Synthesis and Evaluation of Radioiodinated 2-(2(*RS*)-Aminopropyl)-5-iodothiophenes as Brain Imaging Agents

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Methods have been developed for the preparation of 2-(2(*RS*)-aminopropyl)-5-iodothiophenes. The syntheses and physical properties of 2-(2(*RS*)-aminopropyl)-5-iodothiophene and *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene are described. The radioiodinated agents are of interest because of the high expected uptake and prolonged brain retention that may result from binding to high-capacity, relatively nonspecific amine binding sites. Radioiodine was introduced into the 5-position of 2-(2(*RS*)-aminopropyl)-5-iodothiophene and *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene by radioiodination of the corresponding 5-boronic acid or 5-(trimethylstannyl) derivatives. Tissue distribution studies in rats with 2-(2(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene showed high brain uptake (5 min, 2.77% dose/g; 30 min, 2.51% dose/g) and good brain/blood (B/B) ratios (5 min, 6/1; 30 min 3.8/1. A comparison of the brain uptake of the *N*-isopropyl derivative with the 2(*RS*)-aminopropyl analogue demonstrated higher initial brain uptake and brain to blood ratios (5 min, 3.2% dose/g; 10.3/1) but more rapid washout (30 min, 1.37% dose; 2.8/1). These data suggest that radiolabeled 2-(2(*RS*)-aminopropyl)-5-iodothiophenes are potentially useful agents for cerebral perfusion imaging by single-photon-emission computerized tomography (SPECT).

Introduction

Radiopharmaceuticals labeled with single-photon-emitting radionuclides which rapidly cross the blood–brain barrier and show high brain uptake with slow washout are important agents for the clinical evaluation of regional cerebral perfusion using single-photon-emission computed tomography (SPECT) techniques. Iodine-123-labeled organic amines are an extensively investigated class of cerebral perfusion agents. Iodine-123 is an attractive radionuclide for SPECT applications because iodine-123 emits abundant (85%) 159 keV photons, which are nearly ideal for clinical γ-cameras, and has a 13.3-h half-life, which is compatible with the time needed for attaching iodine to organic substrates by a wide variety of currently available synthetic methods. In addition, iodine-123 is available commercially by the ^{127}I, p,5n, ^{123}Xe, β+, ^{123}I method, which affords iodine-123 free of high-energy radionuclide impurities such as iodine-124, which can degrade the image.

Radioiodinated amines are highly lipophilic and are rapidly extracted from the blood into the brain in significant levels by the mechanism of passive diffusion. Once inside the brain, these radiotracers are retained by a specific trapping mechanism for a period of time sufficient to allow image acquisition. The initial uptake of radioactivity by the brain is dependent upon regional blood flow, thus regional cerebral blood flow (rCBF) can be measured from the SPECT image because the initial fixed regional distribution pattern of activity is proportional to blood flow.[1]

The principal strategies have been developed for trapping radioiodinated amines in the brain. One is represented by the central nervous system (CNS) active catecholamine analogue *N*,*N*-dimethyl-2-(4-iodo-2,5-dimethoxyphenyl)isopropylamine[2,3] and the amphetamine analogue *N*-isopropyl-2-(4-iodophenyl)isopropylamine (IMP).[4] These amphetamines are presumably retained in the brain by their affinities to CNS amine binding sites. A second strategy is represented by the diamine *N*,*N*,*N*′-trimethyl-*N*′-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (HIPDM), which is retained by pH gradients across the blood–brain barrier.[5,6] Other strategies to trap radioiodinated amines in the brain for use as potential rCBF agents have been reported.[7,8]

Iodine-123-labeled IMP has been granted a new drug application and is being used on a routine clinical basis. Scans mapping regional blood flow following administration of IMP show defects in patients with stroke,[9] hyperperfusion in patients with epileptic foci[10] and meningiomas,[11,12] and regions of hypoperfusion in patients with

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(1) Blau, M. Radiotracers for Functional Brain Imaging. *Semin. Nucl. Med.* **1985**, *15*, 329–334.
(2) Braun, U.; Shulgin, A. T.; Braun, G.; Sargent, T., III. Synthesis and Body Distribution of Several Iodine-131 Labeled Centrally Acting Drugs. *J. Med. Chem.* **1977**, *20*, 1543–1546.
(3) Sargent, T., III; Shulgin, A. T.; Mathis, C. A. Radiohalogen-Labeled Imaging Agents. 3. Compounds for Measurement of Brain Blood Flow by Emission Tomography. *J. Med. Chem.* **1984**, *27*, 1071–1077.
(4) Winchell, H. S.; Baldwin, R. M.; Lin, T. H. Development of I-123-Labeled Amines for Brain Studies: Localization of I-123 Iodophenylalkyl Amines in Rat Brain. *J. Nucl. Med.* **1980**, *21*, 940–946.
(5) Tramposch, K. M.; Kung, H. F.; Blau, M. Synthesis and Tissue Distribution Study of Iodine-Labeled Benzyl- and Xylylamines. *J. Med. Chem.* **1982**, *25*, 870–873.
(6) Kung, H. F.; Tramposch, K. M.; Blau, M. A New Brain Perfusion Imaging Agent: [I-123]HIPDM:N,N,N′-Trimethyl-N′-[2-Hydroxy-3-Methyl-5-Iodobenzyl-]-1,2-Propanediamine. *J. Nucl. Med.* **1983**, *24*, 66–72.
(7) Tedjamulia, M. L.; Srivastava, P. C.; Knapp, F. F., Jr. Evaluation of the Brain-Specific Delivery of Radiolodinated (Iodophenyl)alkyl-Substituted Amines Coupled to a Dihydropyridine Carrier. *J. Med. Chem.* **1985**, *28*, 1574–1580.
(8) Hanson, R. N. Radioiodinated 1-Substituted-4-Phenylpiperazines As Potential Brain Imaging Agents. *Int. J. Nucl. Med. Biol.* **1985**, *12*, 315–320.
(9) Raynaud, C.; Rancurel, G.; Samson, Y.; Baron, J. C.; Soucy, J. P.; Kieffer, E.; Cabanis, E.; Majdalani, A.; Ricard, S.; Bardy, A.; et al. Pathophysiologic Study of Chronic Infarcts With I-123 Isopropyl Iodo-Amphetamine (IMP): The Importance of Periinfarct Area. *Stroke* **1987**, *18*, 21–29.
(10) Royal, H. D.; Hill, T. C.; Holman, B. L. Clinical Brain Imaging With Isopropyl-Iodoamphetamine and SPECT. *Semin. Nucl. Med.* **1985**, *15*, 357–376.
(11) Nakano, S.; Kinoshita, K.; Jinnouchi, S.; Hoshi, H.; Watanabe, K. Dynamic SPECT With Iodine-123 IMP in Meningiomas. *J. Nucl. Med.* **1988**, *29*, 1627–1632.

