y = 3), 97614-91-0; IV (x = 2, y = 2), 97614-92-1; IV (x = 2, y = 3), 97614-93-2; IV (x = 3, y = 2), 97614-94-3; IV (x = 3, y = 3), 97614-95-4; V (x= 1, y = 2), 84354-31-4; V (x = 1, y = 3), 97614-98-7; V (x = 2, y = 2), 97633-39-1; V (x = 2, y = 3), 97614-99-8; V (x = 3, y = 2), 97615-00-4; V (x = 3, y = 3), 97615-01-5; VI, 75092-39-6; VI (Me5), 33146-99-5; VII (y = 2), 97614-96-5; VII (y = 3), 97614-97-6; VII (y = 4), 97633-83-5; VIII (y = 2), 97615-02-6; VIII (y = 3), 97615-03-7; VIII (y = 4), 97615-04-8; pyrazole-3,5-dicarboxylic acid, 3112-31-0; 9-chloroacridine, 1207-69-8.

Evaluation of the Brain-Specific Delivery of Radioiodinated (Iodophenyl)alkyl-Substituted Amines Coupled to a Dihydropyridine Carrier[†,§]

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To evaluate the potential usefulness of radioiodinated phenylamines attached to dihydropyridine carriers as a means of brain-specific delivery of radiopharmaceuticals, 1-methyl-3-[N-[β-(4-[^{125}I]iodophenyl)ethyl]carbamoyl]-1,4-dihydropyridine ([^{125}I]-**9**) and 1-methyl-3-[N-(4-[^{125}I]iodophenyl)carbamoyl]-1,4-dihydropyridine ([^{125}I]-**13**) have been prepared by dithionite reduction of the corresponding pyridinium precursors, [^{125}I]-**8** and [^{125}I]-**12**, respectively. Formation of **8** involved coupling of (p-aminophenyl)ethylamine with N-succinimidyl (1-methyl-3-pyridinio)formate iodide (**4**) followed by transformation to the corresponding N-piperidinyl- (**6**) or (diethylamino)- (**7**) triazines that were converted to **8** by treatment with HI. Alternatively, **12** was prepared by initial conversion of (4-aminophenyl)mercuric acetate (**10**) to 4-iodoaniline (**11**) by treatment with I_2 and then coupling with **4**. The radioiodinated quaternary products, **8** and **12**, showed low brain uptake and low brain to blood ratios, whereas the dihydropyridine analogues, **9** and **13**, showed comparatively good brain uptake and good brain to blood ratios in rats. These data demonstrate that dihydropyridine-coupled radiopharmaceuticals can cross the blood–brain barrier and the technique may be useful for the measurement of cerebral blood perfusion.

The use of iodine-123-labeled radiopharmaceuticals for measurement of regional cerebral blood flow by either planar or single-photon computerized tomographic techniques (SPECT) provides valuable clinical information for the identification and evaluation of brain lesions.[1] Many lipophilic organic compounds cross the intact blood–brain barrier, with the resulting distribution pattern reflecting regional blood flow.[2] After intravenous administration, the delivery of such lipophilic substances to the brain is flow limited, and thus, the amount of activity appearing initially in the brain is proportional to the regional blood flow. After equilibrium is reached, many agents are cleared or "washed out" from the brain tissue at a rate directly proportional to regional blood flow. Lipophilic compounds that have reversible permeability to the blood–brain barrier (freely enter and exit) are not optimal for brain imaging due to their rapid clearance. A variety of strategies have thus been pursued to design agents that are rapidly extracted in the first pass and show rapid blood clearance with resulting good brain to blood ratios. The key feature for such agents is to exhibit prolonged cerebral retention with minimal redistribution. In this manner, imaging technologies that take prolonged acquisition periods such as SPECT can be used to qualitatively and potentially quantitatively determine the regional distribution of the tracer, which reflects blood perfusion.

Strategies that have been pursued include the high cerebral extraction of amphetamines. A variety of structurally modified radioiodinated amphetamines have been screened.[3] These studies have resulted in the development of p-[^{123}I]iodo-N-isopropylamphetamine (IMP),[4,5] which has been shown to be an excellent agent for SPECT studies in humans, exhibiting high cerebral extraction and slow washout.[5–7] The amphetamines apparently bind strongly to high-affinity nonspecific sites. Another strategy involves the "pH shift" approach using radiolabeled amines that are "trapped" in the brain by the slightly lower cerebral pH in comparison to plasma.[8–10] The extension of this concept has resulted in the development of N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-[^{123}I]iodobenzyl]-1,3-propanediamine (HIPDM),[11,12] which also shows excellent properties in human studies.[13,14]

A unique approach for brain-specific sustained release of therapeutic drugs has recently been described by Bodor et al.[15,16] (Figure 1). This approach involves the chemical

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‡ Present address: The Upjohn Co., La Porte, TX 77571.

