initial rates, k_{obsd} was determined at one allenic amine concentration (2–4-fold greater than K_i), and k_2 was then calculated as $k_2 = k_{obsd}(1 + K_i/[I])$.[41] The value of k_2 for (*S,R*)-**5** was calculated with a forced zero-activity endpoint [i.e., fit to $E = E_0 \exp(-kt)$]. A rough estimate for the inactivation rate of (*S,S*)-**6** was made on the basis of ca. 90% enzyme activity remaining (relative to control) after 260 min of a 0.4 mM incubation.

Acknowledgment. We wish to thank Christer Sahlberg and Alf Claesson for samples of **2** and penta-2,3-dienamine, Valerie Robinson for her valuable contributions to the NMR analyses, and Robin Spencer for helpful discussions. We are also grateful for financial assistance in the form of Natural Sciences and Engineering Research Council (Canada) Industrial Research Fellowships to R.A.S. and R.L.W.

Registry No. (*R*)-**1**, 89290-07-3; (*R*)-**1**·$C_2H_2O_4$, 114351-89-2; (*S*)-**1**, 89290-08-4; (*S*)-**1**·$C_2H_2O_4$, 114351-90-5; (*R*)-**2**, 85506-93-0; (*R*)-**2**·$C_2H_2O_4$, 85506-94-1; (*S*)-**2**, 85506-95-2; (*S*)-**2**·$C_2H_2O_4$, 85506-96-3; (*R,R*)-**3**, 89290-09-5; (*S,S*)-**3**, 89362-15-2; (*R,S*)-**3**, 89362-14-1; (*R,S*)-**3**·HCl, 114351-91-6; (*S,R*)-**3**, 89362-13-0; (*S,R*)-**3**·HCl, 114351-92-7; (*R*)-**4**, 89290-10-8; (*R*)-**4**·$C_2H_2O_4$, 114351-93-8; (*S*)-**4**, 89290-11-9; (*S*)-**4**·$C_2H_2O_4$, 114351-94-9; (*R,R*)-**5**, 89290-12-0; (*R,R*)-**5**·$C_{H2}O_4$, 114351-95-0; (*S,S*)-**5**, 89362-18-5; (*S,S*)-**5**·$C_2H_2O_4$, 114351-96-1; (*R,S*)-**5**, 89362-17-4; (*R,S*)-**5**·$C_2H_2O_4$, 114351-97-2; (*S,R*)-**5**, 89362-16-3; (*S,R*)-**5**·$C_2H_2O_4$, 114377-11-6; (*R,R*)-**6**, 89290-13-1; (*R,R*)-**6**·$C_2H_2O_4$, 114377-12-7; (*S,S*)-**6**, 89362-21-0; (*S,S*)-**6**·$C_2H_2O_4$, 114351-98-3; (*R,S*)-**6**, 89362-20-9; (*R,S*)-**6**·$C_2H_2O_4$, 114351-99-4; (*S,R*)-**6**, 89362-19-6; (*S,R*)-**6**·$C_2H_2O_4$, 114352-00-0; (±)-**7**, 65337-13-5; (±)-**7** (hydrogen phthalate), 42969-62-0; (*R*)-**7**, 42969-65-3; (*R*)-**7** (hydrogen phthalate·(*R*)-PhCH(CH_3)NH_2), 114351-86-9; (*S*)-**7**, 2914-69-4; (*S*)-**7** (hydrogen phthalate·(*S*)-PhCH(CH_3)NH_2), 100837-08-9; (*R*)-**8** (*R*-THP), 114351-87-0; (*R*)-**8** (*S*-THP), 114352-04-4; (*S*)-**8** (*R*-THP), 114352-05-5; (*S*)-**8** (*S*-THP), 114351-88-1; (*R*)-**9** (*R*-THP), 114419-86-2; (*R*)-**9** (*S*-THP), 114419-90-8; (*S*)-**9** (*R*-THP), 114419-91-9; (*S*)-**9** (*S*-THP), 114419-87-3; (*R*)-**10**, 65032-23-7; (*S*)-**10**, 85507-21-7; (*R*)-**11**, 85507-16-0; (*S*)-**11**, 85507-17-1; (*R*)-**13**, 3886-69-9; (*S*)-**13**, 2627-86-3; (*R*)-**14**, 5933-40-4; (*S*)-**14**, 19131-99-8; (±)-**15**, 300-62-9; (*R*)-**15**, 156-34-3; (*R*)-**15**·L-tartrate, 114352-01-1; (*S*)-**15**, 51-64-9; (*S*)-**15**·$^1/_2H_2SO_4$, 51-63-8; (*R*)-**16**, 33817-09-3; (*S*)-**16**, 537-46-2; (±)-**17**, 32908-38-6; (±)-**17**·HCl, 49800-23-9; (*R*)-**17**, 23357-46-2; (*R*)-**17**·L-tartrate, 32908-39-7; (*S*)-**17**, 23357-52-0; (*S*)-**17**·D-tartrate, 114352-02-2; (±)-**18**, 42882-35-9; (*R*)-**18**, 114419-88-4; (*R*)-**18**·(+)-dibenzoyltartrate, 114419-89-5; (*S*)-**18**, 49681-43-8; (*S*)-**18**·(-)-dibenzoyltartrate, 114352-03-3; MAO, 9001-66-5; $(CH_3)_2NH$, 124-40-3; $Ph(CH_2)_2NHCH_3$, 589-08-2; PhCHO, 100-52-7; $C_2H_5NO_2$, 79-24-3; $PhCH{=}C(NO_2)CH_3$, 705-60-2.

