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Synthesis of a Potential Water-Soluble Radiographic Contrast Medium, 2,4,6-Triiodo-3-acetamido-5-*N*-methylcarboxamidophenyl β-D-Glucopyranoside[1]

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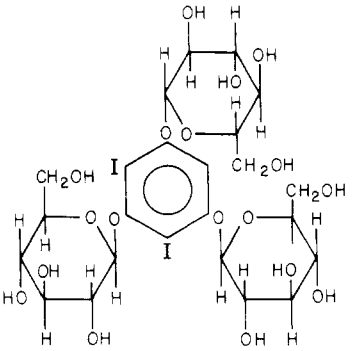
Starting from 3,5-dinitrobenzoic acid, the infinitely water-soluble compound, 2,4,6-triiodo-3-acetamido-5-*N*-methylcarboxamidophenyl β-D-glucopyranoside (**9**), was synthesized in nine steps. Glucoside **9**, the first example of potentially a new class of water-soluble x-ray contrast media, is rapidly excreted from dog's plasma into the urine, unchanged. It has low intravenous toxicity in mice (LD_{50} = 24.5 g/kg). Thin-layer chromatography of aqueous solutions of **9** revealed first appearance of aglycon **7** after 1 week at room temperature.

The current water-soluble contrast media (CM) used for radiodiagnostic visualization of body organ systems are sodium or *N*-methylglucamine salts of various derivatives of triiodobenzoic acid. To achieve a useful degree of opacity, aqueous solutions of these substances must be highly concentrated; thus, their tonicity exceeds that of the body fluids four to five times which leads to perturbances in the organism. Also, due to their ionic character, they have a high acute toxicity manifested by seizures where allowed to come in contact with the brain cortex. These factors, together with their chemotoxicity, on occasion result in adverse clinical reactions to these compounds.[2] The contrast medium currently used in the U.S. for radiographic visualization of the central nervous system and its cavities is the ethyl ester of *p*-iodophenylundecylic acid. This oily compound has no charge and is insoluble in water. Thus, it has no acute neurotoxicity; however, being immiscible with the cerebro–spinal fluid, it globulizes and consequently incompletely delineates the examined structures. Also, it often produces late chronic inflammatory changes.[3a] In an effort to eliminate the charge, Almen suggested synthesis of a nonionic derivative of metrizoic acid.[3b] This compound, 2-(3-acetamido-5-*N*-methylacetamido-2,4,6-triiodobenzamido)-2-deoxy-D-glucose, has high water solubility and low toxicity. The amide bond attaching the carbohydrate moiety, however, is susceptible to hydrolysis and this experimental material thus cannot be dispensed in injection-ready solutions.

Earlier work by this group has been concerned with the studies of the principles and mechanisms of toxicity of CM. We understand the toxicity of water-soluble CM to be due to their hydrophobicity, charge, and hypertonicity of their aqueous solutions. This laboratory previously was able to establish the correlation between hydrophobicity, toxicity, and interaction with the proteins.[4] Based on this experience, in order to further improve the currently used water-soluble radiographic media, we have developed a design concept of a highly hydrophilic, nonionic, stable material and verified it in the synthesis of a diiodophenyl triglucoside (I). This medium, with intravenous toxicity equal to glucose, approaches the ideal of a nontoxic water-soluble and stable radiographic contrast medium, yet it has the disadvantage of relatively low iodine content (29.4%).[5]



