Potential Organ or Tumor Imaging Agents. 11.† Radioiodinated Tyramines

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The lack of suitable radiolabeled agents for photoscanning adrenal medullary tumors prompted synthesis of 4-hydroxy-3-iodo- (**2**), 3-hydroxy-6-iodo- (**3**), and 3-hydroxy-5-iodophenylethylamine (**4**) radiolabeled with iodine-125. Radioiodination by isotope exchange was unsuccessful for **3** and **4**, but the former was obtained by the direct radioiodination of *m*-tyramine hydrochloride. Tissue distribution studies in dogs with **2** and **3** revealed extensive *in vivo* deiodination and no selective localization in adrenal medulla or adrenergically innervated tissues.

Despite the rapid advances in nuclear medicine in recent years, there is still no suitable radiopharmaceutical available to aid in the diagnosis of neural crest tumors such as pheochromocytoma and neuroblastoma.# These tumors are a group of functional tumors which arise from the sympathetic chain and adrenal medulla and are capable of producing large quantities of catecholamines and their metabolites.[2] Unlike pheochromocytoma which occurs in adults, neuroblastoma is the second most common solid malignant tumor of infants and children.[2]

In our design of new radiopharmaceuticals we have concentrated on two approaches, namely (1) radiolabeling drugs which are known or suspected of having a predilection for a particular organ or tumor, and (2) radiolabeling naturally occurring compounds which are known to be synthesized and/or stored within certain organs or tumors. Since these approaches have led to useful diagnostic agents for ocular melanoma[3] and adrenal disease,[4] these same concepts were employed in the present study. In this instance, however, the second or more biochemical of the two approaches is emphasized.

Since malignancies of the adrenal medulla in laboratory animals are rare,[5] our search has focused attention on compounds displaying a predilection for the adrenal medulla. On the basis of their origin, it seemed reasonable that agents selectively concentrating in this tissue should exhibit a similar affinity for functional medullary tumors.

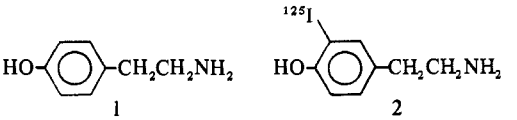
In recent years, considerable information has become available concerning the biochemistry of catecholamines and the adrenal medulla.[6] It is now common knowledge that norepinephrine is synthesized from dopamine in the chromaffin granules of the medulla. This newly formed norepinephrine returns to the cytoplasm where it is N-methylated to form epinephrine which is then stored in the chromaffin granules. Since the observed molar ratio between ATP and catecholamines in the adrenal medulla is 1:4, it is generally accepted that the catecholamines are bound to ATP within these granules.

Although pheochromocytomas usually contain much higher concentrations of catecholamines than the normal adrenal medulla, these tumors usually have ATP concentrations about 30 times lower. This observation has led to the conclusion that pheochromocytoma cells have a defective storage mechanism.[2] Apparently, the tumor cells accumulate high concentrations of catecholamines in the free state in the cytoplasm.[2]

A number of reports cite the ability of [^{3}H]norepinephrine and [^{3}H]epinephrine to selectively accumulate in adrenal tissue.[7,8] Of particular pertinence was the investigation by Morales, *et al.*,[9] in which 26 dogs were injected with ^{14}C-labeled catecholamines, catecholamine precursors, *p*-tyramine, and β-phenylethylamine. Considerable radioactivity was retained by the medulla following administration of radiolabeled dopamine, norepinephrine, and epinephrine. For example, the average adrenal medulla:plasma ratio at 6 hr after [^{14}C]dopamine was 740. This finding was of particular chemical significance because dopamine lacks an asymmetric center. Moreover, a single experiment with [^{14}C]*p*-tyramine showed an adrenal medulla:plasma ratio of approximately 130. In contrast, [^{14}C]β-phenylethylamine showed no predilection for adrenal medullary tissue. Subsequent *in vitro* studies by Slotkin and Kirshner[10] verified the importance of the presence of at least one phenolic hydroxyl for uptake and storage of substituted β-phenylethylamines in adrenal storage vesicles.

