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1-Methyl-3-pyrrolines and 2-methylisoindolines: new classes of cyclic tertiary amine monoamine oxidase B substrates

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Abstract

Both 1-methyl-3-pyrrolines and 2-methylisoindolines are substrates for MAO-B with V_{max}/K_m values ranging from 200 to 2000 $min^{-1} mM^{-1}$ at 37°C. These compounds represent new classes of cyclic tertiary amine substrates for this flavoenzyme. The only other known cyclic amines that are MAO-B substrates are 1,4-disubstituted 1,2,3,6-tetrahydropyridinyl derivatives. The presence of an allylic (benzylic) amino functionality in all of these compounds may be linked to their substrate properties since related piperidinyl and pyrrolidinyl analogs are stable in the presence of MAO-B. This paper discusses energetic and geometric features of these compounds in relationship to their substrate properties and in anticipation of their utility to probe the active site of this flavoenzyme.

1. Introduction

The flavoenzymes monoamine oxidase MAO A and B (MAO-A and MAO-B) catalyze the oxidative deamination of brain neurotransmitters such as dopamine and serotonin as well as a variety of xenobiotic amines [1]. The primary structures of these enzymes have been established from gene sequences [2,3] but little is known about the three dimensional features of their active sites. The parkinsonian inducing nigrostriatal neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP (**1**, R = Ph)] and some of its structurally related analogs are excellent MAO-B and/or MAO-A substrates [4,5]. MAO-B catalyzes the conversion of MPTP to the dihydropyridinium intermediate **2** which undergoes spontaneous oxidation to the pyridinium species **3**, the ultimate neurotoxin (Scheme 1) [6,7]. These partially rigid tetrahydropyridinyl derivatives have been used to examine the catalytic mechanism [8–11] and to investigate the topology of the active sites of both forms of the enzyme [12–14]. To the best of our knowledge, 1,4-disubstituted 1,2,3,6-tetrahydropyridines are the only reported cyclic tertiary amines which display good MAO-B substrate properties. The corresponding piperidinyl analog **4** of MPTP is not a substrate [15] suggesting that the allylamine functionality is important for the catalytic process. Consistent with this view, the MAO-B catalyzed oxidation of MPTP occurs regiospecifically at the C-6 allylic position [16].

In an attempt to evaluate further the potential importance of the allylic moiety in the MAO-B catalyzed oxidations of cyclic tertiary amines, the series of β,γ-unsaturated five membered cyclic tertiary amines (pyrrolines and isoindolines) shown below was synthesized. The substrate properties of these compounds are discussed in terms of their geometric and stereoelectronic properties and are compared to the known structural requirements for the MAO-B catalyzed oxidation of tetrahydropyridinyl derivatives and related compounds.

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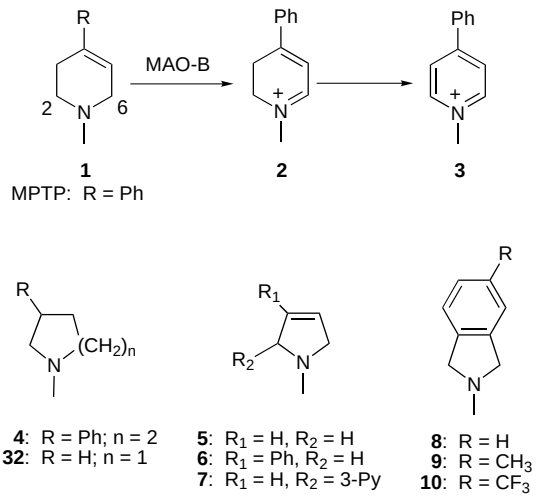


Scheme 1.

