C<u>H</u>$(CH_3)_2$-2, H-2', H-3', H-4', -OH-1); 3.3 - 4.1 (m, 6H, H-1, H-6, H-5'); 4.6 (m, 1H, H-1').

<u>2-Methyl-6-tetrahydropyranyloxy-hexane-1-tosylate</u> **<u>6b</u>**. The primary alcohol **<u>5b</u>** (2.7 g, 12.5 mmol) was treated with *p*-toluenesufonyl chloride (3.57 g, 18.75 mmol) in pyridine (40 mL) to yield the tosylate **<u>6b</u>** as a viscous liquid in quantitative yield (4.6 g, 99%). IR: ν max 1605 cm^{-1} (aromatic =C-H); ^{1}H-NMR: δ 1.0 (d, 3H, J = 6Hz, -CH_3-2); 1.2 - 1.9 (m, 13H, H-2, H-3, H-4, H-5, H-2', H-3', H-4'); 2.4 (s, 3H, -C_6H_5-C<u>H</u>$_3$); 3.3 - 4.1 (m, 6H, H-1, H-6, H-5'); 4.6 (m, 1H, H-1'); 7.2 - 8.0 (d of d, 4H, J = 9Hz, -C_6H_4).

<u>2-Isopropyl-6-tetrahydropyranyloxy-hexane-1-tosylate</u> **<u>6c</u>**. The primary alcohol **<u>5c</u>** (2.4 g, 10.0 mmol) was treated with *p*-toluenesufonyl chloride (2.86 g, 15.0 mmol) in pyridine (40 mL) to yield the tosylate **<u>6c</u>** as a viscous oil in 81% yield (3.2 g). IR: ν max 1606 cm^{-1} (aromatic =C-H); ^{1}H-NMR: δ 0.9 (d, 6H, J = 6Hz, -CH(C<u>H</u>$_3$)$_2$-2); 1.2 - 2.1 (m, 14H, H-2, H-3, H-4, H-5, -C<u>H</u>$(CH_3)_2$-2, H-2', H-3', H-4'); 2.4 (s, 3H, -C_6H_5-C<u>H</u>$_3$); 3.2 - 4.2 (m, 6H, H-1, H-6, H-5'); 4.6 (m, 1H, H-1'); 7.2 - 8.1 (d of d, 4H, J = 9Hz, -C_6H_4).

<u>1-Iodo-2-methyl-6-tetrahydropyranyloxyhexane</u> **<u>7b</u>**. Treatment of the tosylate **<u>6b</u>** (4.6 g, 12.5 mmol) with NaI (7.5 g, 50 mmol) in acetone (150 mL) afforded the iodide **<u>7b</u>** as a pale yellow viscous liquid in 88.3% yield (3.6 g). ^{1}H-NMR: δ 1.0 (d, 3H, J = 6Hz, -CH_3-2); 1.2 - 1.9 (m, 13H, H-2, H-3, H-4, H-5, H-2', H-3', H-4'); 3.2 (d, 6H, J = 7Hz, H-1); 3.3 - 4.1 (m, 4H, H-6, H-5'); 4.6 (m, 1H, H-1').

<u>1-Iodo-2-isopropyl-6-tetrahydropyranyloxyhexane</u> **<u>7c</u>**. Treatment of the tosylate **<u>6c</u>** (3.2 g, 8.0 mmol) with NaI(4.8 g, 32 mmol) in acetone (100 mL) afforded the iodide **<u>7c</u>** as a pale yellow viscous liquid in 88.0% yield (2.5 g). ^{1}H-NMR: δ 0.9 (d, 6H, J = 6Hz, -CH(C<u>H</u>$_3$)$_2$-2); 1.1 - 1.9 (m, 14H, H-2, H-3, H-4, H-5, -C<u>H</u>$(CH_3)_2$-2, H-2', H-3', H-4'); 3.2 (d, 6H, J = 7Hz, H-1); 3.3 - 4.1 (m, 4H, H-6, H-5'); 4.6 (m, 1H, H-1').

