104505-62-6; **34**, 76743-02-7; **35**, 104489-64-7; **36**, 76743-03-8; **37**, 76743-04-9; **38**, 104489-65-8; **39**, 104489-66-9; **40**, 104489-67-0; **41**, 104489-68-1; **42**, 76743-06-1; **43**, 76743-08-3; **44**, 76743-07-2; **45**, 76743-09-4; **46**, 82095-07-6; **47**, 86372-50-1; **48**, 82081-48-9; **49**, 82081-52-5; **50**, 82081-50-3; **51**, 76743-13-0; **52**, 76743-14-1; **53**, 76732-74-6; **54**, 76743-10-7; **55**, 76732-62-2; **56**, 82081-31-0; **57**, 82081-36-5; **58**, 82081-40-1; **59**, 82081-60-5; **60**, 82081-54-7; thiourea, 62-56-6; 1-bromo-3-(1,1-dimethylpropoxy)propane, 64419-02-9; methyl isothiocyanate, 556-61-6; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; methylamine, 74-89-5.

Phenylpiperazine-Based Radiopharmaceuticals for Brain Imaging. 3. Synthesis and Evaluation of Radioiodinated 1-Alkyl-4-phenylpiperazines

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As part of our program in radiopharmaceutical chemistry we have prepared and evaluated a series of radioiodinated 1-alkyl-4-phenylpiperazines as potential brain-imaging agents. The compounds were chosen on the basis of their synthetic versatility, activation toward electrophilic substitution, and ease of purification. The intermediates **1**–**6** were readily obtained and converted to the corresponding radioiodinated products **7**–**12** in 76–91% isolated radiochemical yields. The tissue distribution in rats indicated that the 1-*N*-butyl derivative **9** possesses the best combination of brain uptake (0.28–0.35% ID·kg/g), retention, and selectivity (brain/blood > 20) over the 4-h evaluation period. A subsequent imaging and tissue distribution study in the dog using ^{131}I-labeled **9** supported the results observed in the rat and suggested the potential of this agent as a brain-imaging agent.

The development of single-photon emission computed tomographic (SPECT) instrumentation with sensitivity and resolution approaching that of the positron emission tomographic (PET) devices has stimulated the search for X-ray-emitting compounds capable of crossing the intact blood–brain barrier (BBB) and providing information regarding local cerebral perfusion.[1,2] Many types of brain pathology present themselves as alterations of blood flow and/or metabolic status prior to changes in brain morphology or density that can be detected by conventional radiologic methods. PET scanning has been particularly valuable in identifying many of these disorders, including early stroke, epilepsy, Huntington's chorea, Alzheimer's disease, and others.[3–6] This modality requires an on-site cyclotron, synthetic capability, and a PET scanner to prepare and use the short-lived radiopharmaceuticals. Widespread application of the brain scanning techniques may require the use of radionuclides that are available from generator sources or are sufficiently long-lived to be incorporated into an agent and shipped to the site of use.

Although ^{99m}Tc is the radionuclide of choice in clinical nuclear medicine, the difficulty in preparing a suitable chelate that will bind reduced ^{99m}Tc, readily cross the BBB, and be retained without redistribution long enough to provide useful scintigraphic images slowed its general acceptance.[7–11] Only recently, however, the derivatives of technetium-99m propyleneamine oxime (^{99m}TcPnAO) have been introduced into clinical nuclear medicine[12,13] and demonstrate significant potential. Organic radiopharmaceuticals, however, labeled with iodine radionuclides have been much more successful. The more promising of these radiopharmaceuticals are ^{123}I-labeled *N*-isopropyl-1-(4-iodophenyl)-2-aminopropane (*N*-isopropyl-*p*-iodoamphetamine, IMP)[14,15] and *N*,*N*,*N*′-trimethyl-*N*′-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (HIPDM).[16,17] The utility of IMP as an indicator of cerebral perfusion has been demonstrated in several clinical studies.[18–20] A comparison of HIPDM and IMP in-

Scheme I

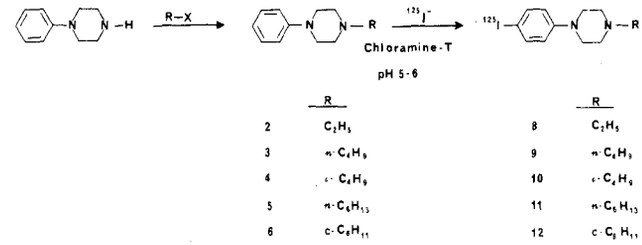

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Table I. Properties of 1-Alkyl-4-phenylpiperazines (2–6)

