

eyelid closure. The presence of normal locomotor activity or exploratory head movements and less than 50% eyelid closure indicated a block of TBZ sedation and ptosis, respectively. Ten mice were used per dosage level of the test compound and in the control group. When the response, sedation and/or ptosis, to TBZ was 90% or less in the control group, the response in the drug-treated group was corrected by using Abbott's formula.¹⁵ Four to five dosage levels of the test compounds were used in obtaining an ED₅₀ value. ED₅₀ values and 95% confidence limits were calculated by probit analysis.¹⁵

Maximal Electroshock Threshold Seizures (MEST) Test. The effect of selected members of the series on electroshock seizures was determined in normal and in TBZ-treated mice. Nonfasted male albino mice of the Swiss Webster strain (Royal Hart Laboratories), weighing 18-24 g, were used in this procedure. The test compound or saline was injected 30 min prior to electroshock. Tetrabenazine methanesulfonate (64 mg/kg) was injected intraperitoneally 15 min after the administration of the test compound. These mice were subjected to electroshock 15 min later. Hind-limb tonic-extensor seizures were induced by the delivery of a 60-Hz current of 8-mA intensity for 0.25 s through ear-clip electrodes. The use of a current intensity of 8 mA for 0.25 s was previously determined to be the minimal current strength required to induce hind-limb tonic-extensor seizures in approximately 100% of mice used in this study (ED₉₉). The incidence of hind-limb tonic-extensor seizures in TBZ-treated mice was also 100% (ED₉₉ = 6.0 mA). Abolition of the hind-limb tonic-extensor seizure indicated activity. The dose ED₅₀ required to block seizures in 50% of normal and TBZ-treated mice was determined. Four to five dosage levels of the test compound were used in obtaining an ED₅₀ value. ED₅₀ values and 95% confidence limits were calculated by probit analysis.¹⁵

Gross Behavioral Effects and Lethality. The gross behavioral effects of selected compounds were observed in mice following intraperitoneal doses of 1, 3, 10, 30, 100, and 300 mg/kg. The mice were held for 4 days following administration of the test compounds. An estimated LD₅₀ range based on lethality count was made on day 4. Three male albino mice of the Swiss Webster

strain (Royal Hart Laboratories), weighing 18-24 g, were used per dosage level of compound administered.

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Note Added in Proof: A brief examination of uptake inhibition of NE, DA, and 5HT for 4, 19, and 37 (according to Horn, A. S.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* 1972, 180, 523) showed rather weak activity. For 4 (100 nM), 19 (1000 nM), and 37 (1000 nM), percent inhibition values were 24, 37, and 26 for DA; 2, 85, and 40 for NE; and 5, 56, and 7 for 5HT, respectively. K_i values for imipramine were >10 000 nM for DA, 12 nM for NE, and 42 nM for 5HT.

Registry No. 4, 90530-62-4; 4-HCl, 90530-63-5; 5, 90530-97-5; 5-HCl, 90530-64-6; 6-fumarate, 90530-66-8; 7, 90530-67-9; 7-fumarate, 90530-68-0; 8, 90552-80-0; 8-HCl, 90552-78-6; 9-dihexamate, 90530-70-4; meso-10, 90530-98-6; dl-10, 90552-81-1; meso-10-HCl, 90530-71-5; dl-10-HCl, 90530-72-6; 11, 90530-99-7; 11-HCl, 90530-73-7; 12 (2-thienyl isomer), 90531-00-3; 12 (2-thienyl isomer)-HCl, 90530-74-8; 12 (3-thienyl isomer), 90531-01-4; 12 (3-thienyl isomer)-HCl, 90530-75-9; 13, 90530-76-0; 13-HClO₄, 90530-77-1; 14, 90530-78-2; 15, 90552-79-7; 16-oxalate, 90530-80-6; 17-HCl, 7351-52-2; 18, 80376-82-5; 18-HCl, 80376-83-6; 19, 7647-54-3; 19-HCl, 13636-10-7; 20, 3139-55-7; 20-HCl, 3139-54-6; 21, 90530-81-7; 21-dihexamate, 90530-82-8; 22, 4382-96-1; 22-HCl, 6949-96-8; 23, 69681-77-2; 23-HCl, 75198-08-2; 24, 85336-82-9; 24-HCl, 21998-53-8; 25-fumarate, 90530-84-0; 26, 90531-02-5; 26-HCl, 90530-85-1; 27, 36756-35-1; 27-HCl, 90530-86-2; 28-oxalate, 90530-88-4; 29, 90530-89-5; 29-HClO₄, 90530-90-8; 30-fumarate, 90530-91-9; 31-hemifumarate, 90530-92-0; 32, 90531-03-6; 32-HCl, 6635-05-8; 33-saccharin, 90530-93-1; 34, 90531-04-7; 34-HCl, 90530-94-2; 35, 90531-05-8; 35-HCl, 22101-74-2; 36-saccharin, 90530-96-4; ethylene oxide, 75-21-8; propylene oxide, 75-56-9; diphenylacetaldehyde, 947-91-1; diethanolamine, 111-42-2.

Supplementary Material Available: Ninety-five percent confidence limits for the biodata presented in Tables I and II (1 page). Ordering information is given on any current masthead page.

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Radiohalogen-Labeled Imaging Agents. 3. Compounds for Measurement of Brain Blood Flow by Emission Tomography

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The radioiodine-labeled amines currently available as brain-imaging agents, based on our previous work and that of others, are prepared either by exchange labeling or by direct iodination of a protected intermediate. The intrinsic slowness of these processes limits their potential for use with the positron-emitting ¹²²I, as it has a half-life of only 3.6 min. This isotope has advantages of a low dose to the patient and availability from a generator containing the parent 20-h ¹²²Xe. To develop a radiopharmaceutical in which ¹²²I could be utilized, we prepared a number of secondary and tertiary amines (maintaining the 2,5-dimethoxy substitution pattern which allows direct iodination at the 4-position) with ¹³¹I. The organ distributions of these compounds were studied, and the best properties were found in the *N,N*-dimethyl homologue (2,5-dimethoxy-*N,N*-dimethyl-4-iodoamphetamine). This compound was successfully synthesized in a matter of seconds, with a chemical yield and radioactive purity both in excess of 90% and an incorporation efficiency of radioiodine of about 40%.

Paper 1 of this series¹ described an amphetamine analogue, 2-(4-[⁸²Br]bromo-2,5-dimethoxyphenyl)isopropylamine, which was the first reported radiohalogen-labeled organic compound that showed uptake and reasonably long

retention in normal human brain. The second paper² described the synthesis of the analogous radioiodinated agent, 2-(4-[¹³¹I]iodo-2,5-dimethoxyphenyl)isopropylamine (1r), which showed first-pass extraction in the monkey from blood to brain. Because of this property, we proposed

(1) Sargent III, T.; Kalbhen, D. A.; Shulgin, A. T.; Braun, G.; Stauffer, H.; Kusubov, N. *Neuropharmacology* 1975, 14, 165, to be considered paper 1 of this series.

