(3) (a) W. I. Howland, J. L. Curry, and A. K. Butler, *Radiology*, **80**, 489 (1963). (b) Metrizamide: *Acta Radiol., Suppl.*, **335**, 3 (1973).
(4) J. H. Lang and E. C. Lasser, *J. Med. Chem.*, **14**, 233 (1971).
(5) M. Sovak, B. Nahlovsky, J. H. Lang, and E. C. Lasser, *Radiology*, in press.
(6) (a) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases", Wiley, New York, N.Y., 1962, Chapter 2; (b) p 66; (c) p 130.
(7) H. Cassebaum and K. Kierback, *Pharmazie*, **21** (3), 167–170 (1966); *Chem. Abstr.*, **67**, 538505 (1967).
(8) J. B. Cohen and D. McCandlish, *J. Chem. Soc.*, 1266 (1905).
(9) It is not presently known which of the three possible diiodo isomers we have reported here. Nevertheless, this derivative served to substantiate the amine HCl structure.
(10) Contaminated with 5–10% acetylated glucose carried over from the glucosidation reaction.
(11) For a review, see H. K. Porter, *Org. React.*, **20**, 455 (1973).
(12) E. Glaser and W. Wulwek, *Biochem. Z.*, **145**, 514 (1924).
(13) F. E. Smith, French Patent 2150805; *Chem. Abstr.*, **80**, 112687 (1974).
(14) C. Hansch, *Farmaco, Ed. Sci.*, **23**, 293 (1968).
(15) "Handbook of Chemistry and Physics", 55th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, p D-129.

Radiopharmaceuticals. 16. Halogenated Dopamine Analogs. Synthesis and Radiolabeling of 6-Iododopamine and Tissue Distribution Studies in Animals[1]

J. S. Fowler,* R. R. MacGregor, A. P. Wolf,

Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973

A. N. Ansari, and H. L. Atkins

Medical Department, Brookhaven National Laboratory, Upton, New York 11973. *Received September 22, 1975*

A simple halogenated derivative of dopamine, 6-iododopamine (1), has been synthesized using two different methods. These synthetic sequences have been applied to the radiolabeling of 1 with carbon-11, iodine-131, and iodine-123. The tissue distribution of 1 in mice, dogs, and rats was determined. The ratio of radioactivity (%/g) in the adrenal medulla–kidney in dogs increases from 3.45 at 2 h postinjection to 33.3 at 24 h postinjection. Thyroid uptakes in mice, dogs, and rats show that in vivo deiodination of 1 is not significant.

Dopamine (3,4-dihydroxyphenethylamine) functions as a neurotransmitter and also as a precursor for norepinephrine, one of the adrenal medullary hormones. We and others have devoted considerable effort to labeling dopamine as well as biogenic amine analogs with nuclides which decay by emission of radiation which can be detected outside the body barrier in the search for a radiopharmaceutical which would allow external visualization of the adrenal medulla and abnormalities associated with adrenal medullary tissue.[2-4]

We have initiated a program to develop synthetic methods leading to simple halogenated analogs of dopamine which can be labeled with halogen or carbon isotopes. The purpose of this work is to develop the synthetic capabilities for varying the physical half-life of a molecule by labeling with nuclides of different half-lives while attempting to retain the desirable biological properties of the natural molecule. Such research into analog synthesis and subsequent biological evaluation has important implications in the study of structure–biological/biochemical activity relationships. It is also useful to be able to modify a radiopharmaceutical by incorporating a radiohalogen or radiocarbon which has decay properties ideal for the particular study.

We have reported a method for labeling of dopamine with carbon-11 ($t_{1/2}$ = 20.4 min) previously.[2a] The first analog to dopamine which we have prepared and studied was ^{18}F-labeled 6-fluorodopamine.[3] The simple halogenated analogs of dopamine which retain the unperturbed catecholamine nucleus had not been previously synthesized in labeled or unlabeled form. We describe here (1) the preparation and characterization of 6-iododopamine (3,4-dihydroxy-6-iodophenylethylamine, **1**) using two different synthetic sequences; (2) the labeling of 6-iododopamine with carbon-11 (carrier-free) and iodine-131 (and iodine-123); and (3) the tissue distribution of C-11 and radioiodine labeled iododopamine in animals.

Chemistry. The synthetic sequences used in the synthesis of 6-iododopamine are shown in Scheme I. The two different routes were developed in order to incorporate the readily available forms of radioactive carbon and radioactive iodine into 6-iododopamine efficiently.

The commercial availability of isotopic carbon in the form of cyanide ($K^{14}C{\equiv}N$, $K^{13}C{\equiv}N$) and the ready availability of ^{11}C-labeled hydrogen cyanide to institutions which have access to a cyclotron should make radiocarbon labeled iododopamine in exceedingly high specific activity available for basic and clinical research using method A. The chemical form of radioactive iodine isotopes commercially available is most commonly sodium iodide. Method B uses molecular iodine which is readily available from radioactive sodium iodide as described in the Experimental Section. The reactions used here are straightforward and in the case of method A the entire sequence can be carried out in <60 min which is necessary with the short-lived carbon-11.