compd	mol. formula	mp, °C	yield, %	recrystn solvent	R_f[a]	calcd C	calcd H	calcd N	found C	found H	found N
ethyl **2**	$C_{12}H_{18}N_2 \cdot 1HCl(0.25H_2O)$	190–191	68	acetone	0.55	62.07	7.79	12.07	62.04	7.91	11.97
butyl **3**	$C_{14}H_{22}N_2 \cdot C_2H_2O_4$	194–196	55	acetone	0.73	62.34	7.74	9.09	62.13	7.81	8.95
1-butyl **4**	$C_{14}H_{22}N_2 \cdot 1HCl(1.0H_2O)$	228–230	65	acetone	0.82	61.65	8.81	10.28	62.08	8.86	10.25
hexyl **5**	$C_{16}H_{26}N_2 \cdot 1HCl(1.75H_2O)$	178–180	79	acetonitrile	0.86	61.15	9.71	8.92	61.27	9.32	8.85
c-hexyl **6**	$C_{16}H_{24}N_2$	101–102[b]	16	water/ethanol	0.72	78.62	9.92	11.46	78.97	10.15	11.57

[a] R_f values determined with use of silica gel plates and *n*-BuOH/H_2O/AcOH (4:2:1) as the mobile phase. [b] Reference 34, 108–109 °C.

dicates that they possess similar tissue distribution,[21] although HIPDM may be superior for studies performed during rapid changes in blood flow. Other labeled agents have been reported that possess properties similar but not significantly superior to these two and therefore have not generated similar clinical acceptance.[22-26]

Although IMP and HIPDM are of significant value, they both possess characteristics that are ultimately undesirable as radiolabeled tracers for cerebral perfusion imaging. Labeling of both agents proceeds via isotope exchange, which inherently leads to a comparatively low specific activity for the agent. The administered dose of the agent therefore contains unlabeled compound that may be pharmacologically active. In the case of IMP, isotopic exchange proceeds at a position that is not activated and rigorous conditions are required to produce reliable yields of the labeled product. The time required for the labeling and purification of the product results in the increased percent of the ^{124}I radionuclide, present as a byproduct of the $^{124}Te(p,2n)^{123}I$ production method, such that the injected dose (mCi/patient) is limited as a result of radiation dosimetric considerations. The production of ^{123}I via the $^{124}Xe(p,2n)^{123}Cs(^{123}Xe)^{123}I$ method,[27] which generates no ^{124}I contaminant, minimizes the dosimetric problem. Also, both radiopharmaceuticals are highly extracted by the lungs with the result that photons arising from that tissue are received by the detectors over the brain and reduce the resolution of the subsequent brain image.

As part of our program to develop new brain-imaging agents we have attempted to overcome some of the problems associated with IMP and HIPDM by identifying precursors that could be easily labeled via electrophilic methods, readily separated from the nonradioactive starting material, and highly extracted and retained by the brain with greatly reduced uptake in the lung. On the basis of our successful utilization of the *N*-phenylpiperazine moiety in the preparation of radioiodinated adrenal and myocardial agents,[28-30] we extended this approach to the synthesis and evaluation of labeled 1-substituted-4-phenylpiperazines with potential as brain-imaging agents.[31,32]

Table II. Radiochemical Yields for Compounds 7–12

compd	isolated radiochemical yield, %	anal.
ethyl **8**	76	HPLC, TLC
butyl **9**	76	HPLC, TLC
isobutyl **10**	85	HPLC, TLC
hexyl **11**	90	HPLC, TLC
c-hexyl **12**	91	HPLC, TLC

We report here the synthesis of a series of radioiodinated 1-alkyl-4-phenylpiperazines at the no-carrier-added (NCA) level and their biodistribution in rats after intravenous administration. The interpretation of the results suggests that several of the agents possess potential as brain-imaging agents.

Chemistry. Compounds **1–12** were synthesized according to Scheme I. The intermediate 4-(unsubstituted phenyl)piperazines **2–6** were prepared by alkylation, with the appropriate alkyl halides, purified, and characterized (Table I). Compound **1** was prepared by the same method and was identical to that obtained commercially. The electrophilic radioiodination of the 4-phenylpiperazines **2–6** proceeded at the no-carrier-added level to give good yields of the desired products, **8–12**, isolated by HPLC (Table II). The labeling of compound **1** has been reported previously.[31] The identity of the products was ascertained by comparison with the authentic nonradioactive 4-iodophenyl compounds prepared with use of *N*-(4-iodophenyl)piperazine and the alkyl halide. Retention times on HPLC were identical, and the radioactivity comigrated with the nonradioactive compound. Since the radiolabeling and isolation procedures could be performed within 2–3 h, the overall method is applicable to general use in nuclear medicine. The radioactive iodine in the products is also chemically stable as the formation of free radioiodide was less than 2%/month when either ^{125}I or ^{131}I was used.