(2) Braun, U.; Shulgin, A. T.; Braun, G.; Sargent III, T. *J. Med. Chem.* 1977, 20, 1543, to be considered paper 2 of this series.

that it would be useful as a brain-imaging agent in nuclear medicine.³ Additional analogues of this compound were subsequently reported by Winchell et al.:⁴ one of them, *N*-isopropyl-2-(*p*-iodophenyl)isopropylamine (termed IMP), was chosen for clinical trials on the basis of its high brain/blood ratio.

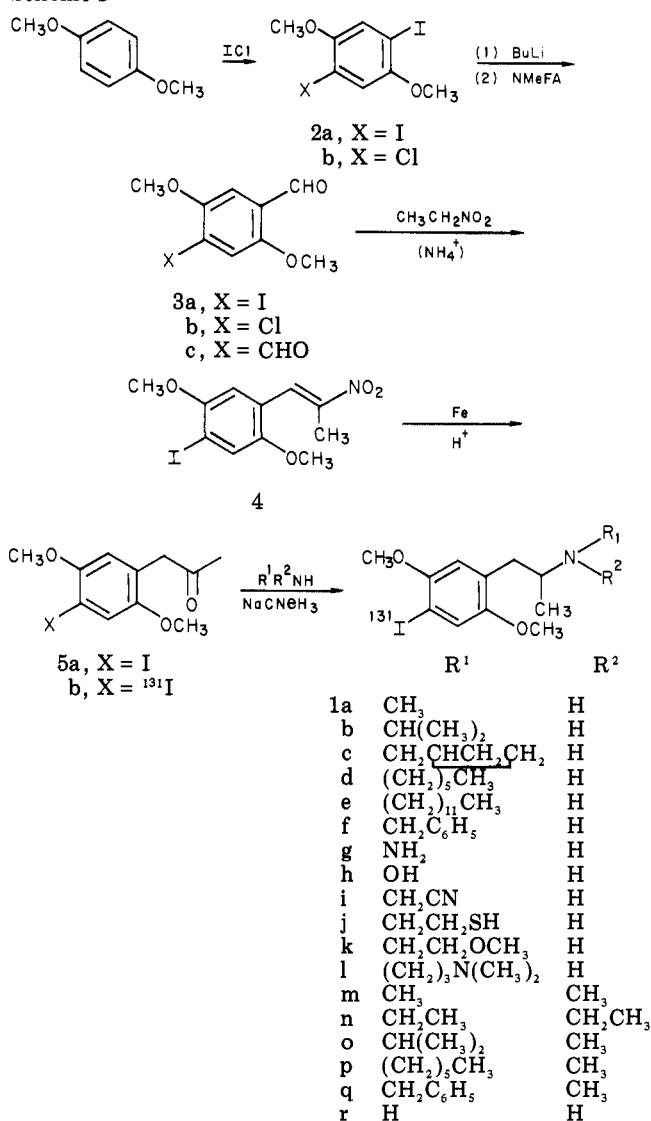
Clinical trials with ¹²³I-labeled IMP using single photon emission computed tomography have shown the usefulness of this agent in measurement of regional brain blood flow.^{5,6} Perfusion deficits in brain, many not detectable by CAT scanning, were shown in patients with stroke. Hyperperfusion was seen in patients with epileptic foci. Other more distantly related compounds labeled with radioiodine have also been reported as potential brain imaging agents.^{7,8}

All of the above agents, with the exception of our original compound with the 2,5-dimethoxy ring substitution pattern, are made by first synthesizing the halogenated compound and then labeling by exchange. Such a process, while convenient for manufacture, has two limitations: (1) the specific activity is inherently limited because of the presence of unlabeled compound, and (2) the exchange labeling reaction is relatively slow; this limits the usable isotopes to those of fairly long half-life. Thirteen-hour ¹²³I is the most useful isotope for this application because its γ energy is ideal for single photon imaging devices.

Positron emission tomograph (PET) imaging systems construct tomographic images by utilizing detection of the coincident 0.51-MeV γ rays from decay of positrons. PET images contain quantitative data on the regional concentration of the isotope within the human body without interference by overlying tissue. PET devices require positron-emitting radioisotopes, and the most feasible among the halogens that are suitable in terms of half-life and radiation dose to the patient are 1.7-h ⁷⁵Br and 3.6-min ¹²²I. Of these, ¹²²I has two advantages; it has a very short half-life, making possible repeat studies at short intervals with lower total radiation dose, and it is the daughter of 20-h ¹²²Xe. A generator system has been described by which the ¹²²I daughter can be repeatedly extracted carrier-free from the ¹²²Xe parent.⁹ This would allow the production and shipping of ¹²²I generators to institutions that do not have cyclotrons.

It is with these considerations in mind that we have investigated the series of compounds reported here. The 2,5-dimethoxy substituents sterically direct halogenation at the para position; if the primary amine function of the precursor is protected, oxidative side reactions are avoided.¹⁰ In our first studies this protection was afforded by a phthalide group, which was removed after iodination. In order to provide the most rapid possible synthesis with ¹²²I, we decided to investigate 2-(4-iodo-2,5-dimethoxy-

Scheme I

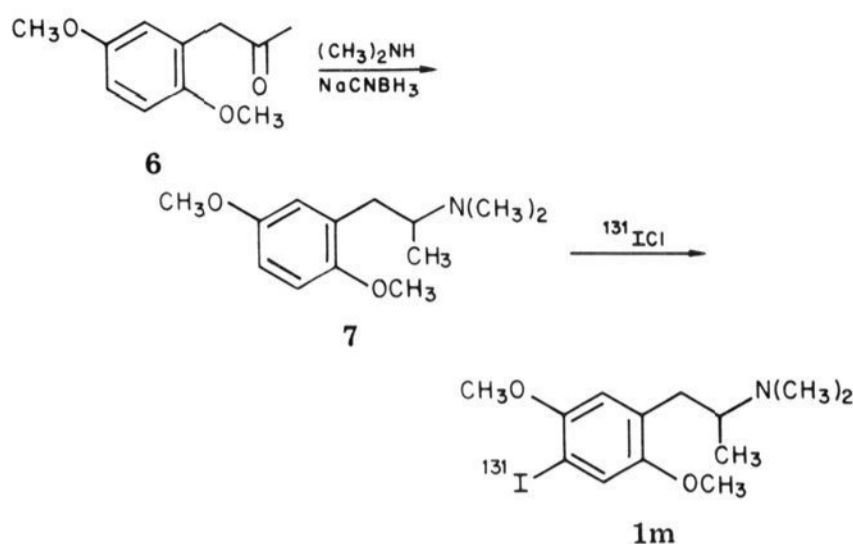


phenyl)isopropylamine with various nitrogen substituents to determine the stability of the precursor to direct iodination. If high brain uptake could be found with one or more of these species, the removal of the protective groups would be unnecessary, and sufficient rapidity of synthesis might be available to utilize labeling with ¹²²I, as well as with more conventional isotopes, such as ¹²³I.

