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Structure Biodistribution Relationship of Radiolabeled Ergolines: Search for Brain Imaging Radiopharmaceuticals

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SUMMARY

A series of ergoline derivatives, analogues of Pergolide **1** and Lysergol **6**, were synthesized, radiolabeled with ^{125}I or ^{75}Se, and evaluated for their ability to cross the Blood Brain Barrier of rats, for potential use as radiopharmaceuticals for imaging the brain. Introduction of the radiolabel was either at the 17- position (attached to the 8ß-methylene) or at the 2- position of the indole portion of the ergoline moiety. Of the 8 radiolabeled compounds tested, two pergolide analogues, 8ß-(methyl-^{75}Se-seleno)-methyl-6-propyl ergoline **5** and 8ß-[^{125}I]-iodomethyl-6-propyl ergoline **2f'** showed the highest uptake in the brain, adrenal and heart with good organ to blood ratios. This work has shown that analogues of pergolide, a dopamine agonist, if labeled with ^{123}I may yield a clinically useful brain imaging radiopharmaceutical.

Keywords: Radiolabeled Ergolines, Brain uptake, Pergolide, Lysergol derivatives.

INTRODUCTION

Aberrant dopamine neuronal transmission has been implicated in the pathogenesis of Parkinsonism (1-6). Other central nervous system diseases such as Huntington's Chorea (2,7,8) Tardive Dyskinesia (9-12), and Schizophrenia (13-15) are also associated with changes in the density of dopaminergic receptors.

Several investigators have labeled and studied different dopamine antagonists, e.g. ^{82}Br-Bromperidol (16-17), ^{77}Br-bromspiroperidol (18-19), ^{18}F-Haloperidol (17,20,21), ^{11}C-Spiroperidol (21), ^{75}/^{77}Br-Benperidol (22) and ^{11}C-MPTP (23). 3-N-[^{11}C]-methylspiperone, a ligand with high affinity for dopamine receptors, labeled with the positron-emitting radionuclide ^{11}C, has been used in imaging the receptors by positron emission tomography scanning in baboons and in humans (24,25).

Pergolide mesylate **1** ([8ß)-8-[(methylthio)methyl]-6-propylergoline methane sulfonic acid), a semi-synthetic ergot alkaloid derivative known to possess central dopaminergic

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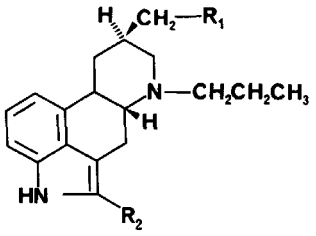
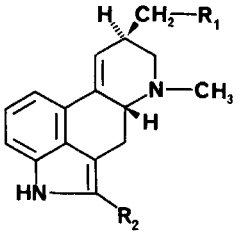
receptor agonistic activity (26), was found to compete with ^{3}H-labeled dopamine and ^{3}H-labeled spiperone binding to brain striatal membranes with a high affinity comparable to that of apomorphine and superior to lergotrile (27). Using the molecule of pergolide and lysergol (another ergot alkaloid) as our model compounds, we have synthesized several ergoline derivatives, with different substituents in the 8-ß position (Figure 1). We radiolabeled these compounds with ^{125}I or ^{75}Se and performed complete biodistribution studies in the rat. In the case of one compound, the Se bioisostere of pergolide **5** a detailed distribution of this compound in the various brain regions of the rat as well as the effect of other dopamine agonists and antagonists on its biodistribution is included.

RESULTS AND DISCUSSION

Chemistry. The synthesis of 8ß-iodomethyl-9-ergolene **2a** and 8ß-[^{125}I]-iodomethyl-9-ergolene **2a'** outlined in Scheme I, uses lysergol **6** to prepare 8ß-(methanesulfonyl)-oxymethyl-6-methyl-9-ergolene **7** which if refluxed with sodium iodide (NaI) produced **2a** or with no-carrier added sodium iodide-^{125}I ($Na^{125}I$) produced **2a'**. **7** was also used to prepare 8ß-(p-bromophenylthio)-methyl-9-ergolene **2d**. We were unsuccessful in exchanging the p-bromo group in **2d** with either non-radioactive iodide to prepare **2e** or radioactive iodide to prepare **2e'**.