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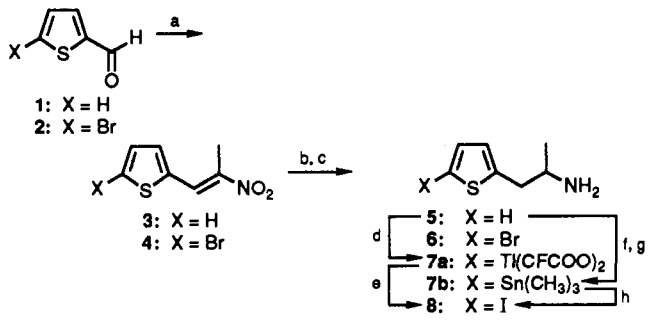
Scheme I[a]



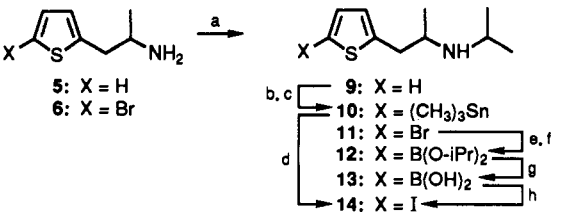
[a] Reagents: (a) $CH_3CH_2NO_2/NH_4OAc$; (b) $NaBH_4/BF_3$–Et_2O; (c) 10% HCl; (d) $Tl(CF_3COO)_3$; (e) KI; (f) *n*-BuLi; (g) $(CH_3)_3SnCl$; (h) I_2.

dementia.[13]

2-(2(*RS*)-Aminopropyl) analogues in which an iodine-123-labeled 5-iodothienyl moiety replaces the 4-iodophenyl group are also attractive candidates to evaluate rCBF by SPECT. 2-(Isopropylamino)thiophene has been reported to exhibit similar physiological properties to amphetamine in laboratory animals[14] and may therefore concentrate and be retained in the brain by the same mechanism as amphetamine. In addition, thienyl biosteres of biologically active phenyl compounds[15] are of interest because the thiophene ring can be substituted at the 5-position by a variety of metals such as thallium,[16,17] boron,[18] tin,[19] and mercury[20] to afford reactive substrates which undergo facile iododemetalation. Iododemetalation is an attractive labeling technique which gives high radiochemical yields at low temperature.[21]

The goals of the present investigation were to develop methods for the syntheses of the model agents 2-(2-(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene and *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-[^{131}I]iodothiophene and to evaluate the distribution properties of these agents in rats.

Scheme II[a]



[a] Reagents: (a) $CH_3COCH_3/NaCNBH_4$; (b) *N*-BuLi; (c) $(CH_3)_3SnCl$; (d) I_2; (e) Mg; (f) $B(O\text{-}iPr)_3$; (g) H_2O; (h) NaI/chloramine-T.

Results and Discussion

Chemistry. The initial stages of this investigation entailed the syntheses of 2-(2(*RS*)-aminopropyl)thiophene (**5**) and 2-(2(*RS*)-aminopropyl)-5-bromothiophene (**6**). The synthetic approach for the preparation of these racemic thienylamphetamine analogues involved formation of α,β-unsaturated nitroalkenes via a 2-substituted thiophenecarboxaldehyde and is shown in Scheme I. Commercially available thiophene-2-carbaldehyde (**1**) and 5-bromothiophene-2-carbaldehyde (**2**) were condensed with nitroethane in the presence of a catalytic amount of ammonium acetate to afford 1-(2-thienyl)-2-nitropropene (**3**) and 1-(5-bromo-2-thienyl)-2-nitropropene (**4**), respectively, by a Knoevenagel reaction. Two approaches were explored for the reduction of nitroalkenes **3** and **4** to the desired saturated amines, 2-(2(*RS*)-aminopropyl)thiophene (**5**) and 2-(2(*RS*)-aminopropyl)-5-bromothiophene (**6**). The first approach involved the use of lithium aluminum hydride, a classic procedure which has been used in the preparation of various 2-(2(*RS*)-aminopropyl)thiophene derivatives.[22] The reduction of the thienyl nitroalkenes to the 2-(2-(*RS*)-aminopropyl)thiophenes using lithium aluminum hydride was reported to proceed in 50–70% yield. Formation of 2-(2(*RS*)-aminopropyl)thiophene (**5**) and 2-(2-(*RS*)-aminopropyl)-5-bromothiophene (**6**) by this approach was not successful and resulted in a complex mixture of products.

The second, and successful, approach involved the recently reported sodium borohydride catalyzed reaction of borane complexes with α,β-unsaturated nitroalkenes.[23,24] In this approach, 2-(2(*RS*)-aminopropyl)thiophene (**5**) and 2-(2(*RS*)-aminopropyl)-5-bromothiophene (**6**) were prepared in 77% and 72% yield, respectively, by the reduction of **3** and **4** with a borane–tetrahydrofuran complex ($B\text{-}H_3$–THF) followed by acid hydrolysis.