Supplementary Material Available: Complete ^{13}C NMR spectral data with peak assignments for compounds 1–6 (3 pages). Ordering information is given on any current masthead page.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Analogues. Inactivation of Monoamine Oxidase by Conformationally Rigid Analogues of *N,N*-Dimethylcinnamylamine

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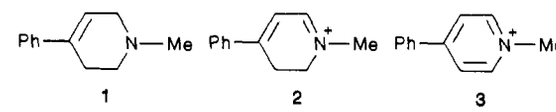
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a potent neurotoxin and also an inactivator of monoamine oxidase (MAO). Since MPTP is a conformationally rigid analogue of *N,N*-dimethylcinnamylamine, other conformationally rigid analogues of *N,N*-dimethylcinnamylamine were synthesized and tested as inhibitors and inactivators of MAO. (*E*)-2-(Phenylmethylene)cyclohexanamine (**5a**), (*E*)-*N,N*-dimethyl-2-(phenylmethylene)cyclohexanamine (**5b**), 3-phenyl-2-cyclohexen-1-amine (**6a**), *N,N*-dimethyl-3-phenyl-2-cyclohexen-1-amine (**6b**), and (*E*)- and (*Z*)-*N*-methyl-3-(phenylmethylene)piperidine (**7** and **8**) are all inhibitors and time-dependent inactivators of MAO B, but none is as potent as MPTP. α-Methylation and methylation of the amino group in all cases increases the K_i value relative to that for the parent compound. Compounds **5a**, **5b**, **6a**, and **6b** are highly cytotoxic, but cytotoxicity is not prevented by pretreatment of the cells with pargyline. There does not appear to be a correlation between the configuration of the *N,N*-dimethylcinnamylamine analogue and its potency as a MAO inactivator.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**, MPTP) is a potent neurotoxin that produces symptoms identical with those associated with Parkinson's disease.[1-3] The neurotoxicity of MPTP is blocked in animals by pretreatment with selective inactivators of monoamine oxidase (MAO), and, therefore, it was concluded that the neurotoxicity of MPTP is derived from a metabolite produced by a MAO-catalyzed oxidation of MPTP.[3,4] Chiba et al.[4] showed that MPTP was metabolized by MAO B to 1-methyl-4-phenyl-2,3-dihydropyridinium ion (**2**, $MPDP^+$) and to 1-methyl-4-phenylpyridinium ion (**3**, MPP^+). Not only is MPTP a substrate for MAO, but it also is a mechanism-based inactivator[5] of MAO.[6-9] Inactivation by [^{14}C]MPTP results in attachment of radioactivity to the enzyme, which remains bound, even after denatura-



1 **2** **3**

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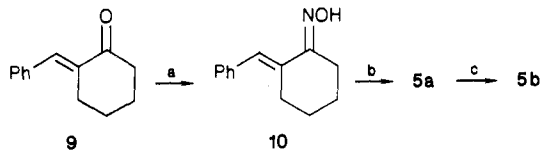
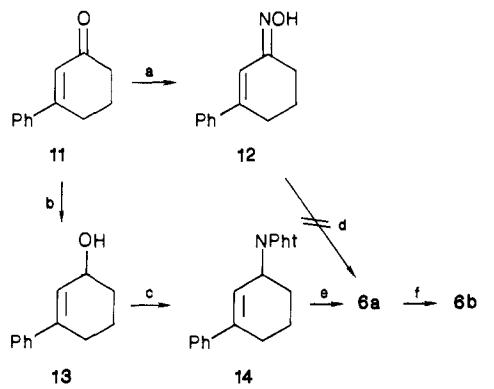
Scheme I. Synthetic Route to **5a** and **5b**[a]



[a] (a) $NH_2OH/NaOH$; (b) Zn/HOAc; (c) 37% HCHO/$NaCNBH_3$.

