SYNTHESIS OF ^{122}I- AND ^{125}I-LABELLED meta-DIMETHOXY-N,N-DIMETHYLIODOPHENYLISOPROPYLAMINES

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SUMMARY

The syntheses of ^{122}I- and ^{125}I-labelled 2,4-dimethoxy-N,N-dimethyl-5-iodophenylisopropylamine, 3,5-dimethoxy-N,N-dimethyl-2-iodophenylisopropylamine and 2,6-dimethoxy-N,N-dimethyl-3-iodophenylisopropylamine are described. The speed (3 min, including purification) and yield (45-85%) obtained in direct iodination procedures utilizing chloramine-T have allowed the use of the short-lived positron emitter ^{122}I ($t_{1/2}$ = 3.6 min) in brain blood flow imaging studies. The three appropriate precursors (the meta-dimethoxy-N,N-dimethylphenylisopropylamines) were prepared from the corresponding phenylacetone analogues by reductive amination employing dimethylamine and $NaCNBH_3$. The ketones were obtained from the appropriate nitrostyrenes through reduction with elemental Fe.

Key Words: meta-dimethoxy-N,N-dimethyliodophenylisopropylamines, iodine-122, iodine-125, brain blood flow agents, iodinated amphetamines.

INTRODUCTION

Two classes of imaging agents for brain blood flow determination exist. One has the properties of high extraction by brain tissue on the first pass and retention by brain for a time period sufficient for imaging; the other depends upon free diffusion in and out of brain tissue. The first example of a retained agent was 4-^{82}Br-2,5-dimethoxyphenylisopropylamine (4-^{82}Br-2,5-dimethoxyamphetamine) (1). Two similar iodinated analogues have been described (2,3), and a chemically related diamine has also been utilized for brain imaging studies (4). These compounds were prepared with gamma-emitting isotopes which were inappropriate for positron emission tomography (PET).

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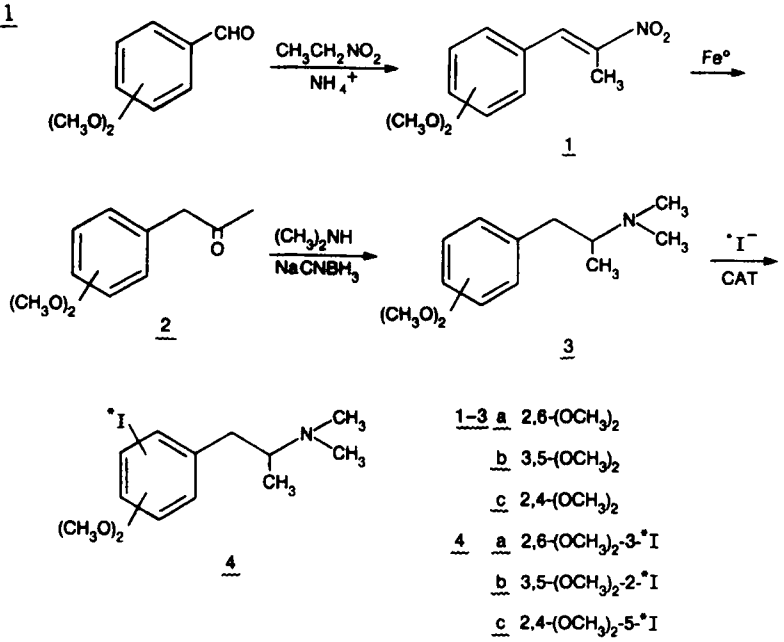
A potentially useful positron-emitting isotope of iodine is ^{122}I ($t_{1/2}$ 3.6 min). This is the daughter of ^{122}Xe ($t_{1/2}$ 20.1 h), making possible a generator from which ^{122}I can be repeatedly milked (5,6). Previously, considerable synthetic time has been required for the incorporation of the radio-iodine into the iodinated amphetamine analogues, either because derivatization was needed to protect the amine from oxidation (2) or a slow halogen-halogen exchange process was used (3,4). Syntheses utilizing ^{123}I ($t_{1/2}$ 13 h) or ^{131}I ($t_{1/2}$ 8 d) can be performed with little loss of the radionuclide in these relatively slow processes; iodinations involving ^{122}I require fast synthetic routes.

Iodination of the 2,5-dimethoxy-N,N-dimethylamphetamine with ICl required high temperature, an organic reaction medium and preformation of radio-labelled ICl (7). The para-dimethoxy orientation of this 2,5-dimethoxy analogue did not activate the ring sufficiently for direct electrophilic iodination by methods such as chloramine-T (8). The syntheses of the corresponding meta-dimethoxy-N,N-dimethylamphetamine counterparts are described here. These compounds have proven sufficiently activated to allow direct radio-iodination employing chloramine-T in an aqueous medium.

