In Vitro O-Demethylation of the Psychotomimetic Amine, 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane[1]

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Received March 11, 1976

The possible relationship between metabolism and psychotomimetic activity among the methoxylated 1-phenyl-2-aminopropanes led to our investigation of the in vitro O-demethylation of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (1, DOM, STP). Employing a sensitive and highly selective stable isotope dilution assay, we observed that rabbit liver homogenates biotransform the amine 1 to its 2-*O*-demethyl, 5-*O*-demethyl, and bis(*O*-demethyl) metabolites. Both monophenolic metabolites are enriched in their *S* enantiomers. The bis(*O*-demethyl) metabolite has structural, chemical, and electrochemical similarities to the sympatholytic agent "6-hydroxydopamine". The possible significance of metabolic O-demethylation in terms of the psychotomimetic properties of amine 1 is discussed.

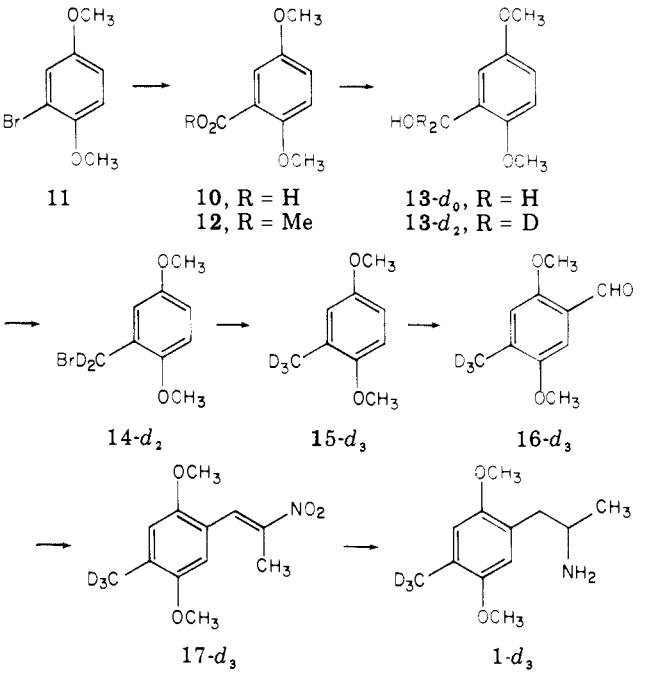
The profound effects of psychotomimetic substances on behavior and perception have been the subject of extensive discussions in both the popular and scientific literature.[2] Interest in this area stems in part from similarities between drug-induced states and human psychotic behavior.[3] Evidence indicating a genetic basis for schizophrenia[4] implies the involvement of a biochemical lesion. This concept is consistent with the controversial[5] report that dopamine β-hydroxylase activities are significantly lower in schizophrenic than in normal postmortem brain tissues.[6] We are interested in the possibility that such biochemical lesions may also be caused by neurotoxic metabolites derived from the psychotomimetic 1-phenyl-2-aminopropanes,[7-9] such as the title compound, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**1**).

In man, (*R,S*)-**1** is reported to be 80 times more potent than mescaline.[7] Human[10] and animal[11] investigations indicate that the *R* enantiomers (**a**) in this series are considerably more psychoactive than the *S* enantiomers (b). In vivo[12] and in vitro[13] metabolic studies have established that (*S*)-**1** (**1b**) is more rapidly metabolized than (*R*)-**1** (**1a**) which may account in part for the observed pharmacological stereoselectivity. Shulgin et al.[7] proposed that the psychotomimetic activity of 1-phenyl-2-aminopropanes may be related to their metabolic conversion to indole derivatives. In the case of amine **1**, this process could involve metabolic bis-O-demethylation to the hydroquinone **2** followed by oxidative cyclization. This metabolic sequence was of special interest to us because hydroquinone **2** is an analogue of the neurotoxin "6-hydroxydopamine" (**3**).[14] [A more correct chemical name for **3** is 2-(2,4,5-trihydroxyphenyl)ethylamine. Chemical Abstracts lists **3** as benzeneethanamine, 2,4,5-trihydroxy.] Both **2**[15] and **3**[16,17] are readily converted to their corresponding indole derivatives **4** and **5**.

Previous studies[12,13,18] have shown that oxidation of the aromatic methyl group of **1** to the hydroxymethyl and carboxy compounds (**6** and **7**) is a major pathway for the metabolism of this compound. A number of aryl alkyl ethers, however, are known to undergo metabolic O-dealkylation[19] and phenolic metabolites of amine **1** have been detected mass spectrometrically.[13] In order to characterize more fully the metabolic fate of **1** and to explore the possible formation of potentially neurotoxic compounds, we investigated the metabolic formation of the hydroquinone **2** and the two monophenols **8** and **9** in 10 000g rabbit liver supernatant fractions. We also examined the stereoselectivity associated with the mono-O-demethylations.

Assays of mono-O-demethylation metabolites used **1**-d_2 (side-chain label) as substrate. For reasons which become apparent below, amine **1**-d_3 (ring methyl label) was used in studies of bis-O-demethylation.

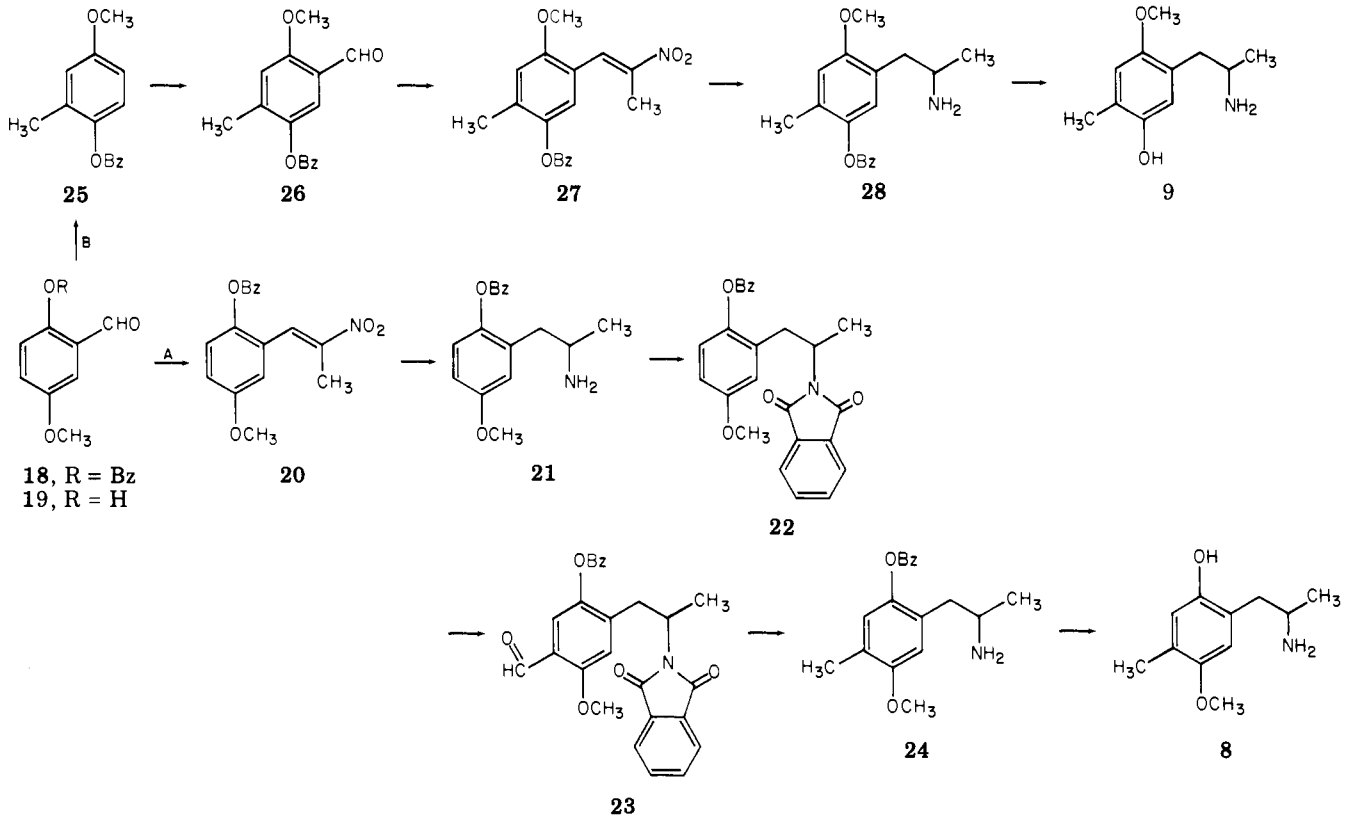
Scheme I. Synthesis of Labeled Substrate **1**-d_3