For purposes of external radioscanning, elements capable of emitting γ-radiation are desirable. Since none of the elements of dopamine or tyramine possess radionuclides with suitable γ emissions, it became necessary to introduce an appropriate element into the catecholamine molecule for this purpose. Iodine-125 was selected for the initial feasibility studies because of its reasonable half-life and ease of handling.

From a synthetic standpoint, it was considered that an aromatic iodo derivative of dopamine would be unstable both *in vitro* and *in vivo*. For this reason it was decided to synthesize a series of radioiodinated tyramine analogs. Accordingly, controlled iodination of *p*-tyramine (**1**) furnished *m*-iodo-*p*-tyramine (**2**). Radioiodine was readily incorporated by isotope exchange with sodium iodide-125 in refluxing ethanol. Preliminary animal studies with this product, however, revealed considerable *in vivo* deiodination and most of the radioactivity appeared in the thyroid. The



1 2

increased chemical instability of iodine ortho to a phenolic function has been previously noted.[11]

It thus became necessary to find sites on the tyramine structure that would be more resistant to *in vivo* deiodination. Consequently, the iodinated *m*-tyramine analogs **3** and **4** seemed appropriate candidates for synthesis and evaluation.

The general susceptability of aromatic iodine atoms to

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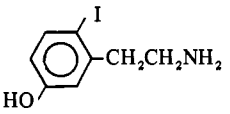
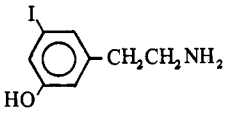
#For reviews on the current status of nuclear medicine, the reader is referred to P. D. R. for radiology and nuclear medicine, Medical Economics, Inc., Oradell, N. J., 1971. See also ref 1.



3



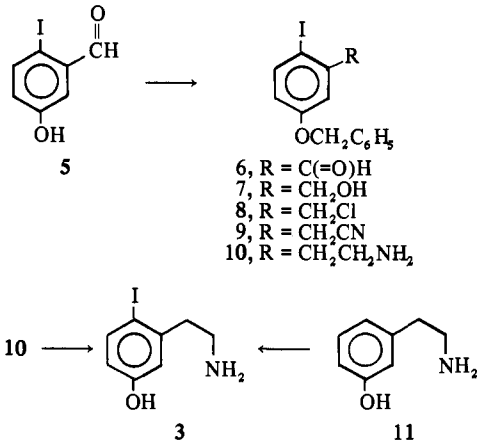
4

hydrogenolysis[12] meant that synthetic approaches to **3** and **4** required procedures where such conditions were avoided. The reported[13] excellence of diborane for the reduction of nitriles to phenylethylamines encouraged us to seek a path to **3** incorporating this transformation. The known aldehyde **5** appeared to be a suitable starting material for this purpose and this was readily converted to the benzyl ether **6** by the method of Daly, *et al.*[14]

Initial attempts to reduce **6** to the alcohol **7** using lithium aluminum hydride resulted in partial hydrogenolysis of the iodine atom, a result which was not unexpected. Although some of the desired alcohol was obtained, the predominant product was the deiodinated alcohol, and it became necessary to examine other reduction methods. An attempt to reduce **6** with sodium borohydride in methanol resulted in the recovery of starting material. The aldehyde could be reduced in good yield, however, with lithium tri-*tert*-butoxyaluminum hydride.

Although the alcohol **7** could be converted to the chloride **8** by refluxing in thionyl chloride, superior results were achieved by using diglyme as solvent. The nitrile **9** was conveniently prepared by subjecting **8** to the action of sodium cyanide in dimethylformamide.

Diborane reduction of **9** and subsequent acid hydrolysis of the benzyl ether **10** did, indeed, produce the desired phenylethylamine **3** although in poor yield. The intermediate benzyl ether **10** was not isolated but was characterized as the picrate salt. Following the completion of this synthesis it was found that **3** could also be obtained directly by controlled iodination of *m*-tyramine hydrochloride (**11**).