The synthetic procedures leading to the three meta-substituted compounds were the same, starting with appropriate precursors, and are outlined in Scheme 1. Dimethoxybenzaldehyde was reacted with nitroethane (as both reagent and solvent) with a catalytic amount of ammonium acetate via the Knoevenagel reaction (9). The resulting nitrostyrene 1 was reduced to the phenylacetone 2 with elemental iron in acetic acid (10). Reductive amination of the ketone with dimethylamine and sodium cyanoborohydride (11) yielded the tertiary amine 3 which was iodinated directly in an aqueous system containing either ^{122}I-iodide or ^{125}I-iodide and chloramine-T (CAT).

The resulting ^{122}I-labelled meta-dimethoxy-N,N-dimethyliodoamphetamines 4 have been utilized in PET studies of cerebral perfusion in mongrel dogs. These agents demonstrate rapid brain uptake and long term retention in cerebral tissue and show promise as brain blood flow radiopharmaceuticals (12,13).

Scheme 1



1-3 a 2,6-$(OCH_3)_2$
b 3,5-$(OCH_3)_2$
c 2,4-$(OCH_3)_2$

4 a 2,6-$(OCH_3)_2$-3-*I
b 3,5-$(OCH_3)_2$-2-*I
c 2,4-$(OCH_3)_2$-5-*I

EXPERIMENTAL

Materials and Methods

The ^{122}Xe was obtained from Crocker Nuclear Laboratory, University of California, Davis. A complete description of the ^{122}Xe-^{122}I generator system is given elsewhere (6). Na ^{125}I in dilute NaOH, used for exploratory procedures, was purchased from New England Nuclear Corporation. 2,4-Dimethoxybenzaldehyde and 3,5-dimethoxybenzaldehyde were obtained commercially (Aldrich Chemical Co.). 2,6-Dimethoxybenzaldehyde was prepared by the procedure of Lambooy (14) except that butyllithium was used to form the lithiation product with meta-dimethoxybenzene (Aldrich Chemical Co.) followed by reaction with N-methylformanilide. Iodinations were conducted in an enclosed, shielded box and activity measurements made with a Capintec CRC 30 radioisotope dose calibrator. NMR spectra were determined on the UC Berkeley

Chemistry Department 200 MHz FT-NMR. Where microanalyses are indicated only by the symbols of the elements, the results obtained were within 0.4% of the theoretical values; analyses were performed by the Galbraith Laboratories, Knoxville, Tenn. All melting points are uncorrected. Distillations were performed using a Kugelrohr apparatus at the temperatures and vacuum pressures indicated. High performance liquid chromatography (HPLC) was conducted with a Waters Assoc. M6000A pump and U6K injector with a Waters Model 450 UV detector (254 nm) and NaI(Tl) detector in series for absorbance and radioactivity detection. Two HPLC analytical separation systems were utilized: a Hamilton PRP-1 reverse phase resin column (4.6 x 250 mm 10 µm) eluted with methanol/2M NH_4OH/1M NH_4NO_3 (650/50/25) and an Altex normal phase silica column (4.6 x 250 mm 10 µm) eluted with dichloromethane/methanol/n-propylamine (250/4/1). Semi-preparative HPLC separations of the iodinated (cold) amphetamine analogues for NMR analyses were performed on a Whatman M9 Partisil column (9 x 500 mm 10 µm) utilizing dichloromethane/methanol/n-propylamine (250/4/1) eluent. Thin layer chromatography (TLC) was performed on Eastman Chromogram 6060 silica gel sheets developed with ethyl acetate/ethanol/ammonium hydroxide (34/4/1).

2,6-Dimethoxy-beta-methyl-beta-nitrostyrene. 1a. To a solution of 10.0 g of 2,6-dimethoxybenzaldehyde in 50 ml nitroethane there was added 0.5 g anhydrous ammonium acetate, and the mixture was held on the steam bath for 2 h. The solvent was removed in vacuo giving a heavy reddish oil which, upon dissolving in 25 ml hot methanol and cooling, yielded bright yellow crystals, 12.0 g (90% yield), m.p. 101.5-102.5°C.

In the same manner, 3,5-dimethoxy-beta-methyl-beta-nitrostyrene (1b) was prepared (94% yield), m.p. 87-88°C (lit. value m.p. 88°C (15)).