PERGOLIDE



LYSERGOL

1 : $R_1 = SCH_3$; $R_2 = H$

2f : $R_1 = I$; $R_2 = H$

2f': $R_1 = {}^{125}I$; $R_2 = H$

2g : R_1 = o-iodobenzylselenide ; $R_2 = H$

2g': R_1 = o-^{125}I-iodobenzylselenide ; $R_2 = H$

3b : $R_1 = SCH_3$; $R_2 = I$

3b': $R_1 = SCH_3$; $R_2 = {}^{125}I$

3c : $R_1 = OSO_2CH_3$; $R_2 = I$

3c': $R_1 = OSO_2CH_3$; $R_2 = {}^{125}I$

4 : $R_1 = SeCH_3$; $R_2 = H$

5 : $R_1 = {}^{75}SeCH_3$; $R_2 = H$

6 : $R_1 = OH$; $R_2 = H$

2a : $R_1 = I$; $R_2 = H$

2a': $R_1 = {}^{125}I$; $R_2 = H$

2b : $R_1 = 4\text{-}I\text{-}C_6H_4SO_3$; $R_2 = H$

2b': $R_1 = 4\text{-}{}^{125}I\text{-}C_6H_4SO_3$; $R_2 = H$

2c : $R_1 = 4\text{-}I\text{-}C_6H_4CO_2$; $R_2 = H$

2c': $R_1 = 4\text{-}{}^{125}I\text{-}C_6H_4CO_2$; $R_2 = H$

2d : $R_1 = 4\text{-}Br\text{-}C_6H_4S$; $R_2 = H$

2e : $R_1 = 4\text{-}I\text{-}C_6H_4S$; $R_2 = H$

2e': $R_1 = 4\text{-}{}^{125}I\text{-}C_6H_4S$; $R_2 = H$

3a : $R_1 = OH$; $R_2 = I$

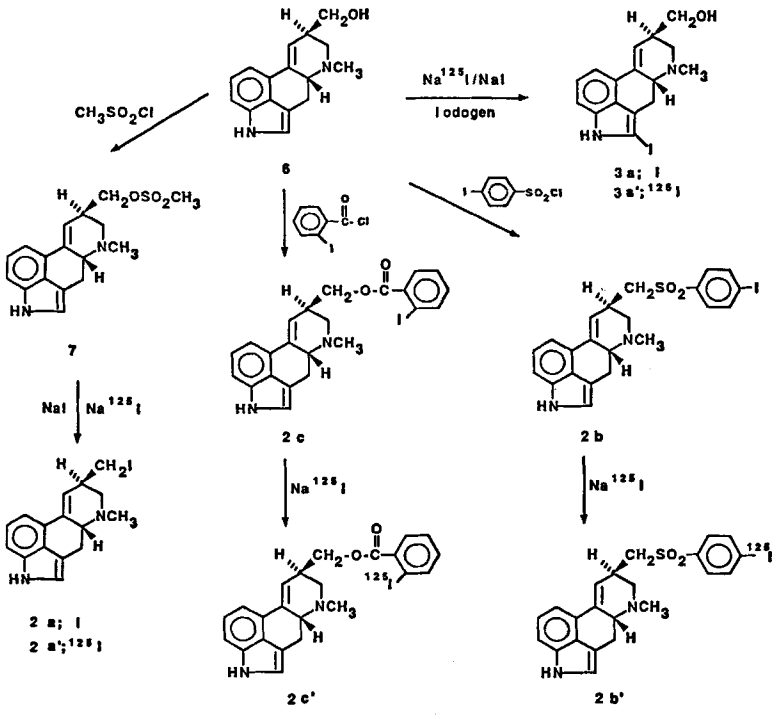
3a': $R_1 = OH$; $R_2 = {}^{125}I$

Figure 1. Structures of non-radioactive and radioactive pergolide and lysergol derivatives.

8ß-(p-iodobenzenesulfonyl)-oxymethyl-6-methyl-9-ergolene **2b** (Scheme I) was prepared and purified by thin layer chromatography yielded **2b'**.

8ß-(o-iodobenzoyl)-oxymethyl-6-methyl-9-ergolene **2c** (Scheme I) was prepared by treating **6** with o-iodobenzoyl chloride in pyridine. **2c'** was obtained when crystalline **2c** was mixed with solid 18-Crown-6 and no-carrier added sodium iodide-^{125}I and the mixture heated for 24 hrs. at 140 ^{0}C.

SCHEME I



8ß-Iodomethyl-6-propylergoline **2f** and 8ß-^{125}I-iodomethyl-6-propylergoline **2f'** were synthesized by refluxing 8ß-(methanesulfonyl)-oxymethyl-6-propylergoline **8** with either sodium iodide to produce **2f** or sodium iodide-^{125}I to produce **2f'** (Scheme II).

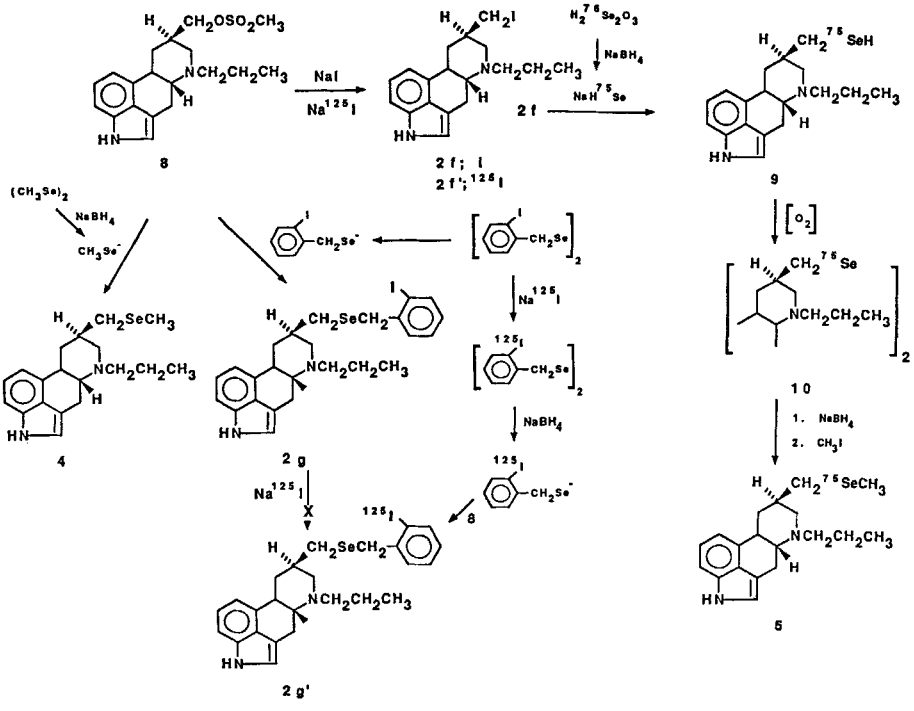
8ß-(o-Iodobenzyl)-selenomethyl-6-propylergoline **2g** was synthesized by treating **8** with sodium (o-iodobenzyl)selenide prepared from di-(o-iodobenzyl)diselenide. Attempts to radioiodinate **2g** with sodium iodide-^{125}I by such methods as iodine exchange in solvents like alcohol and without solvent (melt method) failed. Therefore **2g'** was prepared by radiolabeling di-(o-iodobenzyl)diselenide with sodium iodide-^{125}I and then reducing it with $NaBH_4$ to give sodium (o-[^{125}I]-iodobenzyl)selenide which in turn was reacted with **8** to give **2g'** (Scheme II).

2-Iodo-Lysergol **3a**, 2-Iodo-Pergolide **3b**, and 2-Iodo-8ß-(methanesulfonyl)-oxymethyl-6-propylergoline **3c** were prepared by treating **6**, **1**, and **8** respectively with sodium iodide in

the presence of 1,3,4,6-tetra-chloro-3α,6α-diphenylglycouril (Iodogen) for 2 hours at room temperature. **3a'-c'** were prepared as above except that sodium iodide-^{125}I was used in the reaction (Scheme I, **3a,3a'**).

8ß-(methylseleno)-methyl-6-propylergoline **4** was prepared by treating **8** with methylselenide in THF/Ethanol. This method could not be used to prepare **5** due to the volatility and danger of handling methylselenide-^{75}Se. Therefore 8ß-(methyl[^{75}Se]seleno)-methyl-6-propylergoline **5** was prepared by treating **2f** with sodium hydrogen selenide-^{75}Se prepared from selenious acid-^{75}Se. The iodo group in **2f** was displaced by the HSe^- anion to form the corresponding selenol **9** which upon exposure to air formed the diselenide **10**. Reduction of **10** with $NaBH_4$ and subsequent addition of methyl iodide provided the desired compound **5** (Scheme II).