2. Results and discussion

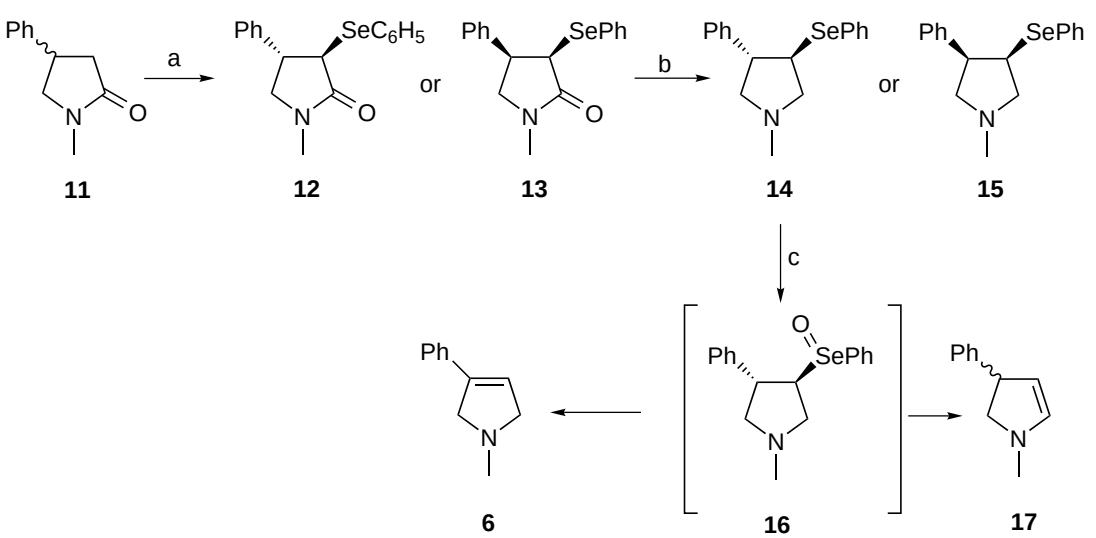
2.1 Synthesis

Synthesis of 1-methyl-3-phenyl-3-pyrroline (**6**) was accomplished via a strategy developed by Chavdarian for the preparation of the corresponding 2-(3-pyridinyl) analog **7** (Scheme 2) [17]. The racemic form of 1-methyl-4-phenyl-2-pyrrolidinone (**11**) was treated with LDA followed by reaction of the resulting lithium enolate with phenylselenyl chloride [18]. The ^{1}H NMR spectrum of the resulting phenylselenyl product (Scheme 2) was consistent with a single diastereoisomer but the spectral features did not allow unambiguous assignment of the geometry about the double bond. Arguments based on steric control of enolate attack on the phenylselenyl chloride from the least hindered side and AM1 semi-empirical calculations (the *trans*-diastereomer **12** is more stable than the *cis*-diastereomer **13** by 7 kcal/mol) support the assignment of this product as the *trans*-isomer **12**. Borane reduction of this lactam gave the pyrrolidine **14** (or its geometric isomer **15**). The corresponding selenoxide (presumably **16**) gave the desired pyrroline **6**, a reaction that should proceed by a *syn* elimination which is consistent with the proposed *trans* geometry for this series. The yield in this reaction was only 30% suggesting that elimination also may have occurred to give the isomeric enamine **17** which may have degraded during work-up of the reaction mixture [17]. The formation of **17** is not unexpected since calculations show that **6** is favored over **17** by only 0.3 kcal/mol.

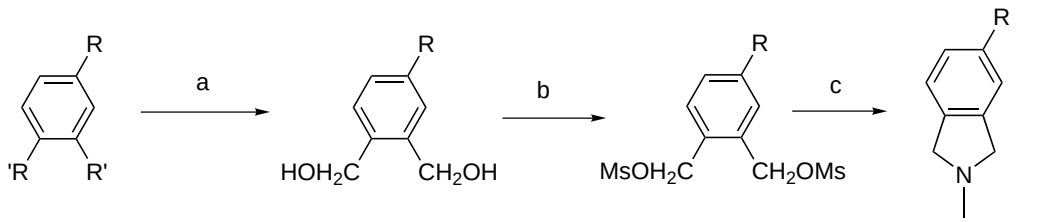
Syntheses of the 2-methylisoindolines **8–10** were achieved according to the reaction sequence summarized in Scheme 3. The starting materials 4-methylphthalic acid (**19**) and 1,2-*bis*-hydroxymethylbenzene (**21**) were commercially available. The 4-trifluoromethyl analog **20** was obtained by oxidation of 1,2-dimethyl-4-trifluoromethylbenzene (**18**) [19]. $LiAlH_4$ reduction of the phthalic acids **19** and **20** [20] provided the corresponding carbinols **22** and **23**. The *bis*mesylates **24–26** then were converted to the desired isoindolines by treatment with methylamine [21].