While **1** was reasonably stable in aqueous solution, removal of the water resulted in a residue which rapidly discolored and hence precluded its isolation as a crystalline solid. However, the (1) NMR spectral data, (2) thin-layer chromatograms, (3) radiolabeling of **1** with two different nuclides with chemical and radiochemical identification of products as well as all intermediate compounds, (4) independent synthesis of **1** via an alternate route, and (5) formation of a derivative (**10**) all verify the formation of **1**·HBr.

6-Iododopamine was synthesized by two independent methods (Scheme I). Demethylation of **5** with BBr_3,[5] which is essential since HI causes extensive deiodination, resulted in the formation of colorless, hygroscopic powder. On the basis of the known formation of tetrahalogenoborates from amines and boron trihalides[6] as well as the formation of bromoboronates[7] from the interaction of catechols with boron tribromide, we have tentatively assigned structure **9** to this compound. Compound **9** would be predicted to hydrolyze to **1**·HBr.[7] The addition of water

Table I. Tissue Distribution of [^{131}I]- and [^{123}I]-6-Iododopamine at Various Time Intervals in Mice (% Dose/Organ ± SD)[a]

Sacrifice time, min	No. of animals	Adrenals	Kidneys	Liver	Thyroid	Blood (%/g)
5	3	0.030 ± 0.005	8.03 ± 0.57	7.1 ± 0.5	0.094 ± 0.012	4.28 ± 0.51
15	3	0.015 ± 0.002	3.44 ± 0.081	3.64 ± 0.07	0.067 ± 0.017	1.52 ± 0.11
30	10	0.014 ± 0.001	1.69 ± 0.21	2.40 ± 0.52	0.084 ± 0.012	1.11 ± 0.08
60	4	0.0087 ± 0.0005	1.00 ± 0.23	1.04 ± 0.01	0.066 ± 0.014	0.50 ± 0.04
120	4	0.020 ± 0.002	0.78 ± 0.14	0.84 ± 0.05	0.176 ± 0.061	0.35 ± 0.03
240	4	0.012 ± 0.002	0.79 ± 0.25	0.94 ± 0.36	0.158 ± 0.028	0.162 ± 0.016

[a] Loading dose, 8–11 × 10^{-8} mol/mouse.

Table II. Tissue Distribution of Radioiodine Labeled 6-Iododopamine in Dogs[a]

Sacrifice time, hr	Blood	Liver	Kidney	Adrenal medulla	Adrenal cortex	Thyroid
			% Dose/Gram			
2	0.023	0.0042	0.0081	0.028	0.0045	0.020
24	0.0002	0.00063	0.00063	0.021	0.003	0.35
			% Dose/Organ			
2		2.24	0.77	0.0062	0.0092	0.026
24		0.48	0.075	0.0021	0.0104	0.48

[a] The values are given for one dog at each time period. Loading dose, 1.29 × 10^{-6} mol/dog.

Table III. Tissue Distribution of [^{131}I]-6-Iododopamine at Various Time Intervals in Rats (% Dose/Organ ± SD of Four Rats)[a]

Sacrifice time	Adrenal medulla	Adrenal cortex	Liver	Kidneys	Thyroid	Blood (%/g)
5 min	0.0247 ± 0.0026	0.0098 ± 0.0017	4.58 ± 0.48	3.55 ± 0.65	0.029 ± 0.005	0.66 ± 0.09
30 min	0.0138 ± 0.0021	0.0062 ± 0.0005	2.36 ± 0.22	2.37 ± 0.28	0.062 ± 0.007	0.48 ± 0.06
60 min	0.0038 ± 0.0013	0.0070 ± 0.0003	0.67 ± 0.04	0.72 ± 0.03	0.080 ± 0.005	0.131 ± 0.007
2 h	0.0035 ± 0.0007	0.0028 ± 0.0013	0.33 ± 0.04	0.168 ± 0.008	0.183 ± 0.009	0.052 ± 0.002
4 h	0.0047 ± 0.0008	0.002 ± 0.001	0.265 ± 0.023	0.194 ± 0.029	0.251 ± 0.022	0.055 ± 0.006
24 h	0.0021 ± 0.0002	0.000081 ± 0.000004	0.072 ± 0.006	0.024 ± 0.002	0.65 ± 0.12	0.0062 ± 0.0004

[a] Loading dose, 3.6 × 10^{-8} mol/rat.