Preparation of Suspected Metabolites and Deuterated Compounds. Substrate amine **1**-d_2 was prepared by $LiAlD_4$ reduction of the corresponding 1-phenyl-2-nitropropene.[12] The resolutions of amines **1**-d_0 and **1**-d_2 were performed by repeated crystallization of their *o*-nitrotartranilate salts.[12] Compounds **1**-d_6,[13] **2**-d_0, and **4**-d_0[15] were available from earlier work.

The synthesis of amine **1**-d_3 (Scheme I) proceeded by way of 2,5-dimethoxybenzoic acid (**10**) which was prepared from the bromobenzene derivative **11** via a Grignard carbonation reaction. The methyl ester **12** was reduced with $LiAlD_4$ to give high yields of the benzyl alcohol **13**-d_0 (or **13**-d_2). The NMR spectrum of **13**-d_0 exhibited a benzyl proton signal as a sharp singlet at δ 4.64 ppm which was absent in the spectrum of **13**-d_2. Upon treatment of the alcohol with tosyl chloride, we found we were unable to isolate the theoretically reducible tosylate, presumably because of the instability of methoxybenzyl tosylates.[20] Instead, the alcohol **13**-d_2 was converted with PBr_3[21] to the corresponding bromo derivative **14**-d_2 which was then reduced with $LiAlD_4$ to the trideuteriomethyl compound **15**-d_3. Formylation of **15**-d_3 gave the benzaldehyde **16**-d_3 which when treated with nitroethane and NH_4OAc yielded the phenylnitropropene **17**-d_3. Finally, $LiAlH_4$ reduction gave the desired amine **1**-d_3, the NMR spectrum of which

Scheme II. Synthesis of Unlabeled Monophenolic Standards 8-d_0 and 9-d_0

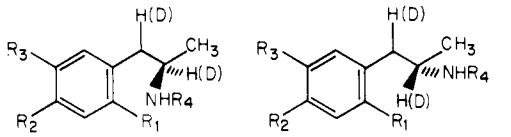


was identical with that of amine 1-d_0 except that the sharp aromatic methyl absorbance at δ 2.23 ppm was undetectable. The chemical ionization (CI) mass spectrum displayed the expected MH^+ ion at 213 with no detectable d_1 or d_2 contaminant. Amine 1-d_3 was stored and used as its high-melting hydrochloride salt.

The syntheses of the two monophenolic compounds 8-d_0 and 9-d_0 are shown in Scheme II. Both pathways started with the benzyl ether **18** of commercially available 2-hydroxy-5-methoxybenzaldehyde (**19**). The sequence to **8** (route A, Scheme II) proceeded via the 1-phenyl-2-nitropropene **20** which was reduced with $LiAlH_4$ to the phenylaminopropane **21**. The C-4 methyl substituent of **8** was introduced by Vilsmeier formylation[22] of the phthalimide **22** to yield aldehyde **23** followed by simultaneous Wolff–Kischner reduction[23] of the resultant benzaldehyde and hydrazinolysis of the phthalimido group. The unique placement at C-4 of the methyl group in intermediate **24** was confirmed by GLC analysis (one peak) and by NMR which showed two singlets at δ 6.73 and 6.82 ppm, consistent with the para orientation of the two aromatic protons. The *O*-benzyl group of amine **24** was cleaved in 12 N HCl at room temperature[24] to give the hydrochloride of the desired aminophenol **8**.

The synthesis of the second unlabeled monophenol **9** (route B, Scheme II) proceeded by reduction of the aldehyde function of **18** with hydrazine and base to yield the toluene derivative **25**. Vilsmeier formylation of **25** and condensation of the resultant benzaldehyde **26** with nitroethane, followed by $LiAlH_4$ reduction of the resulting 1-phenyl-2-nitropropene **27**, gave the benzyloxy-1-phenyl-2-aminopropane **28**. Debenzylation of **28** in 12 N HCl yielded the hydrochloride of aminophenol **9**. Chemical purities of the two monophenolic compounds **8** and **9** were confirmed by elemental and mass spectral analyses. The NMR spectra of **8** and **9** were similar to that of parent amine **1**, except that each compound exhibited only one three-proton singlet near δ 3.9 ppm.

Chart I



a b

Compd	R_1	R_2[a]	R_3	R_4
1-d_0 (d_2)	OCH_3	CH_3	OCH_3	H
1-d_6	OCD_3	CH_3	OCD_3	H
2-d_0	OH	CH_3	OH	H
6	OCH_3	$HOCH_2$	OCH_3	H
7	OCH_3	HOOC	OCH_3	H
8-d_0 (d_2)	OH	CH_3	OCH_3	H
9-d_0 (d_2)	OCH_3	CH_3	OH	H
29-d_0 (d_2)	$OCOC_2F_5$	CH_3	OCH_3	COC_2F_5
30-d_0 (d_2)	OCH_3	CH_3	$OCOC_2F_5$	COC_2F_5
31-d_0 (d_2)	OCH_3	CH_3	OCH_3	COC_2F_5
37-d_0	$OCOC_2F_5$	CH_3	$OCOC_2F_5$	COC_2F_5

[a] For d_3 compounds, $R_2 = CD_3$.

Results and Discussion

Mono-O-demethylation. Because of the chemical instability of the hydroquinone **2**,[18] our initial studies focused on the metabolic formation of the monophenolic compounds **8** and **9**. After incubation of the substrate (1-d_2) with the enzyme system, accurately measured amounts of 8-d_0, 9-d_0, and 1-d_0 were added as internal standards for the mass spectral analyses. The metabolic (d_2) and standard (d_0) monophenols and unconsumed (d_2) and standard (d_0) amine **1** were extracted from the incubation mixtures at pH 9.5–10 and the extracts treated with pentafluoropropionic anhydride (PFPA) to give the acylated derivatives **29**, **30**, and **31** (from **8**, **9**, and **1**, respectively) (see Chart I). Acylation significantly improved the amines' behavior on the GLC column. The effluents whose retention times corresponded to those of authentic

Table I. Mono-O-demethylations of 1-d_2[a]

Substrate, μmol of 1-d_2/g of liver	% metabolized	2-O-Demethyl metabolite obsd: μmol of 8-d_2/g of liver	2-O-Demethyl metabolite obsd: % initial substrate	2-O-Demethyl metabolite obsd: μmol of 9-d_2/g of liver	2-O-Demethyl metabolite obsd: % initial substrate
0.6	97	43	7.0	14	2.3
1.1	81	100	8.8	44	3.8
2.0	39	140	6.8	80	3.7
2.1[b]		220	11.0	130	5.9
2.1[b]		210	10.0	120	5.7

[a] Incubations were carried out for 1 h with shaking at 37 °C in 14.0 ml of 10000 g supernatant fraction (0.25 M sucrose–0.2 M Tris buffer, pH 7.4, equivalent to 2 g of liver) which was added to substrate, NADPH (17 mg), and $MgCl_2$ (1.6 ml of 0.1 M solution). [b] These two incubations used the same liver homogenate.