Chemistry. To evaluate a large number of *N*-substitution patterns for organ distribution, we developed a procedure that allowed a single radiolabeled compound to serve as a precursor (Scheme I). The product of the reaction between *p*-dimethoxybenzene and iodine monochloride depended upon the solvent employed. The relatively polar acetic acid yielded exclusively the diiodo derivative **2a**, whereas the use of methylene chloride provided largely the chloro-iodo counterpart **2b**. Trials with nonpolar solvents, such as hexane, led only to monohalogenation. Reaction of **2** with butyllithium, followed by treatment with *N*-methylformanilide, led to the replacement of the iodine atom with a carboxaldehyde function. In the reaction of **2a** to **3a**, a small amount of dilithiation yielded, as an impurity in **3a**, the known 2,5-dimethoxyterephthalaldehyde **3c**. The ammonia-catalyzed reaction of **3a** with nitroethane and the reduction of the resulting nitrostyrene **4** with iron provided the ketone **5a** with no complications. A number of environments were explored for the exchange of iodine for radioiodine in **5**

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Scheme II



(Table II); the most satisfactory was the use of Na^{131}I in acetic acid at 140°C . Reductive amination of **5b** with various primary or secondary amines and sodium cyanoborohydride provided the corresponding product **1**.

The dimethoxy derivative having the highest brain uptake (**1m**) was prepared by the reductive amination of 2,5-dimethoxyphenylacetone **6** with dimethylamine (Scheme II), followed by the direct iodination of the resulting *N,N*-dimethyl-2-phenylisopropylamine **7** to **1m** with ^{131}I . A nonradioactive reference sample of **1m** was prepared by the direct dimethylation of **1r**. Several iodination procedures were evaluated from the viewpoint of speed, radiochemical purity, radioincorporation yield, reaction scale, and ease and speed of separation from by-products.

Results and Discussion

The uptake in each of the measured organs of each of the ^{131}I -labeled compounds is shown in Table I, as percent of the injected dose in the total organ and as percent of injected dose per gram in each organ. Desirable features of a brain blood flow agent are that it be taken up in brain sufficiently to obtain γ ray imaging and that it be removed from blood rapidly so that the radioactivity imaged in brain will not have a significant contribution from circulating blood. Thus, the parameters of interest are the percent of the injected dose appearing in the brain or other organs and the ratio of organ to blood radioactivity normalized on a weight basis. The time course of these parameters is also of interest because, when a very short-lived isotope is used, it is desirable that optimal values be reached within a few half-lives. Hence, data were obtained at 5 and 30 min for each compound.

Compound **1m** had the highest percent uptake in brain, 3.4%, and also the highest value of brain to blood ratio, 9.0. For compound **1n**, this ratio was 5.0 and for the compound we first reported,³ **1r**, it was 4.7. Thus, the best candidate for a useful brain blood-flow imaging agent is **1m**, the *N,N*-dimethyl analogue. Direct iodination of the precursor **7** to produce **1m** (see Experimental Section) has produced chemical yields of 90% in 10 s, a yield and speed satisfactory for use with ^{122}I . A useful dose of 12 mCi of ^{122}I -labeled **1m** will remain 14.4 min (4 half-lives) after extraction from a 200 mCi ^{122}Xe generator. Methods are currently under development for purification of **1m** within this time span. The reaction yields reported here were achieved at a 1 μg level, obviating pharmacological problems in human applications.

^{131}I -labeled **1m** was further studied by injecting 75 μCi into a dog and measuring brain uptake and blood radioactivity as a function of time, with results shown in Figure 1. Activity in the brain reached a maximum at 5 min, and decreased to 65% of its maximum value by 30 min. Blood

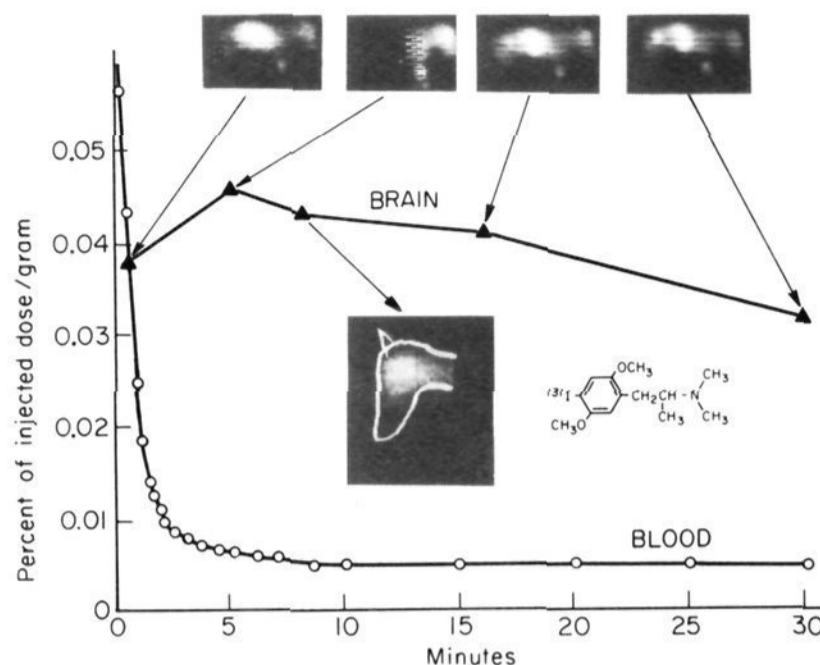


Figure 1. Brain uptake and blood clearance of 2,5-dimethoxy-*N,N*-dimethyl-4- ^{131}I iodoamphetamine in a beagle dog. The scan images are linked to the appropriate time points and an enlarged, left-right reversed image of the head is shown at 8 min, with a sketched outline of the head. Radioactivity is concentrated in the brain, lungs, and liver, at the injection site on the forelimb, and in the last two images, in the bladder.

activity fell rapidly and reached an almost constant value by 5 min, with a brain/blood ratio of approximately 9, in good agreement with the value found in rats. The enlarged image of the head showed clearly the concentration in brain. It should be noted that the gamma energy of ^{131}I and the scanner used produce images of relatively poor resolution. The uptake values for brain are not corrected for tissue attenuation and isotope in overlying tissue; the values on the ordinate for blood and brain were calculated on a slightly different basis (see Experimental Section). The ^{131}I provided the convenience of long half-life, and the entire animal was easily scanned with the Mark II scanner, but ^{123}I with 160-keV γ rays and a scintillation camera would produce much better images. Thus, **1m** appears to have excellent characteristics for the type of brain blood-flow agent we are seeking: rapid uptake and relatively long retention in brain, rapid clearance from blood, a high brain/blood ratio, and rapid synthesis by direct iodination. Studies are now underway to develop the requisite technology and chemistry for production of the ^{122}I -labeled **1m** from a ^{122}Xe - ^{122}I generator.