<u>1-iodo-2-methyl-6-hexanol</u> **<u>8b</u>**. Treatment of the tetrahydropyranyl ether **<u>7b</u>** (3.6 g, 11 mmol) in methanol (150 mL) with a catalytic amount of *p*-toluenesulfonic acid yielded the titled alcohol **<u>8b</u>** as a pale yellow viscous liquid (2.2 g, 82.4%). IR: ν max 3340 cm^{-1} (-OH); ^{1}H-NMR: δ 1.0 (d, 3H, J = 6Hz,-CH_3-2); 1.1 - 2.0 (m, 8H, H-2, H-3, H-4, H-5, -OH-6); 3.2 (d, 6H, J = 7Hz, H-1); 3.7 (t, 2H, J = 6Hz, H-6).

<u>1-iodo-2-isopropyl-6-hexanol</u> **<u>8c</u>**. Treatment of the tetrahydropyranyl ether **<u>7c</u>** (1.0 g, 2.8 mmol) in

methanol (50 mL) with a catalytic amount of *p*-toluenesulfonic acid yielded the titled alcohol **8c** as a pale yellow viscous liquid (0.7 g, 92%). IR: ν max 3328 cm^{-1} (-OH); ^{1}H-NMR: δ 0.9 (d, 6H, J = 6Hz, $-CH(C\underline{H}_3)_2$-2); 1.2 - 2.0 (m, 9H, H-2, H-3, H-4, H-5, -OH-6, $-C\underline{H}(CH_3)_2$-2); 3.3 (d, 6H, J = 7Hz, H-1); 3.7 (t, 2H, J = 6Hz, H-6).

N-(6-Hydroxy-2-methylhexyl)-phthalimide **9b**. Reaction of the iodide **8b** (2.2 g, 9.1 mmol) with potassium phthalimide (2.5 g, 13.65 mmol) in dry DMF (40 mL) afforded the phthalimide **9b** as a pale yellow oil in 76% yield (1.8 g). IR: ν max 3420 cm^{-1} (-OH), 1770 cm^{-1} (-C=O), 1622 cm^{-1} (aromatic =C-H); ^{1}H-NMR: δ 0.9 (d, 3H, J = 6Hz, $-CH_3$-2); 1.2 - 1.8 (m, 8H, H-2, H-3, H-4, H-5, -OH-6); 3.5 (d, 6H, J = 7Hz, H-1); 3.7 (t, 2H, J = 6Hz, H-6); 7.6-7.9 (m, 4H, $-C_6H_4$).

N-(6-Hydroxy-2-isopropylhexyl)-phthalimide **9c**. Reaction of the iodide **8c** (1.35 g, 5.0 mmol) with potassium phthalimide (1.38 g, 7.5 mmol) in dry DMF (20 mL) afforded the phthalimide **9c** as a pale yellow oil in 60% yield (0.86 g). IR: ν max 3435 cm^{-1} (-OH), 1778 cm^{-1} (-C=O); 1622 cm^{-1} (aromatic =C-H); ^{1}H-NMR: δ 0.9 (d, 6H, J = 6Hz, $-CH(C\underline{H}_3)_2$-2); 1.2 - 1.9 (m, 9H, H-2, H-3, H-4, H-5, -OH-6, $-C\underline{H}(CH_3)_2$-2); 3.5 (d, 6H, J = 7Hz, H-1); 3.7 (t, 2H, J = 6Hz, H-6); 7.6 - 7.9 (m, 4H, $-C_6H_4$).

2-Methyl-6-hydoxy-1-hexylamine **10b**. Hydrazinolysis of the phthalimide **9b** (1.2 g, 4.6 mmol) in methanol (30 mL) using hydrazine hydrate (0.35 g, 6.9 mmol) yielded the amine **10b** as a colorless oil (0.35 g, 58%). IR: ν max 3340 cm^{-1} (-OH and $-NH_2$); ^{1}H-NMR: δ 0.9 (d, 3H, J = 6Hz, $-CH_3$-2); 1.0 - 1.7 (m, 8H, H-2, H-3, H-4, H-5, -OH-6); 2.5 (m, 2H, H-1); 3.2 (s, 2H, $-NH_2$-1, exchangeable with D_2O); 3.4 (t, 2H, J = 6Hz, H-6).