Two routes were used for the introduction of iodine into the 5-position of the thiophene ring of a 2-(2(*RS*)-aminopropyl)thiophene (**5**). In one route 2-(2(*RS*)-aminopropyl)-5-iodothiophene (**8**) was prepared via the iododethallation reaction of a 5-[bis(trifluoroacetoxy)]thallium derivative, **7a** (Scheme I). Recently, we employed this method for the preparation of radioiodinated terminal-substituted 5-iodo-2-thienyl fatty acids.[17] Using this approach, heteroaromatic thallation of compound **5** with thallium(III) trifluoroacetate in acetonitrile gave the cor-

(12) Nakano, S.; Kinoshita, K.; Jinnouchi, S.; Hoshi, H.; Watanabe, K. Dynamic SPECT With Technetium-99m HM-PAO in Meningiomas—A Comparison With Iodine-123 IMP. *J. Nucl. Med.* **1989**, *30*, 1101–1105.
(13) Cohen, M. B.; Graham, L. S.; Lake, R.; Metter, E. J.; Fitten, J.; Kulkarni, M. K.; Sevrin, R.; Yamada, L.; Chang, C. C.; Woodruff, N.; et al. Diagnosis of Alzheimer's Disease and Multiple Infarct Dementia By Tomographic Imaging of Iodine-123 IMP. *J. Nucl. Med.* **1986**, *27*, 769–774.
(14) Alles, G. A.; Feigen, G. A. Comparative Physiological Actions of Phenyl-, Thienyl- and Furylisopropylamines. *J. Pharm. Exp. Ther.* **1941**, *72*, 265–275.
(15) Press, J. B. In *Thiophene and Its Derivatives*; Gronowitz, S. Ed.; Wiley: New York, 1986; Vol. II, 354.
(16) McKillop, A.; Fowler, J. S.; Zelesko, M. J.; Hunt, J. D.; Taylor, E. C.; McGillivary, G. Thallium In Organic Synthesis. X. A One-Step Synthesis of Aryl Iodides. *Tetrahedron Lett.* **1969**, 2427.
(17) Goodman, M. M.; Kirsch, G.; Knapp, F. F., Jr. Synthesis and Evaluation of Terminal Radioiodinated Iodothienyl-Substituted Fatty Acids for Myocardial Imaging. *J. Heterocycl. Chem.* **1984**, *21*, 1579.
(18) Johnson, J. R.; Van Campen, M. G., Jr.; Grummitt, O. J. Organoboron Compounds. II. The Reducing Action of Some Organoboronic Acids. *J. Am. Chem. Soc.* **1938**, *60*, 111.
(19) Hanson, R. N.; Franke, L.; Lee, S. H.; Seitz, D. E. Radioiododestannylation: Preparation and Evaluation of Radioiodinated Thienyl Alcohols. *Int. J. Rad. Appl. Instrum. [A]* **1987**, *38*, 641–645.
(20) Hurd, C. D.; Priestly, H. M. Diazo Reactions in the Thiophene and Furan Series. *J. Am. Chem. Soc.* **1947**, *69*, 859.
(21) Goodman, M. M.; Callahan, A. P.; Knapp, F. F., Jr. Design, Synthesis, and Evaluation of ω-Iodovinyl- and ω-Iodoalkyl-Substituted Methyl-Branched Long-Chain Fatty Acids. *J. Med. Chem.* **1985**, *28*, 807–815.
(22) Gilsdorf, R. T.; Nord, F. F. Studies on the Chemistry of Heterocycles. IX. Reduction of Thienyl Nitroolefins with Lithium Aluminum Hydride. *J. Org. Chem.* **1950**, *15*, 807.
(23) Mourad, M. S.; Varma, R. S.; Kabalka, G. W. A Convenient Reduction of α,β-Unsaturated Nitroalkenes to Alkylamines Using Boron Hydrides. *Synth. Commun.* **1984**, *14*, 1099.
(24) Varma, R. S.; Kabalka, G. W. A Simple Route to Alkylamines Via The Reduction of Nitroalkenes. *Synth. Commun.* **1985**, *15*, 843.

Table I. Distribution of Radioactivity in Tissues of Unfasted Fischer 344 Rats following Intravenous Administration of 2-(2(*R,S*)-Aminopropyl)-5-[^{125}I]iodothiophene

tissue	mean % injected dose/g (range) following injection		
	5 min	30 min	60 min
blood	0.46 (0.40–0.55)	0.67 (0.57–0.75)	0.67 (0.56–0.74)
liver	2.32 (2.02–2.78)	1.38 (1.31–1.45)	0.99 (0.95–1.07)
kidneys	3.85 (3.43–4.52)	2.23 (1.98–2.56)	1.46 (1.40–1.60)
heart	1.35 (1.22–1.48)	0.90 (0.84–0.98)	0.58 (0.55–0.63)
lungs	11.91 (10.84–13.77)	5.91 (5.01–7.13)	3.64 (3.37–3.94)
brain	2.77 (1.96–3.72)	2.51 (2.20–2.85)	1.42 (1.36–1.53)
thyroid	15.57 (13.20–17.31)	50.58 (37.97–75.23)	109.68 (81.37–166.09)
thyroid (% dose/organ)	0.19 (0.16–0.20)	0.57 (0.41–0.83)	2.25 (2.16–2.39)
specific activity: 550 mCi/mmol injected dose: 10.7 μCi/animal			

responding 5-[bis(trifluoroacetoxy)thallium] derivative **7a**. The thallium product was treated with an excess of aqueous potassium iodide to give 2-(2(*RS*)-aminopropyl)-5-iodothiophene (**8**) in 36% yield. The NMR spectrum displayed the characteristic AB pattern of a 2,5-disubstituted thiophene centered at 6.77 ppm (J = 4 Hz). The signals of the protons at ring positions 3 and 4 appeared as doublets at 6.50 and 7.7 ppm, respectively. The second route developed for the preparation of compound **8** involved iododestannylation[19] of the trimethylstannyl derivative **7b**. Utilizing this method, 2-(2(*RS*)-aminopropyl)thiophene (**5**) was converted to the corresponding 5-lithio derivative with *n*-butyllithium. 2-(2-(*RS*)-Aminopropyl)-5-(trimethylstannyl)thiophene (**7b**) was prepared by treatment of the 5-lithio derivative with trimethyltin chloride. Iododestannylation of **7b** by treatment with I_2 in methylene chloride gave **8**. 2-(2-(*RS*)-Aminopropyl)-5-iodothiophene (**8**) prepared from both synthetic routes possessed identical chromatographic and spectral properties.

In order to investigate the effects of N-substitution of the thienylamphetamines on brain uptake, an *N*-isopropyl analogue, *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene (**14**), was prepared. Two synthetic routes were developed for the preparation of *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene (**14**). In one route, 2-(2-(*RS*)-aminopropyl)thiophene (**5**) was converted to *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene (**14**) by the three-step sequence of reactions outlined in Scheme II. Reduction amination of acetone with amine **5** and sodium cyanoborohydride gave *N*-isopropyl-2-(2(*RS*)-aminopropyl)thiophene (**9**). Conversion of compound **9** to the 5-(trimethylstannyl) derivative **10**, followed by treatment with I_2 in methylene chloride afforded *N*-isopropyl-2-(2-(*RS*)-aminopropyl)-5-iodothiophene (**14**).