29, **30**, and **31** were collected using a 10:1 effluent flow splitter and subjected to CI mass spectral analysis. Above m/e 100, the mass spectra appeared remarkably clean. The peaks due to deuterated, bis-acylated phenolic metabolites [m/e 490 (**29**-d_2 and **30**-d_2)], unlabeled bis-acylated phenolic internal standards [m/e 488 (**29**-d_0 and **30**-d_0)], unconsumed monoacylated substrate [m/e 358 (**31**-d_2)], and unlabeled monoacylated parent amine [m/e 356 (**31**-d_0)] dominated the spectra. The ratios of molecular ion (MH^+) intensities provided direct measurements of the amounts of deuterated metabolites and unconsumed 1-d_2 since the concentrations of each internal standard were known. In each run, the relevant mass regions were scanned at least three times during which period the ion intensity ratios for the d_2:d_0 species remained essentially constant. High-resolution analyses confirmed the metabolite structure assignments: calcd, 490.105; found, (for **29**-d_2) 490.106, (for **30**-d_2) 490.105. When the entire experiment was carried out in the absence of deuterated substrate, no significant peaks were observed at m/e 358 or 490 although the internal standards were clearly visible.

The results obtained from several incubations are summarized in Table I. Both the 2- and the 5-O-demethylated metabolites were found in substantial amounts in all experiments with compound 8-d_2 accounting for up to 11% of the initial substrate incubated. Higher initial substrate concentrations generally yielded a higher percentage of the monophenols which may indicate that the monophenols themselves are substrates for further metabolic alterations. Since the rates of formation and subsequent metabolism of these compounds are not known, it is not possible to interpret the values listed in Table I in terms of the quantitative importance of the specific metabolic pathways involved.

To investigate the stereochemical composition of monophenolic metabolites **8** and **9**, the incubations were performed using two "pseudoracemic" mixtures (**1a**-d_0:**1b**-d_2 and **1a**-d_2:**1b**-d_0). Following each incubation, a measured amount of amine 1-d_6 was added as an internal standard for estimation of total metabolic consumption of **1**. The amines of interest were purified as described above. Mass spectral analysis of the acylated fractions established the d_0:d_2 ratios for **29**, **30**, and **31** and thus the enantiomeric composition of **8**, **9**, and **1**.

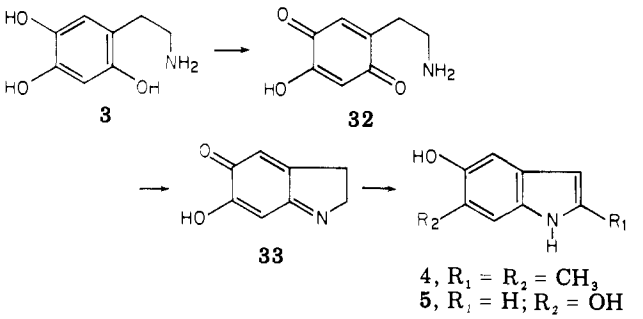
The mono-O-demethylation stereochemical studies (Table II) show that both **8** and **9** accumulate enriched in their *S* (b) enantiomers. The stereoselective effect is more pronounced for the 2- than for the 5-O-demethyl compound and was observed regardless of whether **1a**-d_2:**1b**-d_0 or **1a**-d_0:**1b**-d_2 served as substrate. The ratios of **8b** to **8a** ranged from 6.6 to 12.5 and those of **9b** to **9a** from 1.5 to 3.4. Comparative kinetic profiles for these metabolic conversions will be required before the responsible stereochemical events can be defined. At the present time one can only state that the net effect is the accumulation of the *S* monophenolic metabolites, due either to their stereoselective formation or to stereoselectivity in a subsequent metabolic conversion.

Table II. Stereochemistry of Mono-O-demethylations of 1[a]

"Pseudoracemic" substrate[b]	μmol/g of liver	% metabolized	Final enantiomeric ratios (S/R): 1	8	9
1a-d_2:**1b**-d_0	2.4	60	0.9	12.5	1.5
1a-d_0:**1b**-d_2	2.4	42	0.6	6.6	2.0
1a-d_2:**1b**-d_0	2.0	58	0.4	7.2	2.2
1a-d_0:**1b**-d_2	2.0	63	0.7	9.1	3.4

[a] Incubations were carried out as described in Table I, footnote *a*. [b] Substrates were composed of equal amounts of the *R* and *S* enantiomers in each experiment.

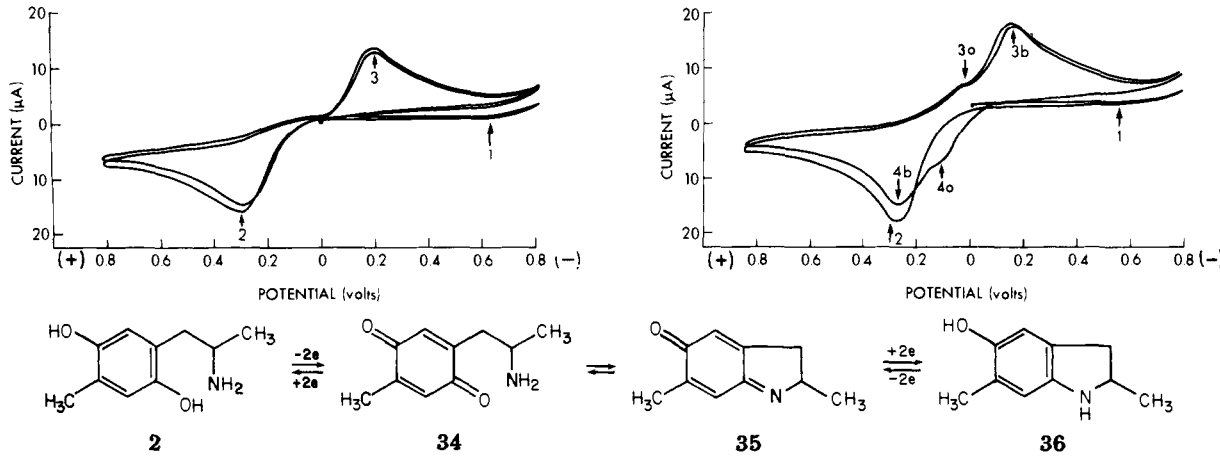
Scheme III



4, $R_1 = R_2 = CH_3$
5, $R_1 = H$; $R_2 = OH$

Bis-O-demethylation. The *p*-hydroquinone **2** is an analogue of the neurodegenerative agent 6-hydroxydopamine (**3**).[25-27] Central administration of this drug causes analogous neurodegenerative effects in brain tissue[28] as well as behavioral changes in animals.[29] On the basis of such evidence Stein and Wise proposed that the etiology of schizophrenia may be associated with the abberant metabolic conversion of brain dopamine to 6-hydroxydopamine.[30]

