Enzyme-Activated Irreversible Inhibitors of Monoamine Oxidase: Phenylallylamine Structure-Activity Relationships

Ian A. McDonald,* Jean Michel Lacoste, Philippe Bey, Michael G. Palfreyman,* and Monique Zreika

Merrell Dow Research Institute, Strasbourg Center, 67084 Strasbourg Cedex, France. *Received May 1, 1984*

Seventeen 2-aryl-3-haloallylamine derivatives were prepared and evaluated as inhibitors of monoamine oxidase (MAO, EC 1.4.3.4). The synthesis of these compounds was achieved from either α-methylstyrene or ring-substituted phenylacetic acid derivatives. With one exception, these 2-arylallylamines were found to be enzyme-activated, irreversible inhibitors of MAO. The most potent inhibitors were ring-substituted derivatives of (*E*)-2-phenyl-3-fluoroallylamine with IC_{50} values ranging from 10^{-6} to 10^{-8} M. Selectivity for the A and B form of MAO was found to depend on the nature of aromatic ring substitution. In general, hydroxyl substitution favored the inactivation of the A form of MAO, while very selective B inhibitors were obtained when the aromatic ring was substituted with a 4-methoxy group. (*E*)-2-(4-Methoxyphenyl)-3-fluoroallylamine and (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine proved to be in vitro as selective for the B form of MAO as deprenyl.

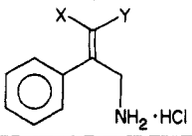
It is now accepted that monoamine oxidase [MAO; monoamine: O_2 oxireductase (deaminating), EC 1.4.3.4] exists in two forms with different distribution amongst organs and across species and different sensitivity to inhibitors.[1] The enzyme form that preferentially oxidizes 5-hydroxytryptamine and norepinephrine and is inhibited by low concentrations of clorgyline is designated type A and the form preferentially deaminating phenethylamine and benzylamine and sensitive to low concentrations of L-deprenyl is called type B.[2]

MAO inhibitors are used in the treatment of depression and certain forms of phobic anxiety and have occasionally been used in the treatment of hypertension.[3] Recently, the use of an MAO inhibitor (L-deprenyl) has been found to be beneficial as an adjunct to the L-Dopa treatment of Parkinson's disease.[4]

Over the past three decades several hundred competitive and irreversible inhibitors of MAO have been reported.[5] The vast majority of these inhibitors show no selectivity for either the A or B form of the enzyme, the major exceptions being the A-selective inhibitors clorgyline, Lilly 51641, harmine, MD 780515, FLA 314, and Ro 11-1163 and the B-selective inhibitors L-deprenyl, pargyline, and Lilly 54761.[6]

Not long after introduction of MAO inhibitors into clinical practice a serious problem associated with their use was discovered.[7] Severe hypertensive crises can arise in MAO inhibitor treated patients after the ingestion of certain foodstuffs (e.g., cheese) containing the pressor amine tyramine. This so-called "cheese effect" appears to be associated essentially with inhibition of the A form of MAO.[8] L-Deprenyl, an irreversible, B-selective inhibitor of MAO which has been extensively studied in the clinic, appears to be free of the cheese effect.[9] This inhibitor, however, has indirect sympathomimetic activity which is probably due to its rapid metabolism to methamphetamine and amphetamine[10] in addition to its property to inhibit monoamine uptake.[11] These secondary effects complicate the interpretation of L-deprenyl's clinical activity solely in terms of inhibition of MAO B. We have recently described[12] the properties of (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (**9**), a selective MAO B inhibitor without indirect sympathomimetic or uptake blocking properties. Since **9** is an interesting member of a new class of MAO inhibitors, we have examined the influence of vinylic halogen substitution and ring substitution of these phenylallylamine derivatives on the potency and/or selectivity for the A and B forms of MAO.

Table I. Influence of Halogen Substitution on MAO Potency



compd	X	Y	mp, °C	formula[a]	IC_{50},[b] M
1	H	H	178–179[c]	$C_9H_{11}N$·HCl	4×10^{-4}
2	F	H	195–196	$C_9H_{10}FN$·HCl	1.8×10^{-8}
3	H	F	144–145	$C_9H_{10}FN$·HCl	1.5×10^{-7}
4	Cl	H	185–186	$C_9H_{10}ClN$·HCl	1×10^{-4}
5	H	Cl	156–157	$C_9H_{10}ClN$·HCl	5×10^{-4}
6	Br	H	190–191	$C_9H_{10}BrN$·HCl	4×10^{-5}
7	F	F	139–140	$C_9H_9F_2N$·HCl	1×10^{-5}
8	Br	Br	243–244	$C_9H_9Br_2N$·HCl	5×10^{-4}
allylamine					5×10^{-4}

[a] Satisfactory C, H, N analyses were obtained for compounds 1–8. [b] IC_{50} values were calculated graphically from the inhibition curves obtained when various concentrations (10^{-3}–10^{-10} M) of the compounds were preincubated with a crude preparation of rat brain mitochondrial MAO for 15 min before measuring the remaining enzyme activity by continuing the incubation for 60 min with tyramine as substrate. [c] Lit.[13b] mp 140–142 °C.

Results and Discussion

Chemistry. The compounds synthesized as a part of this study are listed in Tables I and II. The parent compound 1 has been reported several times[13] and is readily

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(2) (a) Johnston, P. J. *Biochem. Pharmacol.* **1968**, *17*, 1285. (b) Knoll, J.; Magyar, K. *Adv. Biochem. Psychopharmacol.* **1972**, *5*, 393.
(3) Gilman, A. G.; Goodman, L. S.; Gilman, A. "The Pharmacological Basis of Therapeutics", 6th ed.; Macmillan: New York, 1980; p 427.
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(7) (a) Asatoor, A. M.; Levi, A. J.; Milne, M. D. *Lancet* **1963**, 733. (b) Blackwell, B.; Mabbit, L. A. *Lancet* **1965**, 938. (c) Folks, D. G. *J. Clin. Psychopharmacol.* **1983**, *3*, 249.
(8) Youdim, M. B. H.; Finberg, J. P. M. *Mod. Probl. Pharmacopsychiatry* **1983**, *19*, 63.
(9) Elsworth, J. D.; Glover, V.; Reynolds, G. P.; Sandler, M.; Lees, A. J.; Phuapradit, P.; Shaw, K. M.; Stern, G. M.; Kumar, P. *Psychopharmacology (Berlin)* **1978**, *57*, 33.
(10) Reynolds, G. P.; Elsworth, J. D.; Blau, K.; Sandler, M.; Lees, A. J.; Stern, G. M. *Br. J. Clin. Pharmacol.* **1978**, *6*, 542.
(11) Knoll, J. In "Monoamine Oxidase and its Inhibition"; Ciba Foundation Symposium 39; Elsevier/North Holland Biochemical Press: Amsterdam, 1976; p 135.
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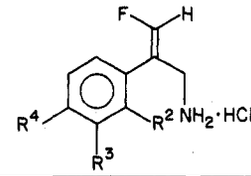
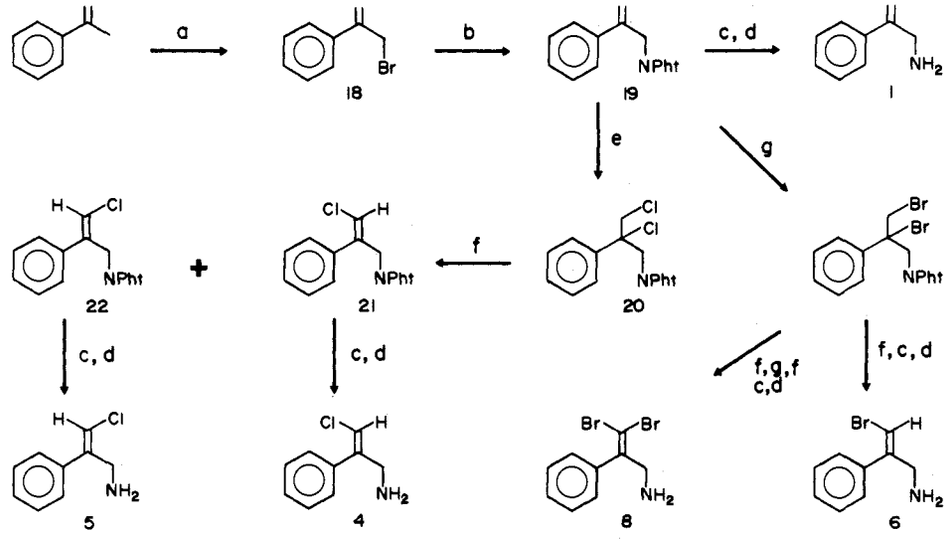
Table II. Influence of Ring Substitution on MAO Potency