(D_2O) to **9** resulted in a solution whose NMR spectrum showed the absence of $-OCH_3$ signals and singlets at δ 6.92 and 7.40 due to the two uncoupled ring protons and a multiplet at δ 2.88–3.36 corresponding to the four protons of the $-CH_2CH_2-$ grouping. Thin-layer chromatography showed one compound which was ninhydrin active indicating the presence of an amine group and ferric chloride–potassium ferricyanide active indicating the catechol moiety. Acetylation of **1** in aqueous solution was carried out according to a procedure often used in the separation of catecholamines from urine or tissue extracts[8] and yielded the triacetylated derivative (**10**) of 6-iododopamine which was characterized (Scheme I). Verification of the formation of **1**·HBr was also obtained by an independent synthesis via the reduction of 3,4-dihydroxy-6-iodophenylacetonitrile (**8**) as shown in Scheme I. A comparison of the NMR spectrum and thin-layer chromatograms of this product showed that it was identical with that formed by the BBr_3 cleavage of **5**. These data are consistent with the formation of **1**·HBr. The NMR spectrum of **1**·HBr was monitored for 3 days and showed no changes. The color of the solution changed slightly, and after 1 day the thin-layer chromatogram showed tailing indicating some decomposition. Although the solution appeared to be stable for several hours, the radiopharmaceutical was used for animal experiments within 30 min after its preparation.

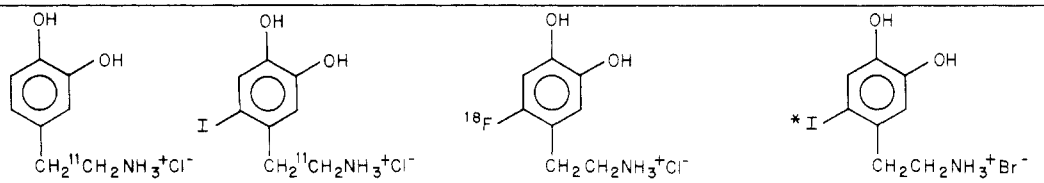
The stability of **1**·HBr in aqueous solution as determined from its NMR spectrum and TLC data certainly appears to be sufficient to allow studies in vivo provided that the solution is injected within a short time period after its preparation. It is well known that an aqueous solution of dopamine itself discolors within a few hours and yet it is used successfully in animal experiments since it is rapidly distributed to amine storage vesicles where it is protected from oxidation. The fate of **1**·HBr in vivo depends on its ability to function as an analog to dopamine. If it is analogous to dopamine in its behavior, one would predict that it would be rapidly presented to organs in vivo depending on the percent of the cardiac output received by the organ and then stored in the organs rich in amine storage vesicles such as the adrenal medulla.[9] The portion of the material remaining in the circulation would be predicted to be enzymatically degraded similarly to the catecholamines.

Radiolabeling of 6-iododopamine with carbon-11 and iodine-131 and iodine-123 was carried out according to Scheme I and the radiochemical as well as the chemical integrity of each intermediate compound as well as the product was confirmed during the syntheses. Since there is not a purification step subsequent to cleavage with BBr_3, the solution of **1** produced by the addition of water to **9** would contain boric acid in a 2:1 molar ratio. Since boric acid is a relatively nontoxic material (LD_{50} = 3 g/kg in rats)[10] no attempt was made to remove it from the final product.

The carbon-11 labeled 6-iododopamine is virtually carrier-free.[11] However, the radioiodine labeled 6-iododopamine, since its synthesis requires the use of molecular iodine, is not carrier-free. The procedure described in the Experimental Section results in the production of 1.29 × 10^{-6} mol of radiolabeled 6-iododopamine. Using 9 mCi of ^{131}I-labeled sodium iodide we have synthesized ^{131}I-labeled 6-iododopamine having a specific activity of 1.6 mCi/1.29 × 10^{-6} mol.