Further study of Table I reveals other compounds of possible interest as radiopharmaceuticals. $^{99\text{m}}\text{Tc}$ micro-particulate agents for scanning of lung are important for diagnosis of emboli and perfusion deficits in a variety of illnesses, and ventilation imaging is currently done with isotopes of gases. Examination of the lung section of Table I reveals five compounds (**1a-d,f**) with a combination of high percent uptake, high percent uptake per gram, and high organ/blood ratio. All of these compounds would appear to be of interest for further evaluation as lung imaging agents. We have earlier reported lung uptake with the bromine congener¹ and suggested use of the iodine analogue as a lung imaging agent.³ In a recent report,¹⁴ the radiation dose to various organs was examined based on uptake of ^{123}IMP , another amphetamine analogue.

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Table I. Organ Distribution of ¹³¹I-Labeled Compounds in the Rat

no.	min ^a	brain			lung		heart		
		% dose/total organ	% dose/g of organ	organ/blood ratio ^b	% dose/g of organ	organ/blood ratio ^b	% dose/total organ	% dose/g of organ	organ/blood ratio ^b
1a	5 (3)	0.97 ± 0.24	0.57 ± 0.14	4.1 ± 1.9	5.9 ± 1.5	42 ± 20	0.65 ± 0.10	0.93 ± 0.32	6.6 ± 3.7
	30 (2)	1.0 ± 0.1	0.62 ± 0.04	2.2 ± 1.0	3.2 ± 0.6	11.4 ± 7	0.32 ± 0.0	0.53 ± 0.0	1.9 ± 0.7
1b	5 (3)	1.2 ± 0.5	0.66 ± 0.32	2.6 ± 2.2	7.7 ± 1.5	31 ± 17	0.79 ± 0.27	1.2 ± 0.5	4.8 ± 3.7
	30 (1)	0.52	0.30	1.3	2.8	12	0.29	0.44	1.9
1c	5 (4)	0.62 ± 0.24	0.33 ± 0.13	2.8 ± 1.3	7.8 ± 2.9	65 ± 30	0.71 ± 0.06	0.91 ± 0.06	7.6 ± 1.1
	30 (1)	0.35	0.19	2.1	2.4	26	0.23	0.30	3.3
1d	5 (3)	0.63 ± 0.12	0.37 ± 0.08	2.3 ± 0.6	7.5 ± 1.5	47 ± 12	1.5 ± 0.4	2.1 ± 0.4	13 ± 3
	30 (1)	0.97	0.57	3.4	4.3	25	0.25	0.36	2.1
1e	5 (3)	0.084 ± 0.001	0.047 ± 0.011	0.10 ± 0.05	6.1 ± 0.9	13 ± 5	1.0 ± 0.1	0.60 ± 0.19	1.2 ± 0.7
	30 (1)	0.046	0.022	0.14	1.3	8.1	0.27	0.19	1.2
1f	5 (3)	1.1 ± 0.5	0.64 ± 0.31	5.3 ± 5.2	8.3 ± 4.5	69 ± 72	0.77 ± 0.24	1.1 ± 0.4	9.2 ± 7.9
	30 (2)	0.90 ± 0.14	0.50 ± 0.08	2.5 ± 0.4	5.0 ± 0.4	25 ± 2	0.34 ± 0.01	0.50 ± 0.06	2.5 ± 0.3
1g	5 (3)	0.72 ± 0.07	0.37 ± 0.03	1.0 ± 0.2	0.87 ± 0.32	2.4 ± 1.1	0.40 ± 0.04	0.46 ± 0.04	1.9 ± 0.2
	30 (1)	0.14	0.08	0.5	0.26	1.5	0.15	1.2	7.1
1h	5 (4)	1.2 ± 0.4	0.69 ± 0.22	3.6 ± 1.5	2.0 ± 0.4	12 ± 3	0.80 ± 0.47	0.66 ± 0.04	3.6 ± 0.6
	30 (1)	1.2	0.63	3.9	3.3	21	0.24	0.30	1.9
1i	5 (2)	0.61 ± 0.14	0.30 ± 0.06	3.0 ± 1.3	2.6 ± 1.1	24 ± 16	0.69 ± 0.24	0.52 ± 0.18	4.7 ± 2.9
	30 (1)	0.61	0.31	2.4	1.9	15	0.30	0.39	3.0
1l	5 (3)	0.05 ± 0.01	0.03 ± 0.01	0.3 ± 0.1	3.8 ± 1.0	34 ± 15	1.9 ± 0.2	1.8 ± 0.3	17 ± 6
	30 (1)	0.04	0.02	0.3	5.4	77	1.6	1.5	21
1m	5 (2)	3.4 ± 0.4	1.8 ± 0.1	9.0 ± 2.3	3.1 ± 0.0	16 ± 3	1.1 ± 0.3	0.8 ± 0.1	4.0 ± 1.3
	30 (3)	1.1 ± 0.4	0.55 ± 0.19	5.0 ± 3.5	1.7 ± 0.2	15 ± 7	0.28 ± 0.09	0.26 ± 0.11	2.4 ± 1.9
1n	5 (2)	0.78 ± 0.59	0.39 ± 0.30	5.6 ± 6.7	2.0 ± 0.8	29 ± 24	0.40 ± 0.26	0.35 ± 0.24	5.0 ± 5.6
	30 (3)	0.26 ± 0.15	0.13 ± 0.07	4.3 ± 1.9	1.2 ± 0.6	20 ± 17	0.20 ± 0.07	0.14 ± 0.04	2.3 ± 1.4
1o	5 (3)	0.23 ± 0.05	0.12 ± 0.03	0.24 ± 0.08	0.53 ± 0.11	1.1 ± 0.3	0.39 ± 0.10	0.34 ± 0.08	0.68 ± 0.24
	30 (1)	0.10	0.05	0.09	0.38	0.72	0.24	0.19	0.36
1q	5 (3)	0.29 ± 0.16	0.15 ± 0.08	1.3 ± 1.1	0.75 ± 0.13	6.3 ± 3.2	1.2 ± 1.5	1.1 ± 1.4	9.2 ± 15
	30 (1)	0.10	0.05	0.09	0.70	7.8	0.21	0.19	2.1
1r	5 (4)	0.64 ± 0.05	0.34 ± 0.02	4.7 ± 1.0	3.3 ± 0.9	47 ± 20	0.92 ± 0.13	0.86 ± 0.11	12 ± 3
	30 (1)	0.76	0.40	6.7	2.8	46	0.32	0.29	14
5b	5 (3)	0.30 ± 0.03	0.15 ± 0.02	0.41 ± 0.08	0.46 ± 0.02	1.2 ± 0.1	0.50 ± 0.02	0.36 ± 0.01	1.0 ± 0.1
	30 (1)	0.06	0.03	0.2	0.18	1.4	0.22	0.15	1.1

^a Number of animals used in parentheses (). ^b Calculated from percent dose per gram of organ.

Particular emphasis was placed on the high uptake of the ¹²³I in the retina and its relatively long retention there, a phenomenon we first reported for **1r** in 1978.³ The high radiation dose to the retina results from the long biological retention; the use of ¹²²I to label **1m** as we propose here will yield good PET images but will have decayed away before it can deliver an appreciable dose to the retina. Because of the possibility that **1m** could also be used for a ¹²³I-labeled radiopharmaceutical, however, we will examine its retina uptake in future studies.

