SYNTHESIS OF DERIVATIVES OF [I-131] PHENYLALKYLAMINES FOR BRAIN MAPPING.

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SUMMARY.- The synthesis and spectral properties of new radioiodinated phenylalkylamines like 2-[^{131}I]-iodo-4,5-dimethoxyphenethylamine, 2-[^{131}I]-iodo-4,5-dimethoxy-*N,N*-dimethyl-phenethylamine 2-[^{131}I]-iodophenethylamine, 2-[^{131}I]-iodo-*N,N*-dimethylphenethylamine, 2-[^{131}I]-iodo-3,4,5-trimethoxy-phenethylamine (mescaline) are described for the first time. These compounds are of biological importance and can be used for brain mapping with SPECT technology.

Keywords: 2-[^{131} I]-Iodo-4,5-dimethoxyphenethylamine, 2-[^{131}I]-iodo-4,5-dimethoxy-*N,N*-dimethylphenethylamine; 2-[^{131} I]-iodophenethylamine; 2-[^{131} I]-iodo-*N,N*-dimethylphenethyl-amine, 2-[^{131}I]-iodomescaline; phenethylamines.

INTRODUCTION

In vivo imaging techniques provide a powerful tool for the evaluation of CNS function in normal or disease states. Despite the attractive features associated with PET studies, for the majority of nuclear medicine clinics, SPECT imaging studies are the only procedures currently available. In view of the biological and pharmaceutical behavior of these compounds, it is important to label them with a γ-emitter to study their properties *in vivo.*

Phenethylamine and its derivatives are known for their physiological activity in brain and have been observed as metabolites in patients with mental disorders [1-10]; some of them had been labelled with I-123[11], or Tc-99m[12] for imaging studies.

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CCC 0362–4803/98/010053–09$17.50

Received 4 July 1997
Revised 20 August 1997

In this paper, we describe the synthesis and spectral properties of 2-[^{131} I]-iodo-4,5-dimethoxyphenethylamine, 2-[^{131}I]-iodo-4,5-dimethoxy-*N,N*-dimethylphenethylamine 2-[^{131} I]-iodophenethylamine, 2-[^{131} I]-iodo-*N,N*-dimethylphenethylamine, 2-[^{131}I]-iodo-3,4,5-trimethoxyphenethylamine (mescaline).

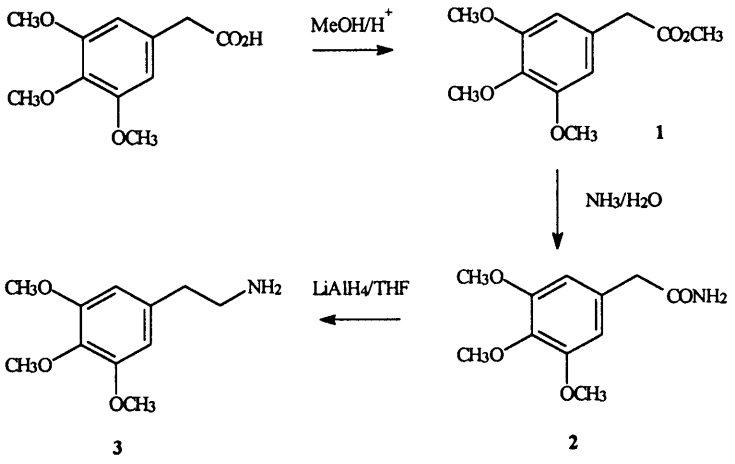
These compounds can be used for brain mapping with SPECT technology. Mescaline and its derivatives have been isolated from plants like *peyote* and other psychoactive cacti[13]. Several synthetic methods have been developed to obtain them for pharmacological purposes with low yields (between 12-35%). Condensation of the substituted benzaldehyde with nitroethane readily afforded the corresponding nitropropene, which was further reduced with $LiAlH_4$/THF[14-17] to yield the amine. *N,N*-Dimethylated derivatives were prepared according to the Eschweiler-Clarke method[18]. 3,4,5-Trimethoxy benzoic acid chloride has also been used as a starting material in a reaction with diazomethane with the formation of the corresponding diazoketone, which was then subjected to Hoffman[19] conditions ($AgNO_3$ /NH_3) to yield the amide, which was further reduced with $LiAlH_4$/THF, leading finally to mescaline. A similar method for preparing the phenethylamines was used by Hadáçek *et al.*[20] who obtained a low yield of the amine. The diazoketone was converted into the corresponding methyl ester of the 3,4,5-trimethoxyacetic acid, which was hydrolyzed and transformed into the acid chloride. After the amide formation with NH_3, it was reduced with $LiAlH_4$/THF to obtain the amine. Iodinated aromatic compounds have been obtained by iodination of the corresponding substrate using sodium iodide in the presence of sodium hypochlorite[21] or hydrogen peroxide[22-23] as oxidants.