SCHEME II



Of the nine radiolabeled compounds, **2a', 2f', 3a', 3b', 3c'** were prepared by no carrier added syntheses. As carrier free (17 Ci/mg, 2125 Ci/mmol) $^{125}I^-$ was used and the radioactive product was separated from the non-radioactive precursor and free I^-, these radioactive compounds had specific activities of 2125 Ci/mmol. In the case of **2b', 2c', 2g'** and **5**, the specific activities were in the range of 2.5-400 mCi/mmol.

Biodistribution Studies. Compound **5** was the first compound synthesized as a true

Se for S analogue of pergolide and was studied more extensively to establish the usefulness of the ergoline nucleus in the design of new dopamine agonists. Table I shows the uptake in the different regions of the brain in rats injected with **5**. The results show that statistically significant uptake was recorded in brain parts known to contain higher amounts of dopamine receptors i.e. locus coeruleus, substantia nigra, pons, medulla oblongata, and corpus striatum than the rest of the brain parts. Also, as see in Table II, the administration of various dopamine agonists and antagonists showed decrease uptake of **5**, as high as 98%, in dopamine receptor rich areas of the brain.

Based on these data and realizing that ^{75}Se is not an ideal imaging radionuclide, we proceeded to synthesize, radiolabel and study the biodistribution of the radioiodinated analogs of the ergoline nucleus.

Except for **2g'** (unstable in-vitro) all the radioactive compounds were formulated as described under the experimental section, and injected into male Sprague-Dawley rats. The animals were sacrificed at various time intervals, appropriate tissues were removed and analyzed for radioactivity. Although many more tissues and at longer time periods were analyzed, only 8 tissues and the shorter time periods are included in Table III, the other

Table I. Rat Brain Distribution of **5***

	Time Period in Minutes				
Tissue	0.25	0.50	1	2	5
Blood	0.19±0.02	0.10±0.02	0.07±0.01	0.04±0.01	0.03±0.00
Brain	0.13±0.01	0.21±0.02	0.24±0.01	0.21±0.01	0.19±0.02
Cerebral Cortex	0.12±0.01	0.16±0.03	0.23±0.02	0.19±0.02	0.18±0.02
Caudate Nucleus	0.11±0.02	0.14±0.02	0.21±0.02	0.19±0.01	0.19±0.02
Cerebellum	0.10±0.02	0.22±0.01	0.21±0.02	0.20±0.01	0.19±0.01
Hippocampus	0.12±0.01	0.16±0.04	0.20±0.01	0.19±0.01	0.16±0.02
Hypothalamus	0.13±0.02	0.20±0.02	0.23±0.03	0.18±0.01	0.17±0.02
Locus Coeruleus	0.17±0.02	0.40±0.03	0.40±0.03	0.29±0.03	0.27±0.03
Midbrain	0.12±0.03	0.20±0.02	0.22±0.01	0.21±0.02	0.21±0.02
Med. Oblongata	0.16±0.02	0.37±0.02	0.28±0.00	0.27±0.02	0.23±0.03
Nucl. Accumbens	0.11±0.02	0.21±0.01	0.21±0.02	0.20±0.02	0.19±0.03
Olfactory Bulbs	0.11±0.02	0.20±0.03	0.19±0.01	0.18±0.02	0.18±0.02
Hypophysis	0.10±0.01	0.18±0.01	0.20±0.01	0.19±0.01	0.18±0.02
Pons	0.17±0.04	0.33±0.06	0.28±0.02	0.25±0.05	0.27±0.01
Substania Nigra	0.13±0.03	0.36±0.03	0.30±0.02	0.25±0.02	0.21±0.01
Corpus Striatum	0.12±0.04	0.25±0.05	0.30±0.06	0.27±0.03	0.24±0.03
Thalamus	0.24±0.04	0.24±0.05	0.24±0.03	0.22±0.02	0.21±0.02

* Values represent the mean %Kg-dose per gram ± standard deviation for five animals per time period.

tissues generally contained low levels of radioactivity. From these data we can make several observations: 1) Except for **2b'** and **3b'** all compounds showed good brain uptake and except for **2b'** all compounds showed relatively high adrenal uptake (presumably adrenal medulla). The reason that **2b'** did not cross the blood brain barrier (BBB) was probably due to its metabolism (hydrolysis) in vivo and the release of [^{125}I]-p-iodobenzene sulfonic acid as evidenced by the high radioactivity content of the kidneys and urine. Although high activity

Table II. Biodistribution of 5 in Various Brain Regions in Rats Preinjected with Dopamine Agonists and Antagonists*

Tissue	1	2	3	4	5	6	7
Brain	0.24	0.14	0.09	0.10	0.09	0.01	0.10
		42%	63%	58%	63%	96%	58%
Caudate Nucleus	0.21	0.11	0.08	0.10	0.08	0.01	0.09
		48%	62%	52%	62%	95%	57%
Corpus Striatum	0.30	0.06	0.14	0.13	0.12	0.01	0.13
		80%	53%	57%	60%	97%	57%
Hypothalamus	0.23	0.09	0.10	0.11	0.06	0.02	0.10
		61%	57%	52%	74%	91%	57%
Locus Coeruleus	0.40	0.18	0.14	0.18	0.16	0.01	0.11
		55%	65%	55%	60%	98%	73%
Nucleus Accumbens	0.21	0.08	0.09	0.09	0.07	0.01	0.11
		62%	57%	57%	67%	95%	48%
Substantia Nigra	0.36	0.10	0.10	0.09	0.09	0.01	0.09
		72%	72%	75%	75%	97%	75%
Thalamus	0.24	0.08	0.09	0.11	0.08	0.01	0.07
		67%	62%	54%	67%	96%	71%

*Values are %Kg-dose/gm at peak uptake times (0.25 - 5 min), and the percentages are total inhibition at that peak time.