Although the issue is controversial,[31] neuronal damage by 6-hydroxydopamine appears to involve oxidation of **3** to form the quinone **32** which will be in equilibrium with **33** (Scheme III).[32] These electron-deficient species may undergo attack by nucleophilic moieties on macromolecules, leading to altered macromolecular structure and function. The redox characteristics and chemical reactivities associated with the oxidation of 6-hydroxydopamine have been investigated by Adams and coworkers.[17] Since the hydroquinone **2** is an analogue of 6-hydroxydopamine, we examined the electrochemical behavior of this compound in buffer at various pH values. Figure 1 (top) displays the cyclic voltammograms of synthetic **2** at pH 6 and 7.4. At pH 6 the reversible couple hydroquinone **2** ⇌ quinone **34** is observed. At pH 7.4, however, the tracing becomes considerably more complex. During the initial reductive (cathodic) pass (1) no flow of current is observed since no reducible species are present. With the first oxidative (anodic) pass current flow (2) corresponding to the oxidation of **2** to quinone **34** is recorded, analogous to the tracing obtained at pH 6. The second reductive pass, however, shows two peaks (3a and 3b). Similarly, the second oxidative pass shows two peaks (4a and 4b). The sequence of reactions associated with these electrochemical events is illustrated structurally in



2 34 35 36

Figure 1. Upper left: cyclic voltammogram of 2 (0.2 mM) in Robinson–Britton buffer at pH 6. Upper right: cyclic voltammogram of 2 (0.2 mM) in Robinson–Britton buffer at pH 7.4. Lower: structural changes occurring during cyclic voltammetry.

Figure 1 (bottom). At pH 7.4 the quinone **34** undergoes intramolecular cyclization to generate the quinone imine **35** which forms a second redox couple with the indoline **36**. Since hydroquinone **2** is readily oxidized at pH 7.4 in the presence of air to generate the strongly UV-absorbing quinone imine **35**, we were able to characterize this reaction sequence spectrophotometrically.[18] As the pH of the solution is raised, **35** rapidly isomerizes to the relatively stable indolol **4**. This sequence is analogous to that suggested for the formation of 5,6-dihydroxyindole (**5**) from 6-hydroxydopamine (**3**).[17]

The chemical reactivity of hydroquinone **2** suggested that 1-d_2 would not be an appropriate substrate for an investigation of the bis-O-demethylation pathway since conversion of **2** to indolol **4** involves partial loss of the side-chain deuterium label. With amine 1-d_3 as substrate it would be possible to monitor the formation of both hydroquinone **2** and indolol **4**.

Following incubation of 1-d_3 (2 μmol/g of liver) with the 10 000g rabbit liver supernatant preparation, measured amounts of 1-d_0 and 4-d_0 were added as internal standards. The pH was adjusted to 9.5–10 and the mixture allowed to stand for 10 min before extraction so that any metabolic hydroquinone 2-d_3 present could undergo conversion to indolol 4-d_3. Since GLC analysis indicated that **4** decomposes upon warming in PFPA, this reagent was unsatisfactory for derivatization. Instead, the crude extracts were analyzed mass spectrometrically at low and high resolution. Metabolic indolol 4-d_3 could not be observed in three separate studies even though substrate consumption was >40% and internal standard 4-d_0 (2.6 μg or 0.016 μmol/g of liver) was readily detected.

Failure to find any indole derived from 1-d_3 did not preclude the possibility that metabolic bis-O-demethylation had occurred. The electron-deficient intermediates **34** and/or **35** could be captured by nucleophiles present in the incubate. Another possibility is that air oxidation of hydroquinone **2** at pH 7.4 is inhibited by constituents of the liver preparations. We[33] and others[34] have observed inhibition of aliphatic hydroxylamine air oxidations in similar systems. We therefore decided to search for the unstable hydroquinone itself. Because of the base sensitivity and polarity of **2**, the isolation of aminophenolic metabolites required cation-exchange chromatography. This, in turn, necessitated substitution of phosphate buffer for the Tris buffer previously used to avoid saturation of the ion-exchange binding sites (see Experimental Section for details). When authentic 2-d_0 (10 μg) was carried through this procedure, it was possible to obtain a clean GLC peak for the expected Tris–PFP derivative, 37-d_0, which gave the required parent (MH^+) ion at 620.

The metabolic study was then undertaken with 1-d_3 as substrate in phosphate buffer. After precipitation of protein with trichloroacetic acid, unlabeled hydroquinone amine 2-d_0, the two unlabeled monophenolic amines, 8-d_0 and 9-d_0, and unlabeled 1-d_0 were added as internal standards. The amines were purified by ion-exchange chromatography, derivatized with PFPA, and separated by GLC. The GLC tracing of the PFP derivatives showed peaks corresponding to **37** and **29** with a small peak for **30** but none for **31**. This is roughly consistent with the observed solubilities of the hydrochlorides of these amines in cold PFPA. Analysis by CI-MS of the collected fractions showed that at an initial substrate concentration of 2.34 μmol of 1-d_3/g of liver, 12% (0.280 μmol/g of liver) appeared as the bis-*O*-demethyl metabolite 2-d_3 while 16% (0.395 μmol/g of liver) appeared as the 2-*O*-demethyl metabolite 8-d_3. Insufficient amounts of the 5-*O*-demethyl derivative were collected for mass spectral analyses. To be certain there was no ether cleavage of 1-d_3 during work-up, 1-d_0 was carried through the entire procedure starting with the trichloroacetic acid treatment. The CI mass spectrum of the acylated residue showed a large peak at m/e 356 (31-d_0) but only background current at m/e 488 and 620, thus confirming the stability of the phenyl methyl ether linkages to work-up conditions. Detailed studies on the chemical stabilities of **8** and **9** confirm that the hydroquinone **2** does not arise as an artifact from these compounds.[35]

The psychotomimetic amine **1** thus undergoes metabolic O-demethylation to give significant amounts of the monophenols **8** and **9** and the hydroquinone **2** in vitro. The chemical behavior of hydroquinone **2** is analogous to the structurally closely related neurotoxin 6-hydroxydopamine. The conjecture that **2** possesses neurotoxic properties analogous to 6-hydroxydopamine arises naturally from these observations. If experimental evidence supports this conjecture, further studies into the potential role of metabolically formed **2** in the psychotomimetic effects of amine **1** would be of great interest.

Experimental Section

Reactions were performed under atmospheres of argon or N_2. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer Model 337 grating spectrophotometer. NMR spectra were taken on a Varian Associates A-60A instrument and chemical shifts are reported in parts per million (δ) downfield relative to Me_4Si (for $CDCl_3$) or Me_2SO-d_6 or DSS (for D_2O). CI-MS analyses were obtained using isobutane (0.7 Torr) as reactant gas and probe temperatures ranging from 180 to 240 °C. All GLC analyses were

performed on a Varian Aerograph 2100 life sciences gas chromatograph equipped with a hydrogen flame ionization detector and using N_2 carrier gas (30 ml/min) and 2 m × 2 mm U-shaped glass columns packed with acid-washed DMCS-treated Chromosorb W coated with 3% OV 25. The cyclic voltammograms were recorded on a three electrode potentiostat.[36] Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., or by the Microanalytical Lab of the University of California, Berkeley.