Experimental Section

Chemistry. General Procedures for Synthesis of Compounds 1–6. To a solution of 3.24 g (20 mmol) of *N*-phenylpiperazine in 30 mL of a suitable solvent, e.g., benzene or acetonitrile, was added 10 mmol of the appropriate alkyl iodide, and the mixture was heated under reflux for 2–3 h. The mixture was then cooled to room temperature and filtered, and the precipitate was discarded. The filtrate was taken and the solvent was evaporated to leave a brown oil, which was dissolved in chloroform and washed three times with water. The chloroform layer was then dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated. The residue was chromatographed on an alumina column (100 g) and eluted with a methanol/chloroform mixture (5:95). The fractions containing the product were collected and evaporated to dryness, and the pure product was then converted

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to the hydrochloride or the oxalate salt for characterization.

Radioiodination Procedure. A. ^{125}I. To 10 μL of a 0.08 N NaOH solution containing 5.0 mCi (2.27 mmol) of $Na^{125}I$ in a sealed vial were added 50 μL of a 5 mM solution of the appropriate 1-alkyl-4-phenylpiperazine in a 5% sodium acetate/acetic acid solution and 50 μL of a 5 mM chloramine-T solution in a 5% sodium acetate/acetic acid mixture (w/v). After the mixture was stirred at ambient temperature for 30 min, the reaction was terminated by the addition of 100 μL of a 5% $Na_2S_2O_5$ solution in water (w/v). The contents were injected onto a C-18 reverse-phase HPLC column and eluted with an ethanol/5 mM ammonium phosphate gradient. The fractions containing the product were combined, and the radiochemicals were isolated in 76–91% radiochemical yields.

B. ^{131}I. The same procedure as above was used to radiolabel 1-butyl-4-phenylpiperazine with 10 mCi of $Na^{131}I$. The pure radiolabeled compound was obtained in 60% radiochemical yield.

Tissue Distribution. A. Rats. Male Sprague–Dawley rats (250–300 g), under ether anesthesia, were injected iv with 0.1 mL of a saline solution containing the appropriate radiopharmaceutical (10–15 μCi). Groups of rats (N = 3) were sacrificed at 0.25, 1, and 4 h after administration. Samples of blood and tissues of interest were removed, weighed, and assayed for activity by using a γ-well scintillation counter. Tissue and blood concentrations are expressed as percentage of injected dose times mass (kg) per gram of tissue (% ID·kg/g),[33] and brain-to-blood ratios were calculated on the basis of the concentrations.

B. Dogs. A female dog weighing 5.7 kg was injected im with 0.6 mL of an acepromazine maleate solution (10 mg/mL) followed 5 min later with 3 mL iv of a mixture of sodium nembutal solution (50 mg/mL)/0.9% saline solution (1:1). The dog was then injected iv with 1.0 mCi of the ^{131}I-labeled 1-butyl-4-(4-iodophenyl)-piperazine. Blood samples were taken at 0.5, 3, 7, 13, 17, 30, 60, and 120 min after administration. Scintigraphic images of the dog skull (posterior oblique) were taken at 15, 38, and 120 min by using a γ-camera with a medium-energy collimator (100 000 counts, 330–380 s). After 2 h the dog was sacrificed by injecting iv 10 mL of sodium nembutal (50 mg/mL), and tissues of interest were excised, weighed (based on body weight, several organs' weights were estimated, blood = 7.5%; fat = 27.5%; muscle = 40%), and assayed for activity. The results were expressed as percentage of injected dose per organ (% ID/organ) and percentage of injected dose per gram of tissue (% ID/g).

Results and Discussion

The two-step synthesis of the simple ^{125}I-labeled 4-phenylpiperazine derivatives **7–12** proceeded readily in good overall yields. The intermediate 1-alkyl-4-phenylpiperazines were easily prepared and isolated via alkylation of the commercially available *N*-phenylpiperazine. This method for obtaining the intermediates appeared to be substantially milder and more general than the use of either bis(chloroethyl)amines[34,35] or anilines[36] or the reaction of the piperazine with an ester followed by lithium aluminum hydride reduction.[37,38] Except for the 1-cyclohexyl derivative **6**, isolated in 16% yield, the yields ranged from 55 to 88% in which the product was separated via a simple column chromatographic step. The radioiodinations of the 1-alkyl-4-phenylpiperazines also proceeded in high isolated radiochemical yields, ranging from 76 to 91%. The use of small quantities of reagents permitted the desired radioactive product to be separated cleanly from the excess starting material using reverse-phase HPLC. As can be seen in Figure 1A (top) there is one major plus a few minor radioactive components in the crude reaction mixture as well as one major UV-absorbing component. Isolation of the radioactive fraction and reinjection of an aliquot indicates only the desired radioactive product and no detectable UV-absorbing components (Figure 1B (bottom)). The isolated product not only was present in high specific activity but also was virtually uncontaminated by starting material.