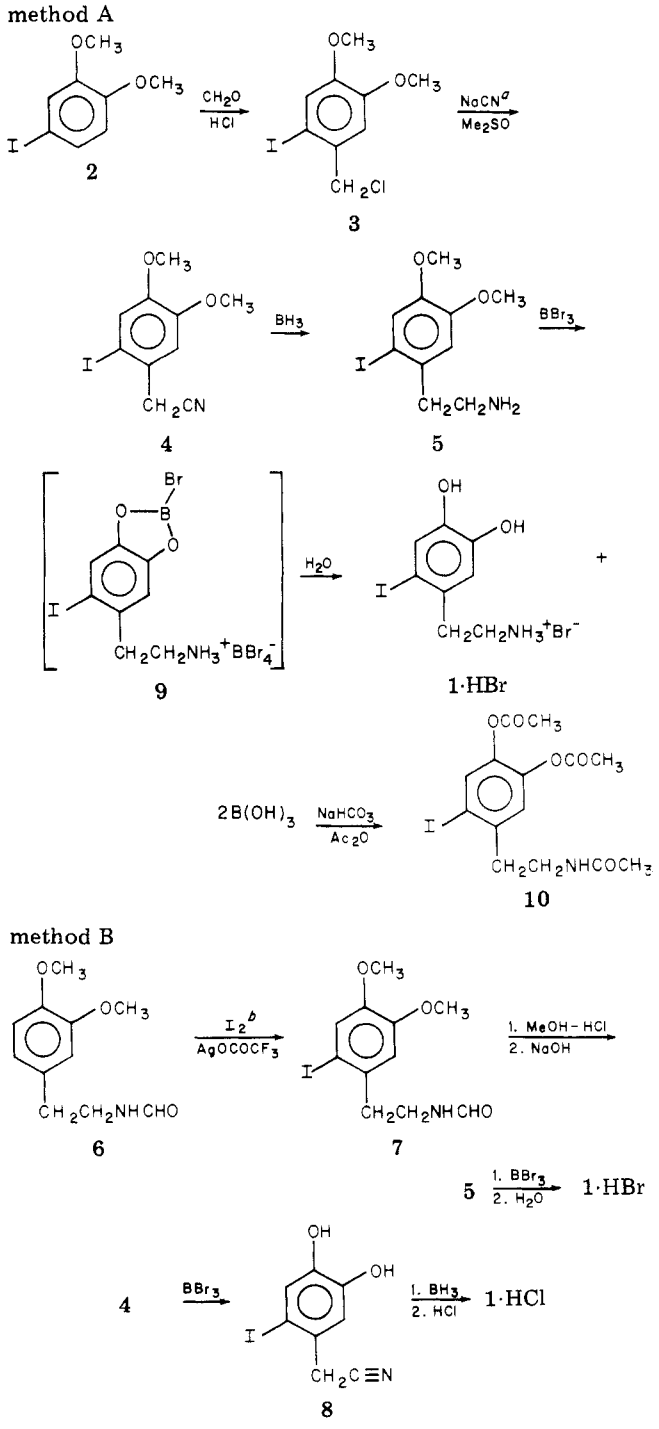
Tissue Distribution Studies. Animal experiments were run with either [^{123}I]- or [^{131}I]-6-iododopamine depending on isotope availability. The tissue distribution as a function of time with [^{131}I]- and [^{123}I]-6-iododopamine in mice, dogs, and rats is shown in Tables I–III. A comparison of the distribution of ^{11}C-labeled and radio-

Table IV. Summary of the Decay Modes of Labeled Dopamine and Labeled Dopamine Analogs



Isotope	Carbon-11	Fluorine-18	Iodine-123	Iodine-131
Half-life	20.4 min	110 min	13.3 h	8 days
Decay mode	β^+	β^+	159 keV γ (83%)	364 keV γ

Scheme I



[a] Isotopic carbon introduced at this point with Na*CN. [b] Isotopic iodine introduced at this point with Na*I.

iodine labeled 6-iododopamine in mice showed no significant differences at 5-, 15-, and 30-min sacrifice times even though the loading doses were different (8–11 × 10^{-8} mol/mouse for radioiodine labeled 6-iododopamine and 5 × 10^{-11} mol/mouse for carbon-11 labeled 6-iododopamine).

Since our primary interest in radioiodinated 6-iododopamine is to evaluate it as an imaging agent for the adrenal medulla, we studied the relative uptakes of radioactivity by the adrenals and the kidneys as a function of time. Ideally, the radioactivity should remain constant in the adrenals and clear from the nearest interfering organ, the kidney. As can be seen from Table II the ratio of adrenal medulla–kidney (%/g) in dogs increases from 3.45 at 2 h to 33.3 at 24 h. Although the concentration of radioactivity in the adrenal medulla remains constant over a 24-h time period, the uptake is probably not high enough to allow imaging. We found a marked increase in uptake in the adrenal medulla with carbon-11 labeled dopamine when "carrier-free" radiopharmaceutical was used. By analogy, carrier-free radioiodine labeled dopamine may be useful as a scanning agent.

In vivo deiodination is a problem associated with many radioiodinated pharmaceuticals.[4,12] To assess the extent to which deiodination occurs in animals with radioiodinated 1, the radioactivity localized in the thyroid of mice, dogs, and rats as a function of time was measured (Tables I–III). The values for mice in Table I show a value of 0.158% per organ at 4 h. The thyroid uptake (%/organ) for two dogs sacrificed at 2 and 24 h is 0.026 and 0.48%. Studies with rats showed 0.65% of the radioactivity to be concentrated in the thyroid at 24 h. Thus our preliminary results in mice and dogs show that in vivo deiodination is a minor metabolic pathway for 6-iododopamine. Pretreatment of animals with thyroid blocking agents was not tried since thyroid uptake was used as a measure of in vivo deiodination.