compd	R^2	R^3	R^4	mp, °C	formula[a]	IC_{50},[b] M	selectivity[c]
2	H	H	H	195–196	$C_9H_{10}FN·HCl$	1.8×10^{-8}	10
9	H	OCH_3	OCH_3	216–217	$C_{11}H_{14}FNO_2·HCl$	2.5×10^{-6}	100
10	OCH_3	H	H	224–225	$C_{10}H_{12}FNO·HCl$	2.5×10^{-6}	2
11	H	OCH_3	H	146–147	$C_{10}H_{12}FNO·HCl$	5×10^{-9}	4
12	H	H	OCH_3	172–173	$C_{10}H_{12}FNO·HCl$	6×10^{-8}	100
13	H	H	Cl	189–190	$C_9H_9ClFN·HCl$	2×10^{-8}	10
14	H	H	CH_3	169–170	$C_{10}H_{12}FN·HCl$	1×10^{-8}	5
15	H	CF_3	H	174–175	$C_{10}H_9F_4N·HCl$	7×10^{-9}	2
16	H	OH	H	142–143	$C_9H_{10}FNO·HCl$	5×10^{-8}	0.1
17	H	OH	OH	192–193	$C_9H_{10}FNO_2·HCl$	1×10^{-7}	0.1
clorgyline						5×10^{-5}	<0.01
L-deprenyl						2.5×10^{-8}	100

[a] Satisfactory C, H, N analyses were obtained for the new compounds. [b] IC_{50} values were calculated graphically from the inhibition curves obtained when various concentrations (10^{-3}–10^{-10} M) of the compounds were preincubated with a crude preparation of rat brain mitochondrial MAO for 15 min before measuring the remaining enzyme activity by continuing the incubation for 60 min with tyramine as substrate. [c] The selectivity for the B form relative to the A form of MAO was estimated from the ratio of the concentrations of the inhibitors needed to decrease the activity of both forms of the enzyme at the same rate.

Scheme I. Synthesis of 3-Bromo and 3-Chloro Derivatives of 2-Phenylallylamine[a]



[a] Reagents: (a) NBS, (b) potassium phthalimide, (c) $NH_2NH_2·H_2O$, (d) HCl, (e) Cl_2, (f) DBU, (g) Br_2.

available from α-methylstyrene (Scheme I). Thus, treatment of α-(bromomethyl)styrene[14] (**18**) with potassium phthalimide in DMF afforded **19** from which **1** could be obtained by hydrazinolysis.[13a] The phthalimido derivative **19** also served as a key intermediate for the synthesis of the bromo- and chlorovinylic analogues. Chlorination of **19** afforded dichloride **20**, which was regioselectively dehydrochlorinated with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in Me_2SO to yield a separable mixture of vinyl chlorides **21** and **22**. Deprotection of the pure isomers afforded (*E*)- and (*Z*)-2-phenyl-3-chloroallylamine **4** and **5**, respectively. Similarly, bromination of **19**, followed by dehydrobromination gave a major product which appeared to be the (*E*)-phthalimido derivative, the deprotection of which afforded (*E*)-2-phenyl-3-bromoallylamine (**6**). Further bromination of this phthalimido derivative gave a tribromide which was dehydrobrominated and deprotected to yield 2-phenyl-3,3-dibromallylamine (**8**).

The syntheses of compounds **2**, **7**, and **9** to **15** follow the chemistry shown in Scheme II in which the preparation of (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (**9**) is described as a particular example. The mixed malonate ester (**24**) was prepared in a straightforward manner from **23**, good yields being obtained when 2 equiv of lithium diisopropylamide (LDA) was used as base. Although the introduction of the difluoromethyl group proceded well under the previously described conditions,[15] somewhat better yields were obtained when sodium *tert*-butoxide was used as base instead of sodium hydride.[16] Decarboxylative fluoride elimination from **25** was achieved in two steps: trifluoroacetic acid to remove the *tert*-butyl ester to give **26**, followed by treatment with 1 equiv of sodium hydroxide in aqueous THF. The resulting acrylate ester **27**

(13) (a) Lattrell, R.; Lohaus, G. *Liebigs Ann. Chem.* **1974**, 870. (b) Tiffeneau, M.; Gahnmann, H. *Bull. Soc. Chim. Fr.* **1935**, *2*, 1876. (c) Patanova, I. M.; Spryskov, A. A.; Belyaev, V. A. *Chem. Abstr.* **1975**, *83*, 58304g.

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(15) Bey, P.; Schirlin, D. *Tetrahedron Lett.* **1978**, 5225.
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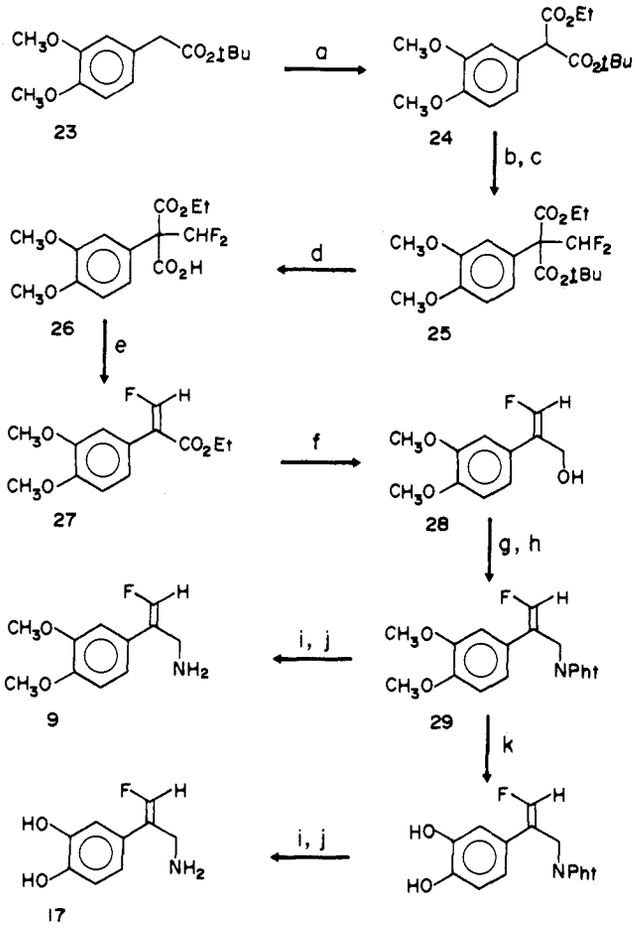
Scheme II. Synthesis of (*E*)-2-(3,4-Dimethoxyphenyl)-3-fluoroallylamine (9) and (*E*)-2-(3,4-Dihydroxyphenyl)-3-fluoroallylamine (17)[a]



[a] Reagents: (a) LDA, $ClCO_2Et$, (b) sodium *tert*-butoxide, (c) Freon 22 ($ClCHF_2$), (d) CF_3CO_2H, (e) NaOH, (f) Dibal, (g) PBr_3, (h) potassium phthalimide, (i) $NH_2NH_2 \cdot H_2O$, (j) HCl, (k) BBr_3.

was selectively reduced with diisobutylaluminum hydride (Dibal) in hexane to give **28** and the phthalimide group was introduced either directly (triphenylphosphine, diethyl azodicarboxylate, phthalimide) or via the bromide (PBr_3; then potassium phthalimide in DMF). Deprotection of **29** with hydrazine readily afforded (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (**9**). In some cases, when the final product did not readily crystallize as its hydrochloride salt, it was found preferable to prepare and purify the *N-tert*-butoxycarbonyl derivative. The amine could then be regenerated as its hydrochloride salt by treatment with hydrogen chloride in anhydrous ether.