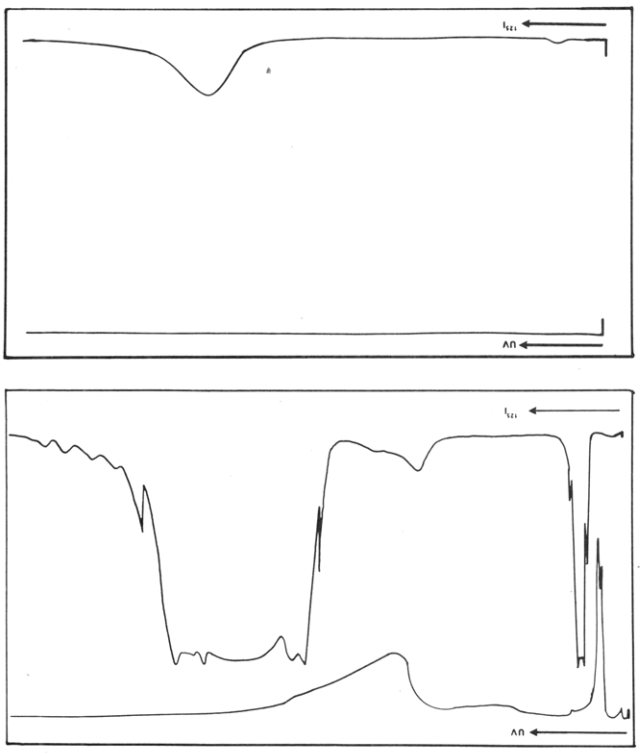


Figure 1. (A, top) HPLC chromatogram of crude reaction mixture from the radioiodination of 1-cyclohexyl-4-phenylpiperazine (**6**). The upper trace is the UV absorption at 254 nm, and the lower trace is the radioactivity for ^{125}I. (B, bottom) HPLC chromatogram of the reinjected sample of the major component isolated from the radioiodination of 1-cyclohexyl-4-phenylpiperazine (**6**).

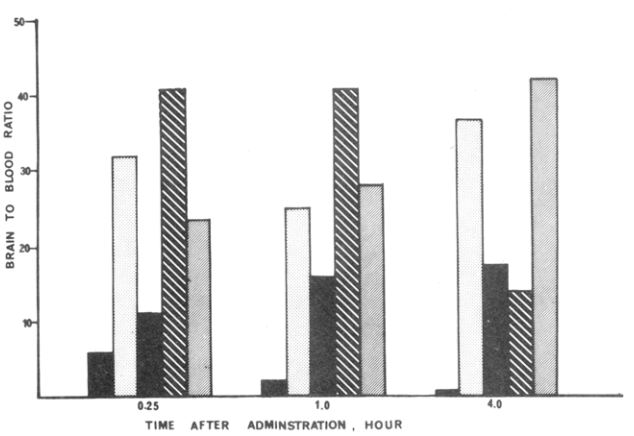


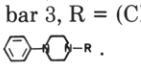
Figure 2. Brain-to-blood ratios for compounds **8–12** in rats at 0.25, 1.0, and 4.0 h: bar 1, R = CH_2CH_3; bar 2, R = $(CH_2)_3CH_3$; bar 3, R = $(CH_2)_5CH_3$; bar 4, R = $CH_2CH(CH_3)_2$; bar 5, R =  .

Table III shows the biodistribution of ^{125}I-labeled **7–12** in rats after intravenous injection. The early brain concentrations, 15 min after injection, ranged from 0.13 to 0.53% ID·kg/g body weight. At 1 h there was substantial retention in the brain for **9–12**; however, the brain levels for the lower homologues, **7** and **8**, were markedly reduced.

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Table III. Distribution of Radioactivity in Rats after Intravenous Administration of ^{125}I-Labeled Alkyl-4-phenylpiperazine