Metalloiodination has also been recently used for iodination or radioiodination of aromatic compounds[24-27].

RESULTS AND DISCUSSION

Preparation of phenethylamines: In this paper we describe an easy method of preparing some derivatives of phenethylamine under mild conditions with yields higher than those reported in the previous methods together with several new iodinated and radioiodinated derivatives. Commercial 3,4,5-dimethoxyphenylacetic acid, 3,4-dimethoxyphenethylamine and phenethylamine are used as starting materials. The main metabolite of mescaline is 3,4,5-trimethoxyphenylacetic acid, which appears to be produced enzymatically by a diamine oxidase[3]. We used this compound as starting material for the synthesis of mescaline, using a similar reaction sequence to that previously developed in our laboratories[28]. The acid was esterified with methanol and the product was added to an excess of aqueous ammonia. After isolation of the amide it was reduced with lithium aluminum hydride in THF (**Scheme 1**). The overall yield was 55 %.

Scheme 1



For preparation of 3,4-dimethoxy- *N,N*-dimethylphenethylamine, the starting amine was methylated by two different methods: the classic methylation with iodomethane and with $NaCNBH_3$ /formaldehyde.

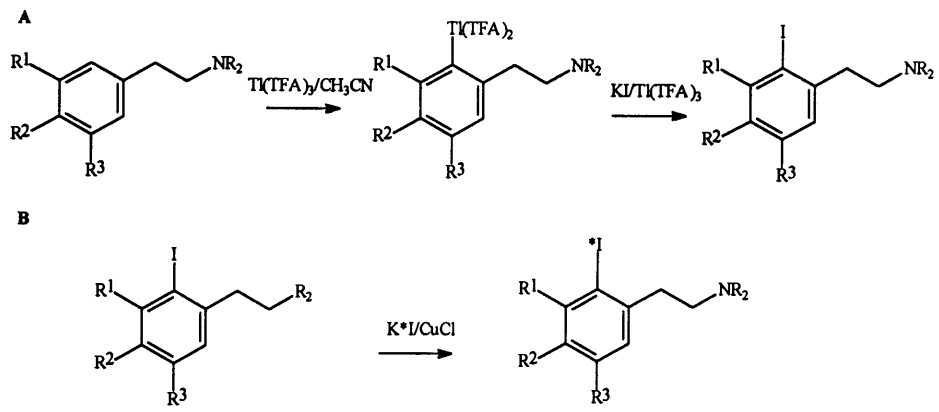
For the protection of the amino group before iodination, 3,4-dimethoxyphenethylamine and the phenethylamine were converted into the corresponding phthalimides by reaction with phthalic anhydride. This is an easy way of preparing these substituted phenethylamines under mild conditions with high yields in a few steps.