2.2 Enzymology

Repeated UV scans (450 to 250 nm) of incubation mixtures containing 500 μM of each of the five test



Scheme 2. Synthetic pathway to 1-methyl-4-phenyl-3-pyrroline (**6**). (a) i. LDA, THF, ii. PhSeCl; (b) BH_3·THF, THF; (c) H_2O_2 30%.



18: R = CF_3; R' = CH_3
19: R = CH_3; R' = COOH
20: R = CF_3; R' = COOH

21: R = H
22: R = CH_3
23: R = CF_3

24: R = H
25: R = CH_3
26: R = CF_3

8: R = H
9: R = CH_3
10: R = CF_3

Scheme 3. Synthetic pathway to the isoindolines **8–10**. (a) $LiAlH_4$, THF; (b) MsCl, NEt_3; (c) $MeNH_2$.

compounds (**5**, **6**, and **8–10**) and 0.16 μM MAO-B were examined to evaluate qualitatively their MAO-B substrate properties. The time dependent formation of new chromophores established that all compounds were substrates for MAO-B. Consequently, 3-pyrrolines and isoindolines join 1,2,3,6-tetrahydropyridines as cyclic tertiary amine MAO-B substrates. As with the 6-membered series, the fully reduced azacycle, 1-methylpyrrolidine (**32**), was stable in the presence of MAO-B. Kinetic studies on the MAO-B catalyzed oxidations of these compounds led in all cases to linear initial rate plots at substrate concentrations that bracketed the K_m values. The V_{max} and K_m values (Table 1) were obtained from the corresponding Lineweaver–Burke double reciprocal plots using the reported molar extinction coefficients for **27**, **28** and **29**. Since we have assumed that the molar extinction coefficients for the methyl (**30**) and trifluoromethyl (**31**) analogs are the same as the value reported for **29**, kinetic estimates are only approximate.

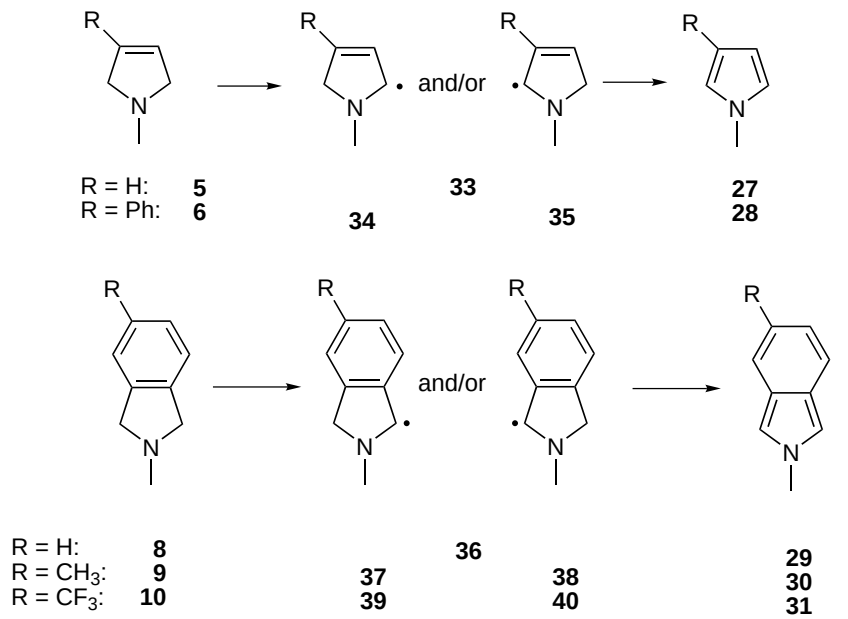
Summarized in Scheme 4 are possible reaction sequences to account for product formation with these two series. Calculations (Table 2) were performed at the semi-empirical level (AM1) to estimate the change in energy involved in the conversion of the substrate molecules to the proposed allylic radicals (**33–40**) that are likely to be formed as intermediates leading to the pyrrolyl and isoindolyl metabolites. In this analysis no effort was made to distinguish between the single electron transfer [22] versus hydrogen atom transfer [23] mechanisms which have been proposed for the MAO catalytic pathway.