tissue[a]	time, h	methyl **7**[b]	ethyl **8**	*n*-butyl **9**	*i*-butyl **10**	*n*-hexyl **11**	c-hexyl **12**
brain	0.25	0.22 (0.19–0.26)	0.24 (0.23–0.25)	0.35 (0.32–0.38)	0.25 (0.25–0.25)	0.13 (0.10–0.16)	0.27 (0.25–0.30)
	1.0	0.09 (0.09–0.09)	0.16 (0.14–0.15)	0.28 (0.28–0.28)	0.27 (0.23–0.32)	0.09 (0.08–0.10)	0.24 (0.21–0.27)
	4.0	0.05 (0.05–0.05)	0.04 (0.04–0.05)	0.32 (0.25–0.41)	0.20 (0.19–0.21)	0.09 (0.09–0.09)	0.12 (0.11–0.13)
blood	0.25	0.04 (0.04–0.04)	0.04 (0.04–0.04)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)
	1.0	0.04 (0.03–0.05)	0.07 (0.06–0.07)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)
	4.0	0.02 (0.02–0.02)	0.08 (0.06–0.09)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)
lung	0.25	0.22 (0.19–0.25)	0.57 (0.52–0.58)	1.02 (0.81–1.16)	0.56 (0.55–0.57)	1.06 (1.00–1.14)	1.20 (1.14–1.30)
	1.0	0.20 (0.19–0.22)	0.37 (0.34–0.43)	1.17 (1.20–1.42)	0.35 (0.33–0.37)	0.76 (0.65–0.85)	0.91 (0.86–0.96)
	4.0	0.09 (0.09–0.09)	0.17 (0.16–0.17)	0.54 (0.45–0.67)	0.22 (0.19–0.25)	0.57 (0.53–0.59)	0.35 (0.34–0.36)
thyroid[c]	0.25	0.96 (0.75–1.15)	1.74 (1.31–2.46)	3.27 (3.39–4.05)	1.18 (1.12–1.29)	1.65 (1.44–2.04)	2.28 (2.05–2.47)
	1.0	2.49 (2.04–2.76)	2.89 (2.56–3.24)	2.09 (1.69–2.41)	1.30 (1.22–1.36)	1.60 (1.41–1.72)	2.64 (2.47–2.81)
	4.0	2.98 (2.48–3.53)	14.85 (14.14–15.81)	5.09 (4.85–5.46)	3.95 (3.21–5.02)	2.70 (2.64–2.80)	2.99 (2.51–3.60)
liver	0.25	0.34 (0.24–0.40)	0.80 (0.69–1.03)	0.32 (0.27–0.39)	0.23 (0.19–0.27)	0.55 (0.45–0.60)	0.36 (0.32–0.39)
	1.0	0.35 (0.27–0.47)	0.56 (0.54–0.58)	0.21 (0.19–0.24)	0.35 (0.34–0.44)	0.66 (0.46–0.90)	0.33 (0.30–0.36)
	4.0	0.20 (0.19–0.21)	0.48 (0.40–0.61)	0.45 (0.40–0.52)	0.49 (0.42–0.55)	0.78 (0.77–0.78)	0.20 (0.19–0.22)
adrenal	0.25	0.28 (0.22–0.37)	1.37 (1.25–1.44)	1.57 (1.43–1.71)	0.59 (0.58–0.61)	0.87 (0.84–0.91)	1.23 (0.97–1.66)
	1.0	0.15 (0.12–0.19)	0.98 (0.84–1.04)	0.97 (0.80–1.14)	0.84 (0.83–0.85)	1.09 (0.78–1.46)	0.86 (0.61–1.12)
	4.0	0.12 (0.11–0.13)	0.26 (0.20–0.32)	1.00 (0.81–1.19)	0.93 (0.90–0.97)	1.14 (1.09–1.22)	0.42 (0.39–0.45)
heart	0.25	0.10 (0.10–0.11)	0.10 (0.10–0.10)	0.29 (0.26–0.32)	0.12 (0.11–0.15)	0.24 (0.24–0.24)	0.26 (0.23–0.28)
	1.0	0.13 (0.12–0.14)	0.09 (0.08–0.09)	0.31 (0.26–0.37)	0.09 (0.09–0.09)	0.16 (0.14–0.18)	0.18 (0.16–0.21)
	4.0	0.12 (0.11–0.13)	0.05 (0.04–0.06)	0.13 (0.11–0.15)	0.06 (0.05–0.07)	0.12 (0.11–0.13)	0.08 (0.07–0.08)
kidney	0.25	0.35 (0.31–0.38)	0.32 (0.28–0.38)	0.53 (0.48–0.58)	0.40 (0.37–0.45)	0.37 (0.35–0.39)	0.55 (0.49–0.61)
	1.0	0.31 (0.28–0.33)	0.28 (0.26–0.35)	0.55 (0.52–0.61)	0.33 (0.29–0.35)	0.34 (0.27–0.42)	0.46 (0.43–0.47)
	4.0	0.17 (0.14–0.21)	0.27 (0.21–0.35)	0.37 (0.32–0.42)	0.20 (0.18–0.23)	0.29 (0.28–0.30)	0.23 (0.23–0.24)
fat	0.25	0.08 (0.07–0.09)	0.09 (0.08–0.09)	0.04 (0.03–0.05)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.01 (0.01–0.01)
	1.0	0.10 (0.08–0.12)	0.08 (0.07–0.09)	0.01 (0.01–0.01)	0.02 (0.02–0.02)	0.02 (0.02–0.02)	0.01 (0.01–0.01)
	4.0	0.06 (0.05–0.07)	0.07 (0.05–0.09)	0.02 (0.02–0.02)	0.04 (0.03–0.04)	0.03 (0.02–0.04)	0.01 (0.01–0.01)
muscle	0.25	0.06 (0.05–0.07)	0.03 (0.03–0.04)	0.03 (0.03–0.03)	0.03 (0.03–0.03)	0.03 (0.03–0.03)	0.03 (0.02–0.03)
	1.0	0.04 (0.03–0.05)	0.04 (0.03–0.04)	0.04 (0.04–0.04)	0.02 (0.02–0.02)	0.02 (0.02–0.02)	0.03 (0.03–0.03)
	4.0	0.02 (0.02–0.02)	0.02 (0.02–0.02)	0.03 (0.02–0.04)	0.03 (0.02–0.03)	0.02 (0.02–0.02)	0.01 (0.01–0.01)

[a] Mean % ID·kg/g (range) for $N = 3$ rats. [b] From ref 28. [c] % ID.