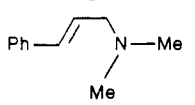
Scheme II. Synthetic Route to **6a** and **6b**[a]



[a] (a) $NH_2OH/NaOH$; (b) $NaBH_4$; (c) Ph_3P, phthalimide, diethyl azodicarboxylate; (d) Zn/HOAc; (e) NH_2NH_2; (f) 37% HCHO/$NaCNBH_3$.

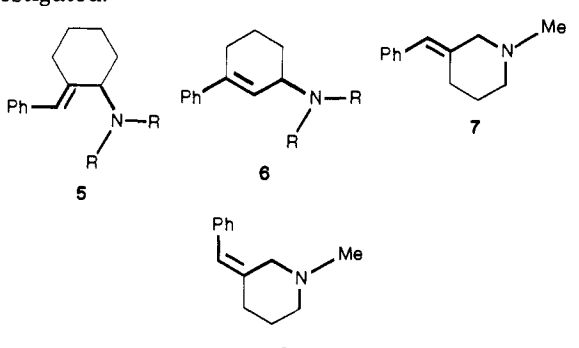
tion.[7] Upon denaturation the flavin spectrum of inactivated enzyme remains similar to that of native MAO, suggesting that attachment is to an active-site amino acid, not to the flavin.

MPTP is a conformationally rigid analogue of *N,N*-dimethylcinnamylamine as depicted by **4**. Since MPTP is



4

a more potent inactivator of MAO than is *N,N*-dimethylcinnamylamine (vide infra), we thought that other conformationally rigid analogues of *N,N*-dimethylcinnamylamine may be inactivators of MAO as well. In order to determine the importance of the conformation of *N,N*-dimethylcinnamylamine to inactivation of MAO, compounds **5**–**8** (the *N,N*-dimethylcinnamylamine part is darkened) were designed to span a variety of configurations. These compounds were synthesized and their inhibition and inactivation properties toward MAO were investigated.

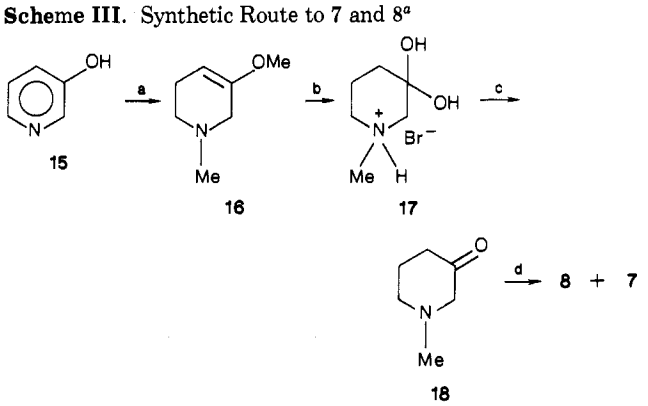


a, R=H; **b** = Me

Results and Discussion

If the trans-s-cis configuration of oxidized MPTP (i.e., $MPDP^+$) is taken as the standard, then compounds **5**, also possessing a trans-s-cis configuration after oxidation, are closest in structure to MPTP. Compounds **6** and **7** after oxidation have a trans-s-trans configuration, and oxidized **8** has a cis-s-trans configuration.

Scheme III. Synthetic Route to **7** and **8**[a]



[a] (a) Na, CH_3I; (b) 48% HBr; (c) K_2CO_3; (d) NaH, $(EtO)_2P(O)CH_2Ph$.

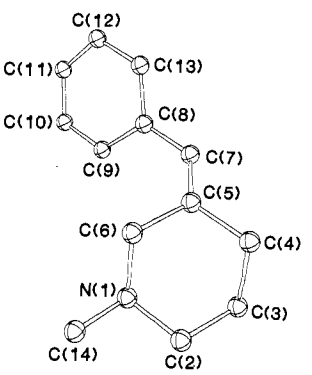


Figure 1. ORTEP drawing of **8**.

Syntheses. The synthetic routes to compounds **5**–**8** are shown in Schemes I–III. 2-(Phenylmethylene)cyclohexanone (**9**), prepared by the method of Walton,[10] was converted smoothly to the oxime **10**; reduction of the oxime with zinc[11] gave compound **5a**. Two methods for bismethylation of the primary amine were used. An Eschweiler–Clarke reductive amination[12] of formaldehyde in formic acid was successful but was not as reproducible, nor gave as high yields, as reductive amination of formaldehyde with sodium cyanoborohydride.[13] This same general approach was taken for the synthesis of **6a**, but it was not successful. Conversion of 3-phenyl-2-cyclohexenone (**11**) to the corresponding oxime (**12**) proceeded in good yields. However, **12** underwent decomposition to unidentified products during zinc reduction. The alternative route shown in Scheme II was successful. The Eschweiler–Clarke reductive alkylation method[12] gave a low yield of desired product, but the sodium cyanoborohydride method[13] worked well.