Discussion

The two synthetic sequences described involve a series of rapid reactions and are ideal for labeling with short-lived nuclides. Since carbon-11 labeled 6-iododopamine can be produced in exceedingly high specific activity,[11] this material would be useful in studies where the chemical loading dose is important or when a very high specific activity material is required.[13]

Table IV shows the interrelation of labeled dopamine and labeled dopamine analogs and lists the pertinent radioactive properties of each compound. It can be seen that the radioactive properties of these compounds vary widely. Thus assuming similar or identical biological behavior, it is possible to vary the "half-life" (relative to half-life of incorporated isotope) of a compound over a wide range and, in effect, to tailor its properties for use in clinical applications in nuclear medicine to suit the diagnostic procedure in question. For example, if shelf life is a problem, then radioiodinated dopamine can be used; if serial studies of short duration are necessary then ^{11}C- or ^{18}F-labeled dopamine can be used.

Although the immediate purpose of this study was to

explore catecholamine analogs which show specificity for the adrenal medulla, it should be noted that 6-iododopamine, while retaining the structural features of natural dopamine, possesses rather large steric perturbation caused by the iodine substituent ortho to the ethylamine side chain. A study of the biological activity of this molecule as well as its ability to function as a substrate for various enzymes involved in catecholamine metabolism would be of interest in evaluating the importance of this part of the molecule to its interaction with the various enzymes involved in catecholamine metabolism.

Experimental Section

Melting points are uncorrected. NMR spectra were obtained on a JEOL MH-100 spectrophotometer and use Me_4Si as an internal standard. NMR spectra in D_2O use sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. Mass spectra were run on a Hitachi Perkin-Elmer RMU 7. Analyses were carried out by Schwarzkopf Microanalytical Laboratories.

3,4-Dimethoxy-6-iodobenzyl Chloride (3). To 2 g (0.00843 mol) of 4-iodoveratrole[14] was added 1.5 ml of 37% formalin solution. HCl gas was passed through the reaction mixture until it solidified (ca. 30 min). Recrystallization from CCl_4–ether gave 1.2 g of **3** in 45% yield: mp 86–88°; NMR ($CDCl_3$) 6 H at δ 3.84 (s), 2 H at δ 4.60 (s), 1 H at δ 6.95 (s), 1 H at δ 7.20 (s). Anal. ($C_9H_{10}ClIO_2$) C, H.

3,4-Dimethoxy-6-iodophenylacetonitrile (4). To 0.8 g (0.00255 mol) of **3** in 5 ml of Me_2SO was added 0.24 g (0.0049 mol) of sodium cyanide and the reaction mixture was heated at 120° with stirring for 15 min. After reaction, 5 ml of H_2O was added and the precipitated solid filtered, washed with water, and dried. The solid was dissolved in CCl_4, treated with decolorizing carbon, and evaporated to give 0.32 g of **4** in 41% yield: mp 111–115°. Recrystallization from ethanol–ether gave the analytical sample: mp 116–117°; NMR ($CDCl_3$) 2 H at δ 3.74 (s), 3 H at δ 3.84 (s), 3 H at δ 3.86 (s), 1 H at δ 6.96 (s), 1 H at δ 7.22 (s); ir (KBr) 4.5 (nitrile). Anal. ($C_{10}H_{10}INO_2$) C, H.

3,4-Dimethoxy-6-iodophenylethylamine Hydrochloride (5·HCl). To 0.075 g (2.47×10^{-4} mol) of **4** in 0.5 ml of THF was added 2.3 ml of borane solution (Alfa, 1.1 M in THF). This was allowed to stand for a few minutes at 25°, the solvent removed with a stream of N_2, and 0.8 ml of 3 M HCl added. This was extracted with ether and 0.8 ml of 10 M NaOH added to the HCl layer. The reaction mixture was extracted with ether. The ether extracts were dried (K_2CO_3) and purged with dry HCl. The resulting solid was recrystallized from ethanol–ether to give 0.034 g of **5**·HCl in 39% yield: mp >250°; NMR (D_2O) 4 H at δ 2.76–3.48 (m), 3 H at δ 3.84 (s), 3 H at δ 3.88 (s), 1 H at δ 6.96 (s), and 1 H at δ 7.34 (s); λ_{max} (1 N HCl) 284 nm (ε 3934). Anal. ($C_{10}H_{15}ClINO_2$) C, H, N.

3,4-Dihydroxy-6-iodophenylethylamine Hydrobromide (1·HBr). To 0.021 g (6.8×10^{-5} mol) of **5** in 0.1 ml of CH_2Cl_2 was added 0.5 ml of a 10% BBr_3–CH_2Cl_2 solution. This was allowed to stand at 25° for 10 min and blown to dryness to leave 0.023 g (48%) of a white powder presumed to be **9**. This became tan and gummy on exposure to air. A uv spectrum of the weighed sample of the white powder in water showed a λ_{max} at 287 nm and an approximate molecular weight of 692 assuming $\epsilon \simeq 3900$ (based on ε 3892 for **8**). This corresponds approximately to **9** (mol wt 699). An ir of this material was run immediately after removal of solvent: ir (KBr) 3.4 (s, broad), 6.9 (s, broad), 7.9 (w, broad), 8.42 (s, broad), 8.42 (s, broad), 12.50 (w, broad), 15.50 (w, broad), 18.52 (w, broad). The remainder of the material was dissolved in D_2O and the TLC (silica G, 15:3:5 BuOH–HOAc–H_2O) showed one spot (uv active) with R_f 0.65 and which stains prussian blue with $K_3Fe(CN)_6$–$FeCl_3$ reagent and rose gray with ninhydrin reagent; NMR (D_2O + DSS) showed 4 H at δ 2.88–3.36 (m), 1 H at δ 6.92 (s), and 1 H at δ 7.40 (s). The NMR spectrum of the solution was monitored for over a 3-day period and showed no changes although a faint color developed. On evaporation of the water the residue rapidly turned brown.