Radiopharmaceuticals for imaging the heart are also of interest for study of cardiac disorders. Because the heart is essentially surrounded by lung in the human, it is important that uptake of the agent by the lung be as low as possible. Compound **1l** has a significant heart uptake, and although it has a high lung uptake as well, this compound or analogues of it may warrant further investigation for application as a cardiac imaging agent.

Experimental Section

Melting points were taken on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Beckman Acculab spectrometer. NMR spectra were obtained on a Nicolet FT-200. Distillations were carried out bulb to bulb in an Aldrich Kugelrohr oven. Microanalyses were performed either by Galbraith Laboratories, Knoxville, TN, or by the Department of Chemistry, University of California, Berkeley; they are indicated by the elements analyzed for, unless falling outside 0.4% of the theoretical values. All TLC analyses (unless otherwise noted) were performed on silica gel G plates (Brinkmann), developed with methylene chloride, and visualized by quenching of 254-nm fluorescence. HPLC assays were performed on a Waters 205 System.

Tissue Distribution Studies. Male Sprague-Dawley rats weighing 200–300 g had free access to food and water prior to administration of the radiolabeled compounds. Injections were

made in the tail veins of rats restrained in plastic holders and lightly anesthetized with ether. Bolus injections of 0.2 mL of a saline solution containing 10–20 μCi of the ¹³¹I-labeled compound were made, and the rats were sacrificed by decapitation. The organs of interest were excised immediately after sacrifice, weighed, and counted in a Searle Model 1185 gamma well counter. A calibrated external standard was prepared by serial dilution of the injected compound, and percent dose per organ of the injected amount was determined.

Blood clearance in the beagle dog was measured by serial venous sampling. Brain uptake was measured by whole-body scanning with the Anger Mark II whole-body scanner and determining radioactivity in the brain from a region of interest defined over the brain with an HP5047A data analyzer. The percent dose per gram was calculated from the events in the region of interest divided by the events in a region covering the whole body times 100, divided by an assumed brain weight of 90 g.

2,5-Diiodo-1,4-dimethoxybenzene (2a). To a solution of 6.9 g of *p*-dimethoxybenzene (50 mmol) in 50 mL of acetic acid there was added over the course of 3 min a solution of 20 g of ICl in 20 mL of acetic acid. The mixture was heated on a steam bath for 2 h and then cooled with external ice-water, resulting in the formation of a heavy steel-gray crystalline mass. This was removed by filtration, washed sparingly with cold acetic acid, and suspended in 200 mL of water. With good stirring, there was added small portions of Na₂S₂O₄ until the color of the suspended solids had changed from gray to white. This product was removed by filtration, washed with water, and when reasonably dry, recrystallized from 50 mL of boiling acetonitrile. There was thus obtained 7.1 g (36% yield) of a white product, mp 161–165 °C. An analytical sample that was recrystallized again from acetonitrile had mp 167–168 °C (lit.¹¹ mp 171 °C); NMR (CDCl₃) δ 3.82 (6 H, OCH₃), 7.19 (2 H, Ar H). Anal. (C₈H₈I₂O₂) C, H.

2-Chloro-5-iodo-1,4-dimethoxybenzene (2b). To a solution of 6.9 g of *p*-dimethoxybenzene (50 mmol) in 30 mL of CH₂Cl₂ there was added 20 g of ICl in 30 mL of CH₂Cl₂. After stirring for 1 h, the solution was held at reflux for 20 min (steam bath), cooled, and diluted with water. Solid Na₂S₂O₄ was added with

liver			kidney			blood:
% dose/total organ	% dose/g of organ	organ/blood ratio ^b	% dose/total organ	% dose/g of organ	organ/blood ratio ^b	% dose/g of organ
5.3 ± 1.5	0.76 ± 0.23	5.4 ± 2.8				0.14 ± 0.03
11 ± 1	1.8 ± 0.9	6.4 ± 5.7				0.28 ± 0.11
7.2 ± 1.0	1.1 ± 0.3	4.4 ± 2.8				0.25 ± 0.09
6.0	1.2	5.2				0.23
3.9 ± 1.0	0.55 ± 0.15	4.5 ± 1.6	2.0 ± 0.6	1.1 ± 0.3	9.2 ± 3.3	0.12 ± 0.01
8.9	0.97	11	1.7	0.77	8.6	0.09
4.6 ± 0.4	0.58 ± 0.17	5.4 ± 1.3				0.16 ± 0.01
9.4	1.6	9.4				0.17
17 ± 3	1.2 ± 0.3	2.5 ± 1.2	1.8 ± 0.1	0.58 ± 0.09	1.2	0.48 ± 0.11
7.9	0.53	3.3	0.69	0.22	1.4	0.16
4.0 ± 1.4	0.72 ± 0.31	6.0 ± 5.6				0.12 ± 0.06
5.4 ± 1.6	0.95 ± 0.22	4.7 ± 1.1				0.20 ± 0.0
12 ± 2	1.3 ± 0.3	3.6 ± 1.1	2.2 ± 0.6	1.2 ± 0.3	3.3 ± 1.1	0.36 ± 0.03
5.0	0.29	1.7	1.5	0.77	4.5	0.17
8.6 ± 2.0	1.5 ± 1.2	9.5 ± 7.1	2.5 ± 0.7	1.4 ± 0.3	6.8 ± 2.4	0.19 ± 0.02
6.6	0.72	4.5	2.1	1.2	7.5	0.16
8.4 ± 3.0	0.53 ± 0.18	4.8 ± 3.0	4.8 ± 1.3	1.5 ± 0.6	15 ± 9	0.11 ± 0.03
9.5	1.2	9.2	2.2	1.2	9.2	0.13
11 ± 3	0.66 ± 0.39	6.0 ± 4.6	57 ± 2.2	2.0 ± 0.8	16 ± 11	0.11 ± 0.02
7.7	0.55	7.8	5.7	2.0	29	0.07
16 ± 2	1.1 ± 0.1	5.5 ± 1.6	6.8 ± 1.4	2.4 ± 0.1	5.5 ± 2.9	0.20 ± 0.04
12 ± 4	0.89 ± 0.27	8.1 ± 5.4	2.4 ± 0.9	0.90 ± 0.36	8.4 ± 6.2	0.11 ± 0.04
6.0 ± 4.2	0.46 ± 0.33	5.5 ± 7.5	1.8 ± 2.1	0.69 ± 0.41	9.6 ± 10	0.07 ± 0.03
4.3 ± 2.0	0.32 ± 0.16	8.1 ± 4.4	1.1 ± 0.6	0.39 ± 0.20	6.5 ± 5.5	0.06 ± 0.02
10 ± 7	0.76 ± 0.55	1.6 ± 1.3	1.5 ± 0.2	0.53 ± 0.06	1.1 ± 0.2	0.50 ± 0.06
4.6	0.32	0.60	1.1	0.38	0.72	0.53
12 ± 7	0.80 ± 0.44	6.7 ± 5.9	1.8 ± 0.6	0.63 ± 0.16	5.3 ± 3.1	0.12 ± 0.04
7.6	0.62	6.9	1.3	0.52	5.8	0.09
5.6 ± 1.1	0.83 ± 0.85	12 ± 14	3.2 ± 0.5	1.2 ± 0.2	17 ± 5	0.07 ± 0.01
10	0.80	13	2.8	1.1	18	0.06
6.7 ± 5.8	0.91 ± 0.06	2.4 ± 0.3	3.1 ± 0.8	0.95 ± 0.16	2.0 ± 0.6	0.37 ± 0.02
5.8	0.35	2.7	1.1	0.35	2.7	0.13