2,5-Dimethoxybenzoic Acid (10). Magnesium turnings (1.12 g, 46.1 mmol) were placed in a three-neck flask fitted with a magnetic stirring bar and dropping funnel and the entire system was flame dried. A few milliliters of a solution of 2,5-dimethoxybromobenzene (11, 10.0 g, 46.1 mmol) in 60 ml of anhydrous ether was added to the turnings and the reaction was initiated with a small amount of iodoethane. The remaining bromobenzene solution was added dropwise over 20 min and the stirring was continued until the reaction had subsided. Additional Mg (1 g) was added; the reaction was stirred for an additional hour at room temperature and then heated at reflux for 10 min. The cooled reaction mixture was poured slowly with vigorous stirring into a beaker containing 30 g of crushed dry ice. After the carbonation reaction had subsided, the remaining Grignard adduct was washed into the dry ice slurry with ether. Once the excess dry ice had sublimed, ice (20 g) followed by water (20 ml) was added with vigorous stirring. The mixture was cautiously acidified with 20 ml of 12 N HCl and extracted twice with 50-ml portions of ether. The combined ether extracts were shaken with 10% NaOH (2 × 40 ml). The combined basic washings were decolorized with Norit and, after cooling to 3 °C, acidified with 12 N HCl. The oil which settled to the bottom of the flask was extracted with chloroform (2 × 40 ml) and the dried ($MgSO_4$) extract concentrated to give 4.89 g (26.9 mmol, 58%) of the crude product which was crystallized from ethanol–water to yield pure acid (4.20 g, 23.1 mmol, 50%): mp 71–75 °C (lit.[37] mp 76 °C); NMR ($CDCl_2$) δ 10.80 (s, OH), 7.6, 7.1 (m, ArH), 4.06 and 3.81 (s, CH_3). The methyl ester **12** was obtained by heating the acid (50 g, 275 mmol) in freshly distilled thionyl chloride under reflux (65.5 g, 550 mmol) for 3 h followed (after cooling to 3 °C) by addition of methanol (55 g, 1.7 mmol). The neutral fraction was isolated and distilled [bp 125 °C (0.5 mm) [lit.[38] bp 167–168 °C (14 mm)]] to give pure ester (50 g, 255 mmol, 93%): NMR ($CDCl_3$) δ 7.4, 7.0 (m, ArH), 3.90, 3.85, 3.78 (s, CH_3O).

2,5-Dimethoxybenzyl Alcohol-α,α-d_2 (13-d_2). A magnetically stirred suspension of $LiAlD_4$ (1.16 g, 27.6 mmol) in dry THF (75 ml) was cooled to 3 °C. A solution of ester **12** (6.00 g, 30.6 mmol) in dry THF (50 ml) was added dropwise over 15 min and the reaction mixture was stirred overnight. After cooling and dropwise addition of 1.2 ml of water, 1.2 ml of 15% NaOH, and 3.3 ml of water, the reaction mixture was stirred for an additional 30 min and then filtered. The white aluminate salts were washed with ether; the combined filtrate and washings were dried ($MgSO_4$) and concentrated to give 5.73 g of a clear oil. This oil was distilled under vacuum to yield 4.70 g (90%) of pure **13**-d_2: bp 98–115 °C (100 μm) (lit.[39] bp 278–279 °C); NMR ($CDCl_3$) δ 6.95, 6.76 (m, ArH), 3.71, 3.69 (s, CH_3O), 3.26 (s, OH, exchangable with D_2O); no detectable benzyl proton signal at δ 4.64 ppm.

2,5-Dimethoxybenzyl Bromide-α,α-d_2 (14-d_2). A solution of **13**-d_2 (2.80 g, 16.7 mmol) in 25 ml of dry carbon tetrachloride was cooled to 3 °C and then PBr_3 (1.50 g, 5.54 mmol) in 10 ml of dry carbon tetrachloride was added dropwise with stirring. Upon addition of the first few milliliters of PBr_3 solution, a white precipitate formed; this precipitate dissolved as more PBr_3 was added. The reaction mixture was stirred overnight at room temperature and then filtered to remove a brownish residue. The filter paper was washed with a few milliliters of carbon tetrachloride; the combined filtrate and washings were dried ($MgSO_4$) and concentrated to give 3.58 g of a yellow oil. Sublimation at 90–100 °C (100 μm) gave pure **14**-d_2 (2.5 g, 12.6 mmol, 75%): mp 73–75 °C (lit.[21] mp 75–76 °C); NMR ($CDCl_3$) δ 6.92 (m, ArH), 3.88, 3.80 (s, CH_3O); no detectable benzyl proton signal at δ 4.55 ppm.

2,5-Dimethoxytoluene-α,α,α-d_3 (15-d_3). A stirred suspension of $LiAlD_4$ (2.00 g, 47.6 mmol) in dry THF (50 ml) was cooled to 3 °C and a solution of **14**-d_2 (19.4 g, 96.7 mmol) in 50 ml of dry THF was added dropwise with stirring. The mixture was stirred for an additional hour at room temperature and then at reflux for 45 h. After cooling to 3 °C, 2 ml of water, 2 ml of 15% NaOH, and 6 ml of water were added. The mixture was stirred for an additional 30 min and then filtered. The precipitate was washed with ether; the combined filtrate and washings were dried ($MgSO_4$) and concentrated to give 12.0 g of a yellowish oil. Distillation gave 11.5 g of pure **15**-d_3 (74%): bp 78–81 °C (4 mm) (lit.[40] bp 214–218 °C); NMR ($CDCl_3$) δ 6.70 ppm (s, ArH), 3.75, 3.73 (s, CH_3O), no detectable aromatic methyl signal.

2,5-Dimethoxy-4-trideuteriomethylbenzaldehyde (16-d_3). Freshly distilled $POCl_3$ (22.3 g, 146 mmol) was added dropwise to magnetically stirred *N*-methylformanilide (19.7 g, 146 mmol) over the course of 10 min during which time the mixture turned deep red. After an additional 20 min, **15**-d_3 (11.3 g, 72.9 mmol) was added dropwise with continued stirring. The reaction was allowed to proceed an additional 15 min at room temperature and then at 105 °C for 2 h. After cooling, the mixture was poured onto ice with vigorous stirring. The pH of the resulting dark-colored mixture was adjusted to 8 by addition of solid K_2CO_3 and the mixture was extracted with ether (2 × 150 ml). The extracts were dried ($MgSO_4$) and concentrated to give a brown oil which solidified (14.5 g) on standing in vacuo. The crude aldehyde was stirred for 15 min with $NaHSO_3$ (50 g, 4.80 mmol) in 25% ethanol–water and the mixture then was filtered. The solid bisulfite addition product was washed with ether (60 ml) which removed most of the color and then was stirred for 15 min with 2 N HCl. The precipitate was collected, washed with water, and crystallized from ethanol to give yellow crystals (3.8 g). Recrystallization from ethanol yielded 2.3 g (17%) of pure product: mp 82–83 °C (lit.[41] mp 85–87 °C); NMR, no detectable aromatic methyl signal.

1-(2,5-Dimethoxy-4-trideuteriomethylphenyl)-2-nitropropene (17-d_3). A mixture of **16**-d_3 (2.25 g, 12.3 mmol) and NH_4OAc (0.474 g, 6.16 mmol) in nitroethane (26.1 g, 347 mmol, 25 ml) was held at reflux for 4 h. After cooling to room temperature, the mixture was concentrated under vacuum. Recrystallization of the yellow solid from ethanol gave 2.32 g (9.6 mmol, 79%) of yellow crystals: mp 90–91 °C (lit.[12] mp 85–87 °C); NMR, no detectable aromatic methyl signal.

