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SYNTHESIS OF N,N-DIMETHYL-[β-(3,4-DIACETOXY-6-^{123}I-IODOPHENYL)]-ETHYLAMINE (IDDE): A POTENTIAL RADIOTRACER FOR THE STUDY OF THE DOPAMINERGIC SYSTEM

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Abstract

N,N-Dimethyl-[β-(3,4-Diacetoxy-6-^{123}I-Iodophenyl)]ethylamine (IDDE) was synthesized by the iododemercuration reaction with [^{123}I]-NaI and Chloramine-T. The iodinated compound was deprotected with BBr_3, acetylated and purified by HPLC to give the final product in 43% radiochemical yield. The radiochemical purity was >97%.

Key Words: [^{123}I], dopamine metabolism, SPECT, MAO

Introduction

In this paper we report the synthesis and radiolabelling of N,N-Dimethyl- [β-(3,4-Diacetoxy-6-^{123}I-Iodophenyl)]ethylamine (IDDE), an iododopamine derivative in which the catechol group has been acetylated and the amine group dimethylated.

We based our selection of this particular dopamine derivative on the previous work of Borgman and co-workers (1) which showed that the non iodinated analog of IDDE exhibits high dopaminergic activity. This suggested that both O-acetylation and N-alkylation of the dopamine molecule are required to provide entry into the CNS while retaining intrinsic dopaminergic activity.

Modification of the catechol moiety in conjuction with alkylation of the nitrogen atom produce dopamine derivatives that are more lipophilic and potentially able to cross the blood brain barrier (BBB) while at the same time retaining dopaminergic properties on D-1 and D-2 receptors (2,3,4,5,6,).

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Structural modifications of the dopamine molecule at the ethylamine side chain and / or the aromatic ring, while keeping the catechol moiety intact, has produced dopamine derivatives that, as expected, do not cross the BBB but are useful to study renal vascular dopamine receptors (7,8,9,10).

Our aim was to synthesize and radioiodinate an iododopamine derivative with the ability to cross the BBB and with high dopaminergic activity in the brain for use as a SPECT imaging agent.

Since it has been reported that the primary amine function of dopamine is not an essential requirement for dopaminergic activity (11,12), we anticipate that once inside the brain the acetyl groups of IDDE may be hydrolyzed, as was the non iodinated analog (1), producing [^{123}I]- N,N-dimethyliododopamine 4 (Scheme 1) which could enter the dopamine metabolic pathway in the brain or bind to dopamine receptors. Based on the findings of Halldin and co-workers (13) and Inoue and co-workers (14) the [^{123}I]- N,N-dimethyliododopamine which may be formed from the deacetylation of IDDE may also be metabolized by MAO-B generating the corresponding metabolite [^{123}I]-dihydroxyiodophenyl acetaldehyde. Due to its hydrophilicity this compound may not be able to clear from the brain and therefore, may also be useful as a tracer for MAO function.

Experimental

General

3,4-dimethoxy-β-phenethylamine was purchased from Sigma. Chloramine-T was purchased from Aldrich and no carrier added Na^{123}I was obtained from Nordion International. All other chemicals were purchased commercially and were used with no further purification.

NMR spectroscopy was performed on a 300 MHz spectrometer, mass spectroscopy was done at the B.C. Regional Mass Spectroscopy Center, UBC, Vancouver. Elemental Analyses were performed by Canadian Microanalytical Service, Ltd., Delta, B.C. All melting points were determined on a capillary oil bath instrument and are uncorrected. High Performance Liquid Chromatography (HPLC) was carried out on a Spectra Physics System with an analytical Waters column (RCM, Silica, 10 cm x 0.8 cm, 4 μm, λ 280 nm, flow 3 mL/min) or a semi-preparative Phenomenex Ultremex 5 column (Silica, 25 cm x 1 cm, flow 3 mL/min, λ 280 nm) using a mixture of (60:40) CH_3CN/4mM NH_4OAc as the eluant. Reverse phase HPLC was performed using a C-18 analytical Waters RCM column

(10 cm x 0.8 cm, 4 μm, 8NV C-18, λ 280 nm) with a flow rate of 3 mL/min and using (90:10) 0.02 M KOAc/MeOH eluant adjusted to pH 3.9 with glacial acetic acid.