5

6, R = C(=O)H
7, R = CH_2OH
8, R = CH_2Cl
9, R = CH_2CN
10, R = $CH_2CH_2NH_2$

3 11

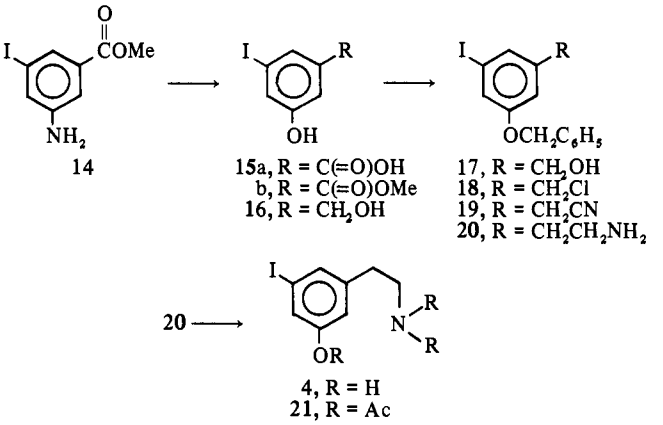
The successful synthesis of **3** suggested that a similar synthetic approach would be suitable for the preparation of 2-(3-hydroxy-5-iodophenyl)ethylamine (**4**). The most suitable and most readily available starting material for this synthesis was 3-iodo-5-nitrobenzoic acid (**12**). Thus, initial efforts were directed toward the conversion of the starting benzoic acid **12** to 3-benzyloxy-5-iodobenzyl cyanide (**20**).

Direct reduction of the aromatic nitro group of **12** would yield an amino acid as the product and similar free amino acids have a tendency to polymerize under catalytic reducing conditions. Furthermore, amino acids introduce problems of isolation. In order to avoid these difficulties, the methyl ester **13** was prepared through the acid chloride.

The nitro group was smoothly reduced in good yield with iron and acetic acid to give methyl 3-amino-5-iodobenzoate (**14**). Equally efficient results were obtained using stannous chloride and hydrochloric acid.

Diazotization of **14** in aqueous sulfuric acid gave the diazonium salt which was decomposed in aqueous sulfuric acid to introduce the phenolic function. This was accompanied by partial hydrolysis of the methyl ester so that both 3-hydroxy-5-iodobenzoic acid (**15a**, 65.8%) and the corresponding methyl ester **15b** (12.7%) were isolated.

Diborane reduction smoothly converted the acid **15a** into the benzyl alcohol **16** which could now be selectively benzylated on the phenolic hydroxyl to give **17**. Treatment of **17** with thionyl chloride afforded **18** which was readily converted to the substituted phenylacetonitrile **19** by the action of NaCN in DMF. Diborane reduction of **19** gave amine **20** which was subsequently debenzylated by acid hydrolysis to furnish the desired iodotyramine **4**.



14

15a, R = C(=O)OH
b, R = C(=O)OMe
16, R = CH_2OH

17, R = CH_2OH
18, R = CH_2Cl
19, R = CH_2CN
20, R = $CH_2CH_2NH_2$

4, R = H
21, R = Ac

Previous papers in this series[3,15] have illustrated the practicality of introducing radioiodine onto aromatic rings by isotope exchange of iodoaryl compounds with inorganic radioiodide in an appropriate solvent. Unfortunately, unless the halogen atom is in a somewhat activated position, it is often necessary to use temperatures approaching 175° before appreciable exchange occurs. In the present study, all attempts to radioiodinate **3** or **4** by this method led to extensive decomposition which prevented isolation of the desired products. Even attempts to radioiodinate the triacetate derivative **21** by the exchange method were unsuccessful. It was subsequently found, however, that direct radioiodination of tyramine hydrochloride afforded the desired radioiodinated **3** after fractional crystallization.

Intravenous administration to dogs of a tracer dose of **3** radiolabeled with ^{125}I showed no selective localization of radioactivity in the adrenal medulla at 2 hr. On the other hand, high levels of radioactivity were apprent in the thyroid indicative of considerable *in vivo* deiodination.** As a consequence of these discouraging results, other chemical approaches to the problem are now under investigation.