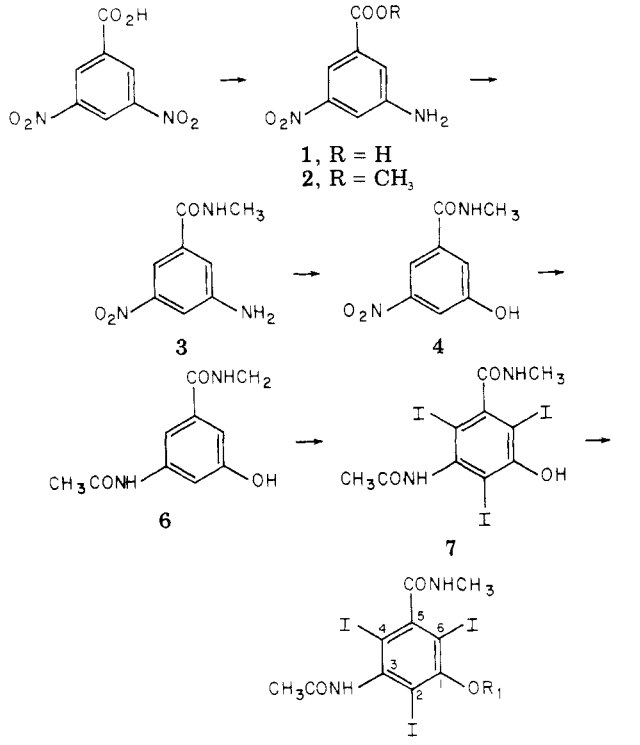
I

In the following, we present the account of the synthesis of another nonionic compound, 2,4,6-triiodo-3-acetamido-5-*N*-methylcarboxamidophenyl β-D-glucopyranoside (50.9% I) (**9**).

Results and Discussion

A. Chemistry. The Zinnin reduction[11] of 3,5-dinitrobenzoic acid (Scheme I) using Na_2S for 2 h at 80° gave typically a 70% yield of **1** compared to only 10% yield using the reported[7] 6–8 h reduction time. Amino ester **2** was prepared as described[8] except that both free amine and amine HCl were isolated. The weak HCl salt was converted to **2** merely by trituration with H_2O. Ester **2** gave amide **3** upon treatment with hot methanolic H_2NCH_3 in excess. The yield of amidophenol **4** was quite dependent upon the concentration of H_2SO_4 used for diazotization of **3** giving 40% with 20% (w/w) H_2SO_4 and 70% with 31.5% H_2SO_4. It was anticipated that a higher concentration of H_2SO_4 would be necessary to diazotize the weakly basic amine **3** but that hydrolysis of amide

Scheme I



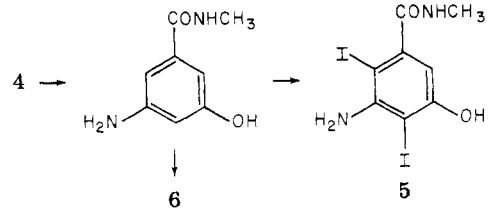
1, R = H
2, R = CH_3

3 4

6 7

8, R_1 = β-D-2,3,4,6-tetraacetylglucopyranosyl
9, R_1 = β-D-glucopyranosyl

Scheme II



6 5

group during diazonium salt decomposition would limit the yield of 4. Catalytic reduction of nitrophenol 4 with Pd/C gave an aminophenol which was used in situ to prepare 5 and 6 (Scheme II). Direct iodination of aminophenol solutions with ICl gave a diiodo derivative 5.[9] Selective N-acetylation of the aminophenol gave 6 which was triiodinated to 7 using ICl in aqueous acetic acid at 80°.

A modification[12] of the Koenigs–Knorr reaction was applied in the preparation of 8 from 7 using 2,3,4,6-tetraacetyl-α-D-glucopyranosyl bromide in aqueous acetone at pH 8. By analogy to previous assignments[12] it is expected that 8 is the β anomer. Deacetylation of 8 was accomplished in 6 N NH_3–MeOH thereby avoiding the alternative NaOMe–MeOH system which is known to generate the acetamido anion ($-NCOCH_3$) of triiodinated benzoic acid derivatives.[13] Glucose free 9 was eluted from neutral alumina with 30% aqueous EtOH even when crude 9 was known to contain 5–10% glucose initially. Lyophilization of aqueous solutions of early column fractions gave pure 9 in hydrated form. The only impurity eluted from alumina, in later fractions, was aglycon 7 due to hydrolysis of the glucoside acetal bond in 9 during work-up (Table I).

Just as in the case of Metrizamide, glycoside 9 cannot be formulated in aqueous solutions for clinical use but would have to be dissolved prior to the injection.

The butanol–water partition studies were done using a modified approach of Hansch.[14] The p values for Metrizamide were 0.42, for compound 7, 8.43, and for compound 9, 0.54. There is thus no significant difference between the hydrophilic character of Metrizamide and 9. Introduction of the carbohydrate moiety into compound 7 proved to greatly decrease its hydrophobicity.

Table I. Approximate Hydrolytic Stability Based on TLC[a] Examination of 1% Distilled Water Solutions of Glucoside 9

Temp, °C	First appearance of aglycon 7
22	1 week
38	1 day
70	1 h

[a] Mixture of glucoside 9 and aglycon 7 exhibited R_f 0.48 and R_f 0.73, respectively, when TLC's were developed in butanol-AcOH-H_2O (4:1:1) and visualized with uv.