Iodination and radioiodination: Two methods were assayed for the preparation of iodinated derivatives (**Scheme 2**), (**A**) the McKillop method for iodination of aromatic compounds using thallium derivatives as intermediates[29], and (**B**) from the iodinated precursor by isotopic exchange catalyzed by Cu (I). The McKillop method led to radioiodinated products at carrier-free levels. ^{131}I derivatives were prepared by using both methods with a radiochemical purity over 97 %. So this proved to be a useful way for the preparation of five radioiodinated derivatives of phenethylamines that can be used for mapping or metabolic studies.

EXPERIMENTAL

General methods. Solvents were of the maximum purity available and checked by gas chromatography. Starting material, like 3,4,5-trimethoxyphenylacetic acid, 3,4-dimethoxy-phenethylamine and phenethylamine were purchased from Aldrich, carrier-free $Na^{131}I$ from

Scheme 2



Compd.	4	5	6	7	8	9	10	11	12
R^1	MeO	MeO	H	H	MeO	MeO	MeO	H	H
R^2	MeO	MeO	H	H	MeO	MeO	MeO	H	H
R^3	H	H	H	H	MeO	H	H	H	H
R	MeO	Phthal	MeO	Phthal	H	MeO	Phthal	MeO	Phthal

Phthal: Phthalimide

Amersham. TLC analyses were performed on aluminum-backed silica gel 60 F_{254} plates (0.2 mm) obtained from Merck and were visualized using ultraviolet light (254 nm) or I_2. Gas chromatography-mass spectrometry was achieved on a Trio 2 VG spectrometer operating at 70 eV. Melting points were recorded in a Fisher-Jones apparatus and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded on a Bruker ACE 200 in $CDCl_3$ or CD_3OD as stated. Resonances are reported downfield from internal tetramethylsilane. Infrared spectra were recorded on a Mattson 3000 FTIR spectrometer. Samples were counted using an automatic gamma detector (Clinigamma Pharmacia).

Synthesis of mescaline

3,4,5-Trimethoxyphenylacetate-methyl ester **(1):** A solution of 1.20 g (5.3 mmol) of 3,4,5-trimethoxyphenylacetic acid in 70 ml of methanol with a few drops of concentrated sulfuric acid was heated under reflux for 2 h until complete disappearance of the acid as checked by TLC on silicagel plates/ ethylacetate: R_f (acid) 0.7, 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 recrystallized from methanol to give 1.20 g (5.0 mmol, 96%). Mp= 40-41°C. IR 1743 cm^1 (CO).

3,4,5-Trimethoxyphenylacetamide (**2**): The ester **1** (1.07 g, 4.8 mmol) was dissolved in 20 ml of concentrated aqueous ammonia and stirred at 20 °C for 24 h; the reaction was tested by TLC on silicagel plates/ ethylacetate Rf (amide) = 0.1. To avoid hydrolysis the excess of ammonia was extracted under reduced pressure. The product crystallized from methanol to give 0.90 g (4.0 mmol, 84%). Mp = 125-126 °C . IR 1640 cm^{-1} (CO).

3,4,5-Trimethoxyphenethylamine (Mescaline) (**3**): To a stirred suspension of $LiAlH_4$ (0.40 g, 10.5 mmol) in dry THF (15 ml), the amide **2** (0.44 g, 1.98 mmol) in dry dichloromethane (25 ml) was added slowly. The mixture was refluxed for 36 h under nitrogen until complete disappearance of the amide 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 filtered to remove any remaining solids, dried over anh. $MgSO_4$, and solvents removed. The yield was 76% (0.32 g, 1.5 mmol) of a colorless oil, which crystallized in the freezer (-20 °C). Mp = 35-36°C. Acid sulfate 157-158 °C .