N,N-dimethyl-[β-(3,4-dimethoxyphenyl)]ethylamine (1)

To a stirred solution of 3,4-dimethoxy-β-phenethylamine (27.15 g, 0.15 mol) and formaldehyde (37 %, 1.03 mol) in acetonitrile (300 mL) was added sodium cyanoborohydride (15 g, 0.24 mol). A vigorous exothermic reaction ensued which was stirred for 15 minutes. Glacial acetic acid added dropwise until the solution tested neutral on wet pH paper. Stirring was continued for an additional 45 minutes. The solvent was evaporated under reduced pressure and KOH (2N, 80 mL) was added to the residue. The amine was extracted with dichloromethane (3 X 150 mL). The combined extracts were dried over anhydrous Na_2SO_4 and the solution filtered and evaporated. The slightly yellow oil was distilled under reduced pressure affording 24.5 g of clear oily product (78.2 %), b.p. 110-113° (0.2 mm). A small fraction (~1 g) of this distilled oil was dissolved in anhydrous diethyl ether and treated with a solution of HCl gas in anhydrous diethyl ether. The resulting white precipitate was filtered and washed with anhydrous ether and air dried. Recrystallization was accomplished from ethanol/ethyl acetate, mp 192-193°C (lit. 192-193°C)(1).

TLC (Si, $CHCl_3$:CH_3OH/9:1) showed only one spot for the distilled oil. HPLC (normal phase silica RCM column) with the conditions described above showed one peak with a retention time of 25.66 min. ^{1}H-NMR ($CDCl_3$, oil): δ 2.2 [s, 6H, $N(CH_3)_2$], δ 2.4 [m, 2H, aliphatic CH_2], δ 2.59 [m, 2H, aliphatic CH_2], δ 3.75 [s,3H, CH_3O], δ 3.80 [s, 3H, CH_3O] δ 6.74 [m, 3H, aromatic-H].

N,N-dimethyl-[β-(3,4-dimethoxy-6-mercurictrifluoroacetyl phenyl)]ethylamine (2)

To a stirred solution of the oil **1** (3.38 g, 16.2 mmol) in dry methanol (30 mL) was added a solution of $Hg(CF_3CO_2)_2$ (8.36 g, 19.6 mmol) in dry methanol(20 mL) . The reaction mixture was left stirring at room temperature for 5 days. The solvent was evaporated under reduced pressure, the residue dissolved in 3-5 mL of methanol, filtered (Millex SR, 0.5 μm) and the mixture was cooled overnight to afford a white solid. The liquid was decanted and the solid dissolved in methanol, filtered and evaporated under reduced pressure affording a yellowish solid.

The solid was washed with ethyl acetate which solubilized the yellowish material, leaving the

insoluble white mercury compound. The solid was filtered, washed with cold ethyl acetate and vacuum dried. Yield 4.6 g (55%), mp 149-150° (dec.) *Anal.* calcd. for $C_{14}H_{18}NO_4F_3Hg \bullet CF_3CO_2H$: C 30.22, H 3.01, N 2.20; found: C 30.25, H 3.04, N 2.23. ^{1}H-NMR (DMSO-d_6): δ 2.88 [s, 6H, $N(CH_3)_2$], δ 2.95 [m, 2H, aliphatic CH_2], δ 3.25 [m, 2H, aliphatic CH_2], δ 3.7 [s, 3H, CH_3O], δ 3.75 [s, 3H, CH_3O] δ 6.98 [s, 1H, aromatic H], δ 7.2 [s, 1H, aromatic H]

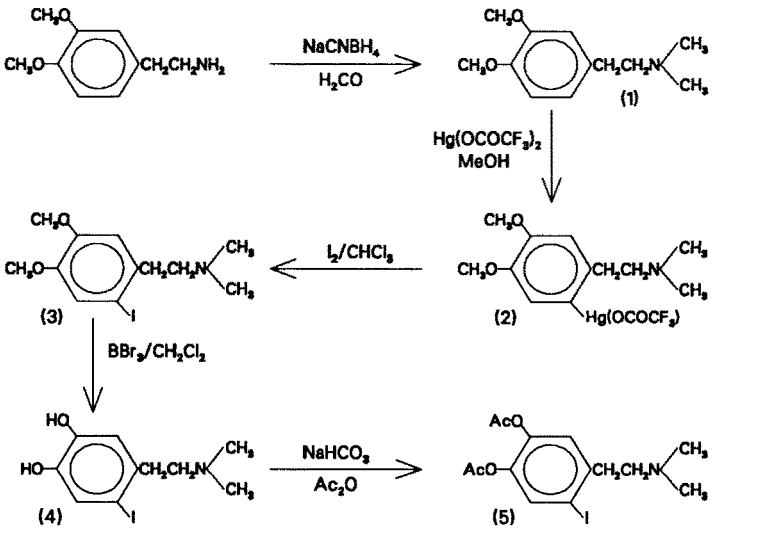
N,N-dimethyl-[β-(3,4-dimethoxy-6-iodophenyl)]ethylamine (3)

To a stirred suspension of **2** (1.01 g, 1.94 mmol) in $CHCl_3$ (30 mL) was added solid iodine (0.984 g, 3.88 mmol) and the mixture stirred at room temperature for 40 hours. The reaction mixture was transferred to a separatory funnel and mixed with a solution of 10% sodium thiosulfate (50 mL) and 5% $NaHSO_3/Na_2S_2O_5$ (30 mL). The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure.