1-(2,5-Dimethoxy-4-trideuteriomethylphenyl)-2-aminopropane Hydrochloride (1-d_3·HCl). A stirred suspension of $LiAlH_4$ (1.45 g, 38.4 mmol) in freshly distilled (from $LiAlH_4$) THF (50 ml) was cooled in an ice bath and a solution of **17**-d_3 (2.32 g, 9.59 mmol) in 30 ml of dry THF was added dropwise. The reaction mixture was stirred overnight and the excess hydride decomposed by the addition of 1.5 ml of water followed by 1.5 ml of 15% NaOH and 4.5 ml of water. Ether (20 ml) was added and the reaction mixture was stirred for an additional 15 min and then filtered. The filter cake was washed with ether and the combined filtrate and washings were dried (K_2CO_3) and concentrated to give 1.98 g of crude product. Sublimation [80–85 °C (100 μm)] gave the pure **1**-d_3 which was dissolved in 75 ml of ether. This solution was filtered and to the filtrate was added a small amount of ether saturated with dry HCl gas. The white amine hydrochloride salt was collected by suction filtration and washed with a small amount of ether to give 1.45 g. Recrystallization from ethanol yielded 1.2 g (4.8 mmol, 50%) of pure **1**-d_3·HCl: mp 187–189 °C (lit.[42] mp 184–185 °C); NMR (D_2O) δ 7.10, 7.07 (s, ArH), 3.97 (s, CH_3O), 3.03 (d, CH_2, J = 7 Hz), 1.40 (d, CH_3, J = 6.5 Hz), no detectable aromatic methyl signal; CI-MS 212 (MH^+), no detectable d_0, d_1, or d_2 contaminant.

1-(2-Benzyloxy-5-methoxyphenyl)-2-nitropropene (20). A mixture of 2-benzyloxy-5-methoxybenzaldehyde (**18**,[43] 30.0 g, 123 mmol), NH_4OAc (4.76 g, 61.5 mmol), and nitroethane (100 ml) was stirred at reflux for 4 h. The solvent was removed under vacuum leaving a yellow solid which was crystallized from ethanol to give 26.6 g (89 mmol, 72%) of the bright yellow product. Recrystallization from ethanol afforded the analytical sample: mp 75.5–77 °C; NMR ($CDCl_3$) δ 8.31 (br, vinyl H), 7.37 (s, C_6H_5), 6.95 (m, ArH), 5.09 (s, CH_2), 3.78 (s, OCH_3), 2.38 (d, CH_3, J = 1 Hz). Anal. ($C_{17}H_{17}NO_4$) C, H, N.

1-(2-Benzyloxy-5-methoxyphenyl)-2-aminopropane Hydrochloride (21·HCl). A stirred suspension of $LiAlH_4$ (12.7 g, 337 mmol) in dry THF (200 ml) was cooled in ice and a solution of **20** (25.0 g, 83.7 mmol) in 100 ml of dry THF was added dropwise. The reaction was allowed to proceed overnight and

the excess hydride was decomposed by the dropwise addition of 12.7 ml of water, 12.7 ml of 15% NaOH, 100 ml of ether, and 38 ml of water. The reaction mixture was stirred for an additional 0.5 h and then was filtered. The white precipitate was washed with ether; the combined filtrate and washings were dried (K_2CO_3) and concentrated under vacuum to give 22.6 g of the crude product. Vacuum distillation gave 17.9 g (66.1 mmol, 79%) of the pure amine: bp 160–165 °C (150 μm); NMR ($CDCl_3$) δ 7.37 (s, C_6H_5), 6.77 (m, ArH), 4.97 (s, OCH_2), 3.69 (s, CH_3O), 3.18 (m, CH), 2.60 (m, CH_2), 1.05 (d, CH_3, J = 6 Hz). For preparation of the analytical sample, a small amount of the distilled amine in ether was treated with ether saturated with dry HCl gas to precipitate the amine hydrochloride. The white solid was collected and recrystallized from ethanol: mp 170–171.5 °C. Anal. ($C_{17}H_{22}NO_2Cl$) C, H, N.

1-(2-Benzyloxy-5-methoxyphenyl)-2-aminopropane-*N*-phthalimide (22). A mixture of free base **21** (12.2 g, 45.0 mmol), phthalic anhydride (6.8 g, 46.0 mmol), and dry toluene (100 ml) in a round-bottom flask equipped with a Dean-Stark trap and drying tube was immersed in an oil bath preheated to 145 °C and was held at reflux for 4 h. At the end of this period the solvent was removed and the residue was recrystallized from ethanol to give 10.6 g (26.4 mmol, 59%) of phthalimide **22**: mp 79–84 °C. Another recrystallization from ethanol afforded the analytical sample: mp 83–85 °C; NMR ($CDCl_3$) δ 7.8–7.3 (m, C_6H_4), 7.42 (m, C_6H_5), 6.70 (m, ArH), 5.03 (s, OCH_2), 4.85 (m, CH), 3.57 (s, CH_3O), 3.25 (m, CH_2), 1.53 (d, CH_3, J = 7 Hz). Anal. ($C_{25}H_{23}NO_4$) C, H, N.

1-(2-Benzyloxy-4-formyl-5-methoxyphenyl)-2-aminopropane-*N*-phthalimide (23). *N*-Methylformanilide (2.08 g, 15.4 mmol) and $POCl_3$ (2.29 g, 15.0 mmol) were stirred for 1 h at room temperature. Compound **22** (1.50 g, 3.75 mmol) was added and the mixture was stirred for 5 h at 95 °C. The mixture was then poured into 200 ml of cold, saturated $KHCO_3$ solution and worked vigorously with a glass stirring rod while being extracted into three 200-ml portions of ether. The organic extracts were dried ($MgSO_4$) and concentrated under vacuum to give 2.4 g of a tan solid. Three recrystallizations from ethanol gave 0.45 g (1.05 mmol, 28%) of pure **23**: mp 124–126 °C; NMR ($CDCl_3$) δ 10.37 (s, CHO), 7.37 (s, C_6H_5), 7.42 (m, C_6H_4), 7.36 (s, ArH), 5.08 (s, OCH_2), 4.90 (m, CH), 3.68 (s, CH_3O), 3.40 (m, CH_2), 1.58 (d, CH_3, J = 6.5 Hz). Anal. ($C_{26}H_{23}NO_5$) C, H, N.

1-(2-Benzyloxy-4-methyl-5-methoxyphenyl)-2-aminopropane Hydrochloride (24·HCl). A mixture of **23** (9.05 g, 21.1 mmol), hydrazine hydrate (16.9 g, 338 mmol), and triethylene glycol (125 ml) was stirred 1 h at 135–145 °C. Potassium hydroxide (5.57 g of 85% pellets, 84.4 mmol) was added and gas evolution was observed by means of a bubbler. When gas evolution was no longer detectable, the bath temperature was raised to 185 °C. The hot mixture was poured into 400 ml of ice water and then extracted into chloroform (3 × 200 ml). The organic extracts were back-washed twice with 75 ml of water, dried (K_2CO_3), and concentrated to give 6.6 g of a yellow oil. The crude amine in 50 ml of dry ether was again dried over K_2CO_3. To the filtered solution was added ether saturated with dry HCl gas until no additional salt precipitated. Two recrystallizations from methanol–ether gave 2.75 g (41%) of analytically pure **24**·HCl: mp 197.5–199 °C; NMR (free amine, $CDCl_3$) δ 7.42 (s, C_6H_5), 6.80, 6.70 (s, ArH), 5.03 (s, $ArCH_2$), 3.81 (s, MeO), 3.25 (m, CH), 2.72 (m, CH_2), 2.20 (s, $ArCH_3$), 1.11 (d, CH_3, J = 6.5 Hz). Anal. ($C_{18}H_{24}NO_2Cl$) C, H, N.

