SYNTHESIS OF ^{131}I DERIVATIVES OF INDOLEALKYLAMINES FOR BRAIN MAPPING

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Dedicated to Prof. Dr. Eduardo G. Gros on the occasion of his 65th anniversary.

SUMMARY.- The synthesis and spectral properties of new radioiodinated indolealkylamines like 2-[^{131}I]-iodo-N,N-dimethyltryptamine , 2-[^{131}I]-iodo-N-methyltryptamine, 2-[^{131}I]-iodo-5-methoxy-N,N-dimethyltryptamine, 2-[^{131}I]-iodo-5-hydroxy-N,N-dimethyltryptamine (2-[^{131}I]-iodo-bufotenine), and 2-[^{131}I]-iodo-tryptamine and the known 2-[^{131}I]-iodo-N-acetyl-5-methoxy-tryptamine (2-[^{131}I]-iodo-melatonine) are described herein. These were synthesized by a high-yield novel method, and their spectral properties are fully described. These compounds are of biological importance and can be used for brain mapping with SPECT technology.

Keywords: 2-[^{131}I]-iodo-N,N-dimethyltryptamine; 2-[^{131}I]-iodo-N-methyltryptamine; 2-[^{131}I]-iodo-5-methoxy-N,N-dimethyltryptamine; 2-[^{131}I]-iodo-5-hydroxy-N,N-dimethyltryptamine); 2-[^{131}I]-iodo-tryptamine; 2-[^{131}I]-melatonine.

INTRODUCTION

Endogenous derivatives of indolealkylamines have been extensively studied [1-11] as usual components of body fluids like blood, cerebrospinal fluid and urine. Also N-methyl derivatives of indolealkylamines have been linked to mental disorders such as schizophrenia[12], and with hallucinogenic properties after their ingestion[13]. In view of the biological and pharmaceutical behaviour of these compounds, it is important to label them with a γ emitter in order to study their properties *in vivo.*

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CCC 0362–4803/97/080677–08$17.50

Received 4 March 1997
Revised 8 April 1997

In this paper, the synthesis and spectral characteristics of 2-[^{131}I]-iodo-N,N-dimethyltryptamine (**8**), 2-[^{131}I]-iodo-N-methyltryptamine (**9**), 2-[^{131}I]-iodo-5-methoxy-N,N-dimethyltryptamine (**11**), 2-[^{131}I]-iodo-5-hydroxy-N,N-dimethyltryptamine (2-[^{131}I]-iodo-bufotenine) (**12**), are described for the first time; also 2-[^{131}I]-iodo-tryptamine (**10**) and 2-[^{131}I]-melatonine (**13**) were prepared in the same way. These compounds can be used for brain mapping with SPECT technology.

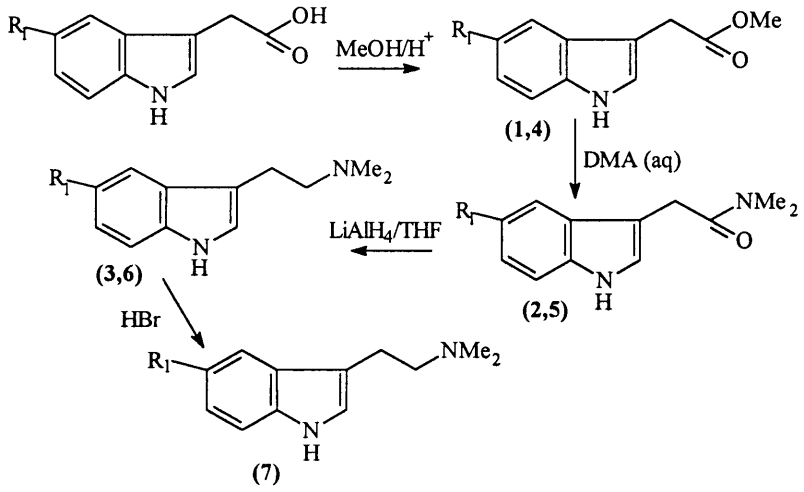
Former derivatives of indolealkylamines like N,N-dimethyltryptamine (**3**) were isolated from plants like *Piptadenia peregrina* and *Psichotria viridis* [14]. Several synthetic methods were developed to obtain them for pharmacological purposes. Serotonine and bufotenine were prepared from nitrile derivatives with an overall yield of 25 %[15]. N,N-Dimethyltryptamine was prepared from indole and oxalyl chloride with yields of 50 % [16-17], by nitroethylation of indole[18-20], from indole-3-acetic acid with an overall yield of 27 %[21], and by the method of Fisher with a yield of 34% [22] and 57 % [23]. Deuterated indolealkylamines have been also prepared for metabolic studies[24], and 2-iodotryptamine and 2-iodo-5-methoxytryptamine have been prepared by previous iodination of the protected indole with *t*-butyllithium and iodine[25].