Table 1
MAO-B catalyzed oxidation of pyrroline and isoindoline derivatives

Substrate	V_{max} (min^{-1})	K_m (mM)	V_{max}/K_m $(min\ mM)^{-1}$
MPTP	273	0.191	1431
5	214	0.248	862
6	397	0.193	2054
8	62	0.267	231
9	80	0.126	639
10	132	0.351	376

As expected, formation of the C-6 allylic radical ($\Delta\Delta Hf = 6.628$ kcal/mol) of MPTP is favored over the corresponding C-2 homoallylic radical ($\Delta\Delta Hf = 18.192$ kcal/mol). The relatively weak energy (58.731 kcal/mol) of the allylic C–H bond is due to the favorable geometry for extended orbital overlap throughout the tetrahydropyridinyl six membered ring of the carbon radical. Similarly, the $\Delta\Delta Hf$ value (21.644 kcal/mol) for formation of the α-carbon radical of 1-methylpyrrolidine (**32**) is considerably greater than the corresponding values for the 3-pyrrolines and isoindolines which range from 10.635 to 16.863 kcal/mol. The substrate properties ($V_{max}/K_m = 862\ min^{-1}\ mM^{-1}$) of 1-methyl-3-pyrroline (**5**), however, were not anticipated since 1,2,3,6-tetrahydropyridine (**1**, R = H) is not an MAO-B substrate [24,25]. The similar $\Delta\Delta Hf$ values for the formation of **33** from **5** (15.857 kcal/mol) and **36** from **8** (16.835 kcal/mol) suggest that the double bond and the fused phenyl ring are equally efficient in stabilizing α-carbon radicals.

Introduction of a phenyl group at C-3 (compound **6**) resulted in an increase in V_{max} and a decrease in K_m values which makes **6** ($V_{max}/K_m = 2054\ min^{-1}\ mM^{-1}$) a better substrate than MPTP ($V_{max}/K_m = 1431\ min^{-1}\ mM^{-1}$) [26]. Two allylic radicals may form from **6**, and therefore the pathway leading to **28** is not obvious. Calculations indicate that the *trans* α-carbon radical **34** is favored over the *cis* isomer **35** by 3.94 kcal/mol. A comparison of the HOMO energy surfaces (Fig. 1) of the two α-carbon radical species provides evidence of better orbital overlap of the unpaired electron with the aromatic ring through the double bond for the *trans* radical **34**. Additional support for the stabilization of **34** by the aromatic group comes from the coplanarity of the phenyl and pyrrolinyl rings ($\theta 1 = 0°$, Fig. 2). In the case of the *cis* isomer **35**, the double bond is more engaged in resonance with the radical and less with the phenyl ring resulting in a greater dihedral angle



Scheme 4. Proposed pathways for the MAO-B catalyzed oxidations of 3-pyrrolines and isoindolines.

($\theta 1 = 9°$, Fig. 3) and reducing the steric interactions between the two rings. Radicals in both the *cis* and *trans* positions increase the *N*-methyl/ring angle $\theta 2$ as a consequence of the better overlap of the nitrogen lone pair with the radical.