good stirring until the color of the mixture had faded to a stable pale yellow. The organic phase and two 75-mL CH₂Cl₂ extracts of the aqueous phase were pooled, and the solvent was removed in vacuo to provide 15.3 g of an amber oil that partially crystallized. The addition of 30 mL of 2-propanol allowed easy filtration to provide 2.4 g of a white solid, mp 109–111 °C. The mother liquors were stripped of solvent, and the residue was distilled (0.2 mmHg) to yield a broad fraction (bp 73–95 °C) that was largely monohalogenated product and unhalogenated starting material. The pot, on cooling, spontaneously crystallized and upon recrystallization from boiling 2-propanol (4 mL/g) yielded an additional 1.0 g of white solid, mp 110–112 °C, for a total yield of **2b** of 3.4 g (23%). An analytical sample was recrystallized again from 2-propanol (mp 114–115 °C) and then from acetonitrile (mp 115–116 °C): NMR (CDCl₃) δ 3.84 (6 H, OCH₃), 6.86 (1 H, Ar H), 7.31 (1 H, Ar H). Anal. (C₈H₈ClIO₂) C, H.

4-Iodo-2,5-dimethoxybenzaldehyde (3a). To a stirred suspension of 19.6 g (50 mmol) of **2a** in 500 mL of anhydrous ether (cooled externally with ice-water) there was added 34 mL of 1.6 N butyllithium in hexane (54 mmol). After 10 min of stirring there was added 8.2 mL of *N*-methylformanilide, converting the loose white precipitate to a thick suspension. This was stirred for 10 min, then held at reflux for about 10 min, and then added to 800 mL of water acidified with HCl. Yellow solids were removed by filtration and washed with ether and acetonitrile (see below). The resulting clear mother liquors were separated, and the organic fraction was stripped in vacuo to yield, after air-drying, 17 g of a pale-yellow solid. This product was triturated under 20 mL of methanol, filtered free of solvent, air-dried (7.5 g), and finally recrystallized from 60 mL of boiling 95% ethanol to yield 5.2 g of pale-yellow crystals of **3a**: mp 136–137 °C; NMR (CDCl₃) δ 3.88 (3 H, OCH₃), 3.90 (3 H, OCH₃), 7.22 (1 H, Ar H), 7.47 (1 H, Ar H), 10.40 (1 H, CHO); IR (M.O. mull) 1675 (C=O), 1133, 1029, 969, 878, 717, 663 cm⁻¹. Anal. (C₉H₉IO₂) C, H.

The yellow insolubles obtained above (4.8 g) were ground under CH₃CN, filtered free of solvent, and recrystallized from 35 mL of boiling CH₃CN to yield 0.6 g of the yellow bisaldehyde **3c**, mp 196–200 °C with sublimation (lit.¹² mp 207 °C).

Attempts to iodinate 2,5-dimethoxybenzaldehyde in the 4-position with ICl employing the procedure in ref 13 were unsuccessful.

4-Chloro-2,5-dimethoxybenzaldehyde (3b). In a manner similar to the preparation of **3a** above, **2b** was converted to **3b**, again with the concomitant preparation of a small amount of **3c** as an impurity. The product was pale yellow, obtained in a yield of 49%, and had a mp 96–98 °C after recrystallization from methanol: NMR (CDCl₃) δ 3.90 (6 H, OCH₃), 7.07 (1 H, Ar H), 7.26 (1 H, Ar H), 10.39 (1 H, CHO); IR (M.O. mull) 1675 (C=O), 1060, 1031, 983, 880, 730 cm⁻¹. Anal. (C₉H₉ClO₂) C, H.

1-(4-Iodo-2,5-dimethoxyphenyl)-2-nitropropene (4). To a solution of 4.8 g of **3a** (16.4 mmol) in 100 mL of nitroethane was added 0.3 g of ammonium acetate, and the mixture was heated on a steam bath for 6 h. The orange-red solution was decanted from a small amount of insolubles and stripped of nitroethane in vacuo, and the residue was treated with 20 mL of boiling methanol. Crystals of **4** formed spontaneously, removed by filtration, and recrystallized from 65 mL of boiling methanol to yield 2.3 g of product: gold crystals with mp 117–118 °C; yield 40%. An analytical sample obtained by recrystallization from methanol melted at 119–120 °C. Anal. (C₁₁H₁₂INO₄) C, H, I, N.

1-(4-Iodo-2,5-dimethoxyphenyl)-2-propanone (5a). A solution of 2.1 g of **4** (6.6 mmol) in 10 mL of hot acetic acid was added to a suspension of 4 g of electrolytic iron in 20 mL of warm acetic acid. Upon heating on a steam bath, the reaction mixture became very dark, and finally there was the deposition of white solids beneath a heavy black oil. Heating was continued for 1/2 h, the reaction mixture was poured into 500 mL of water, a small amount of unreacted iron and an insoluble brown residue was removed by filtration and washed with CH₂Cl₂, and the mother liquors were separated, with the aqueous phase being extracted with an additional 2 × 75 mL of CH₂Cl₂. The organic phases were pooled, the solvent was removed in vacuo, and the residue (3.9 g of a pale amber oil) was distilled at 0.4 mmHg to yield a fraction, bp 120–130 °C, of a colorless oil (1.1 g, yield 52%) that spontaneously crystallized. Recrystallization of an analytical sample from methylcyclopentane gave white crystals: mp 62–63 °C; NMR

Table II

exchange media	temp, °C	radioyield, %
acetic acid	115	8
ammonium sulfate	115	61
pyridine	115	nil
glycerol	115	nil
acetamide	115	nil
benzyl alcohol	115	9
acetic acid	120	12
ammonium acetate	120	nil
ammonium formate	120	nil
ammonium nitrate	120	17
3,4-dimethoxyphenylacetic acid	120	12
ammonium sulfate	140	56
acetic acid	140	70

Table III

compd no. ^a	radioyield, %	TLC R_f	radiopurity, %
1a	9	0.32	98
1b	5	0.53	69
1c	21	0.21	91
1d	3	0.75	83
1e	10	0.91	94
1f	2	0.81	93
1g	12	0.89	85
1h	32	0.75-0.85	85
1i	4	0.30	62
1j	2		<i>b</i>
1k	2		60
1l	60	0.14	95
1m	13	<i>c, d</i>	
1n	13	<i>c, d</i>	
1o	3	0.90	81
1p	2	0.8-0.9	50
1q	20	0.85	48

^a See Scheme I for structure. ^b Not determined. ^c Prepared by iodination of the preformed amine (see Experimental Section). ^d The reductive aminations employing dimethylamine (to yield 1m), diethylamine (to yield 1n), and β -methoxyethylamine (to yield the corresponding *N*-2-methoxyethyl) analogue of 1) all displayed multiple spots.