In the same manner, 2,4-dimethoxy-beta-methyl-beta-nitrostyrene (1c) was prepared (77% yield), m.p. 78-79°C (lit. value m.p. 76-78°C, (16)).

2,6-Dimethoxybenzylmethyl ketone. 2a. A solution of 11.5 g of 1a in 80 ml warm acetic acid was added to a suspension of 35 g of electrolytic iron dust in 150 ml acetic acid. The mixture was heated on the steam bath until a vigorous

reaction set in. The resulting paste was diluted with another 40 ml acetic acid and heated for an hour. The reaction was quenched in 1.5 L water with stirring, decanted from unreacted Fe and extracted with 3 x 100 ml methylene chloride. The pooled extracts were washed with 50 ml 5% NaOH and the solvent removed in vacuo to yield 10.5 g of a pale amber oil. This was distilled in vacuo giving 8.7 g (86% yield) of a colorless oil (95-105°C/0.4 mmHg). Anal: C,H.

In the same manner, the 3,5-dimethoxybenzylmethyl ketone (2b) colorless oil was prepared (83% yield; 110-130°C/0.3 mmHg). Anal: C,H.

In the same manner, 2,4-dimethoxybenzylmethyl ketone (2c) colorless oil was prepared (65% yield; 125-145°C/0.5 mmHg). Anal: C theor. 68.2%, found 66.1 and 66.5%; H.

2,6-Dimethoxy-N,N-dimethylphenylisopropylamine. 3a. A solution of 7.6 g of 2a in 100 ml methanol was added to a warm solution of 25 g dimethylamine hydrochloride in 60 ml methanol. With vigorous stirring there was added 3.3 g $NaCNBH_3$, followed by conc. HCl dropwise as needed to maintain the reaction medium at a pH of about 6. When acid was no longer required (about 48 h) the methanol was removed in vacuo and the residue poured into 2 L of dilute sulfuric acid. The mixture was extracted with 2 x 100 ml methylene chloride (discarded), made basic with 25% NaOH and reextracted (3 x 100 ml methylene chloride). The pooled extracts were stripped of solvent, giving 2.38 g of a colorless oil which was distilled (110-120°C/0.4 mmHg), yielding 1.49 g (17% yield) of a white oil. The perchlorate salt was recrystallized from isopropanol and ether, m.p. 109-110°C. Anal: C,H,N. NMR of the free base ($CDCl_3$) δ 0.88 (d, 3H, $\underline{CH_3}CH$), 2.35 (6H, $(CH_3)_2N$), 2.65 (m, 2H, CH_2), 2.80 (m, 1H, $\underline{CH}CH_3$), 3.80 (6H, $(CH_3O)_2$), 6.53 (d, 2H, phenyl $C_{3,5}$-H, J_o = 8.3 Hz), 7.13 (t, 1H, phenyl C_4-H, J_o = 8.3 Hz).

In the same manner, 3,5-dimethoxy-N,N-dimethylphenylisopropylamine (3b) was prepared, 3.3 g, from 7.4 g of the ketone (39% yield), m.p. of the perchlorate salt 100-101°C. Anal: C,H,N. NMR of the free base ($CDCl_3$) δ 0.93 (d, 3H,

$\underline{CH_3}CH$), 2.32 (6H, $(CH_3)_2N$), 2.80 (m, 2H, CH_2), 2.95 (m, 1H, $\underline{CH}CH_3$), 3.78 (6H, $(CH_3O)_2$), 6.31 (d, 1H, phenyl C_4-H, J_m = 2.0 Hz), 6.34 (d, 2H, phenyl $C_{2,6}$-H, J_m = 2.1 Hz).

In the same manner, 2,4-dimethoxy-N,N-dimethylphenylisopropylamine (3c) was prepared, 10.6 g from 12.4 g of the ketone (74% yield), m.p. of the perchlorate salt 98-98.5°C. Anal: C,H,N. NMR of the free base ($CDCl_3$) δ 0.89 (d, 3H, $\underline{CH_3}CH$), 2.33 (6H, $(CH_3)_2N$), 2.78 (m, 2H, CH_2) 2.95 (m, 1H, $\underline{CH}CH_3$), 3.79 (6H, $(CH_3O)_2$), 6.38-6.43 (m, 2H, phenyl C_3-H and C_5-H, J_o = 8.1 Hz, J_m = 2.4 Hz), 6.99 (d, 1H, phenyl C_6-H, J_o = 8.1 Hz).