A major advantage of this synthesis is that the compounds were obtained exclusively in the *E* configuration. This is due to the stereochemical outcome of the decarboxylative fluoride elimination step in which the (*E*)-acrylate was obtained as the sole isomer. Although this stereoselectivity has been known for many years for decarboxylative chloride or bromide elimination,[17] it was only recently reported for the fluorine case.[18] X-ray structural analyses[19] of (*E*)-2-(4-methoxyphenyl)-3-fluoroallylamine hydrochloride (**12**, Figure 1A) and (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine hydrochloride (**9**, Figure 1B) confirmed the stereochemistry in the present work.

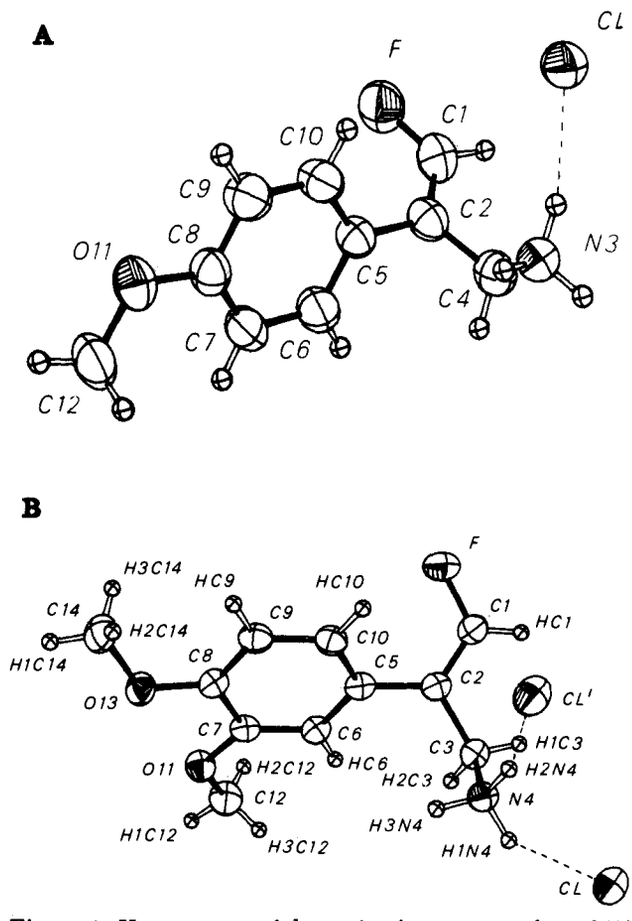
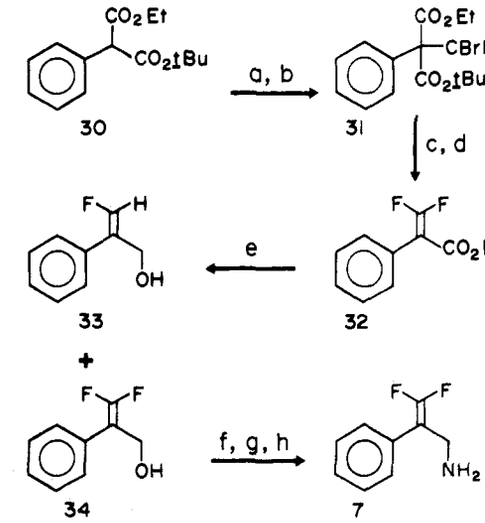


Figure 1. X-ray structural determinations. ORTEP plots of (A) (*E*)-2-(4-methoxyphenyl)-3-fluoroallylamine (**12**) and (B) (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (**9**).

Scheme III. Synthesis of 2-Phenyl-3,3-difluoroallylamine (7)[a]

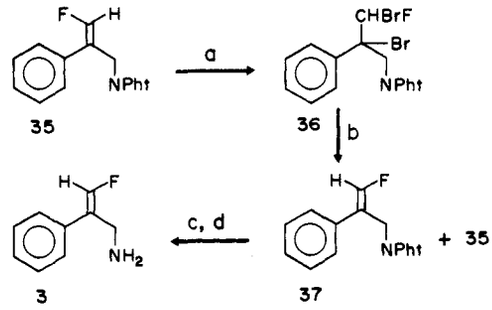


[a] Reagents: (a) LDA, (b) CBr_2F_2, (c) CF_3CO_2H, (d) NaOH, (e) Dibal, (f) triphenylphosphine, diethyl azadicarboxylate, phthalimide, (g) $NH_2NH_2 \cdot H_2O$, (h) HCl.

A complication occurred in the synthesis of 2-phenyl-3,3-difluoroallylamine (**7**). In distinct contrast with all other cases, Dibal reduction of the acrylate ester **32** gave considerable amounts of (*E*)-2-phenyl-3-fluoroallyl alcohol

(17) Krapcho, A. P. *J. Org. Chem.* **1962**, *27*, 2375.
(18) Kosuge, S.; Nakai, H.; Kurono, M. *Prostaglandins* **1979**, *18*, 737.
(19) The X-ray structural analyses were kindly undertaken by Professor R. Weiss at the Laboratoire de Cristallochimie, Institut Le Bel, Université Louis Pasteur, Strasbourg, France.

Scheme IV. Synthesis of (*Z*)-2-Phenyl-3-fluoroallylamine (3)[a]



[a] Reagents: (a) Br_2, (b) NaI, (c) $NH_2NH_2 \cdot H_2O$, (d) HCl.

(33) in addition to the desired 2-phenyl-3,3-difluoroallyl alcohol (34). The ester 32 was obtained in a straightforward manner from the malonate ester 30 with use of dibromodifluoromethane as a means to introduce the bromodifluoromethyl group (Scheme III).

The synthesis of (*Z*)-2-phenyl-3-fluoroallylamine (3) relied upon a cis addition of bromine to the double bond in the phthalimide derivative 35, followed by a sodium iodide mediated trans debromination (Scheme IV). Although this sequence gave adequate amounts of *3*, the initial bromine addition was by no means stereoselective (cis and trans addition approximately 3 to 1), so that careful chromatography was required to separate phthalimide 37 from 35.

In the syntheses of the *m*-tyramine derivative 16 and dopamine derivative 17 (Scheme II), the methoxyl groups could be cleanly removed with BBr_3 when the nitrogen group was protected as the phthaloyl derivative. Subsequent hydrazinolysis proceeded smoothly to afford the air-stable phenol 16 or catecholamine 17.

Biochemistry. The inhibitory properties of compounds 1–17 toward MAO were initially evaluated in vitro by preincubating a crude preparation of rat brain mitochondrial MAO with various concentrations of inhibitors for 15 min before measuring the remaining MAO activity by continuing the incubation a further 60 min in the presence of the mixed substrate tyramine. The approximate IC_{50} values, presented in Tables I and II, were calculated graphically from the inhibition curves obtained with inhibitor concentrations from 10^{-3} to 10^{-10} M. In Table II, the IC_{50} values of clorgyline and L-deprenyl, determined under the same conditions, are included for comparison purposes. The inhibitors were further assessed as time-dependent inhibitors of MAO by using the previously described method.[12] With the exception of the *Z*-chloro analogue 5, which acted as a competitive inhibitor, all inhibitors caused a time-dependent inhibition of MAO when selective substrates were used. Pseudo-first-order kinetics were usually observed[20] for the inactivation of both MAO A and MAO B; i.e., when 5-HT and phenethylamine, respectively, were used as substrates (e.g., for 2 see Figure 2). Selectivity for the A and B forms of the enzyme was approximated by determining for each inhibitor the concentrations necessary to decrease the activity of the A and B forms at the same rate. The concentrations were selected so that 50% loss of enzyme activity occurred within the range of 5–20 min. The ratio of these two concentrations, listed in Table II, was taken as an approximate index of selectivity for the B form relative to the A form of MAO.