RESULTS AND DISCUSSION

Preparation of indolealkylamines: In this paper we describe an easy method of preparation of some derivatives of tryptamine under mild conditions, as well as their iodinated and radioiodinated derivatives. Commercial indole-3-acetic acid, and 5-methoxy-indole-3-acetic acid are used as starting materials. They were esterified with methyl alcohol and the crude product was added to an excess of 40 % aqueous dimethylamine. After isolation the product was reduced with lithium aluminum hydride in THF (**Scheme 1**). The overall yield was 60 % . The amine was stored as the oxalate derivative before using it for iodination and radioiodination. For preparation of bufotenine (**7**), 5-methoxy- N,N-dimethyltryptamine (**6**) was kept overnight in aqueous HBr to hydrolyse the methoxy group. This is an easy way of preparing the substituted indolealkylamines in a small number of steps under mild conditions and in high yields.

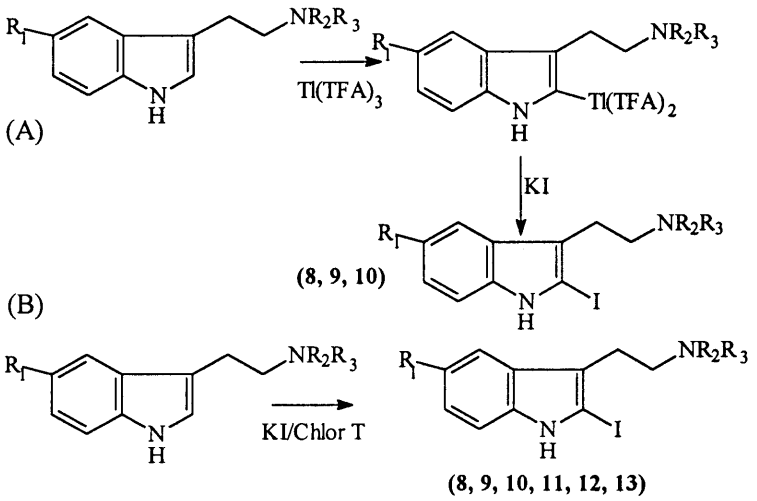
Iodination and radioiodination: Two methods were assayed for the preparation of iodinated derivatives (**Scheme 2**), the McKillop method for iodination of aromatic compounds [26], with thallium derivatives as intermediates (A), and a modification of the method that is used for iodination of peptide compounds with iodide and chloramine-T (B). Both methods were assayed and the compounds were isolated (see experimental). The best results were obtained by the chloramine-T method which was therefore chosen for preparing the [^{131}I]-derivatives with a radiochemical purity over 98 %. This was achieved by a modification of the general method. The labeling with [^{131}I] iodide was performed in a bilayer system chloroform/water. Usually, radioiodination with chloramine-T gives by-products due to substrate oxidation, but under the experimental conditions

Scheme 1



Compds	1	2	3	4	5	6	7
R^1	H	H	H	MeO	MeO	MeO	OH
R^2		Me	Me		Me	Me	Me
R^3		Me	Me		Me	H	Me

Scheme 2.



Compds	8	9	10	11	12	13
R^1	H	H	H	MeO	OH	MeO
R^2	Me	Me	H	Me	Me	Ac
R^3	Me	H	H	Me	Me	H

described herein, the by-products are water soluble and the iodinated amines are soluble in the organic layer, thus resulting in a radiochemical purity over 98%. The radioiodinated amine can be then extracted with water at pH 11. Accordingly this proved to be a useful way for the preparation of four new radioiodinated derivatives of indolealkylamines that can be used for mapping and metabolic studies. Likewise 2-Iodomelatonine (**13**) was prepared with a very good yield and the radioiodinated analogue with a radiochemical purity over 98 %.