Table II

	LD_{50}, g/kg of bw	LD_{50}, g of I/kg of bw
Compound 9	25.5	13.0
Metrizamide	23.5	11.3
Conray 60	13.6	6.4

The acidity of phenol 7, $pK_a = 4.9 \pm 0.1$, was measured in 50% aqueous MeOH due to quite low water solubility. The actual pK_a in water may be even lower than the value reported here due to the normally elevating effect of alcohol on pK_a in binary aqueous systems.[6b] For comparison, the pK_a's of 2,4,6-trichloro-, o-chloro-, and o-iodophenol are 6.00,[15] 8.48, and 8.51,[6c] respectively.

Although the water solubility of glucoside 9 was immeasurably high, the solubility of aglycon 7 was determined to be 4.0% (±0.5%); it is therefore apparent that phenol 7 would not be sufficiently soluble in body fluids to remain in solution in radiodiagnostically meaningful quantities.

B. In Vivo Testing. The intravenous lethal doses of compound 9 were established in male mice weighing between 18 and 21 g. The test compound was sterilized by ultrafiltration and injected in a concentration of 354 mg of I/ml at the rate of 1.1 ml/min. Currently the clinically used N-methylglucosamine salt of iothalamic acid (Conray) (Mallinckrodt Works) and the experimental medium Metrizamide (Nyegaard Co.) were tested under identical conditions for comparison. The results are summarized in Table II. X rays of the survivors of the LD_{50} group showed excellent opacification of the kidneys, which upon sacrifice 1 week later were found histologically normal. When injected intravenously into dogs, compound 9 was rapidly cleared from plasma. Of the injected dose (11 mg/kg bw) 61% was excreted in urine in the first 2 h and 84% in 6 h; 1.6% was excreted into the bile during this 6-h period. Glucoside 9 was recovered from urine and identified by thin-layer chromatography and ir spectroscopy as unchanged. It is rapidly excreted from the organism. It is infinitely soluble in water and has a relatively high iodine content. Compared to the ionic water-soluble contrast media, glucoside 9 proved to have low systemic toxicity. This class of compounds may have potential as radiographic contrast media.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Ir spectra were recorded on a Beckman Acculab 4 spectrophotometer with samples prepared as KBr disks. Optical rotations were measured on a Perkin-Elmer 141 automatic po-

larimeter. ^{1}H NMR spectra were recorded on a Varian T-60 instrument using samples dissolved in Me_2SO-d_6 with Me_4Si as internal standard unless otherwise noted. Microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn., and where noted by symbols of the elements were within ±0.4% of the calculated value. Analytical TLC's were done on 20-cm plates of silica gel 60 F-254 (E. Merck, Darmstadt) and spots were visualized with uv, 40% H_2SO_4 and Tollens reagent at 100°. All evaporations were accomplished with the Buchi rotovapor-RE at 40° using aspirator vacuum. All pH measurements were taken with an Orion Research Model 701 digital pH meter using a combination glass and silver–silver chloride reference electrode (Thomas cat. no. 4094-L15).

Iodinations were achieved with ICl purchased from Matheson Coleman and Bell. Sigma Chemical Co., St. Louis, Mo., supplied the tetraacetyl-α-D-glucopyranosyl bromide.

Determination of p*K* Values. Aqueous methanol solutions (equivolume), 0.002 M in substrate, were titrated at 22° with 0.02 M NaOH and the pH was recorded at intervals. Values of the p*K* were computed from the equation: $pK = pH + \log([BH]/[B^-])$.[6] Solubility at pH 7.35 was determined via a gravimetric procedure.

Synthesis. Compounds 1[7] and 2[8] are not new.

3-Amino-5-nitrobenzoic Acid (1). Reduction of 3,5-dinitrobenzoic acid with $Na_2S \cdot 9H_2O$ was carried out according to the procedure of Cassabaum and Kierbach[7] to obtain a 69% yield of 1: mp 207–209° (lit. 209–211°).

Methyl 3-Amino-5-nitrobenzoate (2). Hot methanolic HCl treatment of 1 gave an 82% yield of 2: mp 158–160° (lit.[8] 158–160°).