Experimental Section††

2-(4-Hydroxy-3-iodophenyl)ethylamine (2). A 1 *N* KI_3 solution (4.4 ml) was added dropwise to a solution of tyramine HCl (302 mg) in NH_4OH (4.4 ml). The solution was allowed to stir at room tempera-

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††Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were taken on a Perkin-Elmer 337 spectrophotometer. The nmr spectra were obtained with a Varian A-60

ture for 45 min. Excess NH_3 was removed under a stream of N_2 whereupon a solid separated. The solution was chilled and the solid collected by filtration. Recrystallization from aqueous MeOH afforded 2 (350 mg, 76%): mp 154–156°; ir and nmr as expected. *Anal.* ($C_8H_{10}INO$) C, H.

2-(4-Hydroxy-3-iodophenyl)ethylamine-^{125}I. $Na^{125}I$ (3 mCi) was added to the solution of 2 (100 mg) in EtOH (5 ml). The solution was refluxed gently with stirring for 6 hr and cooled to room temperature. Refrigeration gave rise to a solid which was collected by filtration and washed with H_2O. Recrystallization from MeOH gave radioiodinated tyramine (75 mg) with a specific activity of 21.65 μCi/mg (72% exchange). Chemical and radiochemical purity was established by tlc using *n*-BuOH–HOAc–H_2O (5:4:1). Analysis under uv light revealed a single spot (R_f 0.38) coincident with the single radioactive area shown by a radiochromatogram scan.

5-Hydroxy-2-iodobenzaldehyde (5). This compound was prepared according to the procedure of Pandya, *et al.*[16] A solution of iodine (37.2 g in 250 ml of 28% aqueous KI solution) was added dropwise to a stirred, ambient temperature solution of *m*-hydroxybenzaldehyde (16 g, 0.131 *M*) in NH_4OH (150 ml). Usually a gummy residue appeared toward the termination of the addition procedure. The reaction mixture was stirred an additional 1 hr and made acid with concentrated HCl. Acidification produced a gummy precipitate which was difficult to crystallize. The precipitate was taken up in Et_2O and washed with aqueous thiosulfate solution. The Et_2O solution was dried ($MgSO_4$) and treated with charcoal. Recrystallization from C_6H_6–petroleum ether (bp 30–40°) yielded 14.48 g (44.5%) of an almost white product: mp 131.5–133.5° (lit. mp 130°); ir and nmr as expected.

5-Benzyloxy-2-iodobenzaldehyde (6). Anhydrous K_2CO_3 (8.3 g, 0.06 *M*) was suspended in a solution of 5 (14 g, 0.056 *M*) and benzyl chloride (7.6 g, 0.06 *M*) in technical DMF (350 ml). The stirred reaction mixture was heated to 100–110° for 2.5 hr. Dilution of the cooled suspension with cold H_2O produced an oil which soon solidified. The crude solid was collected and recrystallized from EtOH to yield 17.17 g (90.7%) of pure 6: mp 81.5–83°; ir and nmr as expected. *Anal.* ($C_{14}H_{11}IO_2$) C, H.

5-Benzyloxy-2-iodobenzyl Alcohol (7). Lithium tri-*tert*-butoxyaluminum hydride (8.17 g, 0.036 *M*) was dissolved in dry THF (50 ml) and the stirred solution was cooled in ice–H_2O. A solution of 6 (4 g, 0.012 *M*) in dry THF (25 ml) was added to the cold metal hydride solution in a dropwise manner, and stirring was continued for an additional 4 hr. The reaction was terminated by pouring the solution into 6% HOAc. Extraction with Et_2O and work-up in the usual manner produced a crude oil (3.7 g) which solidified upon trituration with Et_2O–petroleum ether (bp 30–40°). Recrystallization from C_6H_6–petroleum ether (bp 30–40°) afforded 3 g (75%) of pure 7: mp 62–63.5°; ir and nmr as expected. *Anal.* ($C_{14}H_{13}IO_2$) C, H.