N-Methylation of phenethylamines

N,N-Dimethyl-3,4-dimethoxyphenethylamine (**4**) *and N,N-dimethylphenethylamine* (**6**). **A)** *Eschweiler-Clarke method.* To a stirred suspension of the amine (0.63 mMol) in 5 ml of acetonitrile, formaldehyde (325 µl , 4.3 mMol) was added slowly. The mixture was heated for 15 min under reflux. Sodium cyanoborohydride (62.5 mg, 1.0 mMol) was added and the solution was stirred for 20 min at 20 °C and neutralized with acetic acid (100 µl). The reaction was tested by TLC (neutral alumina), (benzene/ acetone 4:1) (Rf (amine) = 0.3; Rf (dimethylamine) = 0.9). After evaporating the solvent, a light oil was obtained. **B)** *(Iodomethylation).* To a stirred solution of the amine (4.5 mmol), in a mixture of 15 ml of methanol, 5 ml of water and 30 mg of sodium bicarbonate at pH 10-11, 2 ml of iodomethane was added at 20 °C. The product was filtered, dried and crystallized from methanol. The yield of the methiodide was over 95 %. Mp (**4**) = 239-240 °C, Mp (**6**) = 230-231 °C .

Synthesis of N-phthalimides

3,4-Dimethoxyphenethylamine-N-phthalimide (**5**) *and phenethylamine-N-phthalimide* (**7**). 1 Mmol of the amine was heated with 1 mmol of phthalic anhydride until the mixture melted. After cooling at 0 °C the solid was crystallized from methanol with a quantitative yield. Mp (**5**) = 175-176 °C, Mp (**7**) = 158-160 °C. IR 1714 cm^{-1} (CO).

Iodination

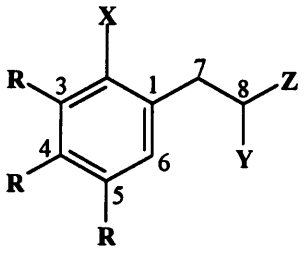
2-Iodo-3,4,5-trimethoxyphenethylamine **(8).** To a solution of thallium trifluoroacetate (0.33 g, 0.61 mmol) in acetonitrile the amine **(3)** (0.12 g, 0.53 mmol) was added slowly. The reaction mixture was heated under reflux for 4 h and the solvent was evaporated under reduced pressure. The solid was dissolved in dichloromethane and a solution of 0.20 g (1.22 mmol) of KI was added. The reaction mixture was stirred at 0 °C for 15 min and filtered to remove the remaining solid (TlI). NaOH (2N) was added to the filtrate until the reaction mixture was basic. After extraction with Cl_2CH_2, the organic layer was dried ($MgSO_4$), and the solvent was removed to give a brown oil. Chromatography on silicagel/methanol yielded 0.12 g of **(8)** (0.37 mmol, 70 %) as a light yellow oil. *2-Iodo-N,N-dimethyl-4,5-dimethoxyphenethylamine* **(9)** and *2-iodo-N,N-dimethylphenethylamine* **(11),** were obtained in the same way.

2-Iodo-4,5-dimethoxyphenethylamine-N-phthalimide **(10),** *2-iodo-phenethylamine-N-phthalimide* **(12).** To a solution of thallium trifluoroacetate (0.33 g, 0.61 mmol), in acetonitrile the amide (0.53 mmol) was added slowly. The reaction mixture was heated under reflux for 4 h and after cooling at 20 °C a solution of 0.20 g (1.22 mmol) of KI was added. The reaction mixture was stirred for 15 minutes and filtered to remove the remaining solid (TlI). The solvent was evaporated under reduced pressure and the solid was recrystallized from methanol to obtain 0.45-0.57 mmol (85-90 %) of **10-12**. Mp **(10)** = 167-168 °C, Mp **(12)** = 143-145 °C.

Radioiodination

The procedure for radioiodination was the same as that described for the synthesis of the corresponding nonradioactive derivatives, while that for radioiodination by isotopic exchange from the iodinated precursor catalyzed by Cu (I) was modified as follows. The iodinated amine was dissolved in 2 ml of PBS (phosphate buffer saline, pH 6.5). 100 ml of a 0.1 M solution of CuCl was added, and then 3 mCi of carrier-free [131-I]-KI was added. The reaction mixture was refluxed for 10 minutes and tested by TLC in alumina/ benzene:acetone (10:7), Rf (2-^{131}I-amine)= 0.1-0.2, Rf (^{131}I-)= 0.45. The radiochemical purity was always over 96 %.