The second route developed for the preparation of compound **14** utilized organoborane chemistry[25,26] and is outlined in Scheme II. 2-(2(*RS*)-Aminopropyl)-5-bromothiophene (**6**) was reacted with acetone and sodium cyanoborohydride to give *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-bromothiophene (**11**). Metalation of compound **11** with magnesium followed by treatment with triisopropoxyborane afforded *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-(diisopropoxyboryl)thiophene (**12**). Hydrolysis of the diisopropoxyborane intermediate **12** afforded *N*-isopropyl-2-(2(*RS*)-aminopropyl)thiophene-5-boronic acid (**13**). Iodination of boronic acid **13** by treatment with sodium iodide and chloramine-T in aqueous THF gave *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene (**14**). The 5-iodothiophene obtained from both synthetic routes (Scheme II) possessed identical physical and spectral properties.

The radioiodinated (aminopropyl)thiophenes 2-(2-(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene (**8**) and *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-[^{131}I]iodothiophene (**14**) were prepared by Na^{125,131}I treatment of their corresponding 5-(trimethylstannyl) or 5-boronic acid derivatives, respectively, with I^+ generated in situ by *N*-chlorosuccinimide or chloramine-T oxidation of radioiodide.

Biological Studies. The distribution of radioactivity expressed as percent dose per gram in tissues of female Fischer 344 rats at 5, 30 and 60 min after intravenous administration of 2-(2(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene is shown in Table I. The initial level of accumulation of radioactivity in the brain after injection of this agent was significant. In contrast to the high brain uptake of [^{125}I]-**8** the activity in the blood was low, resulting in high brain/blood levels. This agent also showed the desired prolonged retention in the brain. The brain uptake exhibited a maximum at 5 min (2.77% dose/g) and exhibited a slight decrease at 30 min (2.51% dose/g). After 60 min, the brain uptake (1.42% dose/g) had decreased to 51% when compared with the peak uptake at 5 min. The brain/blood ratio showed a maximum of 6.3:1 at 5 min and decreased to 2:1 at 60 min. The accumulation of activity in the thyroid was initially low, 0.19% dose/organ at 5 min, but increased gradually to 1.27% dose/organ at 60 min, which demonstrated moderate stability of this agent to in vivo deiodination.

The effects of 5-iodothienyl-2-substitution for a *p*-iodophenyl moiety was assessed by a comparison of 2-(2-(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene with the previously published rat brain uptake of the *R* and *S* isomers of 2-(*p*-iodophenyl)isopropylamine.[4] The brain uptake of activity at 5 min (1.38% dose/g) following administration of the *R* isomer of the iodophenyl analogue was lower than that of the 5-iodothienyl agent, but exhibited a 50% increase at 60 min (2.07% dose/g). The brain/blood ratio of the *R* isomer of 2-(*p*-iodophenyl)isopropylamine was higher at 5 min (10.60:1) than the (*RS*)-5-iodothienyl analogue and reached a maximum at 60 min (18.50:1). On the other hand, the *S* isomer of 2-(*p*-iodophenyl)isopropylamine exhibited lower brain uptake (1.88% dose/g) and brain/blood ratios (11.30:1) at 60 min than did the *R* isomer. Although the brain retention and brain to blood ratios in rats of 2-(2(*RS*)-aminopropyl)-5-iodothiophene was not as high as that observed with either the (*R*)- or the (*S*)-*p*-iodophenyl analogues over a 60-min period, the 5-iodothienyl analogue showed significant brain uptake with good retention and brain/blood ratios. These data

(25) Kabalka, G. W.; Sastry, U.; Sastry, K. A. R.; Knapp, F. F., Jr.; Srivastava, P. C. Synthesis of Arylboronic Acids via the Reaction of Borane Complexes With Arylmagnesium Halides. *J. Organomet. Chem.* **1983**, *259*, 269.

(26) Kabalka, G. W.; Varma, R. S.; Gai, Y.-Z.; Baldwin, R. M. A New Route to Iodine-Labeled N-Isopropyl Iodoamphetamine Via Organoboranes. *Tetrahedron Lett.* **1986**, *27*, 3843.

Table II. Distribution of Radioactivity in Tissues of Unfasted Fischer 344 Rats following Intravenous Administration of N-Isopropyl-2-(2(R,S)-aminopropyl)-5-[^{131}I]iodothiophene

tissue	mean % injected dose/g (range) following injection		
	5 min	30 min	60 min
blood	0.31 (0.28–0.37)	0.49 (0.06–0.63)	0.60 (0.54–0.66)
liver	2.06 (1.64–2.38)	0.71 (0.08–0.90)	0.07 (0.61–0.81)
kidneys	2.72 (2.12–3.14)	1.04 (0.15–1.43)	0.79 (0.74–0.85)
heart	0.94 (0.85–1.13)	0.42 (0.06–0.53)	0.37 (0.33–0.42)
lungs	7.01 (5.92–8.51)	2.76 (0.51–3.71)	1.97 (1.87–2.12)
brain	3.18 (2.57–3.59)	1.37 (0.16–1.76)	0.95 (0.81–1.08)
thyroid	12.51 (7.87–16.51)	26.26 (5.03–36.88)	36.45 (31.90–39.98)
thyroid (% dose/organ)	0.13 (0.08–0.17)	0.28 (0.05–0.38)	1.24 (0.99–1.40)
specific activity: 40 mCi/mmol injected dose: 11.5 μCi/animal			

suggest that radiolabeled 2-(2(*RS*)-aminopropyl)-5-iodothiophenes are potentially useful agents for evaluation of regional cerebral perfusion with single-photon tomography.

It has been shown that the position of substitution of iodine on the benzene ring of derivatives of 2-(iodophenyl)isopropylamine can substantially affect brain uptake, retention, and brain to blood ratios.[4] For *N*-isopropyl-(*RS*)-2-(iodophenyl)isopropylamine brain uptake, retention and brain to blood ratios increase in the order of ortho, meta, and para for the position of the iodine on the benzene ring. Similarly in substituting an iodothienyl for a iodophenyl group of 2-(iodophenyl)isopropylamine, three different thiophene derivatives are also possible: those in which an iodine is introduced onto the 3-, 4-, or 5-position of the thiophene ring. Thus, as has been shown in the iodophenyl series, a comparison of the pharmacological activity of the iodothienyl isomers may give rise to a derivative with greater brain uptake, prolonged retention, and higher brain to blood ratios. To investigate the effects of the substitution pattern of iodine on the thiophene ring on brain uptake and retention, additional synthetic studies are being pursued. These studies include the preparation of radioiodinated (3-iodothienyl) and (4-iodothienyl)-2-(*RS*)-aminopropane.