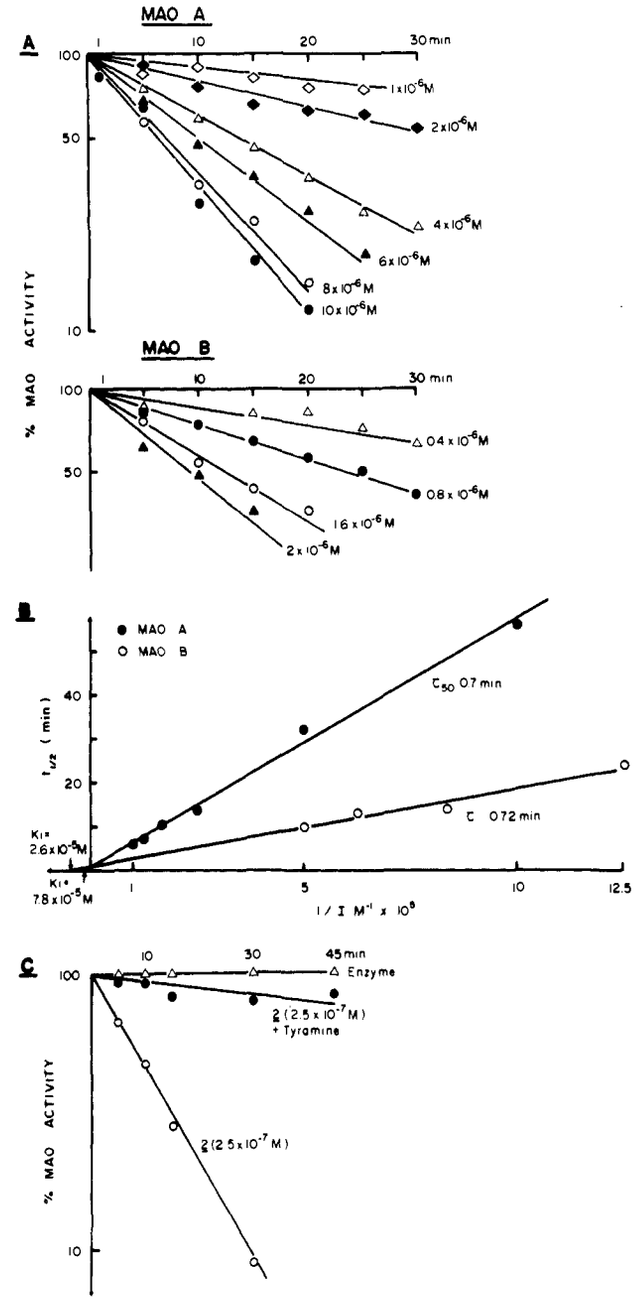


Figure 2. Time-dependent inhibition of MAO by (*E*)-2-phenyl-3-fluoroallylamine (2) at 3 °C.[20] (A) Time-dependent inhibition of MAO measured with the selective substrates 5-HT (upper part) and phenethylamine (lower part); (B) plot of $t_{1/2}$ vs. 1/[I] according to Kitz and Wilson;[30] (C) protection against inactivation by the substrate tyramine (5 mM) at 37 °C.

With use of (*E*)-2-phenyl-3-fluoroallylamine (2) as a representative example, the mechanism of inhibition was investigated. Protection of MAO against inhibition by 2 occurred in the presence of substrate. When the time course of inactivation by 2 (5×10^{-7} M) was followed in the presence of tyramine (5 mM), complete protection was achieved (Figure 2). The rate of inhibition was not modified by the presence of mercaptoethanol (1 mM) in the incubation medium, indicating that the reactive intermediate generated from 2 was not being released from the active site and then inhibiting the enzyme via an affinity labeling mode. Enzyme inactivation was irreversible as shown by the lack of recovery of enzyme activity upon extensive dialysis of the inactivated enzyme. Taken to-

(20) To analyze the kinetic data for some of these compounds (e.g., 2 and 9) it was necessary to work at lower temperatures (3 or 10 °C) in order to reduce the rate of inactivation so that saturation kinetics were clearly apparent.

gether, these results strongly suggest that the fluoroallylamines derivatives are enzyme-activated inhibitors[21] of MAO.

Structure–Activity Relationships. We have confirmed Rando's results[22] that allylamine is a weak inhibitor of MAO ($IC_{50} = 5 \times 10^{-4}$ M) in vitro. Rando also reported[23] that 3-bromo- and 3-chloroallylamine are MAO inhibitors of similar potencies. Modification of the simple allylamine structure by the introduction of a phenyl group did not lead to increased potency, 2-phenylallylamine (**1**) being a relatively poor inhibitor of MAO ($IC_{50} = 4 \times 10^{-4}$ M). Similarly, the vinylic chlorine (**4** and **5**) and bromine (**6** and **8**) derivatives of **1** were weak inhibitors. In marked contrast, the vinylic monofluorine derivatives **2** and **3** were much more potent. The most active compound of the nonsubstituted aromatic ring series (Table I) was the *E* isomer **2** ($IC_{50} = 1.8 \times 10^{-8}$ M).

It is not clear why vinylic fluorine substitution leads to greatly enhanced inhibitory potency in contrast to bromine or chlorine. If the mechanism of inhibition, as suggested by Rando[22] for the inactivation of MAO by bromo- and chloroallylamine, proceeds via addition of an enzyme residue (or the flavin cofactor) to an α,β-unsaturated imine species followed by halogen elimination, fluorine substitution compared to bromine and chlorine could be advantageous. The strong inductive properties of fluorine, coupled with its small size, could act to increase the electrophilicity of the conjugated imine without pertubing the steric environment. The recent availability of radiolabeled **9** should allow us to study the mechanism of inhibition in detail, hopefully leading to an understanding of the importance at fluorine substitution and stereochemistry. The X-ray structural information may be useful in this regard, especially when the *Z* isomer can be studied, a task which is proving difficult due to the relative instability and poor crystal form of this isomer.

Ring substitution in the vinylic fluorine series (Table II; **2** and **9–17**) was shown to have an influence on both inhibitory potency as well as on selectivity for the A and B forms of the enzyme. The most potent compound in this series was the 3-methoxyphenyl derivative **11** ($IC_{50} = 5 \times 10^{-9}$ M), being about 10^5 times more potent than 2-phenylallylamine (**1**). With the exception of the hydroxylated derivatives **16** and **17**, the fluoroallylamine derivatives (Table II) showed selectivity for the B form of the enzyme. The most selective compounds were the 4-methoxy (**12**) and 3,4-dimethoxy (**9**) derivatives, both being in vitro as selective for the B form of MAO as L-deprenyl (approximately 100-fold). On the other hand, hydroxyl substitution in the 3- and/or 4-position of the aromatic ring led to A selectivity (approximately 10-fold).

These observations are in general agreement with what has been reported in the literature concerning substrate preference for one form of the enzyme or the other. For example, at low substrate concentrations the methoxyl-substituted substances 4-methoxyphenethylamine and, to a lesser extent, 3,4-dimethoxyphenethylamine[24,25] would appear to be preferentially oxidized by rat brain mitochondrial MAO B while the hydroxy derivatives norepinephrine[2] and to a lesser extent dopamine[26] and octa-