(CDCl₃) δ 2.13 (3 H, COCH₃), 3.62 (2 H, CH₂CO), 3.74 (3 H, OCH₃), 3.79 (3 H, OCH₃), 6.60 (1 H, Ar H), 7.23 (1 H, Ar H). Anal. (C₁₁H₁₃IO₃) C, H, I.

1-(4-[¹³¹I]iodo-2,5-dimethoxyphenyl)-2-propanone (5b). Several procedures were evaluated for the exchange of ¹³¹I⁻ for the aromatically bound iodine in 5a (Table II). ¹³¹I was employed in this evaluation, as neither speed nor high specific activity (the considerations associated with ¹²²I) were important. A mixture of 5 mg of 5a in 50 mg of the medium being evaluated was treated with 1 μ L (0.02 mCi) of a dilute NaOH solution of no-carrier added Na⁺¹³¹I⁻ (New England Nuclear) in a ground glass stoppered vial and heated to the temperature indicated for 10 min. The percentage incorporation was determined by performing a TLC analysis of a CH₂Cl₂ extraction of the product of the exchange, cleaned up by preliminary washing with both dilute acid and base. The inorganic iodide had an R_f of 0.00 and proved to be greater than 99% radiopure. The R_f of 5 is 0.33. The radioactivity of the UV-quenching spot at this R_f , compared to the remainder of the plate, gave measure of the radioyield of the procedure. The results are tabulated in Table II. The actual high-level exchange runs were performed in acetic acid, at 140 °C, for 10 min, employing 10–20-mCi quantities of Na¹³¹I. Final radiopurity was attained by preparative TLC of the entire exchange product, with the desired band being removed and the actual silica gel scrapings being employed in subsequent reductive amination procedures. The crude exchange product from this process averaged 74% radiopurity, with an average radioyield of 73%. Rechromatography of 5b following preparative purification showed radiopurity in excess of 90%.

N,N-Disubstituted 2-(4-[¹³¹I]iodo-2,5-dimethoxyphenyl)-isopropylamine (1). In a 1-mL ground glass vial there were placed approximately 1 mCi of 5b (suspended on silica gel), 50

mg of the amine R¹R²NH hydrochloride in 0.2 mL of methanol, and approximately 50 mg of NaCNBH₃. The slurry was shaken occasionally over a period of 3 days. The reaction product was partitioned between CH₂Cl₂ and dilute sulfuric acid, the aqueous phase was made basic with dilute sodium hydroxide and reextracted with CH₂Cl₂, and the solvent was removed with a stream of warm dry nitrogen. The radioyield was determined by direct counting of the reaction product before and after purification, and the radiopurity was determined by TLC assay of the purified base fraction on silica gel, employing the solvent system ethyl acetate/methanol/ammonium hydroxide in a 34:4:1, v/v, ratio. These results are tabulated in Table III.

N,N-Dimethyl-2-(2,5-dimethoxyphenyl)isopropylamine (7). A solution of 4.6 g of 1-(2,5-dimethoxyphenyl)-2-propanone (prepared from 2,5-dimethoxybenzaldehyde via the nitrostyrene intermediate and reduction with elemental iron as described for 5a above) in 100 mL of methanol was treated with 15 g of dimethylamine hydrochloride, followed by 2.0 g of NaCNBH₃. The reaction was stirred at room temperature, and concentrated HCl was added as needed to maintain the pH at about 6. When the pH was stable, the volatiles were removed on the rotary evaporator, and the residues were suspended in dilute sulfuric acid. This was extracted several times with CH₂Cl₂, made basic with 25% NaOH, and reextracted with 3 \times 75 mL of CH₂Cl₂. These latter extracts were pooled, the solvent was removed in vacuo, and the residue was distilled [80–100 °C (0.25 mmHg)] to yield 1.5 g of a colorless oil. To a solution of 1.35 g of this oil in 7 mL of 2-propanol there was added a solution of 0.77 g of oxalic acid dihydrate in 10 mL of methanol, followed by 150 mL of ether. There resulted 1.38 g of white granular crystals: mp 133–134 °C; NMR (D₂O) δ 1.29 (d, 3 H, CH₃CH), 2.95 [6 H, (CH₃)₂N], 3.23 (q, 2 H, CH₂), 3.80 (multiplet, 1 H, CHCH₃), 3.86 (3 H, OCH₃), 3.91 (3 H, OCH₃), 7.05 (complex pattern, 3 H, Ar H). Anal. (C₁₅H₂₃NO₆) C, H.

N,N-Dimethyl-2-(4-iodo-2,5-dimethoxyphenyl)isopropylamine (1m, Nonradioactive Form, from 1r). A solution of 0.4 g of 1r as the hydrochloride salt (see ref 2) in 12 mL of methanol and 4 mL of 40% CH₂O was stirred magnetically and treated with 1 g of NaCNBH₃. Concentrated HCl was added periodically to maintain the pH at about 6. After 48 h, the reaction mixture was poured into 250 mL of water, made strongly basic, and extracted with 3 \times 75 mL of CH₂Cl₂. The extracts were pooled and extracted with 2 \times 75 mL of dilute H₂SO₄, and the extract, after pooling and being made basic (4 N NaOH), was again extracted with CH₂Cl₂. Removal of the solvent yielded 0.38 g of a colorless oil, which was dissolved in 2 mL of 2-propanol and treated with a warm solution of 0.13 g of oxalic acid dihydrate in 1.5 mL of 2-propanol and then with ether dropwise until there was a persistent turbidity. Continued stirring allowed the development of a granular white product, which was removed by filtration, washed with ether, and air-dried: weight 0.38 g; mp 145–146 °C with prior sintering at 133 °C; mp with 7 oxalate (mp 133–134 °C) 120–129 °C. The hydrochloride of 1m was hygroscopic: NMR (D₂O) δ 1.27 (d, 3 H, CH₃CH), 2.95 [6 H, (CH₃)₂N], 3.23 (q, 2 H, CH₂), 3.80 (multiplet, 1 H, CHCH₃), 3.84 (3 H, OCH₃), 3.89 (3 H, OCH₃), 6.93 (1 H, Ar H), 7.40 (1 H, Ar H). Anal. (C₁₅H₂₂INO₆) C, H. The radioactive samples were prepared by direct iodination of 7 (see below).