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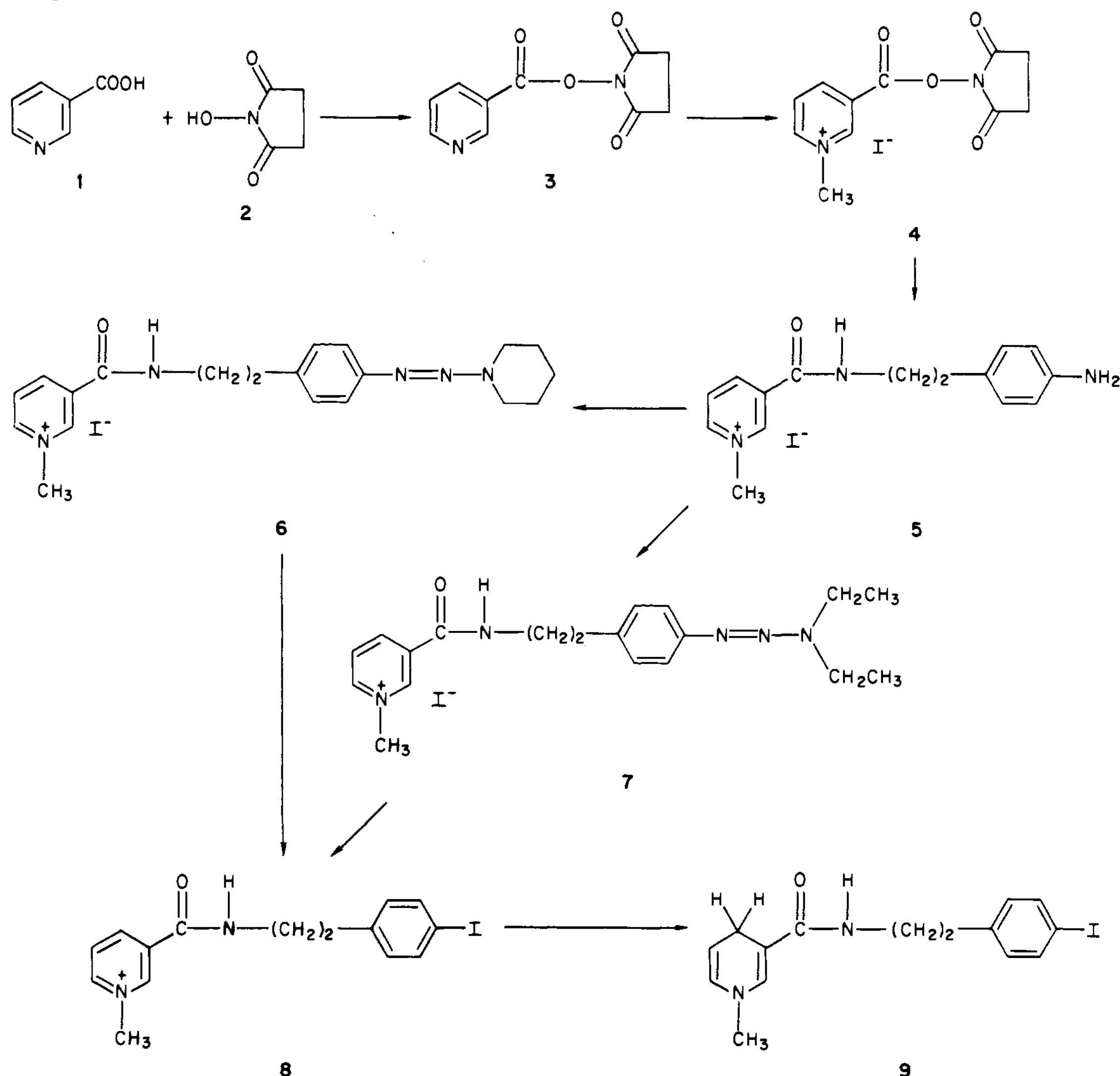
Scheme I



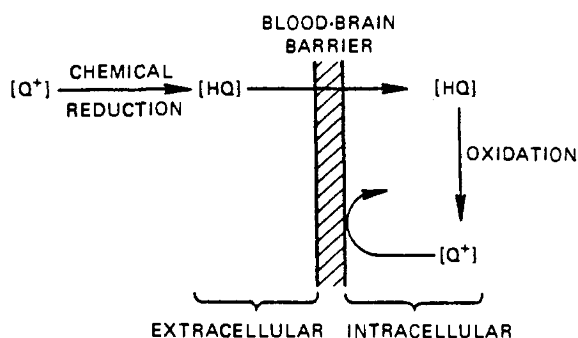


Figure 1.

transformation of the quaternary form of a drug [Q^+], which normally does not penetrate the blood–brain barrier, to a reduced lipid soluble form [HQ]. After intravenous administration the lipid-soluble [HQ] is readily distributed throughout the body and easily crosses the intact blood–brain barrier. The NAD → NADH oxidation, however, regenerates the original impermeable form [Q^+] from [HQ] in the brain. This results in a unique "trapping" of the radiolabeled drug in the brain (intracellular pool). This approach has been successfully used to deliver therapeutic doses of dopamine[17] across the intact blood–brain barrier of rats and prompted us to evaluate the potential utility of this unique approach for the delivery of radiopharmaceuticals to the brain for measurements of cerebral blood perfusion.

It is anticipated that the unique cerebral trapping of the radiolabeled [Q^+] and the hydrophilic nature of Q^+, which will allow its rapid clearance from the blood and other body tissues, will ultimately result in high brain uptake and the high brain to blood ratios required for optimal brain imaging. As a part of our interest in the brain imaging agents, the goals of the present study were to develop a chemical approach to prepare model iodine-125-labeled phenylalkylamines linked to a dihydropyridine carrier and to evaluate the biodistribution properties of these agents in rats.

Results and Discussion

Chemistry. A radioiodinated moiety such as (*p*-iodophenyl)ethylamine coupled with dihydropyridine in the lipid-soluble form (**9**, Scheme I) should be transported across the blood–brain barrier. The agent (**9**) would be oxidized to the quaternary form (**8**) within the brain and remain trapped. At this stage the CO–NH bond could also be potentially cleaved enzymatically, as reported by Bodor et al.,[15,16] to regenerate the radioiodinated phenylethyl-

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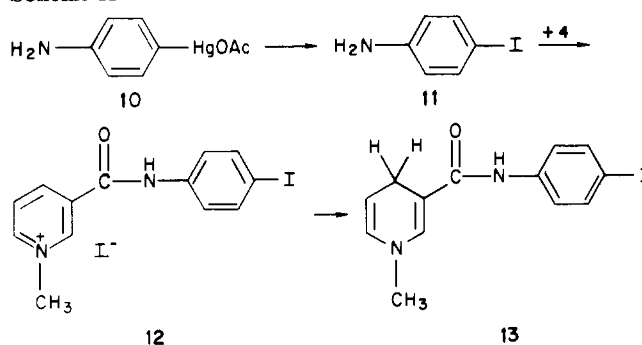
Table I. Distribution of Radioactivity in Tissues of Sprague–Dawley Rats following Intravenous Administration of the Quaternary Compound [^{125}I]-8 and of the Dihydro Compound [^{125}I]-9[a]