Investigations to determine the effects of N-substitution on brain uptake in rats of radioiodinated (*R*)-2-(*p*-iodophenyl)isopropylamine[4] and (*RS*)-2-(4-iodo-2,5-dimethoxyphenyl)isopropylamine (0.34% dose/g at 5 min and 0.4% dose/g at 60 min)[3] have demonstrated that N-substitution by a isopropyl and two methyl groups increased the brain uptake and brain/blood ratio of the *N*-isopropyl *p*-iodophenyl (1.57% dose/g, 12.60:1 at 5 min and 2.14% dose/g, 20.70:1 at 60 min) and the *N,N'*-dimethyl 4-iodo-2,5-dimethoxyphenyl (1.8% dose/g, 9.0:1 at 5 min and 0.55% dose/g, 5.0:1 at 60 min) analogues. The increased brain uptake and brain/blood ratios of (*R*)-*N*-isopropyl-2-(*p*-iodophenyl)isopropylamine, in comparison to the parent primary amine, suggested that *N*-isopropyl-2-(2-(*RS*)-aminopropyl)-5-iodothiophene may exhibit higher brain uptake with higher brain/blood ratios than the corresponding primary amine. Tissue distribution studies in female rats (Table II) after injection of *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-[^{131}I]iodothiophene showed the anticipated initial higher brain uptake and brain to blood ratios. However, retention in the brain was less than that observed with 2-(2(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene. The level of accumulation of radioactivity in the brain after injection of the *N*-isopropyl derivative reached a maximum at 5 min (3.18% dose/g), but decreased rapidly to only 0.97% dose/g at 60 min. The brain/blood ratios reached a maximum of 10:1 at 5 min and decreased to only 1.6:1 at 60 min. The initial higher brain uptake of the *N*-isopropyl derivative in comparison to the parent amine can be explained by an increase in lipophilicity resulting from N-substitution giving rise to a more favorable partition coefficient between the brain tissue and blood than the corresponding primary amine.

Conclusion. Synthetic routes have been developed for the syntheses of 2-(2(*RS*)-aminopropyl)-5-[^{125}I]iodothiophene and *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-[^{131}I]iodothiophene. The model radioiodinated thienylamphetamines show early high brain extraction and brain/blood ratios in rats. The prolonged high brain retention of radioactivity following injection of the parent amine demonstrates that this radioiodinated thienyl analogue exhibits the desired characteristics of an agent for clinical rCBF assessment and is an excellent candidate for further evaluation.

Experimental Section

General. The melting points (mp) were determined in capillary tubes using a Büchi SP apparatus and are uncorrected. The thin-layer chromatographic analyses (TLC) were performed with 250-μm-thick layers of silica gel G PF-254 coated on plastic plates (Whatman). The mass spectra (MS) were determined on a ZAB-EQ (VG Analytical) hybrid high resolution, double-focusing mass spectrometer with collision and analyzing quadrupole. The proton, carbon-13, and boron-11 nuclear magnetic resonance spectra (NMR) were obtained on a JEOL FX-90Q Spectrometer. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN) and, unless noted otherwise, were within ±0.4% of the calculated values. All chemicals and solvents were analytical grade and were used without further purification. The Na^{125}I and Na^{131}I were purchased from Du Pont, Inc. (North Billerica, MA).

Animal Tissue Distribution Experiments. The distribution of radioactivity was determined in tissues of 10 12-week-old female Fischer 344 rats (170–200 g) after intravenous administration of radioiodinated thienylamphetamine. The animals were allowed food and water ad libitum prior to the course of the experiment. The radioiodinated thienylamphetamine was dissolved in 0.9% NaCl and the solution was filtered through a 0.22-μm Millipore filter and injected via a lateral tail vein after anesthesia. The animals were anesthetized with ether and killed by cervical fracture, and the organs excised, rinsed, and blotted dry. The organs were then placed in tared vials. The vials were weighed, the radioactivity of the contents was determined in a Packard autogamma counter, and the percent injected dose per gram of tissue values were then calculated.

Chemistry. 2-(2-Nitropropen-1-yl)thiophene (3). Method A. A mixture of thiophene-2-carbaldehyde (1, 10 g, 89 mmol), nitroethane (10 g, 134 mmol), and NH_4OAc (4 g, 52 mmol) was refluxed for 2 h in 40 mL of acetic acid. The mixture was cooled to room temperature and poured into 200 mL of ice H_2O. The resulting solid was crystallized from methanol to give 7.6 g of 3 (51%) as an orange solid: mp 68–70 °C (lit.[22] mp 68.5 °C).

Method B. A mixture of thiophene-2-carbaldehyde (1, 24.83 g, 23 mmol) and NH_4OAc (10 g, 13 mmol) was refluxed for 7 h in 250 mL of nitroethane. The mixture was cooled to room temperature and the nitroethane was evaporated in vacuo. The resulting orange solid was dissolved in Et_2O and the ether washed several times with water. The ether was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give com-

pound 3 which was identical with the sample prepared by method A. Crystallization from methanol gave 32 g of 3 (80%) as an orange solid: mp 68–70 °C.

2-(2-Nitropropen-1-yl)-5-bromothiophene (4). Method A. A mixture of 5-bromo-2-thiophenecarbaldehyde (3, 10.04 g, 53 mmol), nitroethane (8.66 g, 108.44 mmol), and NH_4OAc (4 g, 52 mmol) was reacted as described for 3. Crystallization from methanol gave 6.41 g of 4 (49%) as yellow needles: mp 147–149 °C; ^{13}C NMR ($CDCl_3$) 14 (CH_3), 120 (C5-thienyl), 127 (C3-thienyl), 131 (C4-thienyl) 135 (C=C), 137 (C-NO_2), 144 ppm (C2-thienyl); ^1H NMR ($CDCl_3$) 2.5 (s, 3 H, CH_3), 7.1 (s, 2 H, aromatic), 8.15 ppm (s, 1 H, HC=C).