1 = 5 (4-7 μCi, IV)
Drug 2 = (+)-Butaclamol.HCl (0.04 mg/Kg, IV, 30 min) followed by 1.
Drug 3 = (-)-Butaclamol.HCl (0.04 mg/Kg, IV, 30 min) followed by 1.
Drug 4 = (±)-Butaclamol.HCl (0.04 mg/Kg, IV, 30 min) followed by 1.
Drug 5 = SKF-38393 (0.04 mg/kg, IV, 30 min) followed by 1.
Drug 6 = SKF-38393 and (+)-Butaclamol.HCl (0.04 mg/Kg, IV, 30 min) followed by 1.
Durg 7 = (-)-Chlorethylnorapomorphine.HCl (0.04 mg/Kg, IV, 30 min) followed by 1.

was present with **3b'** in the adrenal, we cannot explain the low activities detected in the brain at various times. 2) The peak time of radioactivity uptake in the brain ranged from 1 - 15 min, while that in the adrenal ranged from 1 - 5 min, indicating rapid uptake of the radioactivity in these two tissues and also relatively rapid washout from these tissues. At all times, at least a two fold and in some cases a 40 fold amount of radioactivity was present per gm of adrenal tissue versus brain tissue, though more was present in the brain as a whole than in the adrenal. At peak time of radioactivity uptake, the compounds are ranked in decreasing uptake in the brain as follows: **2f' > 5 > 3c' > 2a'=3a' > 2c' > 2b'=3b'** while the same ranking in the adrenal would be **5 > 3b' > 2f' > 3a' > 3c' > 2c' > 2a' > 2b'** . 3) The route of excretion of these radiolabeled compounds is both the kidneys and the hepatobiliary system as evidenced by the high activity in the liver, kidneys and small intestines. In vivo deiodination was minimal in the early time periods when the radioiodine was on an aromatic ring (except for **2b'**) but when it was in the 2-position of the ergoline moiety i.e. **3a', 3b'** or **3c'** appreciable deiodination was noted after 5 min post injection as evidenced by high

radioactivity in the urine. In **2f'**, although the radioiodine is aliphatic, good stability was evidenced up to 30 min post injection. 4) The radiolabeled ergolines being tertiary amines showed as expected high uptake in the lungs except **2b'** as noted above . 5) The heart, known to contain dopaminergic receptor sites, in many cases showed higher uptake of radioactivity than the brain and with a longer half-life. 6) From the data we can also deduce that pergolide derivatives, gave higher brain and adrenal uptake than lysergol derivatives, **2f'** vs **2a'**, presumably due to the longer alkyl chain attachment to N-6, n-propyl vs methyl.

TABLE III - TISSUE BIODISTRIBUTION OF RADIOLABELED ERGOLINE DERIVATIVES*

	Time Period Min	Blood	Adrenal	Brain	Heart	Liver	Kidney	Lung	Intestine	Urine
2a'	1	0.09 ± 0.006	0.22 ± 0.016	0.14 ± 0.009	0.20 ± 0.006	0.17 ± 0.003	0.26 ± 0.019	1.21 ± 0.077	0.14 ± 0.017	0.03 ±0.028
	5	0.06 ± 0.003	0.14 ± 0.006	0.09 ± 0.004	0.07 ± 0.006	0.14 ± 0.029	0.10 ± 0.011	0.35 ± 0.048	0.10 ± 0.014	0.10 ±0.003
	15	0.07 ± 0.001	0.07 ± 0.014	0.07 ± 0.002	0.05 ± 0.001	0.07 ± 0.003	0.08 ± 0.003	0.24 ± 0.022	0.10 ± 0.011	0.12 ±0.036
2b'	1	0.29 ± 0.022	0.03 ± 0.007	0.02 ± 0.002	0.08 ± 0.004	0.13 ± 0.003	0.22 ± 0.010	0.32 ± 0.054	0.30 ± 0.005	0.00 ±0.000
	5	0.17 ± 0.014	0.05 ± 0.010	0.02 ± 0.001	0.04 ± 0.004	0.13 ± 0.008	0.16 ± 0.013	0.15 ± 0.025	0.05 ± 0.017	0.49 ±0.230
	15	0.17 ± 0.008	0.02 ± 0.004	0.01 ± 0.001	0.02 ± 0.004	0.10 ± 0.001	0.10 ± 0.004	0.10 ± 0.006	0.05 ± 0.026	0.06 ±0.039
2c'	1	0.06 ± 0.005	0.39 ± 0.028	0.10 ± 0.002	0.66 ± 0.025	0.23 ± 0.009	0.58 ± 0.027	0.25 ± 0.085	0.09 ± 0.002	0.01 ±0.000
	5	0.04 ± 0.012	0.19 ± 0.094	0.05 ± 0.016	0.20 ± 0.033	0.21 ± 0.065	0.30 ± 0.094	0.63 ± 0.191	0.04 ± 0.018	0.04 ±0.017
	15	0.05 ± 0.002	0.26 ± 0.064	0.07 ± 0.004	0.11 ± 0.008	0.24 ± 0.010	0.32 ± 0.016	0.59 ± 0.169	0.03 ± 0.002	0.84 ±0.365
2f'	1	0.05 ± 0.003	0.30 ± 0.050	0.21 ± 0.016	0.84 ± 0.028	0.24 ± 0.016	0.86 ± 0.023	3.97 ± 0.151	0.18 ± 0.016	0.00 ±0.000
	5	0.04 ± 0.001	0.82 ± 0.146	0.25 ± 0.014	0.37 ± 0.018	0.36 ± 0.012	0.62 ± 0.005	2.33 ± 0.153	0.20 ± 0.017	0.12 ±0.020
	15	0.04 ± 0.003	0.67 ± 0.153	0.29 ± 0.026	0.17 ± 0.022	0.47 ± 0.030	0.45 ± 0.060	1.53 ± 0.227	0.23 ± 0.014	0.54 ±0.106
3a'	1	0.11 ± 0.005	0.72 ± 0.135	0.14 ± 0.010	0.78 ± 0.053	0.44 ± 0.047	1.05 ± 0.065	1.46 ± 0.064	0.25 ± 0.015	0.01 ±0.004
	5	0.06 ± 0.011	0.24 ± 0.037	0.08 ± 0.020	0.14 ± 0.034	0.31 ± 0.009	0.35 ± 0.098	0.33 ± 0.105	0.15 ± 0.005	0.36 ±0.174
	15	0.07 ± 0.005	0.24 ± 0.009	0.08 ± 0.007	0.11 ± 0.012	0.50 ± 0.021	0.29 ± 0.037	0.28 ± 0.075	0.15 ± 0.036	0.79 ±0.793
3b'	1	0.10 ± 0.004	0.55 ± 0.148	0.02 ± 0.004	0.80 ± 0.085	0.49 ± 0.092	1.01 ± 0.119	1.07 ± 0.253	0.26 ± 0.023	0.02 ±0.012
	5	0.01 ± 0.008	0.83 ± 0.088	0.02 ± 0.002	0.31 ± 0.026	0.44 ± 0.015	0.86 ± 0.037	0.67 ± 0.092	0.21 ± 0.028	0.27 ±0.138
	15	0.09 ± 0.004	0.31 ± 0.044	0.02 ± 0.001	0.11 ± 0.015	0.28 ± 0.052	0.33 ± 0.011	0.23 ± 0.025	0.19 ± 0.016	0.81 ±0.254
3c'	1	0.09 ± 0.007	0.61 ± 0.014	0.15 ± 0.003	0.94 ± 0.097	0.33 ± 0.022	1.14 ± 0.082	2.60 ± 0.152	0.25 ± 0.019	0.00 ±0.000
	5	0.05 ± 0.004	0.51 ± 0.010	0.13 ± 0.020	0.40 ± 0.059	0.51 ± 0.044	0.67 ± 0.073	1.24 ± 0.468	0.18 ± 0.029	0.21 ±0.094
	15	0.05 ± 0.002	0.56 ± 0.101	0.07 ± 0.008	0.15 ± 0.001	0.79 ± 0.093	0.39 ± 0.069	0.52 ± 0.116	0.20 ± 0.015	0.53 ±0.307
5	1	0.07 ± 0.012	0.69 ± 0.068	0.24 ± 0.010	0.86 ± 0.020	0.23 ± 0.029	0.58 ± 0.063	4.10 ± 0.184	0.15 ± 0.070	0.00 ±0.001
	5	0.03 ± 0.003	0.96 ± 0.048	0.19 ± 0.019	0.28 ± 0.060	0.41 ± 0.037	0.53 ± 0.077	2.26 ± 0.388	0.21 ± 0.033	0.01 ±0.005
	15	0.02 ± 0.002	0.64 ± 0.120	0.16 ± 0.012	0.10 ± 0.014	0.54 ± 0.054	0.41 ± 0.038	1.19 ± 0.185	0.18 ± 0.011	0.06 ±0.017