The improved substrate properties of **6** relative to **5** may be a consequence of the increased stability of the allylic radical of **34** ($\Delta\Delta Hf = 10.635$ kcal/mol) derived from **6** versus **33** ($\Delta\Delta Hf = 15.875$ kcal/mol) derived from **5**. The geometry of **6**, however, also may contribute to its good substrate properties. The minimum energy conformer of **6** (Fig. 3) shows that the phenyl group occupies space that corresponds to that of the phenyl group of 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (**1**, $R = CH_2Ph$) which is an excellent MAO-B substrate ($V_{max}/K_m = 3580\,min^{-1}\,mM^{-1}$) [26]. It should be noted, however, that the minimum energy conformer of **6** shows a dihedral angle of only 6° between the two rings as opposed to 30–35° for MPTP [27].

The methyl substituted (**9**) and trifluoromethyl substituted (**10**) isoindolinyl derivatives initially were chosen for their similar steric and lipophilic properties (LogP **9** = 1.94, LogP **10** = 2.05) but inverse electronic effects (σ_p **9** = −0.14, σ_p **10** = +0.53). Both substituents led to a moderate enhancement in activity with the electron donating methyl group being more influencial than the electron withdrawing trifluoromethyl group (Table 1). The essentially identical $\Delta\Delta Hf$ values for the formation of the lowest energy species [the *trans* radical in both cases (**37** from **9** and **39** from **10**)], however, do not offer a good opportunity to evaluate electronic effects in this series as anticipated.

In summary, the good substrate properties of these compounds and 1,4-disubstituted 1,2,3,6-tetrahydropyridinyl derivatives, particularly when compared to the lack of substrate properties of the corresponding reduced azacyclic systems, suggest that the allylic functionality plays an important role in the MAO-B catalytic process. A general trend is observed between $\Delta\Delta Hf$ values for conversion of the parent amines to the proposed α-carbon radical intermediates, suggesting that the C–H bond energy at the carbon center undergoing

Table 2
Differences in the heats of formation ($\Delta\Delta Hf$) of allylic or benzylic radicals **32–39** that may be derived from the substrates MPTP, **4–6**, **8–10**, and **32**[a]

Compound	MPTP	**4**	**5**	**6**	**8**	**9**	**10**	**32**
$\Delta\Delta Hf_{C2}$	18.195	19.048	15.875	14.575	16.835	16.731	16.757	21.644
$\Delta\Delta Hf_{C5(C6)}$	6.628	—	—	10.635	—	16.511	16.421	—

[a]Values (kcal/mol) calculated using AM1. NB: $\Delta Hf_H = 52.103$ kcal/mol.

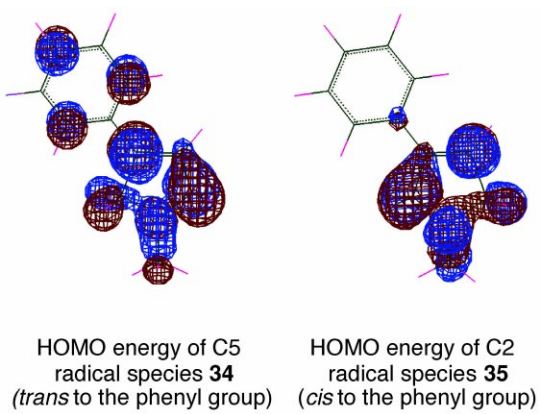


Fig. 1. HOMO energy surfaces of the two possible α-carbon radicals **34** and **35** derived from 1-methyl-3-phenyl-3-pyrroline (**6**).