EXPERIMENTAL

General methods. Solvents were purified to maximum purity prior to use and checked by gas chromatography. Starting materials, e.g. indole-3-acetic acid, 5-methoxyindole-3-acetic acid, N-methyltryptamine, tryptamine and melatonine were purchased from Aldrich, and carrier-free $Na^{131}I$ from Amersham. TLC analyses were performed on silica gel 60 F_{254} aluminum baked plates (0.2 mm) from Merck and were visualized under an ultraviolet light (254 nm) or in an iodine chamber. Gas chromatography-mass spectrometry analyses was achieved on a Trio2 VG spectrometer operating at 70 eV. Melting points were recorded on a Fisher-Johns apparatus and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded on a Bruker ACE 200 using $CDCl_3$ as solvent. Resonances are reported downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded at 75.5 MHz. Infrared spectra were recorded on a Mattson 3000 FTIR spectrometer. Samples were counted in an automatic gamma detector (Clinigamma Pharmacia).

Spectral data: ^{13}C NMR data are shown in Table1; ^1H NMR data are shown in Table 2, and MS data are shown in Table 3.

Table 1. ^{13}C NMR data (δ) for dimethyltryptamine analogues and intermediates

Comp	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C10	C-11	C-12	C-13/C-14
1	122.3	111.1	118.1	118.1	120.7	112.5	127.2	136.1	35.8	173.7	52.1	
2	123.4	111.2	118.7	120.9	118.2	108.1	127.2	136.0	37.2	170.5	34.9/34.6	
3	122.3	111.2	118.1	118.1	120.7	112.5	127.2	136.1	23.0	60.0	45.1	
4	122.8	111.9	99.3	154.8	111.9	109.5	128.0	132.4	31.8	174.7	56.2	54.3
5	123.5	112.0	100.3	153.8	112.0	108.3	127.4	131.1	35.6	171.7	31.3/37.8	55.8
6	122.3	111.8	100.7	154.8	112.9	113.8	127.9	131.5	24.7	58.8	45.5	55.9
7	121.8	111.7	98.3	153.2	112.6	113.7	128.0	130.5	24.5	58.4	45.3	
8	84.2	118.1	118.4	118.6	125.5	110.4	129.5	139.7	20.8	59.1	45.4	
9	83.9	118.9	118.3	118.1	120.9	111.3	129.3	136.1	30.1	51.1	34.7	
10	87.1	111.5	118.8	121.1	118.0	109.3	126.6	136.2	38.3	40.0		
11	84.2	118.8	100.4	153.9	112.1	108.2	127.4	131.2	23.2	57.9	45.5	55.8
12	83.7	111.7	97.9	153.4	112.0	108.1	127.3	131.0	19.8	57.5	45.4	
13	83.8	119.1	98.1	153.6	110.8	108.3	127.5	131.5	23.0	38.5	172.5	20.2/55.7

Table 2. ^{1}H NMR data (δ) for dimethyltryptamine analogues and intermediates.

Comp	H-1	H-2	H-4	H-5	H-6	H-7	H-10	H-11	N-CH3	5-OCH3	
1	8.12	7.07	7.63	7.21	7.12	7.35	3.8	-	3.7	-	
2	8.05	7.08	7.65	7.20	7.13	7.35	3.83	-	3.03/2.98	-	
3	8.14	7.00	7.60	7.15	7.11	7.35	2.68	2.95	2.34	-	
4	8.22	7.01	7.05	-	6.87	7.24	3.81	-	3.67	3.87	
5	8.20	7.04	7.09	-	6.68	7.23	3.79	-	3.03/2.98	3.88	
6	8.10	7.00	7.05	-	6.86	7.25	2.95	2.90	2.34	3.86	
7	8.15	7.00	6.95	-	6.85	7.24	3.00	3.10	2.35	-	5.20(HO)
8	8.17	-	7.45	7.11	6.95	7.32	3.30	3.15	2.35	-	
9	8.15	-	7.50	7.12	6.90	7.30	3.05	3.10	2.35	-	1.05(HN)
10	8.15	-	7.53	7.12	7.07	7.29	2.98	2.84	-		1.24(H_2N)
11	8.30	-	6.98	-	6.76	7.17	3.60	2.97	2.34	3.83	
12	8.25	-	6.90	-	6.75	7.15	3.50	3.00	2.34		
13	8.00	-	7.30	-	7.15	6.90	2.95	2.65	-	3.90	1.95(CH_3)

Table 3. EI MS data for dimethyltryptamine analogues and intermediates.