Compounds **7** and **8** were prepared from a common intermediate by the route shown in Scheme III. Krogsgaard-Larsen and Hjeds[14] reported that *N*-alkyl-3-piperidinones are unstable in the keto form, but that the hydrobromide hydrates are quite stable. *N*-Methyl-3-

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Table I. Kinetic Data for Inhibition and Inactivation of Monoamine Oxidase B by *N,N*-Dimethylcinnamylamine Analogues

	inhibition study			inactivation study		
compd	K_i, mM	type of inhibn	replot shape	K_I, mM	k_{inact}, h^{-1}	concn range, mM
4	1.35	competitive	linear	1.33	12.8	0.8–4
α-MeCA	1.9	competitive	linear	non pseudo first order		1–5
*N,N,*α-Me_3CA	6.2	competitive	linear	non pseudo first order		1–5
MPTP	0.28	competitive	linear	0.50	2.38	1–5
5a	1.94	competitive	parabolic	non pseudo first order		1.7–10
5b	2.3	competitive	linear	non pseudo first order		0.5–2.5
6a	0.51	mixed	linear	non pseudo first order		1–10
6b	1.04	mixed	linear	non pseudo first order		10–50
7	0.69	competitive	parabolic	0.94	0.15	1–10
8	0.38	mixed	linear	0.67	780	0.2–10

piperidinone hydrate hydrobromide (**17**) was prepared from 3-hydroxypyridine (**15**) by a modification of the reported synthesis[14] of *N*-benzyl-3-piperidinone hydrate hydrobromide. Treatment of the free base with diethyl benzylphosphonate gave approximately equal amounts of **7** and **8**. Silica gel did not resolve the two isomers well; however, triethylamine-washed silica gel was quite effective in separating the compounds. Structural assignments for the two isomers were made on the basis of X-ray crystallography of **8**. The ORTEP drawing of **8**, which crystallizes as two independent molecules, is shown in Figure 1 (both independent molecules have similar structures).

Enzymology. Cinnamylamine is an excellent substrate for MAO (K_m = 0.13 mM) that exhibits no inactivation properties, even at 10 mM over a period of 4 h. *N,N*-Dimethylcinnamylamine (**4**), however, is both a substrate and an inactivator of MAO. A summary of the inhibition kinetics (Lineweaver–Burk[15] analysis against the substrate cinnamylamine) and the inactivation kinetics (time-dependent loss of enzyme activity) for MPTP, α-methylcinnamylamine (α-MeCA), *N,N,*α-trimethylcinnamylamine (*N,N,*α-Me_3CA), and compounds **4–8** is presented in Table I. Overall, it is apparent that MPTP is the best inhibitor and inactivator of MAO. There does not appear to be a correlation of structure to K_i, K_I, or k_{inact}. Of the conformationally rigid analogues of *N,N*-dimethylcinnamylamine, only **5b**, which has the same configuration as MPTP, and the cinnamylamine derivatives (**4**, α-MeCA, *N,N,*α-Me_3CA) exhibit the same type of inhibition kinetics as MPTP (competitive with a linear replot). However, the K_i for **5b** is the largest of the K_i values for the conformationally rigid analogues determined in this study. The K_i values for **5** and **6** are larger than those for **7** and **8**. Compounds **5** and **6** can be considered to be α-substituted amines, where the α-substituent is one of the C–C bonds of the 6-membered ring. It is known[16,17] that α-substituted amines are poor substrates for MAO, and, in fact, no appreciable oxidation rate was observed for **5a**, **5b**, **6a**, and **6b**. The K_i for *N,N,*α-Me_3CA is considerably larger than that for **4**, and the K_i for α-MeCA is considerably larger than the K_m for cinnamylamine, thus supporting the hypothesis that the higher K_i values for **5** and **6** may be the result of α-substitution. The analogues other than **5b** show either mixed inhibition kinetics or give a nonlinear (parabolic) curve for the plot of [I] versus the slope of the Lineweaver–Burk plot. These anomalies typically suggest[15] that two molecules of inhibitor may be binding to each enzyme molecule or that dead-end inhibition is occurring and reoxidation of reduced MAO B is blocked. A more detailed kinetic analysis of compound **8** will be presented elsewhere.