N,N-Dimethyl-2-(4-[¹³¹I]iodo-2,5-dimethoxyphenyl)isopropylamine (1m, Radioactive Form, from 7). A solution of 10 μ g of 7 in 0.5 mL of HOAc containing 50 mg of 70% HClO₄ was treated with 100 μ L of acetic acid containing 10 μ g of ¹³¹ICl. This ICl solution resulted from the addition of an appropriate amount of no carrier added Na¹³¹I in aqueous NaOH to 10 μ g of cold ICl in acetic acid. The mixture was heated to the boil with an open flame (ca. 10 s) and then added directly to 10 mL of water containing a trace of Na₂S₂O₄. Sufficient NaOH was added to make the mixture basic (pH >9) and there was added 1 mL of cyclohexane. After vigorous agitation, a small portion of the separated cyclohexane layer was removed for both chemical and radiochemical analysis. These were performed by analytical HPLC employing both a UV (254 nm) and a radioactivity detector. The column employed was an Altex silica 5- μ m 25-cm unit, and the eluting solvent was cyclohexane containing 0.5% (v/v) 2-methoxyethylamine. Typical separations of 7 and 1m were 5.57 and 7.42 min, with complete base line separation between peaks

and a void volume at 1.42 min. With the above concentrations, the radiopurity and chemical purity were consistently in excess of 90%, and the radioincorporation efficiency was in the 30 to 40% range. The reaction gave similar results at 10 and 100 times these concentrations, but at one-tenth this concentration the yields were drastically reduced.

Iodination of 7 to form 1m and the direct synthesis of 1m, when performed with ^{131}I Cl in acetic acid but in the absence of perchloric acid, resulted in a maximum radioincorporation of 12%.

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Registry No. 1a, 90064-53-2; 1b, 90064-54-3; 1c, 90064-55-4; 1d, 90064-56-5; 1e, 90064-57-6; 1f, 90064-58-7; 1g, 90064-59-8; 1h,

90064-60-1; 1i, 90064-61-2; 1k, 90064-67-8; 1l, 90064-62-3; 1m (unlabeled), 85563-10-6; 1m.HCl (unlabeled), 90064-51-0; 1n, 90064-52-1; 1o, 90064-63-4; 1p, 90083-18-4; 1q, 90064-65-6; 1r.HCl (unlabeled), 42203-78-1; 1r, 65756-98-1; 2a, 51560-21-5; 2b, 90064-46-3; 3a, 90064-47-4; 3b, 90064-48-5; 3c, 7310-97-6; 4, 90064-44-1; 5a, 90064-49-6; 5b, 90064-50-9; 6, 14293-24-4; 7, 67707-78-2; 7-oxalate, 90064-45-2; *p*-dimethoxybenzene, 150-78-7; *N*-methylformanilide, 93-61-8; methanamine hydrochloride, 593-51-1; isopropylamine hydrochloride, 15572-56-2; cyclopropanemethanamine hydrochloride, 7252-53-1; hexanamine hydrochloride, 142-81-4; dodecanamine hydrochloride, 929-73-7; benzenemethanamine hydrochloride, 3287-99-8; hydrazine hydrochloride, 14011-37-1; hydroxylamine hydrochloride, 5470-11-1; aminoacetonitrile hydrochloride, 6011-14-9; 2-thioethanamine hydrochloride, 156-57-0; 2-methoxyethanamine hydrochloride, 18600-40-3; *N,N*-dimethyl-1,3-propanediamine hydrochloride, 77642-45-6; diethylamine hydrochloride, 660-68-4; *N*-methyl-2-propanamine hydrochloride, 54565-61-6; *N*-methylhexanamine hydrochloride, 42870-70-2; *N*-methylbenzenemethanamine hydrochloride, 13426-94-3; dimethylamine hydrochloride, 506-59-2.

Antihypertensives. *N*-1*H*-Pyrrol-1-yl-3-pyridazinamines

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The hypothesis that the side effects of hydralazine, such as mutagenicity and lupus erythematosus like syndrome, might be due to the NHNH_2 group prompted us to incorporate part of this moiety into a pyrrole ring. Therefore, we prepared a series of *N*-1*H*-pyrrol-1-yl-3-pyridazinamines and a limited number of *N*-1*H*-pyrrol-1-yl-1-phthalazinamines by reaction of 3-hydrazinopyridazines and 1-hydrazinophthalazines with γ -diketones. Most of these compounds, especially in the pyridazine series, showed moderate to strong antihypertensive activity in spontaneously hypertensive rats. The decrease in blood pressure generally had a slow onset after either oral or intravenous administration. *N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-6-(4-morpholinyl)-3-pyridazinamine hydrochloride (30) (MDL 899) showed no mutagenic activity in several tests and is now in clinical trials in patients.

The pathogenesis of hydralazine-induced lupus erythematosus has been correlated with its rate of hepatic acetylation.¹ With the discovery of a novel urinary hydralazine metabolite in man, namely, 3-(hydroxymethyl)-s-triazolo[3,4-*a*]phthalazine, the hypothesis was advanced² that the functional alcoholic group might provide a handle for the formation of a covalent bond to a protein and, thus, to production of antibodies to the metabolite. The recently discovered mutagenic activity of hydralazine^{3,4} could also be explained by the reactivity of the molecule itself. In particular, the high reactivity of the hydrazine moiety NHNH_2 for carbonyl groups might cause other chemical modifications, resulting in toxic effects. This hypothesis prompted us to incorporate the terminal NH_2 group of some antihypertensive 3-hydrazinopyridazines into a pyrrole ring. Therefore, we prepared a few *N*-1*H*-pyrrol-1-yl-3-pyridazinamines (VI, Scheme II) and tested them for their hypotensive and mutagenic activity. The discovery that three compounds (29-31) endowed with good antihypertensive activity were not mutagenic led us to develop this class. Some compounds having a phthalazine moiety instead of pyridazine were also prepared.

Chemistry. The last intermediates for the preparation of VI are hydrazino derivatives of general formula V (Table

III)(Scheme I), where R represents a tertiary amino group. References^{5,8} for those compounds already known are in Table IV. The new analogues were prepared starting from 3,6-dichloropyridazines I, which were reacted with secondary amines in the presence (method A) or absence (method B) of a solvent, to give 3-amino-6-chloropyridazines II (Table I). The substitution of the chlorine atom with hydrazine to give V was achieved by one of the following three procedures. In the first procedure, reaction with hydrazine hydrate as a solvent (method F, $\text{R}_1 = \text{H}$) was found to be useful only when the final product had a relatively low water solubility. In most cases, the isolation of V as the hydrochloride involved troublesome crystallizations in order to satisfactorily eliminate hydrazine hydrochloride, and the final yields were generally very low. In some cases, after elimination of the hydrazine hydrate, the residues containing the compounds V were used as such for the synthesis of VI. In the second procedure, compounds V were isolated as the benzaldehydes III (Table II), which were easily hydrolyzed in dilute mineral acids when concomitant steam distillation of the benzaldehyde was carried out (methods C and E). In the third procedure, the hydrochlorides of II were reacted with *tert*-butyl carbazate in methylcellosolve, and after mild hydrolysis of the *tert*-butyl esters, the compounds V were isolated as the hydrazones III (method D). One compound, V-24, with a methyl on the hydrazino group ($\text{R}_1 = \text{CH}_3$) was prepared by methylation of the corresponding acetaldehyde hydrazone III-15, followed by hydrolysis of the resulting compound IV. The correct position of the R_1 methyl group was demonstrated by catalytic reduction to the aminopyridazine XI. The new intermediates V are reported in Table III.

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