Comp	M+	100%	M/%	M/%	M/%	M/%	M/%	M%
1	189	130	143/12	59/30				
2	202	130	72/35	58/60				
3	188	58	143/28	130/53	77/20	42/40		
4	219	160	145/32	117/21	89/10			
5	232	160	218/34	145/50	117/38	89/23	72/38	58/65
6	218	58	173/16	160/32	145/10	130/6	117/9	44/54
7	204	146	58/40					
8	314	44	300/8	187/5	186/15	173/24	130/12	71/15
9	300	44	173/35	246/25				
10	286	30	256/57	159/47				
11	344	58	286/23	217/ 23				
12	330	58	272/35	203/38				
13	358	43	315/20	231/8	230/24	117/29	173/59	145/29

Indole-3-methylacetate **(1)**: A solution of 1 g (5.3 mmol) of indole-3-acetic acid in 70 ml of methanol with a few drops of concentrated sulfuric acid was heated under reflux for two hours until complete disappearance of the acid, as checked by TLC on alumina plates using ethylacetate, R_f (acid) 0.1, R_f (ester) 0.9. The solution was neutralized with $CaCO_3$, filtered and the solvent was evaporated under reduced pressure. The crude product was crystallised from methanol to give 0.95 g (5.0 mmol, 95%). Mp = 48°-48.5°C. IR 1722 cm^{-1} (CO).

N,N-Dimethyltryptamide: **(2)**: The ester **1** was dissolved in 20 ml of 40% aqueous solution of dimethylamine (DMA). It was stirred at 20 °C for 40 hrs, the reaction was tested by TLC Silicagel/ ethylacetate, R_f (amide) 0.5; R_f (ester) 0.8. The excess of DMA was evaporated at 20 °C under reduced pressure to avoid hydrolysis. The product was filtered and purified by sublimation under diminished pressure to give 0.8 g (4 mmol, 80%). Mp = 119-120 °C IR 1630 cm^{-1} (CO).

N,N-Dimethyltryptamine **(3)**: To a stirred suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in dry THF (15 ml), the amide **2** (0.4 g, 1.98 mmol) dissolved in dry dichloromethane (25 ml) was added slowly. The mixture was stirred for 48 hrs at room temperature under nitrogen until complete disappearance of the amide was achieved as checked by TLC, silicagel/methanol, Rf (amine) 0.2, Rf (amide) 0.8. The mixture was cooled in an ice bath, and treated with several drops of water to decompose the excess of $LiAlH_4$ reagent. The reaction mixture was vacuum filtered to remove any remaining solids, dried over anh. $MgSO_4$, and solvents removed. The yield was 76% (0.28 g, 1.5 mmol) of a colorless oil which crystallised in the freezer (-20 °C) in one week. Mp = 44-45 °C. Oxalate Mp= 151-151 °C.

5-Methoxyindole-3-methylacetate **(4)**: 5-Methoxyindole-3-acetic acid (1.0 g, 4.9 mmol) was transformed to the ester **4** by the same procedure as that described for **1**. The crude product was crystallised from methanol to give 0.98 g (4.5 mmol, 92%). Mp = 73-74°C. IR 1718 (CO) cm^{-1}.

5-Methoxy-N,N-dimethylacetamide **(5)**: The amide **5** was prepared from **4** (0.95 g, 4.3 mmol) using the procedure described above for **2**. The product was filtered and purified by sublimation under diminished pressure to yield 0.8 g (4 mmol, 82%). Mp = 78-80 °C. IR 1618 (CO) cm^{-1}.

5-Methoxy-N,N-dimethyltryptamine **(6)**: To a stirred suspension of $LiAlH_4$ (0.7 g, 18.4 mmol) in dry THF (20 ml) was gradually added the amide 2 (0.7 g, 3.0 mmol) dissolved in dry dichloromethane (25 ml). The mixture was heated for 9 hrs under reflux with nitrogen until complete disappearance of the amide. TLC silicagel/methanol, Rf (amine) 0.1, Rf (amide) 0.8. The mixture was cooled in an ice bath, and treated with several drops of water to decompose the excess of $LiAlH_4$ reagent. The reaction mixture was vacuum filtered to remove any remaining solids, dried over anh. $MgSO_4$, and solvents removed by vaccum. The colorless oil was crystallised from ethanol, Mp= 50°-51 °C. The yield was 75% (0.49 g, 2.26 mmol).