5-Benzyloxy-2-iodobenzyl Chloride (8). A solution of 7 (13.2 g, 0.039 *M*) in dry diglyme was immersed in a cold H_2O (no ice) bath. $SOCl_2$ (50 ml) was added dropwise to the cool solution and the final reaction mixture stirred for 8 hr. The contents were poured into ice–H_2O (1000 ml) and the product was extracted into Et_2O. The Et_2O extract was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and treated with charcoal. The drying agent and charcoal were removed by filtration. Evaporation of the Et_2O left a white solid (14.7 g) which was recrystallized from EtOH to yield 11.85 g (84%) of a slightly impure product, mp 62.8–65°. Further recrystallization of a small sample afforded pure 8: mp 68.3–69.6°; ir and nmr as expected. *Anal.* ($C_{14}H_{12}ClIO$) C, H.

5-Benzyloxy-2-iodobenzyl Cyanide (9). Sodium cyanide (2 g) was dissolved in a minimum amount of H_2O and added to DMF (100 ml). To this stirred solution was added in a dropwise manner a solution of 8 (8.2 g, 0.023 *M*) in DMF (15 ml). The reaction mixture was stirred for 8 hr at 40–50° and poured into ice–H_2O. The product was isolated by Et_2O extraction and the extracts were dried ($MgSO_4$) and decolorized (charcoal). The residue remaining after removal of the Et_2O was eluted from a silica gel chromatography column (1 × 13 in.) using 20% hexane in C_6H_6. The oil eluted from the column was treated with charcoal in Et_2O solution and subsequently crystallized from C_6H_6–petroleum ether (bp 30–40°) to yield 4.6 g (58%) of product, mp 51–53°. A sample was recrystallized from EtOH: mp 52.7–54°; ir and nmr as expected. *Anal.* ($C_{15}H_{12}INO$) C, H.

2-(5-Benzyloxy-2-iodophenyl)ethylamine (10). A stirred solution of 9 (4.33 g, 0.012 *M*) in dry THF (150 ml) was immersed in a cold H_2O bath. A solution of BH_3 in THF (30 ml of 1 *M* BH_3 in THF) was introduced in a dropwise manner. The solution was stirred for 2 hr after completion of the addition and excess BH_3 was decomposed by the cautious addition of EtOH until effervescence ceased. The solvents were evaporated with a minimum of heat and the residue was taken up in Et_2O. Upon bubbling HCl into the Et_2O solution, a separate liquid phase collected at the bottom of the flask. The Et_2O was removed and the lower phase was dissolved in H_2O. The resulting aqueous solution was made basic with NaOH and the product was reextracted into Et_2O. Evaporation of the Et_2O left 3.2 g (76%) of a crude oil which did not solidify. A small fraction of the product was dissolved in Et_2O and the picrate salt was precipitated by the addition of Et_2O solution of picric acid. The salt was recrystallized from EtOAc. collected, and dried, mp 203.8–205°. *Anal.* ($C_{21}H_{19}IN_4O_8$) C, H.

2-(5-Hydroxy-2-iodophenyl)ethylamine (3). a. By Hydrolysis of Benzyl Ether 10. A solution of crude 10 (3.2 g) in concentrated HCl (40 ml) and glacial HOAc (20 ml) was stirred and heated at 80° for 2 hr. The reaction mixture was made basic with NaOH and extracted with Et_2O. The aqueous residue was titrated with HCl to the cloud point and placed in the refrigerator. After some time a small amount of a brown solid collected in the flask and this was removed by centrifuging. Washing this solid residue with dioxane left a small amount of an almost colorless product. The supernatant yielded a second crop after concentration. Further concentration, however, caused the neutralization salts to precipitate. Both crops of the solid product were combined and recrystallized from EtOH–H_2O to give 0.375 g of pure 3: mp 161–162.5°; ν_{max}^{KBr} 3100–2000 cm^{-1} (NH_2, OH). *Anal.* ($C_8H_{10}INO$) C, H.