Method B. A mixture of 5-bromo-2-thiophenecarbaldehyde (2, 4.14 g, 22 mmol and NH_4OAc (2.5 g, 30 mmol) in 75 mL of nitroethane was reacted as described for 3. Crystallization from ethanol yielded 4.53 g of 4 (82%), as yellow needles, which was identical with the sample prepared by method A: mp 147–149 °C.

2-(2(*RS*)-Aminopropyl)thiophene (5). One hundred and fifty milliliters of a 1.0 M borane–tetrahydrofuran solution under nitrogen was cooled to 0 °C, and 2-(2-nitropropen-1-yl)thiophene (3, 3.4 g, 20 mmol) in 30 mL of dry THF under nitrogen was added with a syringe through a rubber septum. The ice bath was removed, sodium borohydride (0.25 g) was added, and the resulting mixture was refluxed for 26 h. The mixture was cooled to room temperature, slowly poured into 300 mL of ice–H_2O, acidified to pH = 2 with 10% HCl, and stirred at 65–70 °C for 2 h. The resulting mixture was cooled to room temperature and washed with three 50-mL portions of Et_2O. The H_2O phase was basified to pH = 7–8 with sodium hydroxide, washed thoroughly with ether, basified to pH = 10, and extracted with three 10-mL portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to yield 2.16 g of 5 (77%). Pure 2-(2(*RS*)-aminopropyl)thiophene (5, 139 mg, 1 mmol) was obtained by treatment with a 1-mL solution of 4 N HCl in dioxane, the resulting mixture stirred for 15 min, and the solvent removed in vacuo. The resulting residue was crystallized from ethanol–ethyl ether to give 148 mg of hydrochloride salt (75%) as a beige solid: mp 149–150 °C.

2-(2(*RS*)-Aminopropyl)-5-bromothiophene (6). A mixture of 50 mL of 1 M borane–THF, 2-(2-nitropropen-1-yl)-5-bromothiophene (4, 1.93 g, 7.8 mmol), and 0.2 g of sodium borohydride in 25 mL of dry THF was reacted as described for 5. The dried ether extracts were evaporated in vacuo to afford 1.31 g of 6 (77%) of a yellow liquid. Pure 2-(2(*RS*)-aminopropyl)-5-iodothiophene (8, 265 mg, 1 mmol) was obtained by treatment with 1 mL of 4 N HCl in dioxane as described for 5. The dioxane solution was concentrated in vacuo and the residue crystallized from ethanol–ethyl ether to give 165 mg of hydrochloride salt (55%) as a light yellow solid: mp 208–209 °C; ^{13}C NMR ($CDCl_3$) 23 (CH_3), 40 (CH_2), 48 ($CHNH_2$), 109 (C5-thienyl), 125 (C3-thienyl), 129 (C4-thienyl), 143 ppm (C2-thienyl); ^1H NMR ($CDCl_3$) 1.1 (d, J = 6 Hz, 3 H, CH_3), 1.4 (s, 2 H, NH_2), 2.7 (t, J = 8 Hz, 2 H, CH_2), 3.1 (m, 1 H, CH), 6.5 (d, J = 4 Hz, 1 H, aromatic), 6.9 ppm (d, J = 4 Hz, 1 H, aromatic). Anal. ($C_7H_{10}NSBr$) C: calcd, 38.27; found, 38.94. H: calcd, 4.59; found, 5.08.

2-(2(*RS*)-Aminopropyl)-5-(trimethylstannyl)thiophene (7b). 2-(2(*RS*)-Aminopropyl)thiophene (57.0 mg, 0.5 mmol) in 5 mL of dry THF under argon was stirred at room temperature, and 0.6 mL of 1.7 M n-butyllithium (1.0 mmol) solution was added. After the dropwise addition of trimethyltin chloride (400 mg, 1 mmol) in 5 mL of dry THF, the resulting mixture was stirred at room temperature for 60 min. The mixture was added to 50 mL of H_2O and extracted several times with Et_2O. The combined ether extracts were thoroughly washed several times with H_2O, dried with anhydrous sodium sulfate, and concentrated in vacuo to yield 112 mg of 7b (74% yield) as a colorless oil: ^1H NMR ($CDCl_3$) 0.3 (s, 9 H, CH_3), 1.1 (d, J = 6 Hz, 3 H, CH_3), 1.4 (s, 2 H, NH_2), 2.7 (t, J = 8 Hz, 2 H, CH_2), 3.1 (m, 1 H, CH), 6.9 (d, J = 3 Hz, 1 H, aromatic) 7.0 ppm (d, J = 3 Hz, 1 H, aromatic).

2-(2(*RS*)-Aminopropyl)-5-iodothiophene (8). Method A. 2-(2(*RS*)-Aminopropyl)thiophene (5, 211 mg, 1.5 mmol) and thallium(III) trifluoroacetate (1.00 g, 1.8 mmol) in 5 mL of acetonitrile were stirred at room temperature under red lights for 1 h. Potassium iodide (1.5 g, 50 mmol) in 5 mL of H_2O was added, and the resulting mixture stirred at room temperature for 15 min. Sodium thiosulfate (1 g) was then added, and the mixture was stirred for an additional 15 min, poured into 25 mL of 1 N NaOH, and extracted with three 25-mL portions of ether. The ether extracts were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to give 143 mg of 8 (36%) as a colorless liquid. Pure 2-(2(*RS*)-aminopropyl)-5-iodothiophene (8, 265 mg, 1 mmol) was obtained by treatment with 1 mL of 4 N HCl in dioxane as described for 5. The dioxane solution was concentrated in vacuo and the residue crystallized from ethanol–ethyl ether to give 165 mg of hydrochloride salt (55%) as a light yellow solid: mp 208–209 °C; ^1H NMR ($CDCl_3$) 1.1 (d, J = 6 Hz, 3 H, CH_3), 1.3 (s, 2 H, NH_2), 2.7 (t, J = 8 Hz, 2 H, CH_2), 3.1 (m, 1 H, CH), 6.5 (d, J = 4 Hz, 1 H, aromatic) 7.1 ppm (d, J = 4 Hz, 1 H, aromatic).