2-Isopropyl-6-hydroxy-1-hexylamine **10c**. Hydrazinolysis of the phthalimide **9c** (0.4 g, 1.4 mmol) in methanol (30 mL) using hydrazine hydrate (0.105 g, 2.1 mmol) yielded the amine **10c** as a colorless oil (0.12 g, 54%). IR: ν max 3340 cm^{-1} (-OH and $-NH_2$); ^{1}H-NMR: δ 0.9 (d, 6H, J = 6Hz, $-CH(C\underline{H}_3)_2$-2); 1.1 - 1.9 (m, 9H, H-2, H-3, H-4, H-5, -OH-6, $-C\underline{H}(CH_3)_2$-2); 2.6 (m, 2H, H-1); 3.0 (s, 2H, $-NH_2$-1, exchangeable with D_2O); 3.6 (t, 2H, J = 6Hz, H-6).

6-Iodo-1-hexylamine **11a**. PPSE was prepared according to the method of Imamoto *et al.*[21] Phosphorus pentoxide (5 g) and dry hexamethyldisiloxane (12.5 g) was refluxed in toluene (25 mL) under dry nitrogen for 1 h. The solvent was removed under reduced pressure. The residue was reconstituted in 25 mL of MEK, flushed with dry nitrogen and stored under refrigeration in the dark for subsequent use. To a solution of 100 μl of PPSE in MEK was added 6-hydroxy-1-hexylamine (2.3 mg, 0.02 mmol) and NaI (3.6 mg, 0.02 mmol). The mixture was flushed with dry nitrogen and stirred vigorously for 30 m at

60°C. The reaction mixture was analysed by TLC and HPLC. The titled compound was obtained in 73% chemical yield (3.2 mg). ^{1}H-NMR: δ 0.9 - 1.8 (m, 8H, H-2, H-3, H-4, H-5); 2.6 (m, 2H, H-1); 2.8 (s, 2H, -NH_2-1, exchangeable with D_2O); 3.2 (d, 6H, J = 7Hz, H-6); MS: (m/e) 227.

6-Iodo-2-methyl-1-hexylamine **11b**. A mixture of the hydroxyamine **10b** (2.4 mg, 0.02 mmol), NaI (3.6 mg, 0.02 mmol) and PPSE in MEK (100 μL) was stirred for 30 m at 60°C for 30 m. The iodoamine **11b** was obtained in 67% chemical yield (3.0 mg). MS: (m/e) 241.

6-Iodo-2-isopropyl-1-hexylamine **11c**. Reaction of compound **10c** (2 mg, 0.01 mmol), with NaI (2 mg, 0.01 mmol) and PPSE in MEK (100 μL) afforded the titled compound in 60% chemical yield (2.2 mg). MS: (m/e) 269.

6-[^{131}I]-Iodo-1-hexylamine ([^{131}I]-**11a**). The synthesis of [^{131}I]-**11a** was similar to that described for **11a**. 6-Hydroxy-1-hexylamine (1.2 mg, 0.01 mmol) was added to a mixture of [^{131}I]-NaI/NaI and 50 μL of PPSE in MEK. The mixture was stirred at 60° for 30 m. [^{131}I]-**11a** was isolated in 67% radiochemical yield after purification with radio-HPLC (specific activity 340 GBq mmol^{-1}).

6-[^{131}I]-Iodo-2-methyl-1-hexylamine ([^{131}I]-**11b**). Reaction of **11b** (1.5 mg, 0.01 mmol) with [^{131}I]-NaI/NaI and PPSE in MEK (75 μL) afforded the titled compound in 61% radiochemical yield as determined by radio-HPLC (specific activity 340 GBq mmol^{-1}).

6-[^{131}I]-Iodo-2-isopropyl-1-hexylamine ([^{131}I]-**11c**). **11c** (2 mg, 0.01 mmol) was stirred with [^{131}]-NaI/NaI and PPSE in MEK (100 μL) to afford the titled compound in 55% radiochemical yield as determined by radio-HPLC (specific activity 340 GBq mmol^{-1}).

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