compd	time after inj, min	mean percent injected dose/g (range): tissue						brain to blood ratio (mean)
		brain	blood	liver	kidneys	heart	lungs	
[^{125}I]-8	5	0.03 (0.02–0.03)	0.39 (0.34–0.48)	8.03 (6.76–10.44)	16.46 (13.02–19.07)	0.25 (0.24–0.29)	0.47 (0.44–0.56)	0.08
	15	0.03 (0.03–0.03)	0.36 (0.35–0.37)	4.33 (4.01–4.81)	1.46 (1.12–2.04)	0.26 (0.24–0.28)	0.47 (0.40–0.54)	0.08
	60	0.02 (0.02–0.03)	0.27 (0.25–0.32)	0.93 (0.75–1.14)	0.56 (0.48–0.72)	0.20 (0.19–0.23)	0.32 (0.30–0.36)	0.07
[^{125}I]-9	5	0.32 (0.28–0.37)	1.42 (1.38–1.50)	3.10 (2.98–3.22)	4.19 (3.18–4.74)	1.37 (1.24–1.46)	1.48 (1.35–1.74)	0.22
	15	0.22 (0.20–0.25)	1.03 (0.97–1.12)	2.63 (2.43–2.92)	2.54 (2.24–3.12)	1.08 (0.89–1.24)	1.20 (1.05–1.50)	0.21
	30	0.18 (0.17–0.20)	0.77 (0.73–0.85)	1.89 (1.77–2.08)	1.72 (1.56–1.83)	0.86 (0.75–1.03)	0.97 (0.86–1.13)	0.23
	60	0.17 (0.15–0.19)	0.57 (0.54–0.63)	1.24 (1.12–1.44)	1.28 (1.17–1.48)	0.72 (0.64–0.86)	0.66 (0.61–0.86)	0.29

[a] Each animal (five animals per time point) received either 10.5 μCi of [^{125}I]-8 or 2.76 μCi of [^{125}I]-9 by tail vein injection.

amine. For preliminary tissue distribution studies in rats the model radioiodinated compound, 1-methyl-3-[*N*-[β-(4-iodophenyl)ethyl]carbamoyl]-1,4-dihydropyridine (**9**), was prepared as shown in Scheme I. Condensation of nicotinic acid (**1**) with *N*-hydroxysuccinimide (**2**) in dimethylformamide (DMF) in the presence of dicyclohexylcarbodiimide (DCC) gave the activated ester, *N*-succinimidyl pyridine-3-carboxylate (**3**) in 75% yield. The succinimidyl esters are useful intermediates for the formation of the "CONH" bond when coupled with amines.[18] Quaternization of **3** with methyl iodide in boiling acetone yielded (78%) *N*-succinimidyl (1-methyl-3-pyridinio)-formate iodide (**4**). Nucleophilic attack by the primary alkylamine of (*p*-aminophenyl)ethylamine on the activated ester **4** then gave (81%) 1-methyl-3-[*N*-[β-(*p*-aminophenyl)ethyl]carbamoyl]pyridinium iodide (**5**). Diazotization of an aromatic amine in a molecule that also contains a carboxamide group is normally accompanied by a facile intramolecular cyclization.[19] This was not observed in the diazotization of **5** at 0 °C using hydrofluoric acid (HF,[20] 48%) and sodium nitrite. Diazo coupling with piperidine in the presence of potassium carbonate gave after column chromatography the triazene substrate (**6**). Triazene decomposition of **6** with sodium iodide and anhydrous HF in acetone at 0 °C readily furnished 1-methyl-3-[*N*-[β-(4-iodophenyl)ethyl]carbamoyl]pyridinium iodide (**8**) in 67% yield. The anhydrous HF solution was prepared by elution of 48% HF through an anhydrous magnesium sulfate column with acetone. The use of HF instead of HCl was explored due to the fairly inert nature of HF to act as fluorodediazoniating agent that would ensure the formation of only the desired iodo compound. In contrast, HCl could participate as a chlorodediazoniating agent to give the chlorinated product, resulting in contamination and reduced specific activity of the radioiodinated product. In addition, consistently higher yields of **8** were obtained with HF instead of HCl. Sodium dithionite reduction of **8** in aqueous methanol at pH 7.5 ($NaHCO_3$) under argon atmosphere provided the desired compound (**9**) as a low melting solid. Alternatively, **5** was converted to the diethyltriazene **7**, which also readily decomposed with HI to give the product **8**. In order to evaluate the relative in vivo susceptibility to oxidation and

Scheme II



subsequent brain uptake of model dihydropyridine carriers, the 4-iodoaniline-coupled dihydropyridine carrier **13** was also synthesized.

The model agent, 1-methyl-3-[*N*-(4-iodophenyl)carbamoyl]-1,4-dihydropyridine (**13**), was prepared as shown in Scheme II. The general approach for preparation of **12** and **13** encompassed the reaction sequence described earlier (Scheme I). Nucleophilic attack by the amino group of *p*-iodoaniline (**11**) on the activated ester **4** gave (81%) 1-methyl-3-[*N*-(*p*-iodophenyl)carbamoyl]pyridinium iodide (**12**). Iodine-125-labeled **11** was prepared by [^{125}I]-I_2 treatment of readily available[21] (4-aminophenyl)mercuric acetate (**10**). This method has been recently developed in our laboratory for the synthesis of radioiodinated compounds from the corresponding mercuric acetate precursors.[22] To examine the feasibility of this method for the preparation of [^{125}I]-**11**, 4-iodoaniline[21] was first prepared by the I_2 treatment of **10**. Sodium dithionite reduction of **12** in argon-saturated aqueous methanol at pH 7.5 ($NaHCO_3$) under argon atmosphere provided the desired compound (**13**) as a low-melting solid (Scheme II).

Biological Studies. The corresponding ^{125}I-radioiodinated analogues **8** and **9** were prepared by using Na[^{125}I] as shown in Scheme I and cochromatographed with the corresponding unlabeled analogues by thin-layer chromatography. The distribution of compounds [^{125}I]-**8** and [^{125}I]-**9** was evaluated in rats (Table I). The quaternary compound **8** showed very low brain uptake whereas the lipophilic, dihydro compound **9** exhibited significantly higher brain uptake, as expected from the studies reported