3-Amino-5-nitro-*N*-methylbenzamide (3). Into 39.0 g (0.20 mol) of 2 slurried in 400 ml of MeOH was bubbled 15.5 g (0.50 mol) of H_2NCH_3 and the mixture heated to reflux for 48 h. The ice-cold reaction mixture was filtered and washed with MeOH to obtain 33.7 g (85%) of 3: mp 218–221°; ir 3450 (NH_2), 1620 (C=O), 1510 and 1340 cm^{-1} (NO_2); ^{1}H NMR δ 2.78 (d, 3 H, J = 5 Hz, $NHCH_3$). Anal. ($C_8H_9N_3O_3$) C, H, N.

3-Nitro-5-*N*-methylcarboxamidophenol (4). In a warm solution of 20% (v/v) aqueous H_2SO_4 (720 ml of H_2O and 180 ml of concentrated H_2SO_4) was dissolved with stirring 33.6 g (0.175 mol) of 3. Diazotization of this solution was carried out in an ice bath by a 1-h addition of 12.6 g (0.182 mol) of $NaNO_2$ in 25 ml of H_2O. The resulting solution was diluted with 500 ml of H_2O, warmed to room temperature, and converted to phenol by a 2-h addition to a boiling solution of 100 g of Na_2SO_4 in 1750 ml of H_2O and then refluxed an additional hour. The hot phenol solution was decanted from tarry by-products and then sat overnight at ambient temperature to precipitate a tan solid. Additional tan solid was obtained by EtOAc (4 × 200 ml) extraction of the mother liquor for a total yield of 24.1 g (70%) of crude 4. This material after Norite treatment was satisfactory for use in the synthesis of 5. An analytical sample obtained by recrystallization from EtOH–EtOAc–PE gave 4: mp 261–264°; ir 3400 cm^{-1} (OH); ^{1}H NMR δ 2.83 (d, 3 H, J = 4 Hz, $-NHCH_3$), 10.77 (s, 1 H, OH). Anal. ($C_8H_8N_2O_4$) C, H, N.

Catalytic Reduction of 4. To a slurry of 10.0 g (51 mmol) of crude 4 in 150 ml of H_2O was added 0.5 g of 5% Pd/C and 10 ml of 6 N aqueous HCl. Hydrogenation on a Parr shaker at 3 atm for 2.5 h and then removal of the catalyst by filtration gave the crude amine HCl which was used directly for synthesis of 5 and 6.

Diiodo-3-amino-5-*N*-methylcarboxamidophenol (5). To 3.7 mmol of the amine HCl (reduction solution) at ambient temperature was added 15 ml (12 mmol) of 0.8 M ICl in 1.6 M HCl (hood). After 1 h of stirring, a tan precipitate was collected by filtration and then partitioned between EtOAc and aqueous $NaHSO_3$. The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a tan solid. This material was dissolved in aqueous NaOH and then filtered. Addition of 12 N HCl to the filtrate caused a precipitate which was redissolved by further addition of acid. This solution was filtered and then addition of concentrated aqueous NaOH gave a tan solid at pH 4. This material was filtered, washed with H_2O, and dried at ambient temperature in vacuo over P_2O_5 to obtain 0.33 g (21%) of 5: mp 158–160°; ir 3650–3100 (NH_2, OH), 1600 cm^{-1} (C=O); ^{1}H NMR (TFA) δ 3.20 (d, 3 H, J = 5 Hz, $CONHCH_3$). Anal. ($C_8H_8I_2N_2O_2$) N, I.[9]

3-Acetamido-5-*N*-methylcarboxamidophenol (6). Catalytic reduction of 15.0 g (76.5 mmol) of 4 gave 50 ml of an aqueous solution of the amine HCl which was treated with 3.1 g (77.5 mmol) of NaOH followed by 7.8 g (76.5 mmol) of Ac_2O. The reaction solution was stirred overnight at ambient temperature; then the precipitate was removed by filtration, washed with H_2O, and dried to obtain 4.6 g (29%) of 6: mp 281–284°; ir 3410 cm^{-1} (OH); ^{1}H NMR (TFA) δ 2.43 (s, 3 H, $NHCOCH_3$), 3.27 (d, 3 H, J = 5 Hz, $CONHCH_3$). Anal. ($C_{10}H_{12}N_2O_3$) C, H, N.