1-(2-Hydroxy-4-methyl-5-methoxyphenyl)-2-aminopropane Hydrochloride (8·HCl). A mixture of **24**·HCl (1.50 g, 4.67 mmol), 50 ml of 12 N HCl, and 50 ml of benzene was stirred vigorously overnight at room temperature. Concentration under vacuum left a yellow solid which was crystallized from ethyl acetate–ethanol to yield 0.74 g of yellow crystals. Recrystallization from acetonitrile gave 0.61 g of the amine hydrochloride (56%): mp 196–198 °C. Another recrystallization from acetonitrile gave the analytical sample: mp 198–199.5 °C; NMR (D_2O) δ 7.00, 6.92 (s, ArH), 3.90 (s, MeO), 3.11 (m, CH), 2.24 (s, $ArCH_3$), 1.53 (d, CH_3, J = 6.5 Hz); IR (KBr) 3260 (br, OH), 2930 (br, NH_3^+). Anal. ($C_{11}H_{18}NO_2Cl$) C, H, N.

2-Methoxy-4-methyl-5-benzyloxybenzaldehyde (26). A mixture of $POCl_3$ (11.1 g, 66.0 mmol) and *N*-methylformanilide (9.75 g, 72.2 mmol) was stirred for 90 min at room temperature and then 2-benzyloxy-5-methoxytoluene[44] (**25**, 15.0 g, 65.8 mmol) was added dropwise. Stirring was continued overnight during which time the mixture solidified into a gummy mass. The mixture was poured into 150 ml of iced 10% NaOH and worked vigorously with a glass stirring rod. The pH was adjusted to 10 by addition of 10% NaOH and the crude aldehyde was extracted into ether (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum to give an oil which solidified on standing. Two recrystallizations from ethanol afforded 7.2 g of aldehyde **26** (43%): mp 80.5–82 °C; NMR ($CDCl_3$) δ 10.4 (s, CHO), 7.35 (s, C_6H_5), 7.32 (m, ArH), 6.88 (s, ArH), 5.00 (s, CH_2), 3.80 (s, CH_3O), 2.28 (s, CH_3). Anal. ($C_{16}H_{16}O_3$) C, H.

1-(2-Methoxy-4-methyl-5-benzyloxyphenyl)-2-nitropropene (27). A solution of **26** (10.0 g, 39.1 mmol) and NH_4OAc (1.51 g, 19.6 mmol) in 40 ml of nitroethane was stirred at reflux for 2 h. The solvent was then removed under vacuum leaving a yellow solid which, when recrystallized from 2-propanol, afforded 10.1 g (83%) of the yellow nitropropene **27**: mp 101.5–104 °C. Another recrystallization from 2-propanol gave the analytical sample: mp 102–104 °C; NMR ($CDCl_3$) δ 8.32 (s, vinyl H), 7.45 (s, C_6H_5), 6.85 (s, ArH), 5.12 (s, CH_2), 4.87 (s, CH_3O), 2.38 (s, $ArCH_3$), 2.22 (s, allylic CH_3). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

1-(2-Methoxy-4-methyl-5-benzyloxyphenyl)-2-aminopropane Hydrochloride (28·HCl). A stirred suspension of $LiAlH_4$ (4.60 g, 121 mmol) in freshly distilled THF (100 ml) was chilled to 4 °C and a solution of **27** (9.50 g, 30.3 mmol) in THF (50 ml) was added dropwise with vigorous stirring. The reaction was allowed to proceed overnight during which time it warmed to room temperature. The reaction flask was again cooled in an ice bath and to it were added dropwise 4.6 ml of water, 4.6 ml of 15% NaOH, 100 ml of ether, and 14 ml of water. The mixture was stirred for an additional 0.5 h and was then filtered by suction. The gelatinous precipitate was washed with generous portions of ether; the combined filtrate and washings were dried (K_2CO_3) and concentrated to yield the crude amine which was taken up in 60 ml of ether. The amine solution was again dried (K_2CO_3) and to the filtered solution was added a sufficient amount of a solution of dry HCl gas in ether so that no additional precipitate formed. The white solid was collected and washed with a few milliliters of ether to yield 6.7 g (69%) of the crude amine hydrochloride: mp 163–165 °C. A recrystallization from ethanol gave the analytical sample: mp 164–166 °C; NMR (free amine, $CDCl_3$) δ 7.41 (s, C_6H_5), 6.75 (s, ArH), 5.05 (s, CH_2O), 3.80 (s, OCH_3), 3.5–3.0 (d, CH), 2.6 (m, CH_2), 2.3 (s, $ArCH_3$), 1.08 (d, CH_3, J = 6 Hz). Anal. ($C_{18}H_{24}NO_2Cl$) C, H, N.

1-(2-Methoxy-4-methyl-5-hydroxyphenyl)-2-aminopropane Hydrochloride (9·HCl). A mixture of **28**·HCl (1.00 g, 3.11 mmol), 30 ml of benzene, and 30 ml of 12 N HCl was stirred vigorously overnight at room temperature. Concentration under vacuum left an off-white solid which was recrystallized from 2-propanol–ether to give 0.64 g (89%) of white crystals: mp 181–183 °C. Another recrystallization from 2-propanol–ether yielded the analytical sample: mp 183.0–183.5 °C; NMR (Me_2SO-d_6) δ 6.67 (s, ArH), 6.69 (s, ArH), 3.73 (s, CH_3O), 3.28 (m, CH, br), 2.86 (d, CH_2, J = 6.5 Hz), 2.13 (s, $ArCH_3$), 1.12 (d, CH_3); IR (KBr) 3550 (br, OH), 2930 (br, NH_3^+). Anal. ($C_{11}H_{18}NO_2Cl$) C, H, N.