*Values represent the mean %Kg-Dose/gm ± standard deviation for 3-5 animals per time period.

At the present we are studying the no-carrier added labeling and purification parameters of **2f'** with $Na^{123}I$ (a superior imaging radionuclide, $t_{1/2}$=13 hrs., γ=159 KeV) to further test this compound and compare it to **5**.

EXPERIMENTAL

All commercially obtained chemicals and solvents were of reagent grade and were used without purification. Pergolide mesylate **1** and 8ß-(methanesulfonyl)-oxymethyl-6-propylergoline **8** were gifts from Dr. E.C.Kornfeld, Eli Lilly Research Laboratories, Indianapolis,IN. Lysergol **6** was purchased from Sigma Chemical Company, St. Louis,MO. Sodium Iodide-^{125}I (carrier free, in aqueous 0.1N NaOH) was purchased from ICN Chemical and Isotope Division. Selenious acid-^{75}Se (specific activity=305 mCi/mg Se) was purchased from Oak Ridge National Laboratories, Oak Ridge, TN. Proton magnetic resonance spectra were obtained on a Varian EM-360A spectrometer. Mass spectra were obtained on a CEC 110 double-focusing mass spectrometer or a Hewlett Packard 5985 GC/MS system. Melting points (uncorrected) were determined on a Thomas Hoover melting point apparatus. Radiochromatograms were scanned on a LB2723 Dunnschit-Scanner II auto scanner (Berthold, Germany). Radioactivity in tissue samples was assayed with a Packard Multi-Prias 2 gamma counter (United Technologies). Thin layer chromatography (TLC) was performed on silica gel plates containing a fluorescent indicator (Eastman, cat #13181). Van Urk's reagent spray (p-dimethylamino- benzaldehyde 1g., dilute hydrochloric acid (25%) 50 mL, Ethanol (95%) 50 mL) was utilized to identify the presence of ergolines on TLC. Preparative TLC was done on 20X20 cm plates, 500 microns (Analtech, cat #02012). Elemental analyses, where indicated, were performed by Midwest Microlab Inc., Indianapolis, IN, and were within 0.4% of theoretical values. Tissues were weighed on a Mettler AC 100 Digital Electronic Balance.

8ß-(Methanesulfonyl)-oxymethyl-6-methyl-9-ergolene (7). Lysergol **6** (254 mg, 1 mmol) was added to 3 mL acetonitrile under a nitrogen atmosphere, the suspension was cooled to a temperature of 0-5 ^{0}C. To this suspension, was added in a slow dropwise fashion a solution of methansulfonyl chloride (286 mg, 2.5 mmol) in 2 mL acetonitrile. The reaction was stirred at 0-5 ^{0}C for 30 min, the mixture was then allowed to reach room temperature and was stirred for an additional 2 h. The reaction mixture was added gradually to a stirred solution of 5 mL conc. ammonium hydroxide in crushed ice (20 g). This mixture was extracted three times with 75 mL methylene chloride. The combined organic layers were washed two times with 30 mL water, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. Recrystallization from ethyl acetate yielded 210 mg (65%) of **7**; mp 170-175 ^{0}C dec; NMR (DMSO-d_6) δ 2.40-2.55 (3H,s), 3.28-3.35 (3H,s), 4.15-4.32 (2H,d), 6.23-6.32 (2H,s), 6.90-7.29 (3H,m); M.S. m/e 334 (M^+).

8ß-Iodomethyl-9-Ergolene (2a). Compound **7** (100 mg, 0.3 mmol) and sodium iodide (300 mg, 2 mmol) were stirred in 25 mL acetone under a nitrogen atmosphere. The reaction mixture was refluxed for 30 h. After cooling, the solvent was evaporated in vacuo. Cold dilute ammonium hydroxide (2 mL) was added and the suspension extracted three times with 90 mL

ethyl acetate. The combined extracts were washed twice with 30 mL water, and dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The crude product was dissolved in 1 mL ethanol and was purified using preparative TLC, utilizing ethyl acetate as the solvent. The bluish violet zone (R_f 0.2) (when observed under low UV light), was scraped and extracted with 10 mL methanol. The extract was filtered, and the solvent evaporated in vacuo. The product was recrystallized from benzene to yield 20 mg (18%) of **2a**; mp 320-325 ^{0}C dec; NMR ($CDCl_3$) δ 2.55-2.63 (3H,s), 4.98-5.17 (2H,d), 7.20-7.42 (3H,m); M.S. m/e 364 (M^+).