Method B. 2-(2(*RS*)-Aminopropyl)-5-(trimethylstannyl)-thiophene (76 mg, 0.25 mmol) in 5 mL of CH_2Cl_2 cooled to 0–5 °C and protected from light was treated with iodine (127 mg, 0.5 mmol) and stirred until a colorless solution resulted. The reaction mixture was washed with 5% $NaHSO_3$ and dried over anhydrous sodium sulfate. The dried CH_2Cl_2 was removed in vacuo to give 60 mg (90% yield) of 8 as a colorless oil.

***N*-Isopropyl-2-(2(*RS*)-aminopropyl)thiophene (9).** 2-(2-(*RS*)-Aminopropyl)thiophene (5, 2.06 g, 14.6 mmol) in 20 mL of absolute methanol under nitrogen was stirred at room temperature. Sodium cyanohydridoborate (0.43 g, 4.79 mmol), glacial acetic acid (0.8 mL, 13.7 mmol), and dry acetone (6 mL, 82.1 mmol) were added, and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was acidified to pH = 2 with 12 N HCl and the solvent removed in vacuo. The resulting residue was dissolved in 30 mL of H_2O, washed with ether, basified to pH = 7–8 with solid NaOH, washed with ether, basified further to pH = 10 with solid sodium hydroxide, and extracted several times with ether. The combined ether extracts were dried with anhydrous sodium sulfate and concentrated in vacuo to afford 2.09 g of 9 (73% yield) as a colorless liquid. Pure *N*-isopropyl-2-(2(*RS*)-aminopropyl)thiophene (9, 183 mg, 1 mmol) was obtained by treatment with 1 mL of 4 N HCl in dioxane as described for 5. The dioxane solution was concentrated in vacuo and the residue crystallized from ethanol–ethyl ether to give 172 mg of hydrochloride salt (80%) as colorless plates: mp 146–147 °C.

***N*-Isopropyl-2-(2(*RS*)-aminopropyl)-5-(trimethylstannyl)thiophene (10).** *N*-Isopropyl-2-(2(*RS*)-aminopropyl)-thiophene (9, 183 mg, 1 mmol) in 10 mL of dry THF under argon was reacted with 1.5 mL of 1.7 M n-butyllithium (2 mmol) and trimethyltin chloride (400 mg, 1 mmol) as described for 7b. The dried ether extracts were concentrated in vacuo to afford 335 mg of 10 (97%) as a colorless oil.

***N*-Isopropyl-2-(2(*RS*)-aminopropyl)-5-bromothiophene (11).** 2-(2(*RS*)-Aminopropyl)-5-bromothiophene (6, 2.50 g, 11.4 mmol) in 25 mL of absolute methanol under nitrogen was stirred at room temperature. Sodium cyanohydridoborate (0.43 g, 6.84 mmol), glacial acetic acid (0.8 mL, 13.7 mmol), and dry acetone (5.1 mL, 68.4 mmol) were added and the resulting mixture was reacted as described for 10. The combined ether extracts were dried with anhydrous sodium sulfate and concentrated in vacuo to afford 1.99 g of 11 (98%) as a colorless liquid: ^{13}C NMR ($CDCl_3$) 21 (CH_3), 23 (CH_3), 24 (CH_3), 38 (CH_2), 45 [$CH(CH_3)_2$], 51 (CH-NH), 109 (C5-thienyl), 125 (C3-thienyl), 129 (C4-thienyl), 143 ppm (C2-thienyl); ^1H NMR ($CDCl_3$) 1.0 (m, 9 H, CH_3), 2.7 (t, J = 8 Hz, 2 H, CH_2), 3.1 (m, 2 H, CH), 6.5 (d, J = 4 Hz, 1 H, aromatic), 6.9 ppm (d, J = 4 Hz, 1 H, aromatic).

***N*-Isopropyl-2-(2(*RS*)-aminopropyl)thiophene-5-boronic Acid (13).** *N*-Isopropyl-2-(2(*RS*)-aminopropyl)-5-bromothiophene (11, 0.52 g, 2.0 mmol) in 50 mL of dry ether under nitrogen was cooled to −78 °C, and 1.6 mL of 2.5 M n-butyllithium in hexane was added with a syringe through a rubber septum. The resulting mixture was stirred at −78 °C for 60 min. After dropwise addition of 9.2 mL of triisopropyl borate (7.5 g, 20.0 mmol), the mixture was again stirred at −78 °C for 60 min and then at room temperature, for 3 h. The mixture was added to 60 mL of H_2O extracted three times with 20 mL of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate, and the solvent was concentrated in vacuo to give a solid. Trituration of the solid with ether yielded 0.39 g of 13 (86%) as a white solid: ^{13}C NMR (CD_3OD) 28 (CH_3), 30 (CH_3), 31 (CH_3),

45 (CH_2), 57 [$CH(CH_3)_2$], 64 (CHNH), 138 (C3-thienyl), 143 (C4-thienyl), 152 ppm (C2-thienyl); MS m/z 284.15 (M+, 100).

***N*-Isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene (14). Method A.** Boronic acid **13** (0.454 g, 2 mmol) was dissolved in 20 mL of H_2O and the resulting solution was stirred at ambient temperature and shielded from light. After the addition of 2.0 mL of 1.0 M sodium iodide (2 mmol) followed by chloramine-T (0.455, 2 mmol), the reaction mixture was stirred for an additional 30 min. The mixture was extracted three times with 10 mL of ether. The combined ether extracts were dried over sodium sulfate and the solvent was removed in vacuo to yield 170 mg of **14** (30% yield) as a colorless liquid. Pure *N*-isopropyl-2-(2(*RS*)-aminopropyl)-5-iodothiophene (**14**, 478 mg, 1.54 mmol) was obtained by treatment with 1 mL of 4 N HCl in dioxane as described for **5**. The dioxane solution was concentrated in vacuo and the residue crystallized from ethanol–ethyl ether to give 454 mg of hydrochloride salt (85%) as a white solid: mp 165–166 °C, ^{13}C NMR ($CDCl_3$) 20 (CH_3), 23 (CH_3), 38 (CH_2), 45 [$CH(CH_3)_2$], 50 (CHNH), 71 (C5-thienyl), 127 (C3-thienyl), 136 (C4-thienyl), 148 ppm (C2-thienyl); ^1H NMR ($CDCl_3$) 1.0 (m, 9 H, CH_3), 1.8 (s, 1 H, NH), 2.7 (t, J = 8 Hz, 2 H, CH_2), 3.0 (m, 2 H, CH), 6.5 (d, J = 4 Hz, 1 H, aromatic), 7.1 ppm (d, J = 4 Hz, 1 H, aromatic); MS m/z 310.81 (M+, 100).