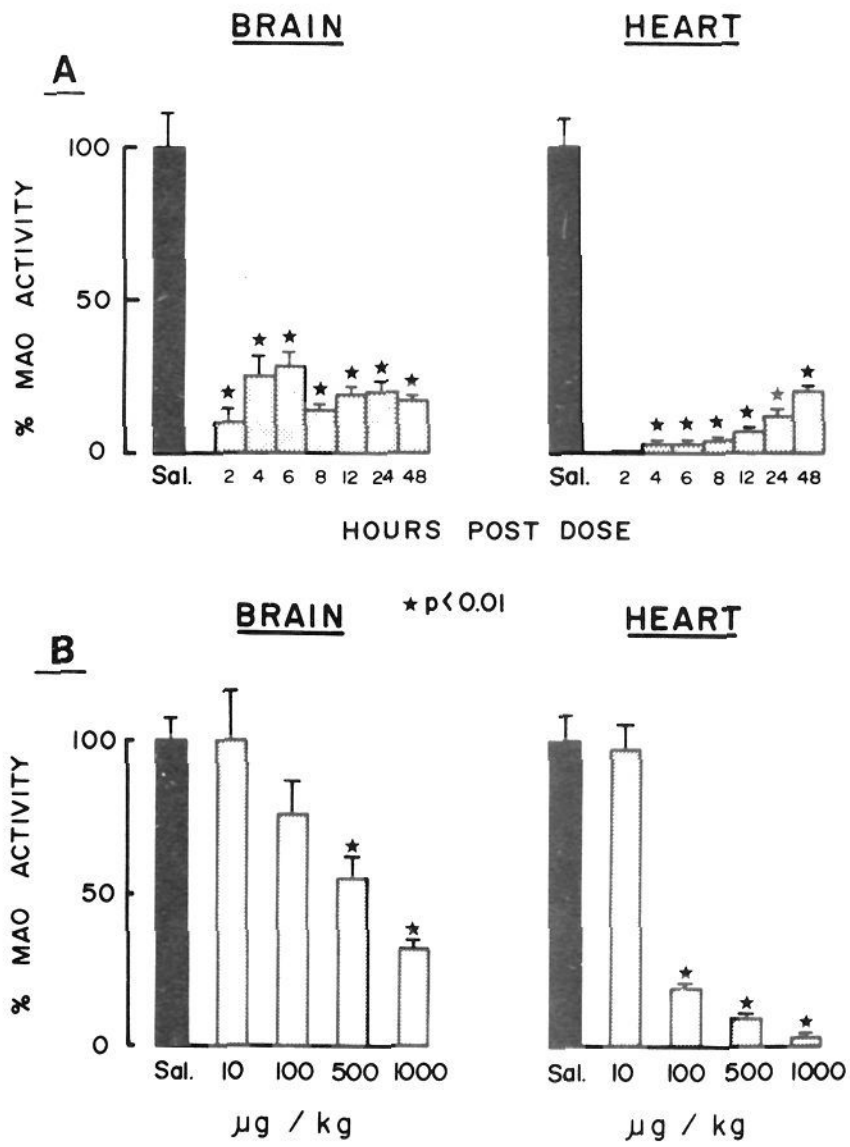


Figure 3. Time course (A) and dose–response (B) of inhibition of MAO in mice ($n = 5$) by (*E*)-2-phenyl-3-fluoroallylamine (**2**). Mice were injected ip with 1 mg/kg. Residual MAO activity was measured 24 h after the dose.

pamine[27] are metabolized mainly by the A form. *p*–Tyramine is considered a mixed substrate. It is conceivable, therefore, that in this series of inhibitors para methoxy substitution leads to B-selective inhibitors and meta hydroxy substitution favors the formation of A-selective inhibitors. Whether this relationship is apparent when the inhibitors are evaluated with MAO from other tissues apart from rat brain has not yet been established. Recently Tipton and Fowler[26] emphasized the importance of the tissue source of MAO with respect to substrate specificity. Preliminary results indicate that the nature of vinylic substitution, whether hydrogen, chlorine, or fluorine, has little influence on selectivity. Finally, all other factors being equal, side-chain β-substitution appears to be associated with selectivity for the B form of the enzyme. This is in agreement with the observation that β-phenylethanolamine is a preferential substrate for MAO B and complements the A selectivity often seen with α-methyl-substituted reversible inhibitors.

Pharmacology. Some of these compounds have been examined as MAO inhibitors in vivo. The non-ring-substituted **2**, for example, given to mice at 1 mg/kg ip, gave good inhibition in the brain and heart (as well as in other tissues), which lasted for at least 48 h (Figures 3A and 3B). This inhibition was accompanied by the expected increases in noradrenaline, dopamine, and 5-hydroxytryptamine with concomitant reduction of their deaminated metabolites (Figure 4).

The most interesting compound in the series, the B-selective inhibitor **9**, has been selected for further development. Preliminary results of current biochemical and

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(22) Rando, R. R.; Eigner, A. *Mol. Pharmacol.* **1977**, *13*, 1005.
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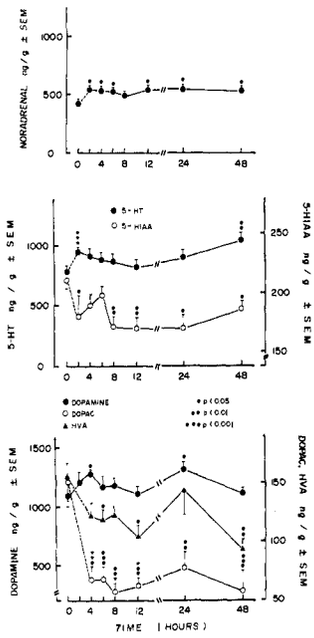

Figure 4. Time course of the effect of a single dose (1 mg/kg ip) of (*E*)-2-phenyl-3-fluoroallylamine (**2**) on mouse brain (n = 5) monoamine and monoamine metabolite concentrations. 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindole-3-acetic acid; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid.

pharmacology studies have recently been reported.[28]

Experimental Section

Chemistry. Melting points were determined on a Mettler FP5 instrument or a Büchi SMP20 instrument and are uncorrected. Microanalyses were obtained on a Perkin-Elmer 240 CHN analyzer. ^{1}H NMR spectra were recorded on a Varian Associates Model T-60 spectrophotometer using trimethylsilane (organic solutions) or 3-(trimethylsilyl)propionic acid-d_4 sodium salt (D_2O solutions) as internal standard.

2-Phenyl-3-phthalimidopropene (19).[13a] A mixture (30.13 g) of α-(bromomethyl)styrene (0.115 mol) and 1-bromo-2-phenylpropene, prepared according to Reed,[14] and potassium phthalimide (21.20 g, 0.115 mol) in DMF (100 mL) was treated at 90 °C for 3 h. The mixture was cooled, diluted with water, and extracted with $CHCl_3$. The $CHCl_3$ extracted was washed with brine, dried, and evaporated to leave a partially solid mass. Trituration with CH_3OH, followed by recrystallization from $CHCl_3$/petroleum ether afforded **19** (18.6 g) as colorless needles; mp 122–124 °C (lit.[13a] mp 122 °C).

2-Phenylallylamine (1).[13a] The hydrochloride salt was recrystallized from EtOH/EtOAc as colorless plates; mp 178–179 °C (lit.[13b] mp 140–142 °C); NMR (D_2O) δ 4.07 (s, 2 H), 5.43 (m, 1 H), 5.66 (s, 1 H), 7.45 (s, 5 H).

1,2-Dichloro-2-phenyl-3-phthalimidopropane (20). Chlorine gas was bubbled for 15 min through a solution of **19** (7.90 g, 30 mmol) in CH_2Cl_2 (100 mL) cooled to 0–5 °C and protected from light. After a further 10 min, the solution was poured into brine and extracted with pentane. The pentane extract was washed with 2% aqueous $NaHCO_3$ and then with water, dried, and evaporated to yield a colorless mass (9.30 g). Recrystallization from n-hexane/CH_2Cl_2 afforded **20** (6.70 g, 67% yield) as colorless needles; mp 114–115 °C; NMR ($CDCl_3$) δ 4.22 (AB, ν_A = 4.50, ν_B = 3.94, J = 12.5 Hz, 2 H), 4.32 (s, 2 H), 7.17–7.97 (m, 5 H). Anal. ($C_{17}H_{13}ClNO_2$) C, H, N.

(*E*)- and (*Z*)-1-Chloro-2-phenyl-3-phthalimidopropane (21 and 22, Respectively). A solution of **20** (4.00 g, 12 mmol) and DBU (2.74 g, 18 mmol) in Me_2SO (200 mL) was heated at 95 °C for 4 h, and then the mixture was cooled, diluted with cold water (300 mL), and extracted with ether. The ether-soluble material (3.98 g, brown oil) was subjected to silica chromatography (10% EtOAc in petroleum ether), and the resulting products were recrystallized from n-hexane/CH_2Cl_2. These were the *E* isomer **21** [0.91 g, 26% yield; mp 106–108 °C; NMR ($CDCl_3$) δ 4.58 (d, J = 1 Hz, 2 H), 6.38 (t, distorted, 1 H), 7.30 (s, 5 H), 7.55–7.88 (m, 4 H); anal. ($C_{17}H_{12}ClNO_2$) C, H, N]; and the *Z* isomer **22** [0.93 g, 26% yield; mp 133–134 °C; NMR ($CDCl_3$) δ 4.95 (d, J = 1.8 Hz, 2 H), 6.42 (t, distorted, 1 H), 7.32 (s, 5 H), 7.57–7.90 (m, 4 H); anal. ($C_{17}H_{12}ClNO_2$) C, H, N].