The crude product was purified by column chromatography (64 g neutral alumina /$CHCl_3$). Several fractions were collected, analyzed by TLC (alumina, $CHCl_3$) and the ones containing only the product were combined and evaporated under reduced pressure yielding a clear oil (0.513 g, 79%). HPLC (RCM, Silica with conditions described above) showed one peak with r.t. of 18.1 min.

The oil (0.15 g) was dissolved in anhydrous ether and treated with a solution of HCl gas in

Synthesis of N,N-Dimethyl-[β-(3,4-Diacetoxy-6-Iodophenyl)]Ethylamine



anhydrous ether. A white precipitate separated, which was cooled, filtered, washed with ether and dried. Recrystallization from isopropanol gave a white solid. Yield 56%, mp 175-6°. *Anal.* calcd. for $C_{12}H_{18}NO_2I{\cdot}HCl$: C 38.80, H 5.16, N 3.77, I 34.16; found: C 38.98, H 5.31, N 3.75, I 33.85. ^{1}H-NMR ($CDCl_3$, oil): δ 2.65 [s, 6H, $N(CH_3)_2$], δ 2.95 [m, 2H aliphatic CH_2], δ 3.10 [m, 2H, aliphatic CH_2], δ 3.83 [s, 3H, CH_3O], δ 3.85 [s, 3H, CH_3O], δ 6.79 [s, 1H, aromatic H], δ 7.22 [s, 1H, aromatic H]. Mass spectra of oil calcd. *m/e*: 335 found: 334 (M-1) ^{13}C-NMR ($CDCl_3$): ppm 38.47 and 59.93 (CH_2), 45.31 [$(CH_3)_2N$], 55.93 and 56.15 (CH_3O), 88.00, 135.21, 145.00, 149.44 (aromatic quaternary carbons), 112.45 and 121.70 (aromatic CH carbons).

N,N-dimethyl-[β-(3,4-diacetoxy-6-iodophenyl)]ethylamine (5)

To a solution of **3** (328 mg, 0.98 mmol) in CH_2Cl_2 (4 mL) at room temperature was added 1M BBr_3/CH_2Cl_2 (4 mL, 4 mmol) and the solution stirred at room temperature for 15 minutes. An aliquot (1 mL) of the mixture was removed and rotoevaporated to dryness. Two successive additions of CH_2Cl_2 were made and the mixtures were again evaporated to dryness. The residue **4** was dissolved in D_2O, filtered through glass wool and used for ^{1}H-NMR: δ 2.9 [s, 6H, $N(CH_3)_2$], δ 2.93 [m, 2H, aliphatic CH_2], δ 3.23 [m, 2H, aliphatic CH_2], δ 6.8 [s, 1H, aromatic H], δ 7.3 [s, 1H, aromatic H]. Reverse phase HPLC analysis showed a retention time of 9.25 min.

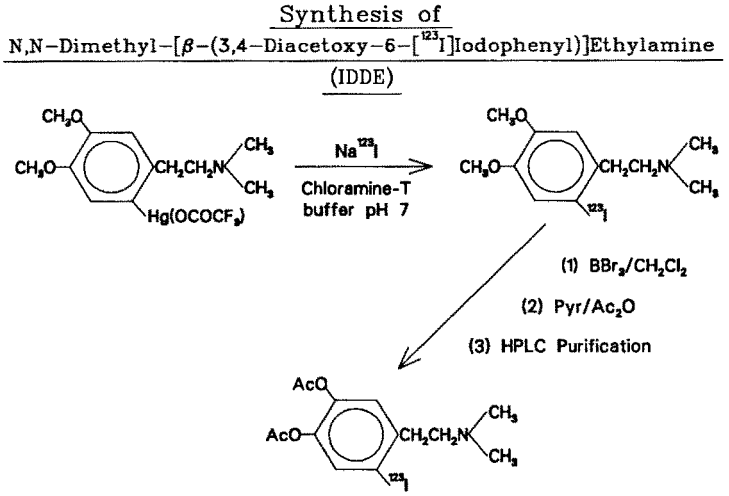
Since ^{1}H-nmr on the aliquot showed hydrolysis was complete, the rest of the reaction mixture was also evaporated to dryness. The residue **4** was dissolved in H_2O (6 mL), separated from the insoluble material, combined with the sample used for ^{1}H-NMR, and rotoevaporated to dryness, dissolved in pyridine (6 mL) followed by dropwise addition of acetic anhydride (6 mL). The mixture was stirred at room temperature for 1h. The solvent was evaporated at reduced pressure and the residue taken up in HCl (2 M) and washed with ether. Excess K_2CO_3 was added and the product extracted with ether, the ethereal solution dried over anhydrous Na_2SO_4, filtered and evaporated to afford 128 mg of yellowish solid, (33% yield). Purification by thick layer chromatography [silica/$CHCl_3$:CH_3OH (9:1)] afforded 45 mg of **4**. HPLC analysis (RCM, silica column, (40:60) 4mM NH_4OAc/CH_3CN, flow rate 3 mL/min, r.t. 9.04 min., semi-preparative silica column (Phenomenex, Ultramex), flow rate 6 mL/min, same eluant, r.t. 30 min.)