Table II. Cytotoxicity of Compounds **5–8**

	% loss of cells		
compd (1.5 mM)	60 min	90 min	120 min
MPTP[a]	12[b]	58	81
5a	100		
5b	37	55	84
6a	28	35	60
6b	100		
7	17	21	20
8	19	18	18
blank	20	19	23
MPTP + pargyline[c]	6	11	15
5a + pargyline	100		
5b + pargyline	32	62	90
6a + pargyline	24	51	69
6b + pargyline	100		
7 + pargyline	21	19	20
8 + pargyline	18	21	18
blank + pargyline	18	15	21

[a] Taken from Figure 3A given in Di Monte et al.[25] [b] Trypan blue uptake. [c] Cells were pretreated with 10 μM pargyline as described by Di Monte et al.[25,26]

All of the compounds listed in Table I are time-dependent inactivators of MAO B. Considering that cinnamylamine does not inactivate MAO, it is curious that compounds **5a** and **6a** do. Of the conformationally rigid analogues, only **7** and **8** gave pseudo-first-order kinetics. The non-pseudo-first-order inactivation kinetics observed for α-MeCA, *N,N,*α-Me_3CA, **5a**, **5b**, **6a**, and **6b** is not the result of rapid inactivator consumption. As mentioned above, these compounds are α-substituted and are poor substrates for MAO B. However, several α-substituted compounds are mechanism-based, pseudo-first-order inactivators of MAO,[18–24] so α-substitution alone does not necessarily interfere with inactivation. The nonlinearity may be the result of multiple binding of the compounds or dead-end inhibition, as discussed above.

Cytotoxicity. The toxicity of compounds **5–8** to rat hepatocytes was measured in the absence and presence of pargyline in order to compare the potential neurotoxicity of these compounds with that of MPTP. As shown in Table II, compounds **5a**, **5b**, and **6b** are more cytotoxic, and **6a** is comparable in cytotoxicity to MPTP, but unlike MPTP, pargyline does not protect the cells from de-

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struction. This suggests that the cytotoxicity of **5a**, **5b**, **6a**, and **6b** is not caused by metabolites generated by MAO in vivo, as is the case for MPTP.[3,4] Compound **4** was reported by Fries et al.[27] not to be a neurotoxin, consistent with the formation of MPP^+ as the cause for neurotoxicity of MPTP.

In summary, there does not appear to be a structure–activity relationship for the conformationally rigid analogues of *N,N*-dimethylcinnamylamine. However, there must be other subtle factors involved in the inactivation, since N,N-dimethylation of cinnamylamine is sufficient to transform an excellent substrate into an inactivator of MAO. This phenomenon also has been observed by Fritz et al.[28] for MPTP; *N*-desmethyl-MPTP is a good substrate for human liver MAO B but does not inactivate it. The *N*-methyl group may be important for the proper orientation of the compounds that leads to inactivation.

Experimental Section

Analytical Methods. Proton NMR spectra were recorded on a Varian EM 390-A spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane as an internal standard. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Silica gel columns for flash chromatography utilized E. Merck silica gel 60 (230–400 mesh ASTM). Analytical thin-layer chromatography was conducted by E. Merck silica gel 60F-254 precoated TLC plates. X-ray crystallography was performed by Dr. Michal Sabat at Northwestern University.

Reagents. 2-(Phenylmethylene)cyclohexanone Oxime (10). 2-(Phenylmethylene)cyclohexanone[10] (**9**) (3.75 g, 20 mmol) was dissolved in ethanol (15 mL) followed by the addition of hydroxylamine hydrochloride (3.0 g, 40 mmol). The reaction solution was heated to reflux, 10 N NaOH (2.0 mL) was added dropwise over a 15 min interval, and the reflux was continued for 1 h. The precipitate that formed during the reaction was removed by suction filtration while the reaction mixture was still hot. The product that crystallized upon being cooled was collected and recrystallized from ethanol to give the oxime (4.0 g, 99%): mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 4 H), 2.64 (m, 4 H), 6.92 (t, 1 H), 7.32 (s, 5 H), 9.59 (br s, 1 H).

(*E*)-2-(Phenylmethylene)cyclohexanamine Hydrochloride (5a). Via a modification of the procedure of Harries and de Osa,[11] **10** (2.0 g, 10 mmol) was partially dissolved in a 50% acetic acid/ethanol solution (30 mL) and cooled to 4 °C. The reaction mixture was stirred while zinc dust (6.4 g, 100 mmol) was added in small increments over a 30-min period. The reaction was allowed to warm to room temperature and was stirred for an additional 30 min. The mixture was filtered, and the solid was washed with ethanol. The combined filtrates were concentrated to less than 5 mL, diluted with ethyl acetate (100 mL), and treated with 10 N NaOH (80 mL), and the organic layer was separated. The aqueous layer was extracted with two additional portions of ethyl acetate (100 mL each), and the combined extracts were dried over $MgSO_4$ and then evaporated to give a pale yellow oil. The oil was treated with ethereal HCl to precipitate the product. Recrystallization from ethyl acetate/ethanol gave the amine hydrochloride as white crystals (1.74 g, 78%): mp 203–204 °C; ^{1}H NMR (D_2O) δ 1.70 (m, 6 H) 2.37 (m, 2 H), 4.33 (m, 1 H), 6.10 (m, 1 H), 7.33 (m, 5 H). Anal. ($C_{13}H_{18}ClN$) C, H, N.