8ß-[^{125}I]-Iodomethyl-9-Ergolene (2a'). Compound **7** (5 mg, 0.015 mmol) was dissolved in 1 mL absolute ethanol under a nitrogen atmosphere. To this solution was added sodium iodide-^{125}I (10 μL, 1 mCi no-carrier added). The reaction mixture was refluxed for 3 h. The solvent was evaporated under nitrogen and the residue extracted with 1.5 mL ethyl acetate and filtered through a glass-wool pledget. The solvent was concentrated to a volume of 0.5 mL under nitrogen and layered on a 5 cm dry packed silica gel column (Kieselgel 40, 0.063-0.2 mm, 10-230 mesh ASTM, cat #10180) and eluted with ethyl acetate. The fractions containing **2a'** were pooled together to give 0.64 mCi (64%). (Sp. Act.= 2125 Ci/mmol). Co-chromatography with **2a** on silica gel eluted with ethyl acetate and scanned with a radiochromatogram scanner, indicated a single radioactive compound with R_f 0.4.

8ß-(p-Iodobenzenesulfonyl)-oxymethyl-6-methyl-9-ergolene (2b). Compound **6** (0.5 g, 1.97 mmol) was stirred in 5 mL THF under a nitrogen atmosphere. To this solution was added triethylamine (0.4 g, 3.93 mmol). p-Iodobenzenesulfonyl chloride (2.5 g, 8.3 mmol) in 25 mL acetonitrile was added dropwise to this solution. The reaction mixture was stirred for 72 h. at room temperature and then added to a cold stirred dilute ammonium hydroxide solution. The product was extracted three times with 60 mL of ethyl acetate. The combined ethyl acetate extracts were washed once with dilute sodium chloride solution, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. Recrystallization from ethyl acetate/hexane yielded 0.6 g (59%) of **2b** ; mp 307-309 ^{0}C dec; NMR (CD_3COOD) δ 2.95-3.11 (3H,s), 4.22-4.35 (2H,s), 7.45-8.15 (7H,m). Anal. ($C_{22}H_{21}O_3N_2SI$) C,H,N,S.

8ß-(p-^{125}I-Iodobenzensulfonyl)-oxymethyl-6-methyl-9-ergolene (2b'). Compound **2b** (5 mg, 0.01 mmol) was dissolved in a mixture of 2 mL absolute ethanol and 0.5 mL THF under a nitrogen atmosphere. To this solution was added sodium iodide-^{125}I (10 μl, 1 mCi no-carrier added). The reaction mixture was refluxed for 20 h. The solvent was evaporated under nitrogen, and the residue dissolved in ethyl acetate and purified by preparative TLC utilizing ethyl acetate as eluent. The middle zone with R_f value 0.4-0.6 was scraped off and extracted with methanol, filtered, and the solvent evaporated under nitrogen. The radioactive **2b'** was assayed to have 0.185 mCi (18%), (Sp. Act.= 18.5 mCi/mmol). Co-chromatography with **2b** on silica gel with ethyl acetate as eluent, and scanned, showed the presence of a single radioactive compound with Rf 0.6.

8ß-(o-Iodobenzoyl)-oxymethyl-6-methyl-9-ergolene (2c). Compound **6** (0.2 g, 0.79 mmol) was

dissolved in 4 mL pyridine. The solution was cooled to 0 C, and stirred under a nitrogen atmosphere. To this solution was added o-iodobenzoyl chloride (0.24 g, 0.9 mmol) in a slow dropwise fashion. The temperature of the reaction mixture was allowed to rise to room temperature, and was gradually heated to 70-80 ^{0}C for 12 h. The reaction mixture was cooled to room temperature, 0.5 mL of water and 3-4 drops of methanol were added to the mixture. The mixture was stirred for 18 h. at room temperature. The solvent was evaporated in vacuo, and the residue extracted with 100 mL ethyl acetate. The organic extract was washed with dilute ammonium hydroxide solution, washed twice with 20 mL water, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Recrystallization from methanol yielded 0.25 g (66%) of **2c** ; mp 175-177 ^{0}C; NMR ($CDCl_3$) δ 2.68-2.70 (3H,s), 4.42-4.55 (2H,d), 7.23-8.15 (7H,m); M.S. m/e 484 (M^+).

8ß-[^{125}I]-(o-Iodobenzoyl)-oxymethyl-6-methyl-9-ergolene (2c'). Compound **2c** (5 mg, 0.01 mmol) was mixed with 0.25 g of 1,4,7,10,13,16-hexa-oxacycloctadecane (18-Crown-6). To this mixture of solids was added $Na^{125}I$ (1 mCi, 10 μL) under a nitrogen atmosphere. The mixture was heated to 140 ^{0}C for 24 h. The reaction mixture after cooling to room temperature was dissolved in 1 mL ethanol. The ethanol solution was passed through an anion exchange cellulose (Cellex D, hydroxide form, BIO-RAD Corp.) packed in a 2 cm column. The radioactive product was eluted with 1.5 mL ethanol and found to contain 0.75 mCi (75%), (Sp. Act.=75 mCi/mmol) of **2c'**. Co-chromatography with **2c** on silica gel with ethyl acetate as eluent showed the presence of only one radioactive compound R_f 0.5.

8ß-(p-Bromophenylthio)-Methyl-6-methyl-9-Ergolene (2d). Compound **7** (0.334 g, 1 mmol) was stirred in a mixture of 1 mL hexamethylphosphoramide (HEMPA) and 0.1 mL water . To this solution was added 4-bromothiophenol (0.567 g, 3 mmol). The reaction mixture was maintained at 70-80 ^{0}C for 20 h. and then allowed to cool to room temperature. The reaction mixture is added dropwise to a stirred solution of 5 mL conc. ammonium hydroxide in 20 g crushed ice. This mixture was then extracted three times with ethyl acetate (90 mL). The combined organic layers were washed two times with 20 mL water, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. Recrystallization of the crude product from a 1:1 mixture of hexane and chloroform yielded 310 g (75.3%) of **2d**; mp 208-211 ^{0}C. NMR (CD_3OD) δ 2.65-2.72 (3H,s), 7.22-7.65 (7H,m); M.S. m/e 426 (M^+).