b. By Direct Iodination of Tyramine Hydrochloride. A solution containing 1 *N* iodine in KI was added in a dropwise manner to a stirred solution of 11 (174 mg) in concentrated NH_4OH (10 ml) at room temperature and stirring was continued for an additional hour. The reaction mixture was warmed on an H_2O bath at 50° for 6 hr and solution stirred overnight until neutral to litmus. The solid that separated was collected and recrystallized from EtOH–H_2O to give 110 mg (42%), mp 160°. This compound was identical in all respects with that obtained by method a.

2-(5-Hydroxy-2-iodophenyl)ethylamine-^{125}I. To a solution of $Na^{125}I$ (1 ml, 10.45 mCi), NaI (15 mg) was added and the solution was left with stirring for 30 min. To this solution was added successively 2 drops of 10% HCl, 2 drops of 30% H_2O_2, KI (100 mg), and iodine (60 mg). The resulting deep colored solution was stoppered and left stirring at room temperature for 1 hr. This solution was then added dropwise to a solution of 11 (44 mg) in NH_4OH (2 ml) and stirred for 1 hr at room temperature. It was then heated in oil bath (70–75°) for 6 hr and left overnight with stirring at room temperature. The solid that separated was collected, washed with H_2O, and recrystallized from EtOH to give 11.0 mg of radioiodinated product with specific activity of 37 μCi/mg (38% exchange). Tlc using *n*-BuOH–HOAc–H_2O (12:3:5) gave a single spot (R_f 0.54) coincident with the single radioactive area shown by a radiochromatogram scan.

Methyl 3-Iodo-5-nitrobenzoate (13). 3-Iodo-5-nitrobenzoic acid (12) (50 g, 0.17 *M*) was refluxed in $SOCl_2$ (100 ml) for 3 hr and the excess reagent was removed by distillation. Absolute MeOH (250 ml) was added slowly to the residual acid chloride with stirring. The solution was refluxed an additional 3 hr and excess MeOH was removed by distillation. H_2O was added to the residue and the ester was extracted into Et_2O. The extract was washed with 5% $NaHCO_3$ and dried ($MgSO_4$). Evaporation of Et_2O yielded 53.3 g (quantitative) of 13: mp 73–76° (lit. mp 88°); ir and nmr as expected. This product was used without further purification for the preparation of 14.

Methyl 3-Amino-5-iodobenzoate (14). a. Reduction with Fe and HOAc. To a mechanically stirred suspension of Fe powder (19 g) in glacial HOAc (80 ml) was added a solution of 13 (9.5 g, 0.031 *M*) in glacial HOAc (80 ml) over 1 hr. The mixture was stirred at room temperature for 4 hr, diluted with H_2O, and neutralized with solid $NaHCO_3$. The neutralized reaction mixture was extracted with Et_2O. The extract was dried (Na_2SO_4) and 8.7 g of the amine HCl was precipitated by adding an Et_2O–HCl solution to the extract. The HCl salt was collected and suspended in dry Et_2O, and NH_3 was bubbled into the suspension. The NH_4Cl formed (1.5 g) was removed by filtration and the Et_2O solution of the free amine was evaporated to dryness yielding 7.5 g (87%) of a tan solid, mp 89–93°. The compound was characterized as the amine HCl which was recrystallized twice from Me_2CO–petroleum ether (bp 30–40°) to yield a pure white solid: mp 160–164°; ir and nmr (CF_3CO_2H) as expected. *Anal.* (C_8H_9ClINO) C, H.

spectrometer in $CDCl_3$ and TMS as an internal standard unless otherwise specified. Tlc were run with Eastman chromagrams cut in 1-in. wide strips and spots were detected with iodine vapor. Chromatograms of radioiodinated compounds were scanned with an Atomic Associates RCS-363 radiochromatogram scanner. Specific activities were ascertained using a Beckman LS 200 liquid scintillation counter.