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Table II. Distribution of Radioactivity in Tissues of Sprague–Dawley Rats following Intravenous Administration of p-[^{125}I]Iodoaniline Conjugates of 1-Methylpyridinium-3-carboxylate ([^{125}I]-12) and the Carrier, 1-Methyl-1,4-dihydropyridine-3-carboxylate ([^{125}I]-13)[a]

compd	time after inj, min	mean percent injected dose/g (range): tissue						brain to blood ratio (mean)
		brain	blood	liver	kidneys	heart	lungs	
[^{125}I]-12	5	0.06 (0.05–0.07)	1.11 (1.00–1.24)	1.18 (1.03–1.31)	2.10 (1.73–2.64)	0.83 (0.79–0.85)	0.84 (0.76–0.91)	0.05
	15	0.05 (0.03–0.06)	0.87 (0.72–1.03)	1.04 (0.81–1.18)	0.74 (0.62–0.92)	0.76 (0.68–0.84)	0.72 (0.58–0.86)	0.06
	30	0.04 (0.03–0.06)	0.75 (0.65–0.83)	0.71 (0.54–0.89)	0.65 (0.58–0.73)	0.68 (0.58–0.82)	0.62 (0.54–0.70)	0.06
	60	0.04 (0.03–0.06)	0.67 (0.58–0.77)	0.49 (0.38–0.57)	0.53 (0.49–0.57)	0.67 (0.58–0.75)	0.57 (0.50–0.65)	0.06
[^{125}I]-13	5	1.14 (0.97–2.17)	0.37 (0.28–0.46)	1.65 (1.06–2.71)	2.36 (1.64–3.43)	2.86 (2.36–3.96)	4.61 (3.62–7.08)	3.87
	15	1.16 (1.05–1.25)	0.35 (0.31–0.40)	1.56 (1.23–1.78)	1.56 (1.42–1.82)	2.43 (2.24–2.58)	3.30 (3.10–3.77)	3.29
	30	1.01 (0.81–1.26)	0.38 (0.35–0.40)	1.18 (1.06–1.29)	1.23 (1.14–1.40)	2.18 (1.96–2.46)	2.43 (2.26–2.89)	2.66
	60	1.12 (0.76–1.42)	0.31 (0.28–0.37)	0.82 (0.47–1.17)	1.07 (0.89–1.19)	1.88 (1.68–2.23)	2.77 (2.11–3.79)	3.6

[a] Each animal (five animals per time point) received either 15.1 μCi of [^{125}I]-12 or 10.6 μCi of [^{125}I]-13 by tail vein injection. During formation vitamin E was added to 13 to inhibit facile oxidation and to 12 as a control.

Table III. Distribution of Radioactivity in Tissues of Sprague–Dawley Rats following Intravenous Administration of p-[^{125}I]Iodoaniline, [^{125}I]-11[a]

time after inj, min	mean percent injected dose/g (range): tissue					
	brain	blood	liver	kidneys	heart	lungs
5	0.58 (0.35–0.72)	0.94 (0.58–1.17)	1.16 (0.73–1.45)	0.97 (0.62–1.13)	0.63 (0.39–0.74)	0.86 (0.54–1.07)
15	0.43 (0.34–0.50)	0.99 (0.95–1.06)	1.57 (1.37–1.74)	1.81 (1.59–2.03)	0.57 (0.52–0.62)	0.81 (0.77–0.86)
30	0.27 (0.18–0.36)	0.77 (0.69–0.84)	1.60 (1.57–1.66)	1.80 (1.67–2.11)	0.39 (0.36–0.42)	0.62 (0.60–0.66)
60	0.06 (0.05–0.06)	0.54 (0.49–0.58)	1.60 (1.36–1.74)	1.12 (0.99–1.24)	0.24 (0.22–0.29)	0.39 (0.36–0.44)

[a] Each animal (five animals per time point) received 12.11 μCi of [^{125}I]-11 by tail vein injection.

by Bodor et al.[15-17] The data from these studies indicate that structurally modified, reduced compounds such as **9** more easily cross the blood–brain barrier as compared to the parent, quaternary drugs, e.g. **8**. Although the absolute brain uptake exhibited by [^{125}I]-**8** was low relative to the expected high extraction for cerebral cardiac output, these studies demonstrated the validity of the concept of preferred cerebral extraction of dihydropyridine agents in comparison to the pyridinium analogues. Subsequent TLC analysis of [^{125}I]-**9** after storage showed rapid conversion to [^{125}I]-**8**, indicating that the low brain uptake probably resulted from the facile oxidation of **9** to the inactive quaternized form **8** during formulation, before administration to the animals.

A second model agent containing the p-iodoanilino moiety was also synthesized to further evaluate the effects of dihydropyridine-coupled aromatic amine structure on brain uptake. The ^{125}I-radioiodinated analogues **12** and **13** were prepared in the same manner using Na[^{125}I]. Oxidation of the oxygen-sensitive product **13** was inhibited, prior to injection, by addition of vitamin E as a stabilizer. Vitamin E was also added to [^{125}I]-**12** prior to administration as a control and to evaluate any effect of vitamin E on the tissue distribution of [^{125}I]-**13**. The tissue distribution of [^{125}I]-**12** and [^{125}I]-**13** was also evaluated in rats (Table II). As expected, the quaternary compound **12** showed low brain uptake and high activity in the blood pool (Figure 2), whereas the lipophilic, dihydro compound **13** showed significant uptake and retention in the brain (Figure 3) and exhibited good brain to blood ratios. We found that iodine-125-labeled 4-iodoaniline (**11**) crosses the blood–brain barrier but exhibits relatively low brain uptake (0.58%/g, 5 min) and rapid clearance (0.06%/g, 60 min)

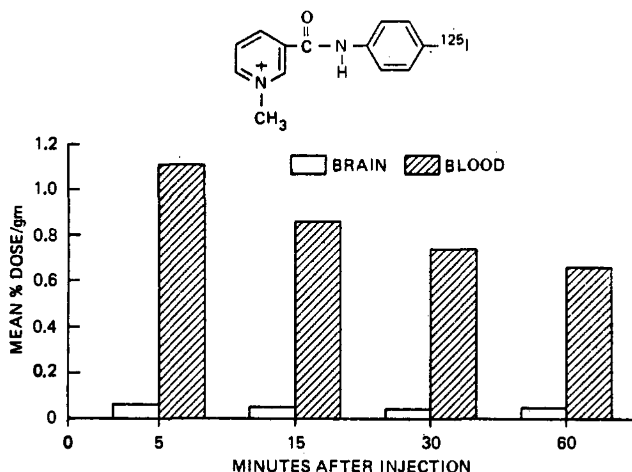

Figure 2. Comparison of the relative brain and blood levels (mean percent dose/g) after administration of [^{125}I]-**12** to Sprague–Dawley rats.

in rats,[23] (Table III) clearly demonstrating that coupling of such radioiodinated amines with an oxidizable carrier (e.g., **13**) may be an effective way to achieve high uptake and retention in the brain.

The two dihydro compounds [^{125}I]-**9** and [^{125}I]-**13** showed different uptake and retention properties in the brain. Whereas the relatively lower brain uptake shown by **9** as compared to **13** could be explained on the basis of facile oxidation of **9** prior to injection (the oxidation of **13** was

(23) Winchell, H. S.; Baldwin, R. M.; Lin, T. H. *J. Nucl. Med.* **1980**, *21*, 940.