8ß-Iodomethyl-6-propylergoline (2f). Compound **8** (0.54 g, 1.48 mmol) was stirred in 15 mL absolute ethanol under a nitrogen atmosphere. To this suspension was added sodium iodide (2 g, 13.3 mmol). The reaction mixture was refluxed for 30 h. and then allowed to cool to room temperature and filtered. The solvent was evaporated in vacuo. The crude product was recrystallized twice from ethyl acetate to yield **2f** 0.22 g (40%); mp 214-216 ^{0}C. NMR (CD_3COOD) δ 0.8-1.1 (3H,t), 1.4-2.0 (4H,m), 2.5-3.0 (13H,m), 6.7-7.2 (4H,m); M.S. m/e 394 (M^+).

8ß-[^{125}I]-Iodomethyl-6-propylergoline (2f'). Compound **8** (5 mg, 0.014 mmol) was added to

1 mL absolute ethanol under a nitrogen atmosphere. To this suspension was added Na I (1 mCi, 10 μL). The reaction mixture was refluxed for 40 h. and was allowed to cool to room temperature. The volume was reduced with nitrogen to about 0.1 mL. This was streaked on a preparative TLC using ethyl acetate as eluent. The radioactive zone R_f 0.5 was scrapped off and eluted with 10 mL methanol, filtered and the solvent removed under a stream of nitrogen to yield **2f*** 0.91 mCi (91%), (Sp. Act.= 2125 Ci/mmol). Co-chromatography on silica gel with **2f** using benzene:methanol (9.5:0.5 v/v) as eluent, showed the presence of one radioactive compound with R_f 0.5.

8ß-(Methylseleno)-methyl-6-propylergoline (4). Sodium borohydride (0.158 g, 4 mmol) dissolved in 2 mL ethanol was added dropwise to a solution of dimethyldiselenide (0.186 g, 1 mmol) in 2 mL THF under nitrogen. After decolorization of the yellow solution, 0.54 g of compound **8** dissolved in 2 mL THF was added, and the solution stirred for 2 h. To the reaction mixture was added 10 mL of water, dropwise, and this mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness. Crystallization from ethanol afforded **4** 0.44 g (81%); mp 196-197 ^{0}C. NMR ($CDCl_3$) δ 0.8-1.1 (3H,t), 1.1-1.9 (4H,m), 2.0 (3H,s), 2.1-3.5 (11H,m), 6.8-7.2 (4H,m), 8.0 (1H,s); M.S. m/e 360 (M^+ for ^{78}Se), 362 (M^+ for ^{80}Se).

8ß-(Methyl-^{75}Se-seleno)-methyl-6-propylergoline (5). To selenious acid (1.29 mg, 10 μmol) in 0.1 mL of phosphate buffer (pH 6.0, 0.5M), was added ^{75}Se-selenious acid ($H_2{}^{75}SeO_3$) (Sp. Act. = 305 mCi/mg Se, 2.7 mCi, 10 μL) (28). The solution was stirred under argon gas, and sodium borohydride (1.14 mg, 30 μmol) in 0.1 mL water was added dropwise until a colorless solution was formed. To this solution, was added 0.5 mL of phosphate buffer (pH 6.0, 0.5M), followed by the addition of **2f** (4 mg, 10 μmol) in 0.2 mL THF. Another 0.5 mL THF was added to the reaction mixture and refluxed for 20 min. The solution was allowed to reach room temperature and then extracted with ether. The ether layer contained 2.25 mCi (83.3%) of the diselenide **10**. The ether layer was evaporated using a stream of nitrogen and the residue dissolved in THF and transferred to a round bottom flask. Sodium borohydride (0.38, 10 μmol) in ethanol was added under argon followed by the addition of methyl iodide (2.9 mg, 20 μmol). After the solution was stirred for 5 min, 2 mL of water was added and the mixture was extracted with chloroform. The organic extract was evaporated to dryness to give 2 mCi (74%) of **5** (Sp. Act.=400 mCi/mmol). The radioactive diselenide **10** and **5** were co-chromatographed with non-radioactive **10** and **4** on silica gel plates using benzene:methanol (9.5:0.5 v/v) as solvent. R_f values for **10** and **5** were 0.09-0.11 and 0.32-0.40 respectively.

8ß-(o-Iodobenzyl)-selenomethyl-6-propylergoline (2g). Di-(o-iodobenzyl)diselenide was synthesized according to the published procedure for diselenide preparation (29). To a solution of di-(o-iodobenzyl)diselenide (208 mg, 0.35 mmol) in 5 mL of THF at room temperature and under nitrogen, was added dropwise sodium borohydride (28 mg, 0.75 mmol) dissolved in 5 ml of absolute ethanol, with magnetic stirring. To the resulting colorless solution

containing the o-iodobenzyl selenide anion was added dropwise a solution of **8** (254 mg, 0.7 mmol) in 50 mL of THF at room temperature. After 36 h of stirring, 20 mL of water was added to the reaction mixture, and the mixture extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The solid residue was dissolved in 2 mL of benzene:methanol (95:5 v/v), layered on a dry packed 2.5 x 40 cm silica gel column (Kieselgel 40, 0.063-0.200 mm, 70-230 mesh ASTM), and eluted with benzene:methanol (95:5 v/v). The fractions containing compound **2g** (identified by TLC on silica gel, eluted with benzene:methanol (95:5 v/v) R_f 0.4, blue color when sprayed with Van Urk's reagent) were pooled together and evaporated under reduced pressure. The crude product when recrystallized twice from boiling absolute ethanol gave **2g** , 51 mg (13%); mp 172-174 ^{0}C. NMR ($CDCl_3$) δ 0.9 (3H,t), 2.1 (2H,d), 3.95 (2H,s), 6.9-7.4 (8H,m), 7.9 (1H,s) M.S. m/e 562 (M^+ for (^{78}Se), 564 (M^+ for (^{80}Se). Anal. ($C_{25}H_{29}N_2SeI$) C,H,N.