By 4 h, only the two butyl derivatives, **9** and **10**, were present in high concentrations whereas the others had declined to 0.04–0.12% ID·kg/g. The brain-to-blood ratios (Figure 2) for three of the ^{125}I-labeled compounds, **9**, **11**, and **12**, were greater than 20:1 at 15 min, and for **9** and **12** the ratios remained high (>20:1) even at 4 h. The best brain-imaging agent in this series was compound **9**, which displayed both a high, consistent brain uptake of 0.28–0.35% ID·kg/g over the 4-h time period and a brain-to-blood ratio that remained in the 25–35:1 range. Although some of the other compounds also demonstrated high uptake or good brain-to-blood ratios at some point, none were as consistent as **9**.

The data in Table II also indicate the rapid and consistent clearance of the radioactivity from the blood. Only the two compounds with the smallest 1-substituents, **7** and **8**, are present in levels >0.01% ID·kg/g at any time. All others are almost completely distributed to the organs or tissues. Activity in the liver, lung, adrenals, and kidneys declined such that the 4-h levels were less than half the initial 15-min values. For **9**–**11**, in particular, the liver and adrenal concentrations remained high for the entire 4 h. Poorly perfused tissues, such as fat, muscle, and myocardium, displayed low uptake at all times, and the thyroid

Table IV. Biodistribution of ^{131}I-Labeled 1-Butyl-4-phenylpiperazine in the Dog, 2 h after Intravenous Administration[a]

tissue	% ID/organ	% ID·kg/g	tissue	% ID/organ	% ID·kg/g
brain	1.824	0.165	heart	0.850	0.182
blood	1.072	0.148	liver	6.584	0.188
lung	1.287	0.143	kidneys	0.850	0.182
thyroid	0.032	0.342	cerebellum	1.571	0.165
muscle	13.680	0.034	medulla	0.076	0.171
fat	9.405	0.034	cortex	0.100	0.171
adrenal	0.121	0.633			

[a] Mass of the animal = 5.7 kg, injected radioactivity = 1.0 mCi.

activity, an indication of in vivo deiodination, in general was relatively low, except for **7**, and the level did not drastically increase over the 4 h.

Because of its distribution characteristics in the rat, **9** was chosen for evaluation in the dog, using both γ scintigraphy and tissue distribution. 1-Butyl-4-phenylpiperazine (**3**) was labeled with ^{131}I in a 60% isolated yield at the no-carrier-added level. Administration of **9** intravenously resulted in rapid uptake in the brain, Figure 3A (top), which remained relatively constant out to 2 h, Figure 3B,C (middle and bottom, respectively). There was some soft tissue uptake as can be seen in the outline of the snout and neck, but visualization of the thyroid is not marked, an indication of the stability of the C–I bond. Not readily apparent in Figure 3A–C is the low level of uptake in the lung, which was not a significant source of localization. The major site of deposition, as determined scintigraphically, was the liver. The results of the tissue distribution study, shown in Table IV, confirm the scintigraphic evaluation, because at 2 h the brain contained 1.82% of the injected dose while the liver and lungs contained 6.58% and 1.29%, respectively. Thyroid activity, which did not appear significant in Figure 3A–C, amounted to only 0.03% ID. The activity in the muscle and fat, major components of soft tissue, represented 13.68% and 1.41% of the administered dose. Activity in the blood fell rapidly during the first 10 min and rose slightly over the next 10 min before declining again for the remaining 100 min of the study. The brain-to-blood ratio was 11:1, which was less than half that observed in the rat. Also significant were the brain-to-muscle and brain-to-fat ratios, which were both 4.8:1 and probably accounted for the appearance of the soft tissue image in the scintiphotos.

In evaluating the potential of the compounds described in this study it is necessary to consider both the chemical and biological characteristics. The most widely used ^{123}I-labeled agents for the clinical evaluation of regional cerebral perfusion are *N*-isopropyl-4-[^{123}I]iodoamphetamine (IMP) and *N,N,N'*-trimethyl-*N'*-(2-hydroxy-3-methyl-5-[^{123}I]iodobenzyl)-1,3-propanediamine (HIPDM). Both of these agents are labeled by using radioisotopic exchange methods, and although labeling HIPDM proceeds readily in contrast to IMP, low specific activities are obtained on the order of 5–10 mCi/mg. Higher specific activities for these compounds can only be achieved at the expense of radiochemical yield. With the compounds in this study, labeling proceeds very easily via electrophilic substitution using radioactive iodine (^{125}I or ^{131}I) at the no-carrier-added level. The introduction of the iodine moiety changes the molecular properties such that a clean separation of the product from the starting material can be made. As a result, very high specific activities are obtained and concerns related to the pharmacological activity of the carrier moiety are minimized. The overall time required for the labeling and isolation procedure is 2–3 h, well within the 13.3-h half-life of the nuclide of choice, ^{123}I, making this a reasonable method for obtaining radiopharmaceuticals.