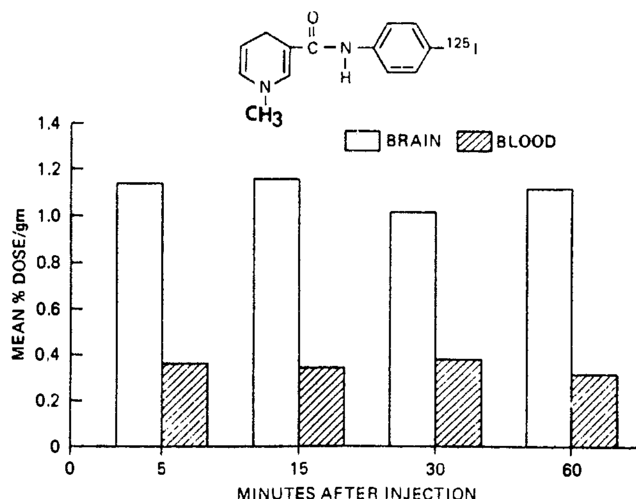

Figure 3. Comparison of the relative brain and blood levels (mean percent dose/g) after administration of [^{125}I]-**13** to Sprague-Dawley rats.

inhibited by adding vitamin E), the relative difference in the retention properties of the two compounds was surprising. Approximately 47% of the radioactivity was lost from the brain in case of [^{125}I]-**9** in 60 min as compared to [^{125}I]-**13**, in which case the levels of radioactivity in the brain remained fairly constant for the same period. Although there is no clear explanation for this difference in the retention properties, it could, however, be attributed to the difference in structural properties of the two compounds. The presence of an additional ethylene group (CH_2CH_2) in **9** could make this analogue and its potential metabolites more lipid soluble and increase their release from the brain in comparison with **13**. Although the partition coefficients and lipid solubilities of **9** and **13** were not determined, both agents are preferentially soluble in the organic phase in an aqueous–chloroform mixture (see the Experimental Section), indicating high partition coefficients. In addition, the "CONH" group in **9** is separated from the phenyl ring by two methylene groups (CH_2CH_2) and is thus less sterically hindered and consequently more susceptible to enzymatic attack and cleavage as compared to **13**. As discussed earlier,[15,16] if such a cleavage were to occur, β-(4-[^{125}I]iodophenyl)ethylamine will be generated in the brain in which case **9** (or generated (iodophenyl)ethylamine) may mimic **11** and show similar retention properties, which indeed appears to be the case.

Summary and Conclusions

These preliminary studies have demonstrated that dihydropyridine-linked radioiodinated amines such as 1-methyl-3-[*N*-[β-(4-iodophenyl)ethyl]carbamoyl]-1,4-dihydropyridine, [^{125}I]-**9**, and 1-methyl-3-[*N*-(4-iodophenyl)carbamoyl]-1,4-dihydropyridine, [^{125}I]-**13**, readily cross the intact blood–brain barrier and show higher brain uptake in rats compared to the corresponding quaternary pyridinium analogues [^{125}I]-**8** and [^{125}I]-**12**. The studies also clearly demonstrate that radioiodinated *p*-iodoaniline when coupled to a dihydropyridine carrier (e.g., **13**) shows significantly higher uptake and retention in the brain as compared to the parent **11** independently. Apparently the lipophilic agents [^{125}I]-**9** and [^{125}I]-**13** cross the blood–brain barrier and are quaternized within the brain. The blood-brain barrier then prevents their release. The oxidized quaternary form, however, being water soluble is washed out from the circulatory system to exhibit high brain to blood ratios. The nonlipophilic quaternary forms [^{125}I]-**8** and [^{125}I]-**12** do not cross the blood–brain barrier and, therefore, do not show brain uptake. We have also shown that the facile oxidation of dihydropyridine compounds to the corresponding quaternary compounds on storage or prior to in vivo administration can be inhibited by adding vitamin E as a stabilizer. These studies have shown that brain-specific delivery of radiopharmaceuticals using the Bodor approach is possible. In addition, these data also suggest that a more detailed evaluation of the brain-specific sustained release of radiopharmaceuticals for potential application in evaluation of regional cerebral blood perfusion should be pursued.

Experimental Section

General Procedures. All chemicals and solvents were analytical grade and were used without further purification. The petroleum ether (pet eth) had a boiling range of 30–60 °C. The iodine-125 was purchased from New England Nuclear, Inc. (North Billierica, MA). The melting points (mp) were determined in capillary tubes on a Buchi SP apparatus and are uncorrected. The thin-layer chromatographic analyses (TLC) were performed by using 250-μm-thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). The proton nuclear magnetic resonance spectra (NMR) were obtained at 60 MHz with a Varian 360-L instrument. Samples (30–40 mg) were dissolved in the solvents indicated, and the resonances (ppm) are reported downfield (δ) from the internal tetramethylsilane standard. The presence of exchangeable protons was confirmed by the addition of D_2O and reintegration. The elemental analyses were determined by Galbraith Laboratories, Knoxville, Tn.

Animal Tissue Distribution Studies. The distribution of radioactivity was determined in tissues of 10–12-week-old female Sprague–Dawley rats (170–200 g) after intravenous administration of the radioiodinated agents. The animals were allowed food and water ad libitum prior to and during the course of the experiment. The radioiodinated compounds were dissolved in a minimal volume of dimethyl sulfoxide (Me_2SO) and diluted with saline to a final concentration of 20% Me_2SO. With [^{125}I]-**12** and [^{125}I]-**13**, vitamin E (~5 mg/mL) was added to the formulation solution. The solution was filtered through a 0.22-μm Millipore and injected via a lateral tail vein into the ether-anesthetized animals. After the times indicated, the animals were killed by cervical fracture, and blood samples were obtained by cardiac puncture. The organs were then removed, rinsed with saline solution, and blotted dry to remove residual blood. The organs were weighed and counted in a NaI autogamma counter (Packard Instruments). Samples of the injected radioactive solutions were also assayed as standards to calculate the percent injected dose per gram of tissue values. The thyroid glands were not weighed directly. The weight of the thyroid glands was calculated in the usual manner by multiplying the animal weight by (7.5 mg/100 g).