b. Reduction with $SnCl_2$ and HCl. To a solution of 13 (53.25 g, 0.173 *M*) in concentrated HCl (118 ml) and MeOH (120 ml) was added with stirring a solution of $SnCl_2$–$2H_2O$ (117.5 g, 0.52 *M*) in MeOH (100 ml). Addition took 30 min and stirring was continued an additional 6 hr at room temperature. At the end of the stirring period, excess MeOH was evaporated and the residue diluted with H_2O. After filtration, the aqueous solution of the amine HCl was made basic and the insoluble product taken up in Et_2O. The dried Et_2O extract ($MgSO_4$, charcoal) was evaporated to afford 14 (46 g, 96%) identical in all respects with that obtained above.

3-Hydroxy-5-iodobenzoic Acid (15a). A solution of 14 (44.6 g, 0.161 *M*) in H_2O (225 ml) and H_2SO_4 (30 ml) was cooled to 0–5°. The stirred suspension of the amine salt was maintained at 0–5° during the dropwise addition of an aqueous solution of $NaNO_2$ (11.2 g in 44 ml of H_2O). The solution of the diazonium salt was stirred an additional 15 min at 0–5° and added slowly to a stirred aqueous solution of H_2SO_4 (300 ml of a 50% solution) maintained at 90°. The decomposed diazonium salt was kept at 90° for an additional 45 min and cooled. The solid products were collected by filtration and taken up in Et_2O. The Et_2O extract was washed well with 5% $NaHCO_3$ and dried ($MgSO_4$). Evaporation of Et_2O yielded 6.7 g of crude methyl ester, mp 133.5–141°. A sample was recrystallized from C_6H_6 to afford pure 15b (5.4 g, 12.7%): mp 148–150°; ir and nmr (CF_3CO_2H) as expected. *Anal.* ($C_8H_7IO_3$) C, H.

The $NaHCO_3$ wash was acidified and the precipitated acid was extracted into Et_2O. The extract was dried ($MgSO_4$) and evaporated to yield 25.9 g (65.8%) of crude 15a, mp 225–232°. A small sample of the acid was recrystallized twice from Me_2CO–H_2O, mp 227–232°. *Anal.* ($C_7H_5IO_3$) C, H.

3-Hydroxy-5-iodobenzyl Alcohol (16). To a solution of 15 (26.1 g, 0.1 *M*) in dry THF (150 ml) was added dropwise with stirring a 1 *M* BH_3 solution in THF (150 ml). The mixture was stirred at room temperature for 3 hr and excess BH_3 was decomposed by the addition of EtOH. The solvents were evaporated with a minimum of heat and the residue was diluted with H_2O. The product was extracted into Et_2O and the extract was washed with 5% $NaHCO_3$. The dried Et_2O solution ($MgSO_4$ and charcoal) was evaporated to dryness to give crude benzyl alcohol (21.6 g, 86%). Recrystallization of a sample from C_6H_6 yielded a pure white solid which gave a positive $FeCl_3$ test for phenols: mp 92–93°; ir and nmr (CF_3CO_2H) as expected. *Anal.* ($C_7H_7IO_2$) C, H.

3-Benzyloxy-5-iodobenzyl Alcohol (17). The benzyl alcohol 16 (20.9 g, 0.084 *M*) and benzyl chloride (11.4 g, 0.09 *M*) were dissolved in technical DMF (200 ml). Anhydrous K_2CO_3 (12.4 g) was suspended in the solution and the whole suspension was heated to 110° and maintained at that temperature for 2 hr with stirring. The cooled reaction mixture was poured onto cracked ice and the product was extracted into Et_2O. The extract was washed with 10% HCl and dried ($MgSO_4$, charcoal). Removal of the Et_2O left a residue which crystallized to yield 17 (23.6 g, 82%) as a white solid: mp 54.5–56.3°; ir and nmr as expected. *Anal.* ($C_{14}H_{13}IO_2$) C, H.