In Vitro Studies (Tris Buffer). All manipulations preceeding the incubation were carried out in a cold room below 4 °C. Male Dutch rabbits (age 6 ± 2 months) were killed by a blow to the neck. The livers were quickly removed (care taken to avoid the gall bladder) and washed in isotonic KCl solution. Small pieces of liver were dried by blotting with filter paper and 5-g portions were placed in each of two 50-ml beakers, each containing 30 ml of 0.2 N Tris buffer (pH 7.4), 0.25 M in sucrose. The liver pieces were minced with scissors and homogenized using a Potter-Elvehjem apparatus. The homogenates were centrifuged at 10000g for 30 min at 4 °C and the supernatants decanted into a chilled 100-ml graduated cylinder (care taken to exclude the solid portions at the bottom of the centrifuge tubes) to give 65 ml of supernatant. Portions of 14 ml (corresponding to 2 g of liver) were added to the appropriate substrates in 25-ml Erlenmeyer flasks. NADPH (17 mg) and $MgCl_2$ (1.6 ml of 0.1 M solution) were added and the mixtures were shaken at 80 rpm at 37 °C for 1 h. Immediately following the incubation, the mixtures were chilled in an ice bath and the pH was adjusted to 9.5–10 by addition of a few drops of 3 N NaOH. The appropriate internal standards were added

immediately and the mixtures were extracted twice with equal volumes of ether. The extracts were concentrated under a stream of dry nitrogen and the residues transferred to conical tubes with the aid of a small amount of ethanol. The ethanol was removed under a stream of nitrogen and the residue was derivatized by heating with PFPA for 15 min at 75 °C. The excess PFPA was removed under a stream of dry nitrogen and the residue was taken up in a few drops of dioxane. The PFP derivatives **29**, **30**, and **31** were isolated by gas chromatography (3% OV-25 on 100–120 Chromosorb W, 6 ft × 2 mm glass column, N_2 carrier gas at 30 ml/min, 100 °C initial column temperature, 10 °C increase/min) and had retention times of 10.4, 14, and 24 min, respectively. These fractions were collected in oven-dried elbow-shaped tubes prepared from 3 mm o.d. soft glass and subjected to CI-MS analysis (isobutane, 0.7 Torr direct probe introduction) from which the isotopic ratios were determined.

The deuterium isotope studies and stereochemical studies were conducted according to this general procedure with the appropriate substrates and internal standards. Generally, ca. 1 mg of substrate was incubated with each portion of liver supernatant (corresponding to 2 g of liver). Usually, ca. 50 μg of each of the monophenolic standards and 500 μg of parent amine standard were added.

In Vitro Studies (Phosphate Buffer). Removal of liver was performed as described above. Small pieces of liver were dried by blotting with filter paper and 5 g of tissue was placed in each of two 50-ml beakers, each containing 30 ml of isotonic KCl with 0.01 M sodium phosphate buffer at pH 7.4. The mincing, homogenization, and centrifugation were performed as previously described. A 14-ml portion of supernatant was incubated with 1.15 mg (4.63 mmol) of 1-d_3·HCl. Following the incubation, the mixture was chilled in an ice bath and the pH adjusted to 3 by addition of 0.5 ml of 25% trichloroacetic acid solution. To the mixture were added the two monophenolic standards **8**·HCl (56.5 μg, 0.245 μmol) and **9**·HCl (51.5 μg, 0.223 μmol), the hydroquinone **2**·HCl (48.5 μg, 0.223 μmol), and unlabeled amine 1·HCl (1.29 mg, 1.75 μmol). The precipitated protein was sedimented by centrifugation at 10 000g for 10 min. The supernatant was passed through a Dowex 50 cation-exchange column prepared by washing 1.0 g of dry resin with 30 ml of 4 N HCl followed by 50 ml of distilled water until all chloride was removed by the $AgNO_3$ test. The column was washed with distilled water until all halide had been removed and then the amines were eluted with 4 N HCl (30 ml). The eluent was concentrated under vacuum with very gentle warming. Residual water was removed azeotropically with ethanol. The white residue was leeched with 2 ml of PFPA for 1 h at room temperature and the mixture was filtered through a plug of glass wool into a test tube. The filtrate was heated at 75 °C for 1 h and the PFPA was driven off with dry nitrogen. The residue was taken up in a few drops of dioxane for GLC (80 °C initial temperature, 4 °C increase/min). The PFP derivatives **37** and **29** had retention times of 12.6 and 16 min, respectively. The PFP derivatives **30** and **31** were not detected. Each fraction was collected and analyzed by CI-MS from which the isotope ratio was determined.

Acknowledgment. These studies were supported by NIMH Research Grant MH 21219 and PHS Training Grant 3920. The authors are grateful to Professor R. Weinkam for providing the chemical ionization mass spectra and to Mr. H. Hundley (FDA, San Francisco District Office) for the cyclic voltammometric analyses.

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2-, 3-, and 4-(α,α,β,β-Tetrafluorophenethyl)benzylamines. A New Class of Antiarrhythmic Agents[1]

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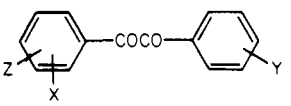
Upon finding 2-(α,α,β,β-tetrafluorophenethyl)benzylamine (4) to be a potent and novel type of antiarrhythmic agent, the title compounds were synthesized. Structure–activity relationships in this series are described.

Among the current drugs for the treatment of cardiac arrhythmias are quinidine and procaine amide, which exhibit similar pharmacologic and electrophysiologic activities. They also share similar disadvantages, especially in terms of myocardial depression. Lidocaine, on the other hand, differs quantitatively in its appreciably less marked alteration of the electrophysiologic properties of the heart. However, it is rapidly metabolized, is usually administered by continuous intravenous infusion, and can cause adverse central nervous system side effects. In the belief that a clinically effective antiarrhythmic agent does not also have to have toxic symptomology, we undertook a search for a nonquinidine type of active structure. This screening program provided a synthetic lead to 2-(α,α,β,β-tetrafluorophenethyl)benzylamine (4), a potent and novel compound. A study pursued to delineate the structure–activity relationships of a series of 2-, 3-, and 4-(α,α,β,β-tetrafluorophenethyl)benzylamines is described.

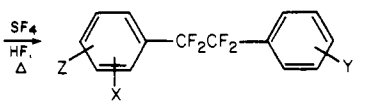
Chemistry. The key intermediates **2** (Table III) in the synthesis of this series were tetrafluorodiphenylethane derivatives with a substituent (X = Br or CH_3) amenable to further chemical modification. These were obtained conveniently and in good yields from the HF-catalyzed reaction of appropriately substituted benzils with SF_4[2] (Scheme I). The requisite benzils **1** (Table II) were prepared by conventional oxidations of the corresponding deoxybenzoins (Table I) or benzoins.

Reaction sequences used are illustrated for the ortho-substituted derivatives in Scheme II. The aryl bromide **2a** gave the nitrile **3a** with CuCN. Reduction of **3a** with $LiAlH_4$ afforded the lead benzylamine **4**. The 5-fluoro derivative **5**, the 4′-fluoro derivative **6**, and the para-substituted analogue **7** were synthesized similarly from the corresponding nitriles (Table IV). The homologue, 2-

Scheme I



1



2

(α,α,β,β,γ,γ-hexafluorophenylpropyl)benzylamine (**8**), was prepared by an analogous sequence from the corresponding bromide **2j**. The precursor of **2j**, 1-(2-bromophenyl)-3-phenylpropane-1,2,3-trione (**1j**), was obtained from 2-bromobenzaldehyde by conventional procedures.[3] The tertiary amine **9** and the secondary amines **10** and **11** were prepared by standard alkylation procedures.

An α-methyl group was introduced into the benzylamine moiety via the Grignard reaction of the nitrile **3a**. Careful work-up of the reaction mixture with ice-cold aqueous HCl gave the ketimine hydrochloride **12** that was reduced with $LiAlH_4$ in THF to the α-methylbenzylamine **13**. Alternatively, the acetophenone **14** obtained by hydrolysis of **12** was converted to the oxime **15** that was reduced to **13**. Application of the latter sequence to the para-substituted nitrile **3d** gave α-methyl-4-(α,α,β,β-tetrafluorophenethyl)benzylamine (**16**). Alkylation of **13** via reduction of the derived formamide yielded the α,*N*-dimethylbenzylamine **17** that was resolved into its enantiomorphs **18** and **19**.

Under forcing conditions and entrainment, the Grignard reagent was obtained from the bromide **2a** and carbonated