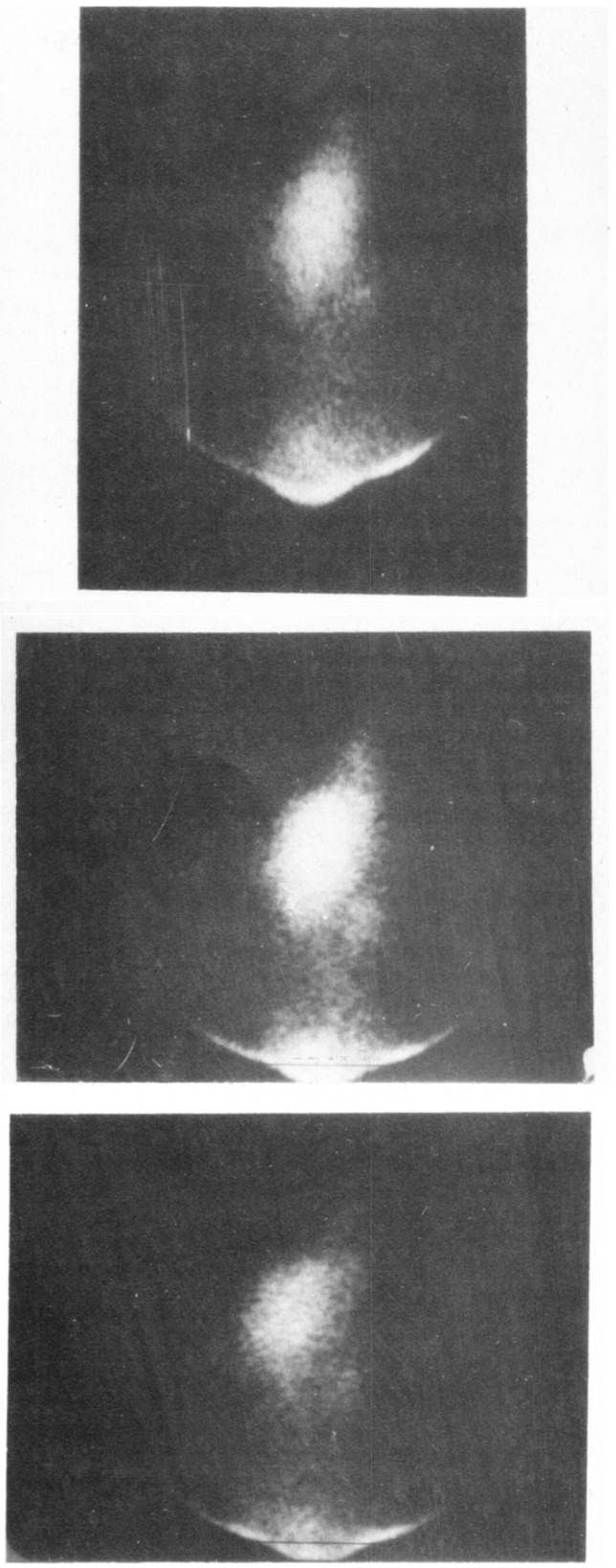

Figure 3. (A, top) Scintiphoto of the radioactivity in the dog brain following the injection of ^{131}I-labeled **8**. The image was taken at 15 min postinjection and represents 100 000 counts acquired in 330 s. (B, middle) Scintiphoto of ^{131}I-labeled **8** in the dog brain at 38 min postinjection, 100 000 counts in 380 s. (C, bottom) Scintiphoto of ^{131}I-labeled **8** in the dog brain at 120 min postinjection, 100 000 counts in 378 s.

The brain uptake, retention, and selectivity demonstrated by the best of this series resemble those of IMP and HIPDM. This particularly is true of the rapid uptake in the brain and its retention over time. The brain-to-blood ratios observed in the rat model are comparable to, if not slightly higher than, those reported for IMP, HIPDM, and other analogues. The significant difference in the tissue distribution between **9** and the other two agents resides in the amount of activity in the lung. This is of concern because of the degradation of scintigraphic image quality and resolution resulting from photons originating in the lung. Over 10% of the IMP dose and over 18% of the HIPDM dose localize in the lung, and this remains relatively constant, whereas the lung activity for **9** is about 5% at 15 min and declines to 2.5% at 2 h in the rat. In larger species, this distribution parameter is even more striking where lung activity for **9** in the dog is only 1.3% ID. For IMP and HIPDM the lung activity in the monkey is 27% and 14–15% ID, respectively. Therefore, one would anticipate that those contributions from the lung activity would be substantially lower.