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



X=H, I
Y=O, H
Z=N, O
R=H, OCH

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

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	CH_3(3)	CH_3(4)	CH_3(5)	Z-CH_3
1	133.1	106.1	144.9	128.0	144.9	106.1	39.9	173.0	56.0	56.0	56.0	52.0
2	133.1	106.1	144.9	128.0	144.9	106.1	41.8	172.7	56.0	56.0	56.0	-
3	133.1	106.1	144.9	128.0	144.9	106.1	40.2	44.4	56.0	56.0	56.0	-
4	132.3	120.8	114.7	142.7	144.1	114.1	35.2	60.7	56.0	56.0	-	41.5
5	132.1	121.8	112.9	143.1	144.3	112.6	34.7	44.5	55.7	55.7	-	-
6	139.4	128.1	128.7	127.4	128.7	128.1	36.3	59.6	-	-	-	41.5
7	140.1	128.0	128.5	127.2	128.5	128.0	35.8	44.7	-	-	-	-
8	143.1	73.8	152.8	130.6	144.5	108.7	38.7	43.5	55.1	56.0	56.0	-
9	142.1	88.5	124.6	145.3	143.6	116.8	33.6	59.8	56.0	55.1	-	41.7
10	140.1	88.2	123.3	146.3	143.2	112.8	32.8	40.8	56.2	55.9	-	-
11	149.3	95.7	138.4	129.8	128.1	130.6	36.0	59.8	-	-	-	42.1
12	149.2	94.8	137.2	128.8	128.0	131.5	34.1	44.3	-	-	-	-

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

Comp	H-2	H-3	H-4	H-5	H-6	H-7	H-8	N-CH3	CH3(3)	CH3(4)	CH3(5)
1	6.11	-	-	-	6.11	3.63	-	3.67(E)	3.73	3.73	3.73
2	6.11	-	-	-	6.11	3.66	-	5.8(NH)	3.73	3.73	3.73
3	6.11	-	-	-	6.11	2.55	2.44	1.0(NH)	3.73	3.73	3.73
4	6.59	6.63	-	-	6.55	3.07	3.85	2.86	3.75	3.73	-
5	6.51	6.61	-	-	6.51	2.71	3.73	-	3.73	3.71	-
6	7.12	7.20	7.09	7.20	7.12	3.05	3.81	2.85	-	-	-
7	7.12	7.20	7.09	7.20	7.12	2.70	3.70	-	-	-	-
8	-	-	-	-	5.93	2.55	2.44	1.10(NH)	3.80	3.66	3.75
9	-	7.20	-	-	6.72	3.09	3.82	2.90	3.79	3.69	-
10	-	7.18	-	-	6.67	3.05	3.91	-	3.81	3.67	-
11	-	7.59	6.88	7.20	6.91	3.08	3.80	2.85	-	-	-
12	-	7.59	6.88	7.20	6.91	3.06	3.90	-	-	-	-

Table 3. MS data for phenethylamine analogs and intermediates.

Comp	M+	M/100%	M /%	M / %	M / %	M / %
1	240	181	225/70	167/23	137/25	
2	225	181	211/18	167/25	148/19	44/47
3	211	181	196/53	167/83	44/44	
4	351	58	209/10	151/45	142/22	127/10
5	311	77	160/38	151/50		
6	291	58	149/15	142/40	127/12	91/6
7	251	160	91/25	77/15		
8	337	180	210/38	166/85	44/49	
9	335	58	208/43	277/85	150/23	77/80
10	437	277	310/43	290/94	160/46	77/71
11	275	58	217/80	147/35	90/22	77/12
12	377	217	250/50	160/45	90/25	

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

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