2,4,6-Triiodo-3-acetamido-5-*N*-methylcarboxamidophenol (7). To 3.1 g (14.9 mmol) of 6 dissolved in 200 ml of AcOH plus 100 ml of H_2O at 80° was added 12.4 g (76.4 mmol) of ICl at once (hood). After 5 h the reaction mixture was allowed to cool to room temperature and stir overnight. A precipitate was collected by filtration and washed well with H_2O, dilute aqueous $Na_2S_2O_3$, and then H_2O. The white solid was dried in vacuo over P_2O_5 to obtain 6.6 g (76%) of 7: mp 245° dec; ir 3350 (OH), 1630 ($CONCH_3$, $NHCOCH_3$), 1540, 1360 cm^{-1}; ^{1}H NMR δ 2.00 (s, 3 H, $NHCOCH_3$), 2.73 (d, 3 H, J = 4 Hz, $CONHCH_3$), 8.23 (1 H, $NHCOCH_3$), 9.73 (s, 1 H, OH). Anal. ($C_{10}H_9I_3N_2O_3$) H, N; C: calcd, 20.50; found, 20.98; I: calcd, 63.61; found, 64.25.

2,4,6-Triiodo-3-acetamido-5-*N*-methylcarboxamidophenyl β-D-2,3,4,6-Tetraacetylglucopyranoside (8). Into a vessel immersed in a room temperature water bath was poured a solution of 5.86 g (10.0 mmol) of 7 and 0.48 g of NaOH in 15 ml of H_2O followed by 20 ml of acetone. To this agitated solution was slowly added 4.11 g (10.0 mmol) of 2,3,4,6-tetracetyl-α-D-glucopyranosyl bromide in 20 ml of acetone at a rate to avoid formation of a separate organic layer. During and after the addition, pH 8 was maintained by periodic addition of 2 N aqueous NaOH. At the end of 6 h the majority of acetone was evaporated in vacuo at 0° and then 30 ml of H_2O was added to give a white precipitate. Filtration of the cold mixture gave a white solid which was washed with 0.01 M $NaHCO_3$ and then H_2O to obtain 6.5 g of crude 8: mp 218–220°. Treatment of this material with Norite in EtOH followed by rapidly heating to boiling and then addition of 5 vol of hot H_2O gave upon cooling 5.1 g (55%) of 8: mp 222–223°; $[\alpha]^{26}D$ −14.4° (1.0, MeOH); ir 3300 (CH), 1730 ($-OCOCH_3$), 1670 and 1620 ($CONHCH_3$, $NHCOCH_3$), 1225, 1040 cm^{-1}; ^{1}H NMR δ 2.02 (s, 12 H, $OCOCH_3$), 2.12 (s, 3 H, $NHCOCH_3$), 2.77 (d, 3 H, $CONHCH_3$); TLC [THF–C_6H_{12}–H_2O (93:7:5)] R_f 0.63. Anal. ($C_{24}H_{27}I_3N_2O_{12}$) H, I, N; C: calcd, 31.49; found 32.15; O: calcd, 20.98; found, 20.49.

2,4,6-Triiodo-3-acetamido-5-*N*-methylcarboxamidophenyl β-D-Glucopyranoside (9). In 200 ml of 6 N methanolic NH_3 was dissolved 21.72 g (23.7 mmol) of crude 8[10] at room temperature and then let sit 22 h at 6°. Evaporation of this solution at ambient temperature gave a syrup which was entered directly onto a (29 in. × 2 in. o.d.) column of neutral, activated aluminum oxide (Ventron, Camag) prepared and eluted with EtOH–H_2O (7:3). The first material off the column, eluted after 1.5 l., contained a single organic substrate. These fractions were evaporated in vacuo at 20° to give a clear, colorless syrup. When this material was lyophilized in 250 ml of H_2O and finally dried in vacuo over P_2O_5 at ambient temperature there was obtained a white solid 9 (10.4 g, 60%): $[\alpha]^{26}D$ +5.6° (1.0, H_2O); ir indicated complete absence of peak at 1730 cm^{-1} ($OCOCH_3$); ^{1}H NMR (D_2O, DSS) δ 2.38 (s, 3 H, $NDCOCH_3$), 3.10 (s, 3 H, $CONDCH_3$), 3.33–4.33 (m, 7 H, CH_2OD and CHOD); TLC [*n*-BuOH–AcOH–H_2O (4:1:1)] R_f 0.48; TLC [THF–C_6H_{12}–H_2O (93:7:5)] R_f 0.47; TLC [C_6H_6–EtOH–Me_2CO (2:2:1)] R_f 0.54. Microanalysis was determined on a sample dried at 80°, 48 h, in vacuo, over P_2O_5. Anal. ($C_{16}H_{19}O_8I_3N_2$) C, H, I, N.

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

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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