(*E*)-*N,N*-Dimethyl-2-(phenylmethylene)cyclohexanamine Hydrochloride (5b). By use of the conditions described by Borch and Hassid,[13] **5a** (669 mg, 3.0 mmol) was dissolved in a solution of 37% formaldehyde (4 mL) in acetonitrile (25 mL). To this was added sodium cyanoborohydride (500 mg, 8.0 mmol). The slightly turbid solution was stirred for 30 min, the pH was adjusted to near neutrality with acetic acid, and the reaction mixture was stirred an additional 90 min. The acetonitrile was removed under reduced pressure, and the residue was dissolved in 1 N NaOH (50 mL) and extracted with three portions of ethyl acetate (50 mL each). The combined extracts were dried over $MgSO_4$, and the solvent was evaporated to an oil. The residual oil was taken up in anhydrous ether and precipitated with ethereal HCl. Recrystallization from ethyl acetate/ethanol gave the tertiary amine hydrochloride as white crystals (650 mg, 87%): mp 208–211 °C; ^{1}H NMR (D_2O) δ 1.66 (m, 6 H), 2.36 (m, 2 H), 2.80 (d, 6 H), 3.67 (m, 1 H), 6.6 (s, 1 H), 7.33 (m, 5 H). Anal. ($C_{15}H_{22}ClN$) C, H, N.

3-Phenyl-2-cyclohexen-1-ol (13). 3-Phenyl-2-cyclohexen-1-one[29] (1.33 g, 7.7 mmol) was dissolved in methanol (12 mL) and cooled to 0 °C. Sodium borohydride (176 mg, 4.64 mmol) was added in two portions over a 5-min period. The reaction mixture was stirred under argon for 30 min at 0 °C and allowed to stir at room temperature for 1 h. The reaction mixture was poured into ethyl acetate (50 mL) and washed with H_2O (25 mL). The aqueous layer was extracted with two portions of ethyl acetate (50 mL each), and the combined organic layers were dried over $MgSO_4$ and evaporated to give the product as a clear oil (1.30 g, 97%): ^{1}H NMR ($CDCl_3$) δ 1.80 (5 H, m), 2.45 (2 H, m), 4.37 (1 H, m), 6.20 (1 H, m), 7.45 (5 H, m).

***N*-(3-Phenyl-2-cyclohexenyl)phthalimide (14).** Via the general procedure of Mitsunobu et al.[30] **13** (1.21 g, 7 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Triphenylphosphine (1.90 g, 7.2 mmol) and phthalimide (1.06 g, 7.2 mmol) were added to the reaction mixture followed by diethyl azodicarboxylate (1.15 mL, 7.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred under argon for 2.5 h. The THF was evaporated, and the residue was flash chromatographed (40 mm × 300 mm) with *n*-hexane (1500 mL) followed by a mixture of *n*-hexane/ethyl acetate (2500 mL, 5:1). The fractions containing the compound with an R_f of 0.47 (*n*-hexane/EtOAc, 5:2) were pooled, and the solvent was evaporated. Recrystallization from ethanol/H_2O gave the phthalimide as a white solid (1.23 g, 58%): mp 154–6 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 4 H), 2.53 (m, 2 H), 5.06 (m, 1 H), 5.90 (s, 1 H), 7.35 (m, 5 H), 7.77 (m, 4 H).

3-Phenyl-2-cyclohexen-1-amine Hydrochloride (6a). *N*-(3-Phenyl-2-cyclohexenyl)phthalimide (230 mg, 0.76 mmol) was partially dissolved in methanol (10 mL). Hydrazine hydrate (49 μL, 1.0 mmol) was added, and the reaction mixture was refluxed for 2 h. After being cooled to room temperature, 2 N HCl (10 mL) was added. The precipitated phthalhydrazide was filtered off and washed with methanol (15 mL) and then H_2O (2 × 10 mL). The combined filtrates were evaporated to a glassy solid and crystallized with ethanol/ether. Recrystallization from ethanol/ethyl acetate gave the product as a white solid (134 mg, 85%): mp 220–221 °C; ^{1}H NMR (D_2O) δ 2.00 (m, 4 H), 2.55 (m, 2 H), 4.15 (m, 1 H), 6.15 (m, 1 H), 7.60 (m, 5 H). Anal. ($C_{12}H_{16}ClN$) C, H, N.