(*E*)-2-Phenyl-3-chloroallylamine (4). A mixture of **21** (445 mg, 1.5 mmol) and hydrazine hydrate (85 mg, 1.7 mmol) in EtOH (3 mL) was refluxed for $1^1/_2$ h, cooled, treated with 18% aqueous HCl, and heated (90 °C) for a further 45 min. The mixture was cooled and then filtered and the filtrate was evaporated to dryness. The residue was extracted with EtOH and the EtOH solution was evaporated to leave a colorless solid. Recrystallization from EtOH/Et_2O gave the hydrochloride of **4** (142 mg, 47% yield) as colorless needles; mp 185–186 °C; NMR (D_2O/DCl) δ 4.07 (br s, 2 H), 6.78 (m, 1 H), 7.50 (s, 5 H).

(*Z*)-2-Phenyl-3-chloroallylamine (5). In a similar manner, **22** (445 mg, 1.5 mmol) was converted to the hydrochloride salt of **5** (152 mg; 50% yield); mp 156–157 °C; NMR (D_2O/DCl) δ 4.32 (s, 2 H), 6.75 (s, 1 H), 7.40 (s, 5 H).

(*E*)-2-Phenyl-3-bromoallylamine (6). The synthesis of **6** from **19** followed essentially the same procedure. Thus, bromination of **19** was achieved with Br_2 in CCl_4 in 91% yield. Dehydrobromination (DBU; 64% yield) to give 1-bromo-2-phenyl-3-phthalimidopropene followed by deprotection (hydrazine hydrate; 69% yield) afforded **6**; colorless needles from EtOH/Et_2O; mp 190–191 °C; NMR (D_2O) δ 4.03 (br s, 2 H), 6.93 (br s, 1 H), 7.48 (s, 5 H).

2-Phenyl-3,3-dibromoallylamine (8). Bromination of 1-bromo-2-phenyl-3-phthalimidopropene followed by dehydrobromination and deprotection as before afforded **8** as colorless needles; mp 243–244 °C; NMR (CD_3OD) δ 4.12 (br s, 2 H), 7.38 (s, 5 H).

Ethyl 2-(*tert*-Butoxycarbonyl)-2-(3,4-dimethoxyphenyl)-acetate (24). A solution of **23** (8.00 g, 31.7 mmol) in THF (50 mL) was added to LDA (63.7 mmol, prepared from 6.43 g of diisopropylamine) in THF (100 mL) at −78 °C. After 1 h at this temperature a solution of ethyl chloroformate (4.15 g, 38.2 mmol) in THF (50 mL) was added, the cooling bath was removed, and the reaction was stirred overnight. The solution was carefully acidified with 6 N aqueous HCl, then the THF was evaporated, and the residue was dissolved in ether. The ether solution was washed with dilute aqueous HCl and then with water, dried, and evaporated. The residue, an almost colorless oil (10.32 g, 100% yield) was used in the following reaction without further purification. From another run a small portion was purified (silica chromatography; 20% Et_2O in petroleum ether) for analysis to give a colorless oil; bp 115 °C (oven) (0.05 mm); NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 1.43 (s, 9 H), 3.75, 3.78 (2 s, 6 H), 4.12 (q, J = 7 Hz, 2 H), 4.25 (s, 1 H), 6.72 (s, 2 H, 6.85 (s, 1 H). Anal. ($C_{17}H_{24}O_6$) C, H.

Ethyl 2-(*tert*-Butoxycarbonyl)-2-(difluoromethyl)-2-(3,4-dimethoxyphenyl)acetate (25). A solution of **24** (10.32 g, 31.9 mmol) in THF (20 mL) was added to a stirred suspension of sodium *tert*-butoxide (6.16 g, 64.2 mmol) in THF (80 mL). After stirring for 15 min, the solution was heated to 40–45 °C and a rapid stream of Freon 22 ($ClCHF_2$) was introduced. The temperature quickly rose to reflux and the addition was continued until the temperature began to drop (after 5–10 min). Stirring was continued for an additional 30 min, and then the mixture was poured into water and extracted with ether. The ether solution was washed with water, dried, and evaporated to afford essentially pure **25** (10.99 g; 92% yield). Distillation of a small portion gave analytically pure material as a colorless oil; bp 105 °C (oven) (0.05 mm); NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H), 1.42 (s, 9 H), 3.73 (s, 6 H), 4.20 (q, J = 7 Hz, 2 H), 6.25 (t, J = 56 Hz,

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1 H), 6.68 (s, 2 H), 6.78 (br s, 1 H). Anal. ($C_{18}H_{24}F_2O_6$) C, H.

Ethyl (*E*)-2-(3,4-Dimethoxyphenyl)-3-fluoroacrylate (27). A solution of **25** (61.70 g, 0.165 mol) in trifluoroacetic acid (150 mL) was stirred at room temperature for 1 h, and then the solution was evaporated under reduced pressure until all the reagent had been removed. The residue was dissolved in THF (70 mL) and treated with 2 M aqueous NaOH (83 mL, 0.166 mol) for 15 min at room temperature. Then the solution was poured into water and the product was isolated by ether extraction and purified by chromatography (silica, 20% EtOAc in petroleum ether) to give **27** as a colorless solid (39.70 g, 95% yield). Recrystallization of a portion from petroleum ether gave colorless plates; mp 71–72 °C; NMR (CCl_4) δ 1.27 (t, J = 7 Hz, 3 H), 3.75 (s, 6 H), 4.15 (q, J = 7 Hz, 2 H), 6.72 (s, 3 H), 7.53 (d, J = 82 Hz, 1 H). Anal. ($C_{13}H_{15}FO_4$) C, H.

(*E*)-2-(3,4-Dimethoxyphenyl)-3-fluoroallyl Alcohol (28). A solution of **27** (30 g, 0.118 mol) in a mixture of dry hexane (170 mL) and dry dichloromethane (40 mL) was cooled to 0 °C. To this was added a 1 M solution of Dibal in hexane (260 mL, 0.26 mol) at such a rate that the temperature did not rise above 10 °C (the temperature was also controlled with an acetone–dry ice bath). When all was added (about 20 min), the solution was stirred at ambient temperature for 1 h and then cooled to about 5 °C. Methanol (130 mL) followed by 6 N hydrochloric acid (83 mL) were added consecutively and the temperature kept below 10 °C with external cooling as before. The organic layer was separated; the aqueous layer was extracted several times with ether, and the combined organic solutions were washed with water, dried, and evaporated to afford essentially pure **28** as a pale yellow solid mass (18.60 g; 74% yield). A small portion was recrystallized from *n*-hexane to give colorless plates; mp 56–57 °C; NMR ($CDCl_3$) δ 2.60 (br s, 1 H), 3.83 (s, 6 H), 4.25 (d, J = 5 Hz, 2 H), 6.78 (d, J = 83 Hz, 1 H), 6.68–7.20 (m, 3 H). Anal. ($C_{11}H_{13}FO_3$) C, H.

(*E*)-1-Fluoro-2-(3,4-dimethoxyphenyl)-3-phthalimidopropene (29). Method A. A solution of **28** (25.00 g, 0.119 mol), triphenylphosphine (31.23 g, 0.119 mol), and phthalimide (17.52 g, 0.119 mol) in THF (450 mL) was treated with a solution of diethyl azodicarboxylate (20.74 g, 0.119 mol) in THF (100 mL) and then allowed to react overnight. The solvent was evaporated, and the byproducts were largely removed by recrystallization (of the byproducts) from toluene and then from ether. The residue was purified by silica chromatography (20% EtOAc in petroleum ether) to give a major fraction (20.48 g) which was recrystallized from *n*-hexane/CH_2Cl_2 to afford **29** (16.50 g; 41% yield) as colorless plates; mp 102–103 °C; NMR ($CDCl_3$) δ 3.80, 3.85 (2 overlapping singlets, 6 H), 4.52 (m, 2 H), 6.32 (s, $^1/_2$ H), 6.68–7.28 (m, 3 H), 7.52–7.88 (m, $4^1/_2$ H). Anal. ($C_{19}H_{16}FNO_4$) ($C_{19}H_{16}FNO_4$) C, H, N.