Method B. Stannane **10** (173 mg, 0.5 mmol) in 5 mL of CH_2Cl_2 was reacted with iodine (127 mg, 0.5 mmol) as described for **8**. The dried CH_2Cl_2 was removed in vacuo to give 152 mg (98% yield) of **14** as a colorless oil.

2-(2(*RS*)-Aminopropyl)-5-[^{125}I]iodothiophene ([^{125}I]-8). A 15-mL round-bottomed flask containing *N*-chlorosuccinimide (1.6 mg, 0.012 mmol) was fitted with a septum inlet and equipped with a magnetic stirring bar and a gas outlet connected to a charcoal trap. Five milliliters of CH_2Cl_2 was introduced via a syringe and the solution cooled to 0–5 °C (ice bath) and stirred. Sodium [^{125}I]iodide (1.5 mg, 0.01 mmol, 5.5 mCi) was introduced via a syringe. The mixture initially turned pink from the formation of ICl. Stannylthiophene **7b** (3.04 mg, 0.01 mmol) in 1 mL of $CHCl_2$ was introduced via a syringe. The mixture initially turned pink from the formation of ICl. The resulting reaction mixture was removed from the ice bath and stirred for 30 min. The solution rapidly became lighter until a colorless solution resulted. The mixture was poured into 20 mL of 5% $NaHSO_3$, basified to pH = 10 with 1 N NaOH, and extracted several times with Et_2O. The combined Et_2O extracts were extracted two times with 15 mL of 1 N HCl. The combined 1 N HCl extracts were basified to pH = 10 with 6 N NaOH and the resulting solution extracted several times with Et_2O. The combined Et_2O extracts were washed with H_2O and dried over anhydrous Na_2SO_4. The Et_2O was evaporated by a stream of argon to give ^{125}I-labeled **8** (1.61 mCi, 29%). TLC (Al_2O_3-GF) ($CHCl_3$–CH_3OH, 98:2) showed one radioactive component (R_f = 0.5) which cochromatographed with the authentic standard.

***N*-Isopropyl-2-(2(*RS*)-aminopropyl)-5-[^{131}I]iodothiophene ([^{131}I]-14). Method A.** A 15-mL round-bottomed flask containing boronic acid **13** (5.6 mg, 0.02 mmol) dissolved in 1 mL of 1 N HCl was fitted with a septum inlet and equipped with a magnetic stirring bar, and a gas outlet was connected to a charcoal trap. The resulting solution was stirred at ambient temperature and shielded from light. Twenty microliters of 1.0 M sodium [^{131}I]-iodide (0.8 mCi, 0.02 mmol) was introduced via a syringe followed by 20 μL of 1.0 M chloramine-T (0.02 mmol), the reaction mixture was stirred for an additional 40 min. The mixture was basified to pH = 10 with 0.3 mL of 5 M KOH extracted with 5 mL of ether. A second 0.5 mL of 5 M KOH was added to the reaction mixture and the resulting solution extracted with 5 mL of ether. The combined ether extracts were dried over sodium sulfate, and the solvent was removed by a stream of nitrogen to yield 0.69 mCi (86% yield). The [^{131}I]-**14** showed a single radioactive component (98%) on thin-layer radiochromatographic analysis (SiO_2-GF, CH_2Cl_2–CH_3OH, 8.5:1) (R_f = 0.32) that cochromatographed with an authentic unlabeled standard (R_f = 0.32).

Method B. Stannane **10** (3.45 mg, 0.01 mmol) in 1 mL of CH_2Cl_2 was reacted with sodium [^{131}I]iodide (0.715 mCi, 0.01 mmol) and *N*-chlorosuccinimide (1.8 mg, 0.01 mmol) dissolved in a mixture of CH_2Cl_2–H_2O (4:1, 5 mL) as described for [^{125}I]-**8**. The dried ether extracts were removed by a stream of nitrogen to yield 0.67 mCi (74% yield). TLC (SiO_2-GF, CH_2Cl_2–CH_3OH, 8.5:1) (R_f = 0.32) of [^{131}I]-**14** showed one radioactive component (R_f = 0.32) which cochromatographed with the authentic standard.

Acknowledgment. Research sponsored by the National Institutes of Health (Grant GM-39081), Grant DDEFG-86 ER 60434 from the Environmental Research Department of Energy, and the Office of Health and Environmental Research Department of Energy under Contract DE-AC05-840 R21400 with Martin Marietta Energy Systems, Inc. The authors thank Valerie Hendrix for assistance in preparing the manuscript.

Phenyl-Substituted Analogues of Oxotremorine as Muscarinic Antagonists

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A series of phenyl-substituted analogues of the muscarinic agent oxotremorine (**1**) have been prepared. The new compounds (**3b–11b** and **9c**) were assayed for antimuscarinic activity on the isolated guinea pig ileum and in intact mice. They were also evaluated for ability to inhibit the binding of the muscarinic antagonist (-)-[^{3}H]-*N*-methylscopolamine to homogenates of the rat cerebral cortex. The phenyl-substituted derivatives were devoid of intrinsic muscarinic activity. Instead, they behaved as competitive muscarinic antagonists in these assays with similar or lower affinity for muscarinic receptors than the corresponding methyl-substituted analogues. The succinimide (**8b**) and the pyrrolidone (**3b**) derivatives of **1** substituted with a phenyl group at position 1 of the butynyl chain showed the highest antimuscarinic potency with dissociation constants (K_D) of 0.10 and 0.20 μM, respectively, in the ileum assay. The phenyl-substituted analogues showed an approximately 10-fold lower in vivo antimuscarinic potency than their corresponding methyl-substituted positional isomers. A correlation was observed between in vitro and in vivo potency within subsets consisting of methyl- and phenyl-substituted derivatives.

Introduction

In general, one or two aryl substituents are present in potent muscarinic antagonists. This situation may be exemplified with antagonists derived from 1,3-dioxolane,[1] 1,3-oxathiolane,[2] esters of ethanolamine,[3] oxadiazole,[4] es-

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(1) Brimblecombe, R. W.; Inch, T. D. Structure–Activity Relations for Anticholinergic Dioxolans. *J. Pharm. Pharmacol.* **1972**, *22*, 881–888.

0022-2623/92/1835-0285$03.00/0