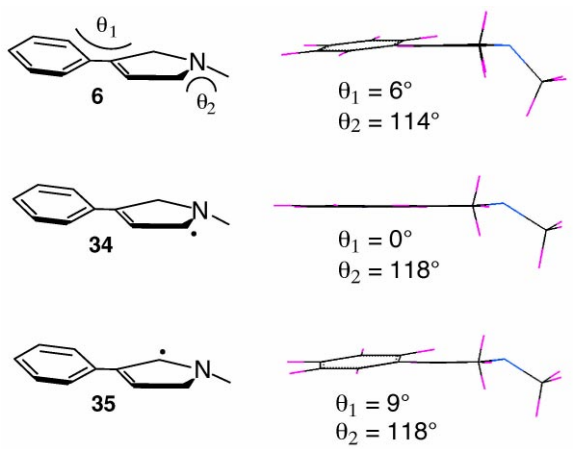


Fig. 2. Geometry of 1-methyl-3-phenyl-3-pyrroline (**6**) and the *trans* (**34**) and *cis* (**35**) α-carbon radicals.

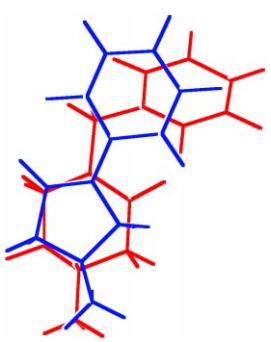


Fig. 3. Overlay of the minimum energy conformers of 1-methyl-3-phenyl-3-pyrroline (**6**) and 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (**1**, R = CH_2Ph).

oxidation may predict substrate properties within this series. It is clear, however, that the enzyme active site also is sensitive to the geometry of these types of compounds. Therefore it may be possible to exploit structural analogs of these azacycles to investigate regions of the active site of MAO-B that are not readily accessed with tetrahydropyridinyl derivatives.

3. Experimental

3.1 General

All chemicals were reagent or HPLC grade. Proton NMR spectra were recorded on a Bruker WP 270 MHz spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS, $\delta = 0$) and spin multiplicities are given as s (singlet), d (doublet), t (triplet), or m (multiplet). Gas chromatography–electron ionization mass spectrometry (GC–EIMS) was performed on a Hewlett-Packard 5890 GC fitted with an HP-1 capillary column (20 m×200 mm×0.33 mm film thickness) which was coupled to a Hewlett-Packard 5870 mass-selective detector. Data were acquired using an HP 5970 ChemStation. Normalized peak heights are reported as a percentage of the base peak. Compound **5** was synthesized according to the literature [28] and was converted to its oxalate salt in dry Et_2O, which was recrystallized from MeOH/Et_2O: mp 137–138°C; ^{1}H NMR (DMSO-d_6) δ 5.91 (s, 2H, vinyl of C3 and C4), 4.02 (s, 4H, CH_2 of C2 and C5), 2.87 (s, 3H, CH_3). The free base of 2-methylisoindoline (**8**) was prepared as reported previously [29] and was converted to its oxalate salt: mp 166–167°C; ^{1}H NMR (DMSO-d_6) δ 7.32–7.41 (m, 4H, phenyl), 4.53 (s, 4H, CH_2 of C1 and C3), 2.94 (s, 3H, CH_3); GC-EIMS (free base) t_R 4.00 min, m/z ($M\cdot^+$) 133. Enzyme kinetic studies were performed on a Beckman Model DU-7400 spectrophotometer. Melting points were determined using a Thomas–Hoover melting point apparatus and are uncorrected.

3.1.1 Trans-*1-methyl-4-phenyl-3-phenylselenyl-2-pyrrolidinone (**12**)*

To a solution of diisopropylamine (2.39 g, 0.0236 mol) in THF (50 ml) was added *n*-BuLi (2.5 M, 8.80 ml, 0.022 mol) at −20°C with stirring under N_2. After the addition the mixture was kept at −20°C for 30 min and then was cooled to −78°C. A solution of 1-methyl-4-phenyl-2-pyrrolidinone [18] (**11**, 1.80 g, 0.01027 mol) in THF (10 ml) was then added dropwise to the LDA solution at −78°C over 15 min. The resulting solution was stirred at −78°C for 40 min and 0°C for 1 h. The solution was quenched with water and extracted with Et_2O. The resulting crude product was chromatographed (silica-gel 35 g, eluent CH_2Cl_2) to give 1.98 g (58%) of pure **12** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.10–7.67

(m, 10H, phenyls), 3.85 (d, 1H, C3, $J_{3-4} = 5.4$ Hz), 3.47 (m, 1H, C4), 3.22–3.38 (m, 2H, C5), 2.84 (s, 3H, CH_3); GC-EIMS t_R 10.11 min, m/z ($M.^+$) 331; HRMS (CI). Calcd for $C_{17}H_{18}NO^{76}Se$: 328.0581. Found: 328.0586.