***N,N*-Dimethyl-3-phenyl-2-cyclohexen-1-amine Hydrochloride (6b).** Via the procedure of Borch and Hassid,[13] **6a** (525 mg, 2.5 mmol) was dissolved in a solution of 37% formaldehyde (2 mL) in acetonitrile (20 mL). Sodium cyanoborohydride (470 mg, 7.5 mmol) was added in one portion at room temperature. After 20 min the pH was adjusted to neutrality with acetic acid, and the reaction mixture was stirred for an additional 1.5 h. The acetonitrile was evaporated, and the residue was dissolved in 1 N NaOH (50 mL) and extracted with three portions of ether (50 mL each). The combined ether extracts were dried over $MgSO_4$ and concentrated to about 50 mL, and then HCl gas was bubbled through the solution to precipitate the product. Recrystallization of the precipitate from ethanol/ethyl acetate gave the tertiary amine hydrochloride as a white solid (334 mg, 56%): mp 205–206 °C; ^{1}H NMR (D_2O) δ 1.9 (m, 6 H), 2.5 (m, 2 H), 3.12 (d, 6 H),

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3.95 (m, 1 H), 6.92 (s, 1 H), 7.62 (m, 5 H); exact mass calcd for $C_{14}H_{19}N$ 201.151 75, found 201.149 40 (2.3 ppm).

***N*-Methyl-3-methoxy-1,2,5,6-tetrahydropyridine (16).** Via a modification of the procedure of Krogsgaard-Larsen and Hjeds,[14] sodium metal (2.60 g, 110 mmol) was dissolved in anhydrous methanol (55 mL). Pyridin-3-ol (9.40 g, 100 mmol) was added to the solution followed by methyl iodide (42.6 g, 300 mmol). The reaction mixture was heated to reflux overnight, and then the excess methyl iodide was removed by distillation. The flask was cooled to 0 °C, and sodium borohydride (7.6 g, 200 mmol) was added portionwise to the reaction vessel over a 1-h period. After the mixture was stirred at room temperature for 2 h, the methanol was removed in vacuo to give a white slurry. To the residue was added H_2O (100 mL), K_2CO_3 (10 g), and ether (100 mL), and the mixture was stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with ether (100 mL). The combined organic layers were dried over $MgSO_4$, evaporated to an oil, and distilled to give a colorless oil (4.39 g, 35%): ^{1}H NMR ($CDCl_3$) δ 2.23 (m, 2 H), 2.37 (s, 3 H), 2.47 (t, 2 H), 2.87 (m, 2 H), 3.53 (s, 3 H), 4.65 (m, 1 H).

***N*-Methyl-3-piperidinone Hydrobromide Hydrate (17).** Compound 16 (3.13 g, 25 mmol) was dissolved in 48% HBr (15 mL) and was refluxed for 5 h. The reaction mixture was cooled and evaporated under reduced pressure to give a glassy light brown residue. Ethanol (15 mL) was added, and the solid (3.36 g, 64%) was collected by filtration. Upon concentration of the mother liquor to 5 mL, more product (1.06 g, 20%) crystallized out of solution. The combined crops were recrystallized from ethanol/ethyl acetate to give 17 as white crystals (4.25 g, 81%): mp 106–107 °C; ^{1}H NMR (D_2O) δ 2.03 (m, 4 H), 3.00 (s, 3 H), 3.10 (m, 2 H), 3.40 (m, 2 H).

***(E)*- and *(Z)*-*N*-Methyl-3-(phenylmethylene)piperidine Hydrochloride (7 and 8).** Sodium hydride (60% in mineral oil; 1.45 g, 36 mmol) was added to DME (40 mL) under argon. The three-necked reaction flask was fitted with two addition funnels and a reflux condenser. Diethyl benzylphosphonate (7.5 mL, 36 mmol) in DME (10 mL) was placed in one of the addition funnels, and *N*-methyl-3-piperidinone (15.7 mmol) in DME (10 mL), prepared by treating 17 (3.34 g, 15.7 mmol) with 2 N K_2CO_3 (50 mL), extracting into ether (3 × 60 mL), drying ($MgSO_4$), and evaporating, was placed in the other dropping funnel. The diethyl phosphonate was added to the NaH/DME mixture over a 5-min period, and then the *N*-methyl-3-piperidinone solution was added dropwise also over a 5-min period. The reaction mixture was refluxed for 1.5 h. Upon being cooled, the reaction mixture became viscous. Water (2 mL) was carefully added to quench any remaining sodium hydride. The addition of water (50 mL) turned the viscous paste into a biphasic mixture, which was poured into 0.2 N HCl (50 mL) and ether (50 mL) and stirred for 10 min. The aqueous layer was raised to pH 10 with 1 N NaOH, extracted with ether (3 × 100 mL), dried over $MgSO_4$, and evaporated to give a pale yellow oil (2.43, 95%). Flash chromatography on triethylamine-treated silica gel 60 (2.5 × 30 cm) with 1:1 petroleum ether/ethyl acetate as eluant gave 1.10 g of the *Z* isomer and 0.95 g of the *E* isomer. The hydrochloride salts were prepared by diluting the free bases in anhydrous ether and precipitating with ethereal HCl.