The literature related to the simple 1-alkyl-4-phenylpiperazines does not provide a clear basis for their localization in the brain. Although a number of derivatives were prepared and evaluated as adrenolytic agents by Bovet[39] and Roth,[40] this work was done prior to the development of sensitive analytical methods. More recently, Caccia et al.[41-46] examined CNS-active drugs containing the 4-arylpiperazine moiety and detected, identified, and measured the levels of the drugs and their arylpiperazine metabolites in the brain and plasma of rats. While the investigators noted a correlation between the lipophilicity of the arylpiperazine metabolite and the brain level and brain-to-plasma concentration ratio, no clear link was established between the arylpiperazine and potential brain receptor interactions based on published receptor affinity data.[47,48] As a result, any model that we would utilize in evaluating our radiochemicals would require the consideration not only of the physicochemical properties of the parent compound but also those of the putative metabolite, iodophenylpiperazine, which may be generated from all the compounds we evaluated.

In our study the results indicate that there is a relationship between the structure of the 1-substituent and the brain uptake and retention; i.e., compounds with small groups, 1-methyl or 1-ethyl, are well-extracted but not retained, whereas those with larger groups, 1-butyl or 1-hexyl, are both extracted and well-retained over a 4-h period. A somewhat similar situation was reported by Larson and Portoghese[49] for the *N*-alkylnormeperidine congeners in which the ED_{50} for narcotic analgesia in mice, a CNS effect, was related to the rate of N-dealkylation of the *N*-alkyl substituent. Since all of the compounds in our study are highly lipophilic, access to the CNS through the blood–brain barrier does not appear to be the limiting factor. The lower uptake for the hexyl derivative can be partially accounted for by its partitioning into other tissues, an effect reported by Larson[49] and Hassain[50] for highly lipophilic compounds. The retention of the compound in the brain would then require the binding of the parent compound to a high-affinity binding site or the conversion of the compound to a metabolite that binds with a high affinity. Although other studies indicate that some arylpiperazines do show potent binding to α-adrenergic or serotonergic receptors, no similar studies have been performed on the 1-alkyl derivatives. Therefore, a receptor-linked mechanism for localization cannot be definitely identified as in the case of muscarinic or dopaminergic agents. The conversion to an active metabolite, e.g., iodophenylpiperazine, would have given results opposite to those observed. The studies by Monem[51] and Larson[49] indicate that N-dealkylation was significantly faster for the *N*-methyl-, *N*-ethyl-, and *N*-propylnormeperidine derivatives than for the *N*-butyl, *N*-hexyl, and *N*-nonyl congeners. It is possible that the metabolite neither readily crosses the blood–brain barrier nor is retained. However, this would appear to be contrary to the results reported by Caccia et al.[46] An alternative is that *N*-oxide formation may compete with N-dealkylation within the brain leading to a metabolite that is retained. The results of the present study do not provide sufficient data to distinguish between the two mechanisms and suggest that a more detailed examination of the brain and blood activity be undertaken with respect to parent and metabolites.

In summary we have identified two radioiodinated phenylpiperazines—the *N*-butyl and *I*-butyl derivatives **8** and **9**—that possessed high brain uptake, prolonged retention, and good brain-to-blood ratios, comparable to IMP and HIPDM. In addition, these derivatives could be readily labeled at the no-carrier-added level and had low lung uptake, properties not demonstrated by either IMP or HIPDM. The pattern of localization for this series suggested a mechanism possibly involving the generation of a highly retained metabolite similar to the mechanism proposed for IMP and HIPDM; however, there is insufficient data to definitively identify that as the mechanism. Future studies will be conducted to further improve the brain localization properties of the labeled phenylpiperazines and to identify the nature of the labeled species in both the brain and plasma. These will aid in the development of the labeled phenylpiperazines as brain perfusion imaging agents for use in single-photon emission computed tomography.

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Registry No. **1**, 92-54-6; **2**, 57498-25-6; **2**·HCl, 64335-22-4; **3**, 80944-47-4; **3**·oxalate, 104393-88-6; **4**, 21048-87-3; **4**·HCl, 104393-89-7; **5**, 104393-81-9; **5**·HCl, 104393-90-0; **6**, 14960-96-4; **8**, 104393-82-0; **9**, 104393-83-1; **10**, 104393-84-2; **11**, 104393-85-3; **12**, 104393-86-4; $Na^{125}I$, 24359-64-6; $Na^{131}I$, 7790-26-3; EtI, 75-03-6; BuI, 542-69-8; i-BuI, 513-38-2; $C_6H_{13}I$, 638-45-9; C-$C_6H_{11}I$, 626-62-0; 1-butyl-4-(4-[^{131}I]iodophenyl)piperazine, 104393-87-5.

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