3.1.2 Trans-*1-methyl-3-phenylselenyl-4-phenylpyrrolidine (**14**)*

To a solution of **12** (1.32 g, 0.004 mol) in THF (15 ml) was added BH_3·THF (1.0 M, 24 ml, 0.024 mol) at room temperature with stirring under N_2. The mixture was kept at room temperature for 30 min and then was heated under reflux for 22 h. After cooling in an ice-water bath, the reaction was quenched with 6 N aqueous HCl and the resulting mixture was heated under reflux for 3 h and then was cooled, made basic with aqueous NaOH and extracted with Et_2O. The residue obtained after rotary evaporation was purified by column chromatography (silica-gel 50 g, eluent CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to give 1.20 g (95%) of pure **14** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.23–7.42 (m, 10H, phenyls), 3.91 (m, 1H, C4), 3.66 (m, 2H, C2), 3.46 (m, 2H, C5), 2.87 (s, 3H, CH_3), 1.68 (m, 1H, C3); GC–EIMS t_R 8.99 min, m/z ($M\cdot^+$) 317; HRMS (CI). Calcd for $C_{17}H_{20}N^{76}Se$: 314.0787. Found: 314.0779.

*3.1.3 Oxalate salt of 1-methyl-3-phenyl-3-pyrroline (**6**)*

To a solution of **14** (0.60 g, 0.0019 mol) in 15 ml THF was added 30% H_2O_2 (0.30 g, 0.0266 mol) dropwise at 0°C with stirring. The mixture was kept at 0°C for 30 min and then at room temperature for 1.5 h. Following the addition of aqueous 10% Na_2SO_3 (5 ml) and 10% aqueous Na_2CO_3 (10 ml), the mixture was extracted with Et_2O. Column chromatography of the organic isolate (silica-gel 25 g, eluents EtOAc to 10% MeOH in EtOAc) gave the free base **6** which was further purified as its oxalate salt (0.14 g, 30%): ^{1}H NMR (CD_3OD) δ 7.25–7.37 (m, 5H, phenyl), 6.18 (m, 1H, C4), 4.44 (s, 2H, C2), 4.21 (unresolved, 1H, C5), 2.98 (s, 3H, CH_3); GC–EIMS (free base) t_R 6.38 min, m/z ($M\cdot^+$) 159; Anal. calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%. Found C, 62.48; H, 6.08; N, 5.53%.

3.1.4 Bis*mesylates **24–26***

To a solution of methanesulfonyl chloride (5.50 g, 0.048 mol) in dry CH_2Cl_2 (40 ml) was added dropwise a solution of diol **21**, **22**, or **23** [21] (0.012 mol) and triethylamine (5.59 g, 0.055 mol) in CH_2Cl_2 (15 ml) at 0°C with stirring under nitrogen. After an additional 30 min at 0°C the reaction mixture was washed successively with 30 ml each of ice-cold water, 10% HCl, saturated $NaHCO_3$ and brine. The organic layer was separated and dried over $MgSO_4$ to give quantitative yields of the oily *bis*mesylates **24**, **25**, and **26** which were used in the next step without further purification: 1,2-*bis*mesyloxybenzene (**24**) ^{1}H NMR ($CDCl_3$) δ 7.41–7.53 (m, 4H, phenyl), 5.36 (s, 4H, CH_2), 2.99 (s, 6H, CH_3); 3,4-*bis*-mesyloxytoluene (**25**) ^{1}H NMR ($CDCl_3$) δ 7.21–7.39 (m, 4H, phenyl), 5.32 (s, 4H, CH_2), 2.99 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 2.39 (s, 3H, CH_3; 1,2-*bis*-mesyloxy-4-trifluoromethylbenzene (**26**) ^{1}H NMR ($CDCl_3$) δ 7.57–7.75 (m, 4H, phenyl), 5.39 (s, 2H, CH_2), 5.38 (s, 2H, CH_2), 3.07 (s, 3H, CH_3), 3.06 (s, 3H, CH_3).