2,4-Dimethoxy-N,N-dimethyl-5-^{125}I-phenylisopropylamine. ^{125}I-4c. The effects of pH and temperature upon the radio-iodination yield were determined for the reaction of 3c with $^{125}I^-$ utilizing CAT as the oxidizing agent. To 500 µl of 0.50 M phosphate buffer solution containing 1 mg of 3c and 70 µCi of $Na^{125}I$ there was added 250 µg of CAT in 10 µl of water. The study at pH 0.3 was made in 500 µl of 0.50 M H_2SO_4. The reactions were quenched at 60 sec by the addition of 5 mg $Na_2S_2O_5$. The results obtained at the pH's over the range of 0.3-9.1 at 60°C are shown in Table 1; the reaction yield was maximized at pH 1.2. The effect of temperature upon the yield over the range of 25-100°C is

Table 1. Effect of pH on the yield of ^{125}I-labelled 2,4-dimethoxy-N,N-dimethyl-5-iodophenylisopropylamine (^{125}I-4c)

pH	Yield of ^{125}I-4c (average of 3 samples)
0.3	90%
1.2	94%
4.3	77%
6.1	81%
7.4	39%
9.1	19%

Table 2. Effect of temperature on the yield of ^{125}I-labelled 2,4-dimethoxy-N,N-dimethyl-5-iodophenylisopropylamine (^{125}I-4c)

T(°C)	Yield of ^{125}I-4c (average of 3 samples)
25	84%
40	89%
60	94%
80	91%
100	92%

shown in Table 2; the yield reached a maximum at temperatures ≥60°C. The speed of the radio-iodination was determined at pH 1.2 and 60°C by quenching the reactions at different times. The iodination reaction was fast; the yield was 86% at 15 sec and 94% at 60, 120 and 300 sec. Optimum reaction conditions were pH 1.2, 60°C and 60 sec. The capacity factors (k') for ^{125}I$^-$, 3a-c and ^{125}I-4a-c on the Hamilton PRP-1 column and on the Altex silica column are given in Table 3. The Rf's of ^{125}I$^-$, 3a-c and ^{125}I-4a-c on silica gel sheets are also listed in Table 3.

Employing the above optimum conditions, 2,6-dimethoxy-N,N-dimethyl-3-^{125}I-phenylisopropylamine (^{125}I-4a) was prepared (50% yield in 1 min).

In the same manner, 3,5-dimethoxy-N,N-dimethyl-2-^{125}I-phenylisopropylamine (^{125}I-4b) was prepared (83% yield in 1 min).

2,6-Dimethoxy-N,N-dimethyl-3-^{122}I-phenylisopropylamine. ^{122}I-4a. Approximately 80 mCi of ^{122}Xe was transferred from a storage vessel to a stainless steel loop at liquid nitrogen temperature, and ^{122}I was allowed to accumulate for 15 min. The ^{122}Xe was cryogenically returned to the storage vessel leaving the ^{122}I on the inside surface of the loop. High vacuum (<5 μm Hg) was applied to the loop for 10 sec while heating to 60°C to remove traces of radio-xenons.[1] Two ml of a 0.20 M phosphoric acid solution (pH 1.3) containing

[1] Less than 1 μCi of radio-xenons were detected in the eluate following the pumping procedure.

Table 3. Summary of chromatographic data and yields of ^{125}I and ^{122}I-labelled meta-dimethoxy-N,N-dimethyliodophenylisopropylamines (4) and precursors (3).

Compound	k' * Hamilton PRP-1 CH_3OH:2M NH_4OH: 1M NH_4NO_3 (650:50:25)	k' * Altex Silica CH_2Cl_2:CH_3OH: n-propylamine (250:4:1)	Rf Silica Gel Sheets EtOAc:EtOH:NH_4OH (34:4:1)	Radiochemical Yield (^{125}I)	(^{122}I)**
$^{125}I^-/^{122}I^-$	0.4	0.1	0.05	---	---
3a	2.8	6.2	0.3	---	---
3b	3.5	1.6	0.2	---	---
3c	4.5	4.1	0.3	---	---
4a	6.6	2.7	0.95	50%	45%
4b	6.7	1.0	0.85	83%	68%
4c	8.1	2.5	0.90	94%	85%

* HPLC flow rate was 2.0 ml/min

**Average of 6 runs each

5 mg of 3a and 100 µg of CAT were added to the loop. The reaction was allowed to proceed for 90 sec at 60°C. The contents of the loop were then loaded onto a 0.9 x 4 cm anion exchange column (BioRad AG1-X8, acetate form). The product (^{122}I-4a) was eluted with 10 ml of a 0.10 M pH 7.4 phosphate buffer solution. Of the activity that was removed from the loop, 55% remained on the anion exchange column and 45% was removed with the eluting buffer. The eluate contained 13.5 mCi of ^{122}I-4a (not decay corrected) which was >98% in radiopurity.[2] The specific activity of the ^{122}I-labelled product exceeded 10^4 Ci/mmole. However, the unlabelled precursor and iodinated product may have similar biological properties resulting in an effective specific activity of ~100 mCi/mmole. The entire radio-synthesis and product cleanup required approximately 3 min (post removal of ^{122}Xe). The chromatographic characteristics of ^{122}I-4a were identical to ^{125}I-4a by HPLC.