***N*-Succinimidyl 3-Pyridinecarboxylate (3).** DCC (45.5 g, 220 mmol) was added to a solution of pyridine-3-carboxylic acid (**1**; 25.0 g, 200 mmol) and *N*-hydroxysuccinimide (**2**) (23.0 g, 250 mmol) in DMF (500 mL). The reaction mixture, which became slightly warm (~45 °C) during the addition of DCC, was allowed to stir at room temperature for 48 h. Glacial acetic acid (4 mL) was added to the reaction mixture to decompose the excess DCC. After the mixture was allowed to stir at room temperature for an additional hour, the white precipitate of dicyclohexylurea was removed by filtration. The filtrate was evaporated in vacuo to yield a pale yellow product that was crystallized from ethyl acetate to give **3** as white crystals: yield 75% (33.0 g); mp 138–139 °C; NMR ($CDCl_3$) δ 2.96 (s, 2 CH_2, 4 H), 7.41–7.78 (m, H-5 (Ar H), 1 H), 8.42–8.66 (dt, J = 2, 8 Hz, H-4 (Ar H), 1 H), 8.98–9.14 (dd, J = 2, 6 Hz, H-6 (Ar H), 1 H), 9.49 (d, J = 2 Hz, H-2 (Ar H), 1 H). Anal. ($C_{10}H_8N_2O_4$) C, H, N.

***N*-Succinimidyl (1-Methyl-3-pyridinio)formate Iodide (4).** A solution of **3** (9.0 g, 41 mmol) and methyl iodide (11.6 g, 5.1 mL, 82 mmol) in anhydrous acetone (40 mL) was heated at 45 °C for 7 h in a flask equipped with an efficient condenser. A pale yellow product separated from the solution. The product was collected by filtration, washed thoroughly with acetone, and dried to yield (78%, 11.6 g) **4** as pale yellow crystals: mp 222–223 °C; NMR (Me_2SO-d_6) δ 3.0 (s, 2 CH_2, 4 H), 4.53 (s, CH_3, 3 H), 8.31–8.62

(m, H-5 (Ar H), 1 H), 9.12–9.63 (m, H-4 and H-6 (Ar H), 2 H), 9.86 (s, H-2 (Ar H), 1 H). Anal. $C_{11}H_{11}IN_2O_4$) C, H, I, N.

1-Methyl-3-[N-[β-(p-aminophenyl)ethyl]carbamoyl]-pyridinium Iodide (5). A solution of (p-aminophenyl)ethylamine (3.2 g, 23 mmol) in DMF (5 mL) was added slowly to a solution of compound 4 (7.8 g, 22 mmol) in DMF (25 mL) placed in a round-bottom flask. The reaction mixture was stirred at room temperature for 8 h. The DMF was evaporated in vacuo to give a yellow solid that was crystallized from methanol to yield (81%, 6.8 g) pale yellow crystals: mp 209 °C; NMR (Me_2SO-d_6) δ 2.58–3.00 (m, NCH_2, 2 H), 3.22–3.70 (m, CH_2Ph, 2 H), 4.51 (s, CH_3, 3 H), 4.83 (br s, NH_2, 2 H), 6.78 (q, J = 8, 24 Hz, Ph H, 4 H), 8.12–8.51 (m, H-5 (Ar H), 1 H), 8.88–9.43 (m, CONH and H-4 and H-6 (Ar H), 3 H), 9.53 (s, H-2 (Ar H), 1 H). Anal. ($C_{15}H_{18}IN_3O$) C, H, I, N.

1-Methyl-3-[N-[β-[p-(3,3-pentane-1,5-diyltriazen-1-yl)-phenyl]ethyl]carbamoyl]pyridinium Iodide (6). A solution of 5 (450 mg, 1.17 mmol) in hydrofluoric acid (48% solution, 54 mg, 1.29 mmol) was cooled (0 °C) in an ice–methanol bath. A solution of sodium nitrite (111 mg, 1.30 mmol) in water (2 mL) was added dropwise while the reaction temperature was maintained at 0 ± 4 °C. A cold solution of piperidine (106.4 mg, 1.25 mmol) and potassium carbonate (219 mg, 1.58 mmol) in water (3.5 mL) was added. The solution was stirred and allowed to reach room temperature slowly. After stirring for 5 h, the reaction mixture was filtered to remove the hydrodediazoniated by product, 1-methyl-3-[N-(β-4-phenylethyl)carbamoyl]pyridinium iodide, mp 135–136 °C dec (lit.[16] mp 134–136 °C dec). Sodium iodide (439 mg, 2.93 mmol) and three drops of a concentrated solution of sodium metabisulfite were added to the filtrate. The resulting mixture was allowed to stir for 10 min, and it was extracted with chloroform (3 × 50 mL). The combined chloroform portion was dried (Na_2SO_4), evaporated in vacuo, and crystallized with chloroform–hexane to yield 342 mg (61%) of 6. An analytical sample was prepared by silica gel (Sigma, SIL-B-200) column chromatography using methanol–chloroform (1:9 (v/v)) as the eluting solvent. Recrystallization (chloroform–hexane) gave 6: mp 146–147 °C; NMR ($CDCl_3$) δ 1.66 (br s, CH_2-3, CH_2-4, and CH_2-5 (piperidine), 6 H), 2.80–3.18 (m, $CONHCH_2$, 2 H), 3.50–3.89 (m, CH_2CH_2Ph, 2 H), 3.71 (br s, CH_2-2 and CH_2-6 (piperidine), 4 H), 4.56 (s, CH_3, 3 H), 7.31 (s, ph H, Ar H, 4 H), 7.90–8.20 (m, H-5 (Ar H), 1 H), 9.22 (t, J = 5 Hz, H-4 (Ar H), 1 H), 9.67–9.96 (m, H-6 (Ar H), 1 H), 10.24 (s, H-2 (Ar H), 1 H). Anal. ($C_{20}H_{26}IN_5O$) C, H, I, N.

1-Methyl-3-[N-[β-[p-(3,3-diethyltriazen-1-yl)phenyl]-ethyl]carbamoyl]pyridinium Iodide (7). Compound 7 was prepared from compound 5 (730 mg, 1.9 mmol) in a manner similar to that described for 6, except that diethylamine (150 mg, 2.05 mmol) was used instead of piperidine. Crystallization from chloroform–hexane gave 7 as orange crystals: mp 162–163 °C; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 2 CH_2CH_3, 6 H), 2.90–3.28 (m, $CONHCH_2$, 2 H), 3.44–3.92 (m, CH_2 Ph, 2 H), 4.75 (q, J = 8, 16 Hz, 2 CH_2CH_3, 4 H), 4.60 (s, CH_3, 3 H), 7.32 (s, Ph H (Ar H), 4 H), 7.88–8.21 (m, H-5 (Ar H), 1 H), 9.03–9.35 (m, H-4 (Ar H), 1 H), 9.55–9.95 (m, H-6 (Ar H), 1 H), 10.20 (s, H-2 (Ar H), 1 H). Anal. ($C_{19}H_{26}IN_5O$) C, H, I, N.