8ß-(-o-[^{125}I]-Iodobenzyl)-selenomethyl-6-propylergoline (2g'). Attempts to directly radioiodinate **2g** by using several established iodine exchange methods were not successful. Therefore **2g'** was synthesized as follows: Di-(o-iodobenzyl)diselenide (2.4 mg, 4 μmol) was dissolved in 1 ml of absolute ethanol in a 5 cc glass ampoule. To this was added sodium iodide-^{125}I (1 mCi, 10 μL), and the solvent was evaporated to dryness with a stream of nitrogen. The ampoule was sealed, and placed in a oven at 94 ^{0}C for 12 hours. The ampoule was then allowed to cool to room temperature, cut open and 0.5 mL of chloroform added to dissolve the contents. The crude product was purified by preparative TLC utilizing chloroform:hexane (1:9 v/v) as solvent system. The middle zone of R_f value 0.37-0.43 was scraped off and extracted with three 5 mL portions of ethyl acetate. The combined extracts were filtered, the filtrate was evaporated in vacuo to yield di-(o-[^{125}I]-iodobenzyl)diselenide 0.12 mCi (18%), (Sp. Act.=30 mCi/mmol). Co-chromatography with non-radioactive di-(o-iodobenzyl)diselenide on silica gel with solvent systems chloroform:hexane (1:9 v/v) and benzene:methanol (95:5 v/v) showed a single radioactive compound with R_f 0.45 and 0.70 respectively. To a solution of di-(o-[^{125}I]-iodobenzyl) diselenide (0.12 mCi, 4 μmol) in THF at room temperature was added dropwise a solution of sodium borohydride (0.38 mg, 10 μmol) in 1 mL of absolute ethanol with magnetic stirring under nitrogen. To the colorless mixture was added dropwise a solution of **8** (2.9 mg, 8 μmol) in 1 mL of THF. After 16 h of stirring, the reaction mixture was evaporated to dryness using a stream of nitrogen, redissolved in 2 mL of chloroform and filtered. The filtrate was concentrated and streaked on a preparative TLC utilizing benzene:methanol (95:5 v/v) as solvent system. The middle zone of R_f value of 0.4-0.5 was scraped off and extracted with 5 ml portions of ethyl acetate, filtered and evaporated in vacuo to yield **2g'** 20 μCi (16%), (Sp. Act.= 2.5 mCi/mmol). Co-chromatography with **2g** on silica gel and solvent system benzene:methanol (95:5 v/v) showed a single radioactive peak R_f 0.44.

General procedure for the Synthesis of 2-Iodo Ergolines. Compound **6** (63.5 mg, 0.25 mmol)

was dissolved in 5 mL of 0.1N tartaric acid solution (with slight warming). This solution was added to a round bottom flask containing 1,3,4,6-tetrachloro-3α,6α-diphenylglycouril (IODOGEN) (108 mg, 0.25 mmol) and sodium iodide (52.5 mg, 0.35 mmol). The suspension was stirred under nitrogen for 2 h. at room temperature, filtered, made basic with 1N NaOH, and extracted three times with 25 mL ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, reduced in volume to about 5 mL and petroleum ether added to start the precipitation of an amorphous solid which was completed overnight at 4 ^{0}C. The solid was recrystallized twice from chloroform:hexane to give **3a** 26 mg (27%); mp 192-194 ^{0}C dec. Chromatography of **3a** on silica gel TLC with acetone as solvent shows the presence of a single compound with R_f 0.33, greenish-blue fluorescence when viewed under short UV light, and no color development when sprayed with Van Urk's reagent, indicating the presence of a substituent at position 2, while lysergol has an R_f of 0.28, shows blue fluorescence when viewed under short UV light, and a violet-blue color when sprayed with Van Urk's reagent. M.S. m/e 380 (M^+); Analysis ($C_{12}H_{17}ON_2I$) C,H,N. Using the above procedure **2-Iodo-Pergolide 3b** was prepared in a low yield of 9%, mp 211-215 ^{0}C dec; mass spectrum m/e 440 (M^+); and **2-Iodo-8ß-(methanesulfonyl)-oxymethyl-6-propylergoline 3c** was prepared in a yield of 12%, mp 179-185 ^{0}C dec; M.S. m/e 476 (M^+).

General procedure for the Synthesis of 2-[^{125}I]-Iodo Ergolines. IODOGEN (2.5 mg, 5.8 μmol) dissolved in 0.5 mL chloroform is added to a 12 x 7.5 mm test tube. The chloroform is evaporated under a stream of nitrogen while the tube is rotated to give a coating of IODOGEN on the test tube wall. To this test tube is added a solution of **6** (1.5 mg, 5.8 μmol) in 1 mL of 0.1N tartaric acid solution, and sodium iodide-^{125}I (1 mCi, 10 μL). The tube is shaken gently at intervals and left at room temperature for 2 h. The solution is carefully aspirated with a pasteur pipette, filtered through a pledget of glass-wool and made alkaline with 10% Na_2CO_3 solution and extracted three times with 5 ml of chloroform. The chloroform extracts were washed twice with 3 ml of 0.01N NaOH solution, dried over anhydrous sodium sulfate, and the solvent evaporated under a stream of nitrogen to yield **2-[^{125}I]-Iodo-Lysergol 3a'** 0.38 mCi (38%), (Sp. Act.= 2125 Ci/mmol). Using this procedure, **2-[^{125}I]-Iodo-Pergolide 3b'** was prepared in 25% yield, 0.25 mCi, (Sp. Act.= 2125 Ci/mmol) from **1**, and **2-[^{125}I]-Iodo-8ß-(methanesulfonyl)-oxymethyl-6-propylergoline 3c'**was prepared in 33.4% yield, 0.33 mCi (Sp. Act.= 2125 Ci/mmol) from **8**. Purification by preparative TLC, and co-chromatography with their corresponding non-radioactive compounds on silica gel with different eluting solvents showed the presence of a single radioactive compound.

Biodistribution Studies. The radiolabeled compounds (greater than 98% radiochemical purity) were dissolved in 2 mL 0.1% tartaric acid solution, filtered through 0.22 μm Millipore (type GS) filter, and adjusted to a specific volume with sterile physiological saline to contain 4-12 μCi in 0.15-0.2 mL of injectable solution. The radiolabeled compounds in the above formulation were administered intravenously to male Sprague-Dawley rats (125-300 gm).

Three to five animals were used per time period for each radiolabeled compound. While the animals were still under sodium pentobarbital anesthesia, they were sacrificed by exsanguination via cardiac puncture and 2 mL of blood was quickly aspirated into a heparinized syringe. A urine sample (1 mL) was aspirated from the bladder. Organs and tissues of interest (adrenal, lungs, liver, small intestines, kidneys, muscle, spleen, brain, femur, fat, and testes) were excised at predetermined time intervals. Each tissue or organ was stripped of fat and adipose tissue, washed with physiological saline, blotted dry, weighed and counted for radioactivity. In the brain distribution studies with compound **5** and the various agonists and antagonists, the whole brain after isolation was dissected into the different brain regions using a modification of literature techniques (30). The percent injected dose per gram of tissue was normalized to 1 Kg animal body weight, and the values expressed as %Kg-Dose/gm.

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