*3.1.5 Oxalate salts of isoindolines **9** and **10***

To a solution of each of the *bis*mesylates **25** and **26** (0.084 mol) was added dropwise a solution of methylamine in THF (2M, 12.6 ml, 0.0252 mol) at 0°C with stirring. The mixtures were kept at 0°C for an additional 4 h and then at room temperature for 15 h. The resulting mixtures were washed successively with water and brine. The oxalate salts were prepared in dry Et_2O and recrystallized from MeOH/Et_2O. The oxalate salt of 2,5-dimethylisoindoline (**9**) was obtained in 36% yield: mp 177–178°C; ^{1}H NMR (DMSO-d_6) δ 7.14–7.27 (m, 3H, phenyl), 4.49 (s, 4H, CH_2 of C1 and C3), 2.93 (s, 3H, N-CH_3), 2.31 (s, 3H, CH_3 of C5); GC-EIMS (free base) t_R 4.60 min, m/z ($M.^+$) 147. Anal. calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%. Found C, 60.50; H, 6.28; N, 5.85%. The oxalate salt of 2-methyl-5-trifluoromethylisoindoline (**10**) was obtained in 45% yield: mp 174–175°C; ^{1}H NMR (DMSO-d_6) δ 7.59–7.79 (m, 3H, phenyl), 4.51 (s, 4H, CH_2 of C1 and C3), 2.93 (s, 3H, N-CH_3); GC-EIMS (free base) t_R 4.09 min, m/z ($M.^+$) 201. Anal. calcd for $C_{12}H_{12}F_3NO_4$: C, 49.49; H, 4.15; N, 4.81%. Found C, 49.26; H, 4.18; N, 4.72%.

3.2 Enzyme substrate studies

The isolation and purification of MAO-B from beef liver were carried out using the procedures reported by Salach [30] with the following modifications. We did not subject the MAO-B preparation to the glucose gradient purification step. The specific activity of MAO-B (9 nmol/ml) was established with MPTP as substrate at 30°C ($V_{max} = 204\ min^{-1}$) as reported earlier [31]. The MAO-B preparation was found to be stable when stored at −15°C over the period of this study.

Solutions of the oxalate salts of the test compounds in phosphate buffer (pH 7.4, 0.5 mM, final volume 500 μl) in a 1 ml quartz cuvette were treated with 10 μl of the MAO-B preparation (final concentration 0.16 μM) and the cuvette was placed in a Beckman Model DU-7400 spectrophotometer maintained at 37°C. The substrate properties were evaluated qualitatively by obtaining a series of scans (450–250 nm) versus time over a 1 h period for each compound.

Kinetic studies with MAO-B were carried out using a Beckman DU-7400 spectrophotometer. Solutions of the test compounds (final volume 510 μl, final substrate concentrations 125 to 4000 μM) in 100 mM sodium

phosphate (pH 7.4) were incubated in the presence of 0.16μM MAO-B. The rates of oxidation were obtained by monitoring the increment in absorbance of the metabolic aromatic products **27–31** over a 30–120 s time period. The V_{max} and K_m values were calculated from double reciprocal plots.

3.3 Calculations

Molecular properties were determined using the semi-empirical method AM1 [32] within MacSpartan software (1996, Wavefunction, Inc.). Calculations used the default restricted Hartree–Fock (RHF) method for the self-consistent field (SCF) except for calculations on the radical species that were performed using the unrestricted Hartree–Fock (UHF) model. The ACD/LogP 1.0 software from ACD/Labs was used to calculate the LogP values.

Acknowledgements

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