1-Methyl-3-[N-[β-(4-iodophenyl)ethyl]carbamoyl]-pyridinium Iodide (8). Method A. Hydrofluoric acid (HF, 48% solution, 0.044 mL) was dried by passing through a column (Pasteur pipet) packed with anhydrous $MgSO_4$ (0.5 mL) that was eluted with acetone (3 mL). Sodium iodide (25.5 mg, 0.17 mmol) was added, and the solution was cooled to 0 °C. A solution of 6 (40.8 mg, 0.085 mmol) in anhydrous acetone (1 mL) was added. The reaction mixture was stirred at room temperature for 1 h and filtered. The filtrate was evaporated in vacuo. Water (5 mL) and chloroform (40 mL) were added to the residue, followed by the addition of sodium iodide (51 mg, 0.34 mmol) and a concentrated solution of sodium metabisulfite (3 drops). The reaction mixture was stirred at room temperature for 10 min. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The chloroform and ethyl acetate portions were combined and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave 8 as a crude product in 67% yield (28.2 mg). An analytical sample was prepared by silica gel (SIL-B-200) column chromatography using methanol–chloroform (1:9) as the eluting solvent. Recrystallization from acetone gave pure 8: mp 214–215 °C; NMR (Me_2SO-d_6) δ 2.60–3.08 (m, $CONHCH_2$, 2 H), 3.12–3.71 (m, CH_2 Ph, 2 H), 4.43 (s, CH_3, 3 H), 7.45 (q, J = 8, 34 Hz, Ph H (Ar H), 4 H), 8.31 (t, J = 6 Hz, H-5 (Ar H), 1 H), 8.78–9.35 (m, H-4 and H-6 (Ar H), 2 H), 9.47 (s, H-2 (Ar H), 1 H). Anal. ($C_{15}H_{16}I_2N_2O$) C, H, I, N.

Method B. Compound 8 was also prepared from 7 in a manner similar to that described from 6 in Method A. Pale yellow crystals (mp 214–215 °C) were obtained in 64% yield.

1-Methyl-3-[N-[β-(4-iodophenyl)ethyl]carbamoyl]-1,4-dihydropyridine (9). Sodium dithionite (68 mg, 0.39 mmol) was added with stirring to an argon-flushed mixture of 8 (45 mg, 0.09 mmol) and sodium bicarbonate (58 mg, 0.69 mmol) in methanol (6 mL). Argon was bubbled through the reaction mixture during the entire course of this reaction. Water (~10 mL) was added dropwise until the reaction mixture became homogeneous. The solution was stirred vigorously for 10 min, $CHCl_3$ (45 mL) was added, and the stirring was continued for an additional hour. The $CHCl_3$ layer was separated; the aqueous layer was extracted once with $CHCl_3$ (25 mL). The $CHCl_3$ portions were combined, dried (Na_2SO_4), and evaporated in vacuo to afford 9 as a syrup. Purification on a silica gel (SIL-B-200) column using 2.5% methanol in chloroform as the eluting solvent yielded (78%, 26 mg) pure 9 as a syrup: NMR ($CDCl_3$) δ 2.74 (q, J = 8, 12 Hz, $CONHCH_2$, 2 H), 2.92 (s, CH_3, 3 H), 3.03 (d, J = 2 Hz, H-4 of dihydropyridine, 2 H), 3.55 (q, J = 8, 12 Hz, CH_2 Ph, 2 H), 4.50–4.85 (m, H-5 of dihydropyridine, 1 H), 5.06–5.39 (br s, CONH, 1 H), 5.67–5.86 (dd, J = 2, 8 Hz, H-6 of dihydropyridine, 1 H), 7.22 (q, J = 8, 40 Hz, Ph H (Ar H), 4 H), 7.36 (d, J = 2 Hz, H-2 of dihyropyridine, 1 H). Anal. ($C_{15}H_{17}IN_2O$) C, H, I, N.

p-Iodoaniline (11). A solution of iodine (25.2 mg, 0.1 mmol) in methanol (1 mL) was added to a stirred suspension of (4-aminophenyl)mercuric acetate (70 mg, 0.2 mmol) in methanol (2 mL). Th iodine color disappeared immediately. The mixture was stirred for 5 min and then diluted with water (15 mL) and extracted with ethyl ether. The ether portion was washed with an aqueous sodium bisulfite (10%) solution followed by water and dried (Na_2SO_4). Evaporation of ether gave iodoaniline, which was found to be identical (mp 65 °C, TLC, NMR) when compared with a commercial sample.

1-Methyl-3-[N-(p-iodophenyl)carbamoyl]pyridinium Iodide (12). A solution of N-succinimidyl ester 4 (537 mg, 1.48 mmol) and p-iodoaniline (325 mg, 1.48 mmol) in DMF (6.0 mL) was stirred at room temperature for 5 h. The DMF was evaporated in vacuo, and the residual syrup was triturated with methanol. The yellow crystalline product was collected by filtration and dried: yield 485 mg (71%); mp 247–248 °C; recrystallization from methanol and water gave the analytical sample. Anal. ($C_{13}H_{12}I_2N_2O$) C, H, N, I.

1-Methyl-3-[N-(4-iodophenyl)]carbamoyl]-1,4-dihydropyridine (13). A suspension of 12 (40 mg, 86 μmol), sodium bicarbonate (55 mg, 0.65 mmol), and sodium dithionite (64 mg, 0.36 mmol) in methanol (5 ml) was saturated with argon which was bubbled through the reaction mixture continuously. The reaction mixture was stirred vigorously, and water was added dropwise until the residue dissolved. Chloroform (15 mL) was added and the mixture stirred for 30 min. The mixture was diluted with water; the chloroform layer was separated and dried (Na_2SO_4). Evaporation of chloroform gave 25 mg (82%) of the desired product as a low-melting solid.