The assignment of the iodine substitution position and the chromatographic characteristics of nonradioactive 4a were established by a separate synthesis employing millimolar quantities of sodium iodide and 3a. To a solution containing 150 mg (0.67 mmole) 3a and 120 mg (0.80 mmole) NaI in 30 ml 0.25 M H_3PO_4 there was added 229 mg (1.0 mmole) CAT. The reaction was allowed to proceed at 60°C for 5 min and was quenched with 300 mg (1.6 mmole) $Na_2S_2O_5$. The solution was made basic with NaOH and extracted with CH_2Cl_2 (3 x 30 ml). The iodinated product (46% yield) was separated from the starting material (3a) and side products by semi-preparative HPLC. NMR of the free base ($CDCl_3$) δ 0.88 (d, 3H, $\underline{CH_3}CH$), 2.37 (6H, $(CH_3)_2N$), 2.66 (m, 2H, CH_2), 2.86 (m, 1H, $\underline{CH}CH_3$), 3.79 (3H, CH_3O), 3.80 (3H, CH_3O), 6.46 (d, 1H, phenyl C_5-H, J_o = 8.7 Hz), 7.57 (d, 1H, phenyl C_4-H, J_o = 8.7 Hz). The HPLC and TLC chromatographic characteristics of 4a were identical to ^{125}I-4a and ^{122}I-4a. The major

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2 The ^{122}Xe gas contained approximately an equal quantity of ^{125}Xe ($t_{1/2}$ 17 h) as an impurity from the production of ^{122}Xe (6). ^{125}Xe decays to ^{125}I, and a small amount of ^{125}I-labelled product was found in the eluate. A 15 min in-growth period resulted in ~10 µCi of ^{125}I-labelled 4a-c (^{122}I/^{125}I ≈ 10^3).

side-product (20% yield) using a stoichiometric excess of CAT in these nonradioactive procedures proved to be the 3-chloro analog (3-chloro-2,6-dimethoxy-N,N-dimethylphenylisopropylamine) as established by NMR of a chromatographically separated sample. The positional assignment of both halides (as shown by NMR, q.v.) is the same as that reported for the bromination of 2,6-dimethoxyphenylisopropylamine (17).

In the same manner, 3,5-dimethoxy-N,N-dimethyl-2-^{122}I-phenylisopropylamine (^{122}I-4b) was prepared (68% incorporation of ^{122}I removed from the loop). The synthesis of nonradioactive 4b (60% yield) was conducted as with 4a. NMR of the free base ($CDCl_3$) δ 0.99 (d, 3H, $\underline{CH_3}CH$), 2.42 (6H, $(CH_3)_2N$), 2.66 (q, 2H, CH_2), 3.06 (m, 1H, $CH_3\underline{CH}$), 3.80 (3H, CH_3O), 3.85 (3H, CH_3O), 6.30 (d, 1H, phenyl C_4-H, J_m = 2.7 Hz), 6.43 (d, 1H, phenyl C_6-H, J_m = 2.7 Hz). The chromatographic characteristics of 4b were identical to ^{125}I-4b and ^{122}I-4b.

In the same manner, 2,4-dimethoxy-N,N-dimethyl-5-^{122}I-phenylisopropylamine (^{122}I-4c) was prepared (85% incorporation of ^{122}I removed from the loop). The synthesis of nonradioactive 4c (65% yield) was conducted as with 4a. NMR of the free base ($CDCl_3$) δ 0.91 (d, 3H, $\underline{CH_3}CH$), 2.34 (6H, $(CH_3)_2N$), 2.76 (m, 2H, CH_2), 2.85 (m, 1H, $\underline{CH}CH_3$), 3.83 (3H, CH_3O), 3.88 (3H, CH_3O), 6.40 (1H, phenyl C_3-H), 7.43 (1H, phenyl C_6-H). The chromatographic characteristics of 4c were identical to ^{125}I-4c and ^{122}I-4c.

A summary of the yields of ^{125}I- and ^{122}I-labelled 4a, 4b and 4c and the chromatographic data is given in Table 3.

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