3-Benzyloxy-5-iodobenzyl Chloride (18). Alcohol 17 (23.6 g, 0.07 *M*) was dissolved in dry diglyme (50 ml) and $SOCl_2$ (10 ml) was added dropwise to the stirred solution maintained at room temperature. The mixture was stirred 8 hr at room temperature and poured into ice–H_2O. The product was taken up in Et_2O and the Et_2O solution washed with 5% $NaHCO_3$ and dried ($MgSO_4$, charcoal). Evaporation of Et_2O left crude 18 (25 g, quantitative) which was essentially pure by tlc (C_6H_6–hexane 1:1). Recrystallization from petroleum ether (bp 30–40°) afforded pure 18: mp 56–58.5°; ir and nmr as expected. *Anal.* ($C_{14}H_{12}ClIO$) C, H.

3-Benzyloxy-5-iodobenzyl Cyanide (19). A solution of 18 (25 g, 0.09 *M*) in technical DMF (25 ml) was added dropwise to a stirred solution of NaCN (9.8 g, 0.2 *M*) in H_2O (15 ml) and technical DMF (100 ml). The reaction mixture was kept at 60° for 3 hr (including the addition time) and stirred overnight at room temperature. The mixture was diluted with ice–H_2O and the product was taken up in Et_2O. The extract was washed with 10% HCl and dried ($MgSO_4$, charcoal). Evaporation of Et_2O left an oily residue (22.8 g). Direct crystallization from EtOH yielded a first crop of solid product. The remaining liquors from the crystallization were evaporated and chromatographed on a silica gel column (14 × 1 in.) using 20% hexane in C_6H_6 as the eluent. The chromatographed product was crystallized from EtOH. Combination of the two products gave essentially pure 19 (18 g, 74%), mp 68.5–71°. A sample was recrystallized twice from EtOH to yield pure 19: mp 69.5–71.5°; ir and nmr as expected. *Anal.* ($C_{15}H_{12}INO$) C, H.

2-(3-Benzyloxy-5-iodophenyl)ethylamine (20). To a solution of 19 (8.4 g, 0.024 *M*) in dry THF (150 ml) at room temperature was added dropwise with stirring a 1 *M* solution of BH_3 in THF (60 ml). The reaction mixture was stirred overnight at room temperature and EtOH was added to decompose the excess BH_3. HCl (g) was passed into the solution and the solvent was evaporated. The residue was washed with a large volume of hot C_6H_6. Evaporation of C_6H_6 yielded a residue (9.2 g) which was recrystallized from C_6H_6 to give pure 20 (4.5 g, 50%) as the HCl salt: mp 156–159°; ir as expected. *Anal.* ($C_{15}H_{17}ClINO$) C, H.

2-(3-Hydroxy-5-iodophenyl)ethylamine (4). The benzyl ether 20 (900 mg) was dissolved in HOAc (4 ml) and HCl (2 ml). The reaction mixture was heated for 2 hr under N_2 at 45° and excess solvent evaporated. Aqueous NaOH was added to effect solution of the product and the aqueous phase was washed with Et_2O. The aqueous phase was titrated with 10% HCl until a solid precipitated. The precipitate was collected and treated with charcoal in THF. The THF was removed by evaporation and the residue was washed with a small quantity of cold EtOH to yield 4 (0.323 g) as a white solid, mp 161.6–163.5°. Recrystallization from EtOH–H_2O gave pure 4: mp 163–163.5°; ir and nmr (CF_3CO_2H) as expected. *Anal.* ($C_8H_{10}INO$) C, H.

***N,N*-Diacetyl-2-(3-acetoxy-5-iodophenyl)ethylamine (21).** A solution of 4 (200 mg) in HOAc (2 ml) and acetic anhydride (2 ml) was heated to gentle reflux for 18 hr. Solvent was removed *in vacuo*, the residue dissolved in H_2O (3 ml), and the resulting solution made basic with 10% NaOH solution. The solid was collected, washed with H_2O, and recrystallized from aqueous EtOH to give 21 (120 mg, 41%) as colorless crystals: mp 97–99°; ir and nmr as expected. *Anal.* ($C_{14}H_{16}INO_4$) C, H.

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