Radiochemical Synthesis of [^{125}I]-8 and [^{125}I]-9. The [^{125}I]-8 was prepared from the triazine substrate 6 as described in method A. The commercial Na[^{125}I] was neutralized with 48% HF solution and passed through a small column (Pasteur pipet) packed with $MgSO_4$ (0.5 mL). Elution with acetone gave anhydrous radioiodide. A 2.5-mCi aliquot of anhydrous iodine-125 in acetone (~1.5 mL) was added to a stirred cold (10 ± 5 °C) solution of the triazene substrate 6 (20 mg, 0.042 mmol) and NaI (0.087 mmol) in acetone (0.5 mL). The reaction solution was stirred for 1 h, extracted with $CHCl_3$, and purified by silica gel column chromatography as described in method A to give [^{125}I]-8 (radiochemical yield 982 μCi, (39%); sp act. 59 mCi/mmol). The product was identical with an unlabeled sample of 8 when examined on TLC (20% MeOH in $CHCl_3$). The [^{125}I]-8 (737 μCi) was reduced as described for the corresponding unlabeled compounds using $NaHCO_3$ (5.3 mg) and sodium dithionite ($Na_2S_2O_4$, 8.0 mg) to provide [^{125}I]-9 in 38% (284 μCi) radiochemical yield. Purification

by silica gel (Sigma Sil B-200) column chromatography and elution with 2.5% methanol in $CHCl_3$ gave (175 μCi (24% yield); sp act. 59 mCi/mmol) pure [^{125}I]-**9**, which cochromatographed with unlabeled **9** on TLC (25% MeOH in $CHCl_3$).

Radiochemical Synthesis of [^{125}I]-11, [^{125}I]-12, and [^{125}I]-13. The commercial sample of iodine-125 (21.8 mCi) was received in 0.1 N NaOH and was first neutralized with a hydrofluoric acid (HF) solution (prepared by diluting 48% aqueous HF with methanol). A solution of iodine (one atom equivalent of the substrate, 12.7 mg) in methanol (2 mL) was added to the radioiodide solution. The resulting solution was made homogeneous and added to a cold (ice–water bath) stirred suspension of finely powdered 4-(aminophenyl)mercuric acetate (0.1 mmol). An instantaneous reaction with iodine color discharge was observed. The reaction mixture was stirred for 5–10 min, diluted with water (25 mL), and extracted with ethyl ether. The ether portion was washed with 10% aqueous sodium bisulfite solution followed by water and dried (Na_2SO_4). Evaporation of ether provided 4-[^{125}I]iodoaniline (15.8 mCi, 73% radiochemical yield) with a specific activity of 218 mCi/mmol. Further purification could be achieved by silica gel column chromatography by elution with $CHCl_3$ without significant loss of the product. The 4-[^{125}I]iodoaniline prepared by this method was characterized by comparing with an authentic unlabeled sample[21] of **11**. The [^{125}I]-**11** (15.8 mCi) and the succinimidyl ester **4** (27 mg, 0.075 mmol) were dissolved in DMF (1 mL). The solution was stirred for 4 h and applied to a 16 × 1.2 cm column packed with silica gel (Sigma Sil B-200) in $CHCl_3$. Elution of the column with $CHCl_3$ provided unreacted [^{125}I]-**11** (5.52 mCi). Further elution with 20% MeOH in $CHCl_3$ (v/v) gave [^{125}I]-**12** (5.67 mCi, 35.8% radiochemical yield) in 70% yield with a specific activity of 137 mCi/mmol on the basis of recovered [^{125}I]-11. The [^{125}I]-**12** was reduced into [^{125}I]-**13** in an argon atmosphere, using $NaHCO_3$ (25 mg) and $Na_2S_2O_4$ (35 mg) as described for [^{125}I]-**9** in 13% (719 μCi) radiochemical yield.

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Registry No. **1**, 59-67-6; **2**, 6066-82-6; **3**, 78348-28-4; **4**, 97807-17-5; **5**, 97807-18-6; **6**, 97807-19-7; **7**, 97807-20-0; **8**, 97807-21-1; [^{125}I]-**8**, 97807-22-2; **9**, 97807-23-3; [^{125}I]-**9**, 97807-24-4; **10**, 6283-24-5; [^{125}I]-**11**, 77718-00-4; **12**, 97807-25-5; [^{125}I]-**12**, 97807-26-6; **13**, 97807-27-7; [^{125}I]-**13**, 97807-28-8; p-$H_2NC_6H_4(CH_2)_2NH_2$, 13472-00-9; $NHEt_2$, 109-89-7; piperidine, 110-89-4; **11**, 540-37-4; 1-methyl-3-[N-(2-phenylethyl)carbamoyl]pyridinium iodide, 84254-38-6.

Synthesis and in Vitro Pharmacology of 7-Oxabicyclo[2.2.1]heptane Analogues of Thromboxane A_2/PGH_2

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A series of chemically stable TXA_2/PGH_2 analogues modeled after the structure of the natural products was prepared in search of useful inhibitors of TXA_2/PGH_2-mediated pathophysiology. Each of the 16 isomers implied in structure 1 was prepared in chiral form and evaluated for activity in vitro in platelets and smooth muscle. Depending on relative side chain and carbinol stereochemistry, TXA_2/PGH_2 agonist and antagonist and, surprisingly, PGD_2/PGI_2 agonist activities were observed. The enantiomers possessing the α heterocycle shown in 1 were generally more potent than their mirror-image isomers.

The adversary relationship between prostacyclin and thromboxane-A_2 (TXA_2), which modulates coronary blood vessel caliber[1] and platelet aggregation,[2] presents a novel opportunity for therapeutic intervention in cardiovascular events. Substances that inhibit TXA_2 synthetase or interfere at the TXA_2 receptor would be expected to normalize pathological events caused by oversynthesis of TXA_2. Thus, the synthesis of compounds modeled after TXA_2 has been the goal of our research group since publication of its structure in 1975.[3]

Topologically, TXA_2 and its biosynthetic precursor PGH_2 can be represented by three areas of polar functionality (carboxyl, heterocycle, carbinol) connected by linkages of precise length and stereochemistry. Medicinally useful agents modeled after TXA_2 or PGH_2 will require structural modifications in each area to overcome the chemical and metabolic instability and undesired activity inherent in the nature products. Currently, active research is directed toward identifying advantageous replacement functionality in each area. However, the major emphasis has centered on the chemically labile dioxabicyclo[3.1.1]heptane ring system. Stable surrogate ring systems in which oxygen is replaced by carbon,[4,7,8] nitrogen,[5] or

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