Method B. A solution of **28** (13.72 g, 65.3 mmol) in dry toluene (200 mL) was cooled to about 10 °C and treated with a solution of phosphorus tribromide (7.59 g, 28.1 mmol) in toluene (200 mL). The cooling bath was removed and the reaction was allowed to continue for $1^1/_2$ h during which time some tar formed. The supernatant was poured into saturated aqueous K_2CO_3 and the product was isolated by ether extraction in the normal way to give brown crystals (16.0 g). This product (16.0 g) and potassium phthalimide (11.32 g, 61.2 mmol) were heated in dry DMF (130 mL) at 65 °C for 4 h, and then the mixture was poured into water and extracted with ether. The ether solution was washed with water, dried, and evaporated to give a solid mass. Recrystallization from *n*-hexane/CH_2Cl_2 afforded **29** (15.95 g, 72% overall yield) as before.

(*E*)-2-(3,4-Dimethoxyphenyl)-3-fluoroallylamine (9). A mixture of **29** (6.82 g, 20 mmol) and hydrazine hydrate (1.10 g, 22 mmol) in CH_3OH (45 mL) was refluxed for 3 h. Aqueous HCl (18%; 12 mL) was added and refluxing was continued for 30 min, and then the mixture was cooled and filtered. Evaporation of the filtrate left a solid residue which was triturated with CH_3OH and then recrystallized from EtOH/Et_2O to afford **9** (2.56 g, 52% yield) as colorless plates; mp 216–217 °C; NMR (D_2O) δ 3.87 (s, 6 H overlapping 4.00, br d, J = 4 Hz, 2 H), 7.10 (br s, 3 H), 7.17 (d, J = 82 Hz, 1 H).

(*E*)-2-Aryl-3-fluoroallylamines 2 and 10–15. The syntheses of these compounds from the corresponding *tert*-butyl phenylacetates followed the procedures outlined for the synthesis of **9** from **23**. Exceptions to this general procedure were as follows: (1) deprotonation of ethyl 2-(*tert*-butoxycarbonyl)-2-(2-methoxyphenyl)acetate was achieved with *n*-butyllithium/potassium *tert*-butoxide instead of sodium *tert*-butoxide (in the synthesis of **10**); (2) decarboxylate fluoride elmimination to prepare ethyl (*E*)-2-[3-(trifluoromethyl)phenyl]-3-fluoroacrylate was achieved with triethylamine (2.5 equiv) in CH_2Cl_2 at room temperature (in the synthesis of **15**); and (3) Dibal reduction of **32** (see below).

Ethyl 2-(*tert*-Butoxycarbonyl)-2-(bromodifluoromethyl)phenylacetate (31). Following the procedure described for the preparation of **25**, ethyl 2-(*tert*-butoxycarbonyl)phenylacetate (15.84 g, 60 mmol) was converted to **31** (19.69 g, 83% yield after chromatography) with use of dibromodifluoromethane in place of Freon 22; NMR (CCl_4) δ 1.28 (t, J = 7 Hz, 3 H), 1.52 (s, 9 H), 4.25 (q, J = 7 Hz, 2 H), 7.13–7.55 (m, 5 H). Small peaks corresponding to the difluoromethyl and dibromofluoromethyl analogues were also evident in the spectrum.

Ethyl 2-Phenyl-3,3-difluoroacrylate (32). Following the procedure described for the preparation of **27**, **31** (20.95 g, 53.3 mmol) was converted to **32** (10.80 g, 96% yield) which was distilled as a colorless oil; bp 70 °C (oven) (0.05 mm); NMR (CCl_4) δ 1.25 (t, J = 7 Hz, 3 H); 4.15 (q, J = 7 Hz, 2 H); 7.18 (br s, 5 H). This product was contaminated with a small amount of ethyl 2-phenyl-3-bromo-3-fluoroacrylate.

Dibal Reduction of 32. A solution of **32** (7.13 g, 33.6 mmol) in THF (180 mL) was cooled to about −78 °C and a solution of Dibal in hexane (1.3 M solution, 105 mL, 135.6 mmol) was added. The cooling bath was removed and the temperature was allowed to rise over 45 min, and then the solution was cooled to 0–5 °C and treated slowly with methanol (50 mL) and then with 10% aqueous KOH (13.5 mL). The mixture was then dried ($MgSO_4$), filtered, and evaporated to yield a yellowish oil (4.60 g). Chromatography (silica, 20% EtOAc in petroleum ether) allowed the separation of two products. The first-eluted substance was **34** (1.94 g, 34% yield, colorless oil); NMR (CCl_4) δ 2.70 (s, 1 H), 4.13–4.43 (m, 2 H), 6.98–7.35 (m, 5 H). The second substance was **33** (1.42 g, 28% yield, colorless oil); NMR ($CDCl_3$) δ 1.68 (s, 1 H), 4.33 (broadened d, J = 5 Hz, 2 H), 6.17 (s, $^1/_2$ H), 7.20–7.63 (m, $5^1/_2$ H). In addition, a mixture (1.00 g) of these two substances was obtained.

2-Phenyl-3,3-difluoroallylamine (7). Alcohol **34** (1.94 g, 11.4 mmol) was converted to 1,1-difluoro-2-phenyl-3-phthalimidopropene (2.12 g, 62% yield) by method A above. This product recrystallized from hexane as colorless needles; mp 102–103 °C; NMR (CCl_4) δ 4.67 (m, 2 H), 7.28 (br s, 5 H), 7.57–7.88 (m, 4 H). Anal. ($C_{17}H_{11}F_2NO_2$) C, H, N. Treatment of this substance (0.60 g, 2 mmol) with hydrazine hydrate in the normal way gave almost pure amine **7** (0.41 g). Purification was achieved by conversion to the *N*-Boc-protected derivative; colorless needles; mp 44–45 °C; NMR (CCl_4) δ 1.33 (s, 9 H), 3.93–4.27 (m, 2 H), 4.60 (br s, 1 H), 7.27 (s, 5 H). Anal. ($C_{14}H_{17}F_2NO_2$) C, H, N. Deprotection of this Boc derivative (0.14 g) was achieved with ether/hydrogen chloride whereupon the hydrochloride salt of **7** (0.07 g, 65% yield) crystallized as colorless needles; mp 139–140 °C; NMR (D_2O) δ 4.10 (broadened s, 2 H), 7.43 (s, 5 H).

(*Z*)-2-Phenyl-3-fluoroallylamine (3). In the dark a solution of bromine (0.35 g, 2.2 mmol) in CH_2Cl_2 (5 mL) was added to a cold (0–5 °C) stirred solution of **35** (0.56 g, 2 mmol) in CH_2Cl_2 (30 mL). The cooling bath was then removed and stirring was continued for 24 h. More CH_2Cl_2 was added and the solution was washed consecutively with aqueous Na_2SO_3 and water, dried, and evaporated to leave a colorless solid. Recrystallization from *n*-hexane/CH_2Cl_2 gave **36** (0.66 g, 75% yield) as colorless needles; mp 163–164 °C; NMR ($CDCl_3$) δ 4.50 (m, 2 H), 7.83 (d, J = 47 Hz, 1 H); 7.07–7.90 (m, 9 H). A mixture of **36** (0.66 g, 1.5 mmol) and NaI (15 g, 0.1 mol) in acetone (100 mL) was refluxed for 4 h, cooled, and decolorized with Na_2SO_3. The acetone was evaporated, and the products were isolated by ether extraction. Chromatography (silica; 10% EtOAc in petroleum ether) of the resulting product (0.36 g) gave two pure substances. The first eluted product was the *Z* isomer **37** (0.25 g; 59% yield); colorless needles from CH_2Cl_2/*n*-hexane; mp 78–79 °C; NMR ($CDCl_3$) δ 4.78 (dd, J = 3 Hz, 1.5 Hz), 2 H), 6.80 (dt, J = 82 Hz, 1.5 Hz, 1 H), 7.07–7.87 (m, 9 H). Anal. ($C_{17}H_{12}FNO_2$) C, H, N. The second product was the *E* isomer **35** (0.08 g, 19% yield); colorless needles from *n*-hexane/CH_2Cl_2; mp 98–99 °C; NMR ($CDCl_3$) δ 4.55 (m, 2 H), 6.32 (broadened s, $^1/_2$ H), 7.13–7.93 (m, $9^1/_2$ H). Anal.