3,4-Dihydroxy-6-iodophenylethylamine-*1*-^{11}C Hydrobromide. [^{11}C]Hydrogen cyanide[15] was trapped in 0.2 ml of 0.05 M NaOH (1.0×10^{-5} mol) and the resulting solution evaporated to dryness. To this was added 0.025 ml of H_2O and 0.0031 mg of **3** in 0.1 ml of CH_3CN. This was heated for 5 min at 90° and evaporated to dryness at 25°. After addition of 0.1 ml of H_2O the reaction mixture was extracted four times with ether (total volume = 2 ml). The extracts were dried over K_2CO_3, the ether was removed, and 0.3 ml of borane solution (Alfa, 1.1 M in THF) was added. This was allowed to stand at 25° for a few minutes; the solvent was removed using a N_2 stream and 0.3 ml of 1 N HCl added. This was extracted with ether and the ether discarded. The reaction mixture was made alkaline by the addition of 0.1 ml of 10 M NaOH and extracted with ether, the ether extracts were filtered through K_2CO_3, and the ether was removed using a N_2 stream. To the residue was added 0.1 ml of CH_2Cl_2 and 0.2 ml of a 10% BBr_3–CH_2Cl_2 solution. This was allowed to stand for a few minutes at room temperature and blown to dryness. Water or saline was added and the material used for animal experiments. A TLC (silica G, 15:3:5 BuOH–HOAc–H_2O) was run on the basic ether with carrier **5** added and showed all of the radioactivity coincident with the spot corresponding to **5**. A TLC of the final solution using the same solvent showed all of the radioactivity concentrated in one spot corresponding to the R_f of **1**·HBr. The radiochemical yield was 11%.

***N*-Formyl-3,4-dimethoxy-6-iodophenylethylamine (7).** To 0.033 g (1.79×10^{-4} mol) of **6**[16] was added 0.053 g (2.39×10^{-4} mol) of silver trifluoroacetate and a solution of 1.79×10^{-4} mol of iodine in CCl_4. This was stirred for 5 min. When the color was discharged, the solution was filtered and evaporated to give 0.059 g of an oil which after two crystallizations from ethanol–ether gave 0.012 g of **7** in 19.8% yield: mp 108.5–110°; NMR of the oil ($CDCl_3$) 2 H at δ 2.76–3.04 (m), 2 H at δ 3.28–3.72 (m), 6 H at δ 3.82 (s), 1 H at δ 5.84 (s, broad), 1 H at 6.72 (s), 1 H at δ 7.16 (s), and 1 H at δ 8.12 (s). Anal. ($C_{11}H_{14}INO_3$) C, H.

3,4-Dimethoxy-6-iodophenylethylamine Hydrochloride (5·HCl). To 0.012 g (3.58×10^{-5} mol) of **7** was added 1 ml of a 1 N HCl–CH_3OH solution. This was allowed to stand at 25° for 24 h (or sealed and heated 15 min at 115°) and the solvent removed to yield **5**·HCl in 64% yield, with identical spectral properties to **5**·HCl prepared by reduction of **4**.

3,4-Dihydroxy-6-iodophenylethylamine-*6*-^{131}I *or* -^{123}I Hydrobromide.[17] ^{131}I-Labeled I_2 (3.52×10^{-6} mol) was generated as follows. To 0.020 ml of a 5% solution of KI, 0.120 ml of a 5% solution of KIO_3, a known amount (radioactivity) of $Na^{131}I$ (carrier-free reductant-free in 0.1 N NaOH, New England Nuclear, no. NEZ-035A), and 0.5 ml of CCl_4 was added 0.040 ml of 9 N H_2SO_4. This was stirred until the water layer was colorless. The CCl_4 solution of [^{131}I]-I_2 was dried by filtering through a 0.5 × 0.5 cm column of Sephadex G-25.