E isomer: mp 170–171 °C; NMR of free amine ($CDCl_3$) δ 1.69 (m, 2 H), 2.35 (s, 3 H, and t, 2 H), 2.53 (t, 2 H), 3.00 (s, 2 H), 6.42 (s, 1 H), 7.23 (m, 5 H); NMR of HCl salt (D_2O) δ 1.6–2.6 (br m, 4 H), 2.7–3.5 (m, 2 H), 3.07 (s, 3 H), 3.5–4.3 (m, 3 H), 6.82 (s, 1 H), 7.51 (s, 5 H). Anal. ($C_{13}H_{18}ClN$) C, H, N.

Z isomer: mp 193–195 °C; NMR of free amine ($CDCl_3$) δ 1.77 (m, 2 H), 2.27 (s, 3 H), 2.30 (t, 2 H), 2.50 (t, 2 H), 3.10 (s, 2 H), 6.33 (s, 1 H), 7.23 (m, 5 H); NMR of HCl salt (D_2O) δ 1.55–2.55 (br m, 4 H), 2.7–3.4 (m, 2 H), 3.00 (s, 3 H), 3.5–4.2 (m, 3 H), 6.79 (s, 1 H), 7.48 (s, 5 H). Anal. ($C_{13}H_{18}ClN$) C, H, N.

Inactivation Experiments. Inactivations of MAO B by the different analogues were performed analogous to the procedure described below for 8.

Inactivation of MAO B by 8. A 5-μL aliquot of 120 μM beef liver MAO B[31] in 50 mM potassium phosphate, pH 7.2, was added to varying concentrations of 8 (0.0, 1.0, 1.25, 1.67, 2.5, 5.0, and 10.0 mM) in 100 mM potassium phosphate, pH 7.2, and incubated at 25 °C. Aliquots were removed periodically and assayed for enzyme activity (see enzymes and assays). The percent of residual activity was calculated on the basis of the t_0 value for the inactivation, and these values were plotted as ln % activity vs time. The $t_{1/2}$ values for the different 8 concentrations were estimated from the semilog plots and plotted versus the reciprocals of the corresponding concentration of 8. From these plots the K_I and k_{inact} values were derived.[32]

Inhibition Experiments. Studies of the inhibition of MAO oxidation of cinnamylamine by the different analogues were performed analogous to the procedure described below for 8.

Inhibition of MAO B Oxidation of Cinnamylamine by 8. A 5-μL aliquot of 4.0 μM MAO B in 100 mM potassium phosphate, pH 7.2, was added to 495 μL of a solution containing varying concentrations of cinnamylamine (0.1, 0.125, 0.167, 0.25, and 0.5 mM) and 8 (0.0, 1.0, 2.0, 3.0, 4.0, and 5.0 mM) at 25 °C. The initial rates of oxidation were measured by recording the increase in the 290-nm absorbance with time. The rate data were treated by the method of Lineweaver and Burk,[15] and kinetic constants were derived from linear regression analysis of the slope versus [8] replots.

Cytotoxicity Studies. These studies were carried out by Dr. Donato Di Monte by the procedure described previously.[25,26]

Registry No. 1, 28289-54-5; 4, 33962-90-2; **5a**, 105206-09-5; **5a**·HCl, 114506-91-1; **5b**, 114506-95-5; **5b**·HCl, 114506-92-2; **6a**, 114506-96-6; **6a**·HCl, 114506-94-4; **6b**, 114506-98-8; **6b**·HCl, 114506-97-7; **7**, 114507-01-6; **7**·HCl, 114507-02-7; **8**, 114507-00-5; **8**·HCl, 114507-03-8; **9**, 1467-15-8; **10**, 114506-90-0; 11, 10345-87-6; **12**, 88141-37-1; **13**, 17488-64-1; 14, 114506-93-3; **15**, 109-00-2; **16**, 98435-42-8; **17**, 114506-99-9; **18**, 5519-50-6; α-MeCA, 53309-95-8; Me_3Ca, 34097-92-2; diethyl benzylphosphonate, 1080-32-6; cinnamylamine, 4360-51-4; monoamine oxidase B, 9001-66-5.

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