5-Hydroxy-N,N-dimethyltryptamine **(7).** 0.2 g (0.9 mmol) of 5-methoxy-N,N-dimethyltryptamine (**6**) was stirred overnight with aqueous HBr to hydrolyse the methoxy group. The amine **7** was extracted into dichloromethane to give a colorless oil, which crystallised from ethyl acetate, Mp= 146-147 °C. Yield 60% (0.11 g, 0.55 mmol).

IODINATION

2-Iodo-N,N-dimethyltryptamine **(8)** *(Method A)*: To a solution of thallium trifluoroacetate ($Tl(TFA)_3$) (0.33 g, 0.61 mmol), in acetonitrile the amine **3** (0.1 g, 0.53 mmol) was added slowly. The reaction mixture was heated under reflux for 4 hrs and the solvent was evaporated under reduced pressure. The crude solid was dissolved in dichloromethane, and a solution of 0.2 g (1.22 mmol) of KI was added. The reaction mixture was stirred at room temperature for 15 min and vacuum filtered to remove the remaining solid (TlI). NaOH (2N) was added to the filtrate until basic reaction, and extracted with CH_2Cl_2; the organic layer was dried anh. ($MgSO_4$), and removed to give

a brown oil. Column chromatography on silicagel/methanol yielded 0.12 g of **8** (0.37 mmol, 70 %) as a light yellow oil.

(Method B): The amine **3** (0.10 g, 0.53 mmol) in chloroform (5 ml) was added to a solution of of chloramine-T (0.15 g, 0.73 mmol) in 5 ml of water. An aqueous solution of KI (0.12 g , 0.73 mmol) was added to the reaction mixture, stirred for 5 min and decoloured with sodium metabisulfite (0.02 g, 0.10 mmol); the organic layer was dried with anh. ($MgSO_4$), and the solvent removed under reduced pressure to obtain 0.14 g of a light yellow oil **8** (0.45 mmol, 85 %).

2-Iodo-N-methyltryptamine **(9)** *and 2-iodo-tryptamine* **(10).** 2-Iodo-derivatives of the amines were prepared using the same procedure as that described for the synthesis of **8**. Method A and method B yielded 74 and 87 % of the derivative **9**, respectively, as a colourless oil, while only method B was used in order to obtain 2-Iodo-5-Methoxy-N,N-dimethyltryptamine **(11)** with 88% yield; only method B was used to obtain 2-iodo-5-hydroxy-tryptamine **(12)** which crystallised from methanol/hexane to yield 83% (0.13 g, 0.4 mmol) of a light yellow solid (Mp= 105-108 °C), and finally 2-Iodo-Melatonine **(13)** in 87 % yield.

RADIOIODINATION

The general procedure for radioiodination of the amines was similar to the synthesis of the respective non-radioactive derivatives. Three mother solutions were prepared: an aqueous solution of chloramine-T (1.0 mg in 3 ml of water) (solution A); a solution of 3 mg of amine in 1 ml of chloroform (solution B), and a solution of sodium metabisulfite (0.7 mg in 1 ml of water) (solution C). 300 µl of A (0.6 µmol) and 400 µl of B (6 µmol) were mixed in an assay tube with 1 mCi of $Na^{131}I$ in 20 µl of NaOH solution. The reaction mixture was stirred in a vortex for 3 min and then 80 µl of C (0.25 µmol) were added, the organic and aqueous layers (OL and AL, respectively) being counted separately. The chloroform was allowed to evaporate to dryness and the iodinated amine was dissolved in 200 µl of PBS (phosphate buffer saline, pH 7.4). The reaction was tested by TLC in alumina/ benzene:acetone (7:10), Rf (2-^{131}I-DMT)= 0.1, Rf (^{131}I-)= 0.45. A series of blank assays

Table 4. Experimental parameters for the radioiodination of the amines **8-13**.

Comp.	Labeling Efficiency %=(OL-AL*r)/(OL+AL)*100	Radiochemical purity %=(OL-AL*r)/OL*100
8	81.6	98.0
9	85.6	98.5
10	90.0	99.0
11	81.6	98.0
12	81.6	98.0
13	90.0	99.0

were performed (without solution B), and both layers (OL and AL) were counted, leading to a coefficient r = OL/(AL + OL) of 0.10 +/- 0.05. The results are shown in Table 4. TLC analysis of the organic layers confirmed the results in the table.

ACKNOWLEDGEMENTS.- Thanks are due to CONICET and Universidad de Buenos Aires (UBA; Argentina) for financial support. One of us, (J.A.S), also thanks CONICET, (Argentina) for a research fellowship.

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