($C_{17}H_{12}FNO_2$) C, H, N. Deprotection of **37** (0.25 g) with hydrazine hydrate gave **3** (0.19 g); the hydrochloride salt recrystallized from $EtOH/Et_2O$ as colorless needles; mp 144–145 °C; NMR (D_2O) δ 4.20 (broadened d, J = 3 Hz, 2 H), 7.13 (d, J = 82 Hz, 1 H), 7.50 (m, 5 H).

(*E*)-2-(3,4-Dihydroxyphenyl)-3-fluoroallylamine (17). A solution of **29** (3.20 g, 9.4 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C and treated with BBr_3 (molar solution in CH_2Cl_2; 31 mL, 31 mmol). After 15 min, the cooling bath was removed and the stirring was continued for 30 min. The solution was poured into water and stirred for 30 min, and then the product was isolated by CH_2Cl_2 extraction as a solid mass. Recrystallization from EtOAc/*n*-hexane gave (*E*)-1-fluoro-2-(3,4-dihydroxyphenyl)-3-phthalimidopropene (2.58 g, 88% yield) as cream needles; mp 184–185 °C; NMR (acetone-d_6) δ 4.17 (dd, J = 3 Hz, 1.5 Hz, 2 H), 6.10–6.33 (m, 3 H), 6.37 (d, J = 84 Hz, 1 H), 7.17 (s, 4 H), 7.37 (s, 2 H). Anal. ($C_{17}H_{12}FNO_4$) C, H, N. This substance was deprotected in the normal way to afford the catecholamine (**17**) which was purified via its *N*-Boc derivative (mp 145–146 °C) whereupon colorless needles of the hydrochloride salt were obtained; mp 192–193 °C NMR (D_2O) δ 3.92 (d, J = 3 Hz, 2 H), 6.97 (m, 3 H), 7.07 (d, J = 81 Hz, 1 H).

MAO Inhibition. Determination of IC_{50} Values. Monoamine oxidase (MAO) determination in vitro: Partially purified mitochondrial MAO was prepared from rat brain by homogenization of tissue in 0.1 M phosphate buffer (pH 7.2; 1:2.5 w/v) followed by centrifugation at 12000*g* for 10 min at 4 °C. The supernatant was recentrifuged at 40000*g* for 30 min at 4 °C to obtain a mitochondrial pellet which was resuspended in 0.1 M phosphate buffer (pH 7.2; 2.5 mL/g of rat brain). MAO specific activity in the mitochondrial suspension determined using [^{14}C]tyramine as substrate was 25 nmol (mg protein)$^{-1}$ h^{-1}. The inhibitors (10^{-3}–10^{-10} M) were preincubated for 15 min with the mitochondrial preparation in 0.1 M phosphate buffer (pH 7.2; 2 mL) and then [^{14}C]tyramine (20 μL; prepared by diluting [^{14}C]tyramine 5 μCi; sp act. 50 mCi/mmol with tyramine (100 mM) in 0.1 M phosphate buffer; pH 7.2 to a final volume of 1 mL) was added and the incubation was continued at 37 °C for a further 60 min. Aqueous HCl (2 M, 300 μL) was added and the mixture was extracted with toluene (7 mL). Radioactivity in the toluene extract was counted by liquid scintillation spectrometry with Econofluor (N.E.N) as the scintillant. Blanks containing either no enzyme or acid-inactivated enzyme were similarly treated. Molar concentrations of inhibitors producing 50% inhibition (IC_{50}) were determined graphically.

Time-Dependent Inhibition. Time-dependent inhibitory kinetics, characteristic of an enzyme-activated irreversible mechanism of action,[21] were determined by preincubating for various times with different concentrations of the inhibitors the partially purified mitochondrial preparation. Remaining enzyme activity was then determined following a 200-fold dilution of the enzyme. Incubation in 0.1 M phosphate buffer (pH 7.2, 2 mL) of the substrate (either [^{14}C]tyramine (5 μM), [^{14}C]-5-HT (10 μM), or [^{14}C]phenethylamine (5 μM)) was continued for a further 30 min at 37 °C (1 h with tyramine), and then 2 M aqueous HCl (300 μL) was added. The products were extracted into either toluene/ethyl acetate (1:1) for the 5-HT and phenethylamine metabolites or toluene for tyramine metabolites. Radioactivity was measured as before.

Further Biochemistry. The inhibitor **2** (5×10^{-7} M) was incubated in the presence of tyramine (5 mM), and then time-dependent kinetics were determined with [^{14}C]tyramine as substrate. Similarly, **2** (5×10^{-7} M) was incubated in the presence of mercaptoethanol (1 mM). Partially inhibited enzyme (approximately 80% inhibited) was either dialysed against two changes of 0.1 M phosphate buffer (pH 7.2) for 24 h at 4 °C or washed with water (×5). Enzyme activity (using [^{14}C]tyramine) was measured before and after these treatments by using the procedure described for the determination of IC_{50} values.

MAO Determinations ex Vivo. Groups of mice (male CD_1 albino) were injected intraperitoneally (ip) with various doses of inhibitor and killed 24 h later. In separate experiments mice were injected ip with a single dose of compound and killed at various times after treatment. MAO activity was determined in homogenates of brain and heart with [^{14}C]tyramine as substrate.

Monoamine and Monoamine Metabolite Determinations. Brains and hearts from the mice treated with the MAO inhibitors were analyzed for their monoamine and metabolite content by HPLC with electrochemical detection according to the method of Wagner et al.[29] Statistical evaluation of MAO activity and monoamine determinations was undertaken by using Student's "*t*" test in comparison to control animals.

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Registry No. 1, 28144-67-4; 1·HCl, 56132-76-4; **2**, 85278-69-9; **2**·HCl, 85278-05-3; **3**, 93605-75-5; **3**·HCl, 85278-84-8; **4**, 93605-76-6; **4**·HCl, 85278-24-6; **5**, 93605-77-7; **5**·HCl, 85278-23-5; **6**, 93605-79-9; **6**·HCl, 93605-78-8; **7**, 85278-36-0; **7**·HCl, 85278-38-2; **7** *N*-Boc deriv, 85278-37-1; **8**, 93605-80-2; **8**·HCl, 85278-19-9; **9**, 85278-66-6; **9**·HCl, 85278-04-2; **10**, 85278-70-2; **10**·HCl, 85278-07-5; 11, 85278-25-7; 11·HCl, 85278-06-4; **12**, 85278-71-3; **12**·HCl, 85278-11-1; **13**, 85278-75-7; **13**·HCl, 85278-08-6; 14, 85278-74-6; **14**·HCl, 85278-64-4; **15**, 85278-73-5; **15**·HCl, 85278-67-7; **16**, 85278-68-8; **16**·HCl, 85278-55-3; **17**, 85278-52-0; **17**·HCl, 85278-54-2; **17** *N*-Boc deriv, 85278-53-1; **18**, 3360-54-1; **19**, 16307-59-8; **20**, 85278-20-2; **21**, 85278-21-3; **22**, 85278-22-4; **23**, 13790-42-6; **24**, 85277-60-7; **25**, 85277-70-9; **27**, 85277-77-6; **28**, 85277-86-7; **29**, 85277-95-8; **31**, 85278-30-4; **32**, 85278-32-6; **33**, 85277-87-8; **34**, 85278-33-7; **35**, 85277-96-9; **36**, 93605-81-3; **37**, 85278-44-0; MAO, 9001-66-5; potassium phthalimide, 1074-82-4; 2,3-dibromo-2-phenylphthalimidopropane, 85278-16-6; 1-bromo-2-phenyl-3-phthalimidopropene, 93605-82-4; ethyl chloroformate, 541-41-3; Freon 22, 75-45-6; phthalimide, 85-41-6; dibromodifluoromethane, 75-61-6; 1,1-difluoro-2-phenyl-3-phthalimidopropene, 85278-35-9; (*E*)-1-fluoro-2-(3,4-dihydroxyphenyl)-3-phthalimidopropene, 85278-85-9.

Supplementary Material Available: Physical data for the new phenylallylamine derivatives are recorded (27 pages). Ordering information is given on any current masthead page.