Anal. calcd. for $C_{14}H_{18}O_4NI$: C 42.98, H 4.64, N 3.58; found: C 42.79, H 4.74, N 3.53. ^{1}H-

NMR ($CDCl_3$): δ 2.2 [s, 6H, $COCH_3$], δ 2.45 [s, 6H, $N(CH_3)_2$, δ 2.59 [m, 2H, aliphatic CH_2], δ 2.9 [m, 2H, aliphatic CH_2], δ 7.05 [2, 1H, aromatic H], δ 7.59 [s, 1H, aromatic H], *m/e*: 391 (M + 1).

N,N-dimethyl-[β-(3,4-diacetoxy-6-^{123}I-iodophenyl)]ethylamine (IDDE)

To a 1 mL v-vial with teflon septum, screw cap and magnetic stirring bar containing a solution of **2**(500 μL) in phosphate buffer pH 7 (1 mg, from a solution of 4 mg/2 mL) was added $Na^{123}I$ (10 μL, 20.4 mCi). After stirring for 2-3 minutes a solution of freshly prepared Chloramine-T (75 μL , 10 mg/mL in buffer pH 7) was added. After 20 minutes of stirring at room temperature, the reaction was quenched by the addition of a solution of $NaHSO_3$ containing $Na_2S_2O_5$ (100 μL, 40 mg/mL).



The reaction mixture dissolved in methanol was passed through a C-18 Sep Pak and the methanol solution was evaporated under nitrogen. The residue was dissolved in dichloromethane (2 mL) and to this was added BBr_3 (1 M solution in dichloromethane, 1 mL). The mixture was stirred for 15 minutes at room temperature. The product was extracted with water (5 mL) and the aqueous layer evaporated to dryness. To the residue was added pyridine (2 mL) and acetic anhydride (2 mL).

The mixture was stirred for 20 min at room temperature and evaporated to dryness. The residue was dissolved in H_2O (800 μL), filtered, and the flask and filter washed with additional H_2O (400 μL) (7.8 mCi/1.2 mL H_2O). The entire solution was purified by HPLC using a semi-preparative silica column (Phenomenex, Ultramex) with 4mM NH_4OAc/CH_3CN (40:60) as eluant with a flow rate of

6 mL/min and u.v. detection at 280 nm. The radioactive product with retention time 29.5 min., corresponding to IDDE, was collected (two minor radioactive products plus free $^{123}I^-$ were observed, retention times 9.59 min., 21 min. and 2 min. respectively). The collected solution was evaporated to dryness under reduced pressure and the residue dissolved in EtOH (1.5 mL) and then diluted with H_2O (4 mL) to give 8.77 mCi (43%) of the product (decay corrected).

Results and Discussion

^{123}I-labelled IDDE was prepared from the iododemercuration of a fully protected mercury dopamine derivative followed by removal of the O-methoxy groups and subsequent O-acetylation. Direct radioiodination of the corresponding mercurated precursor was chosen over an exchange method in order to obtain the product in high specific activity. The mercury precursor was readily prepared by the reaction of mercuric bis-trifluoroacetate on the protected dopamine derivative. The synthesis of N,N-dimethyl-[β-(3,4- dimethoxyphenyl)]ethylamine was accomplished by reductive amination using sodium cyanoborohydride (15).

The radiochemical purity was greater than 97% (no other radioactive components were detected upon re-injection of the HPLC purified product). The estimated specific activity was calculated to be greater than 30,000 Ci/mmol at E.O.S. (based on limits of U.V. detection).

Animal studies are currently in progress to evaluate this compound.

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