To 0.75 mg (3.5×10^{-6} mol) of **6** was added 1.5 mg of $AgOCOCF_3$ (previously dissolved in 0.150 ml of ether and blown dry in the presence of **6**) and to this was added the dry solution of [^{131}I]-I_2. This was stirred at 40° for 10 min at which time the color was nearly discharged and AgI precipitated. The iodine color was completely discharged by the addition of ca. 2 mg of dry $AgOCOCF_3$ and stirring for 5 min. The CCl_4 solution was filtered through Sephadex and the CCl_4 removed using a stream of N_2. To the residue was added 1 ml of 1 N HCl–CH_3OH; the vessel was sealed and heated for 20 min at 110°. The solvent was removed using a stream of N_2, 0.2 ml of 1 N HCl was added, and the mixture was extracted with ether. To the HCl was added 0.2 ml of 5 M NaOH and this was extracted with ether and the extracts were dried over K_2CO_3. The ether was removed with N_2 and 0.1 ml of CH_2Cl_2 and 0.2 ml of 10% BBr_3–CH_2Cl_2 were added. This was allowed to stand at 25° for 10 min and the solvent removed. The residue was dissolved in water or saline and used for animal experiments. TLC's were run at points in the synthesis corresponding to the preparation of **7**, **5**, and **1** and showed all of the radioactivity coincident with the spots corresponding to these compounds. The radiochemical yield was 40%.[18] The chemical yield (from uv analysis) was 37% (1.29×10^{-6} mol).

3,4-Dihydroxy-6-iodophenylacetonitrile (8). To 0.1 g (0.00033 mol) of **4** in 1 ml of CH_2Cl_2 at 0° was added 2.6 ml of a 10% BBr_3–CH_2Cl_2 solution. The reaction mixture was stirred at 25° for 5 min and the solvent and excess BBr_3 were removed in a stream of nitrogen. The residue was triturated with 2 ml of water. The white solid was filtered and dried to give 0.071 g (78%) of **8**: mp 180–185° (>150° dec). The analytical sample

was obtained by dissolving the white solid in ether, treating with decolorizing carbon, and triturating the product with ether–pentane (1:1): NMR (acetone-d_6) 2 H at δ 3.80 (s), 1 H at δ 7.08 (s), 1 H at δ 7.32 (s), and 2 H at δ 8.36 (s, broad); ir (KBr) 4.42 μ (nitrile); λ_{max} (ethanol) 290 nm (ϵ 3892). Anal. ($C_8H_6INO_2$) C, H.

3,4-Dihydroxy-6-iodophenylethylamine Hydrochloride (1·HCl). To 0.025 g (9.1×10^{-5} mol) of **8** in 0.2 ml of THF was added 0.8 ml of borane solution (Alfa, 1.1 M in THF) and the reaction mixture was allowed to stand at 25° for 10 min. The solvent was removed using a stream of N_2 and 1 ml of D_2O acidified with HCl added. This was evaporated to dryness and D_2O added. A TLC of the resulting solution on silica G using 15:3:5 BuOH–HOAc–H_2O showed one spot (uv active) with R_f 0.65 which stains prussian blue with $K_3Fe(CN)_6$–$FeCl_3$ reagent and rose gray with ninhydrin reagent. The NMR (D_2O + DSS) was identical with that of the material produced by BBr_3 cleavage of **5**.

Acetylation of 5. To 0.111 g of **5**·HCl (3.23×10^{-4} mol) in 2 ml of H_2O was added 0.5 ml of 10 M NaOH. The free base was extracted into ethyl acetate–ether (1:1). The extracts were dried (K_2CO_3) and the solvent was removed using a stream of nitrogen. To 2 ml of CH_2Cl_2 and 2 ml of BBr_3 solution (10% in CH_2Cl_2) was added, with stirring, the amine in 3 ml of CH_2Cl_2. This was stirred for 10 min and the solvent and excess BBr_3 were removed with a stream of nitrogen. An additional 2 ml of CH_2Cl_2 was added to the residue and the solvent removed again. The residue was dissolved in 3 ml of water and 1 g of $NaHCO_3$ was added followed by the dropwise addition 0.5 ml of acetic anhydride. The mixture was stirred for 15 min or until gas evolution ceased. The mixture was extracted with CH_2Cl_2, the extracts were washed with water and dried over K_2CO_3, and the solvent was removed to yield 0.098 g (75%) of **10** as a colorless oil which slowly crystallized on standing in ether: mp 76.5–78°; NMR ($CDCl_3$) 3 H at δ 1.92 (s), 6 H at δ 2.24 (s), 2 H at δ 2.8–3.0 (m), 2 H at δ 3.2–3.6 (m), 1 H at δ 5.92 (s, broad), 1 H at δ 6.96 (s), and 1 H at δ 7.54 (s); ir (KBr) 1771 cm^{-1} (C=O); MS (80 eV) m/e 405 (M^+, 8), 278 (M^+ – I, 34), 262 (100), 249 (80), 236 (40), 194 (52), 136 (85). Anal. ($C_{14}H_{16}INO_5$) C, H, N.

Animal Experiments. Two mongrel dogs (anesthetized with Surital) were injected with 100–1500 μCi of radioiodinated 6-iododopamine (1.29×10^{-6} mol) in saline. The dogs were sacrificed at 2 and 24 h. Three samples of large organs were taken and averaged and small organs (ovaries, adrenals, and thyroids) were taken intact and counted. Mice and rats were injected intravenously ($8–11 \times 10^{-8}$ mol/mouse and 3.6×10^{-8} mol/rat) and sacrificed by ether overdose. Whole organs were counted.

Acknowledgment. We thank Dr. David Christman for running the mass spectra.

References and Notes

(1) Research performed under the auspices of the U.S. Energy Research and Development Administration. By acceptance of this article, the publisher and/or recipient acknowledges the U.S. Government's right to retain a nonexclusive, royalty-free license in and to any copyright covering this paper.
(2) (a) J. S. Fowler, A. N. Ansari, H. L. Atkins, P. R. Bradley-Moore, R. R. MacGregor, and A. P. Wolf, *J. Nucl. Med.*, **14**, 867 (1973); (b) R. D. Ice, D. M. Wieland, W. H. Beierwaltes, and R. G. Lawton, *ibid.*, **15**, 503 (1974).
(3) For a preliminary report of the synthesis of [^{18}F]-6-fluorodopamine, see R. R. MacGregor, A. N. Ansari, H. L. Atkins, D. R. Christman, J. S. Fowler, and A. P. Wolf, *J. Nucl. Med.*, **15**, 513 (1974).
(4) R. E. Counsell, T. D. Smith, V. V. Ranade, O. P. D. Noronha, and P. Desai, *J. Med. Chem.*, **16**, 684 (1973).
(5) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).
(6) I. M. Butcher and W. Gerrard, *J. Inorg. Nucl. Chem.*, **27**, 823 (1965).
(7) W. Gerrard, M. F. Lappert, and B. A. Mountfield, *J. Chem. Soc.*, 1529 (1959).
(8) M. Goldstein, A. J. Friedhoff, and C. Simmons, *Experientia*, **15**, 80 (1959).
(9) R. J. Wurtman, *N. Engl. J. Med.*, **273**, 693 (1965).
(10) P. G. Stecher, Ed., "The Merck Index", Merck and Co., Rahway, N.J., 1968, p 160.
(11) In the synthesis of [^{11}C]-6-iododopamine no cold sodium cyanide is added in the synthesis. However, hydrocarbon contaminants, present in the gases which make up the target, are converted to hydrogen cyanide in the system. This causes a dilution of ~5000 relative to strictly carrier-free material (1×10^7 Ci/mmol) to produce a compound having a specific activity of at least 2×10^3 Ci/mmol.[15]
(12) R. E. Counsell and R. D. Ice in "Drug Design", Vol. 6, E. J. Ariens, Ed., Academic Press, New York, N.Y., 1975, p 172.
(13) In studies involving identification of membrane-bound receptor structures the need for very high specific activity has been recognized. For example, see P. Cuatrecasas, G. P. E. Tell, V. Sica, I. Parikh, and K-J. Chang, *Nature (London)*, **247**, 92 (1974), and C. D. Aurbach, S. A. Fedak, C. J. Woodard, J. S. Palmer, D. Hauser, and F. Troxler, *Science*, **186**, 1223 (1974).
(14) M. E. Gutzke, D. W. Fox, L. S. Ciceresko, and S. H. Wender, *J. Org. Chem.*, **22**, 1271 (1957).
(15) D. R. Christman, R. D. Finn, K. I. Karlstrom, and A. P. Wolf, *J. Nucl. Med.*, **14**, 864 (1973); *Int. J. Appl. Radiat. Isot.*, **26**, 435 (1975).
(16) W. M. Whaley and M. Meadow, *J. Chem. Soc.*, 1067 (1953).
(17) Na^{123}I was obtained as reductant-free saline solution from the Brookhaven Linac Isotope Producer (BLIP) to which NaOH was added to give a 0.1 N NaOH solution.
(18) Radiochemical yield = activity in product × 2 (statistical correction)/starting activity.

Antimalarials. 8. Synthesis of Amino Ethers as Candidate Antimalarials

M. P. LaMontagne,* M. S. Ao, A. Markovac, and J. R. Menke

Ash Stevens Inc., Detroit, Michigan 48202. *Received May 22, 1975*

Based upon the antimalarial activities demonstrated by compounds I and II a series of amino ethers represented by structures III–VI was synthesized. These structures incorporated several modifications of compound II. The compounds prepared displayed no activity in either the Rane *P. berghei* mouse screen or the Rane *P. gallinaceum* sporozoite-induced chick test.

A series of substituted tetrahydrofuran derivatives was recently synthesized by Marxer.[1-3] One of these, 2-(4-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (I), was found to possess both prophylactic and curative antimalarial activity in animals.[3] More recently, McCaustland et al.[4] synthesized a number of compounds structurally