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4-(AMINOMETHYL)-1-ARYL-2-PYRROLIDINONES, A NEW CLASS OF MONOAMINE OXIDASE B INACTIVATORS

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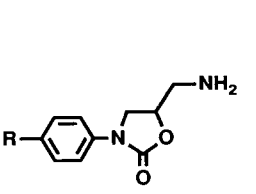
Both 4-(aminomethyl)-1-phenyl-2-pyrrolidinone (**4a**) and 4-(aminomethyl)-1-(methoxyphenyl)-2-pyrrolidinone (**4b**) hydrochlorides were synthesized via a six-step sequence, which represents a general approach to 1,4-disubstituted 2-pyrrolidinones. Both of these compounds inactivated monoamine oxidase B and represent the first in a new class of monomamine oxidase inactivators.

KEY WORDS: Monoamine oxidase B, inactivation, 4-(aminomethyl)-1-aryl-2-pyrrolidinones.

INTRODUCTION

Compounds that inactivate mitochondrial monoamine oxidase B (MAO, EC 1.4.3.4) block the destruction of brain dopamine and, as a result, have been shown to be important adjuncts in the treatment of Parkinson's Disease.[1] *L*-Deprenyl, a potent and selective inactivator of MAO B, currently is used worldwide in combination with *L*-dopa for the treatment of this disease.[2] Recently we have been studying the mechanism of inactivation of MAO B by 5-(aminomethyl)-3-aryl-2-oxazolidinones (**1**),[3,4] a class of MAO B inactivators reported during the 1980's.[5,6] Our conclusion regarding that inactivation mechanism[3] was that attachment to the enzyme by this class of compounds at the aminomethyl methylene group (**2**) was



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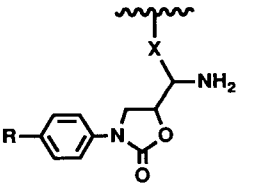

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stabilized by the electron-withdrawing ability of the oxazolidinone ring. Consequently, the corresponding lactones, 5-(aminomethyl)-3-aryldihydrofuran-2(3H)-ones (**3**),

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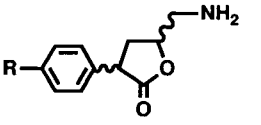

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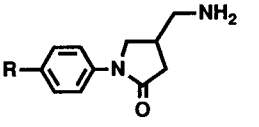
were synthesized, and both of the diastereomeric racemates also were shown to inactivate MAO B.[7] This is consistent with the hypothesis that the electron-withdrawing ability is important. Here we show that the corresponding lactams, the 4-(aminomethyl)-1-aryl-2-pyrrolidinones (**4**), also inactivate MAO B. These compounds represent yet another new class of MAO B inactivators. In addition to the



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pharmacological potential for this class of compounds as adjuncts in treatment for Parkinson's disease, 1,4-disubstituted 2-pyrrolidinones, in general, exhibit a wide spectrum of other pharmacological activities including antidepressant, anticonvulsant,[8] antiulcer,[9] antiasthmatic[10] and antiallergic activity.[11] Some 1,4-disubstituted 2-pyrrolidinones also have a promising transdermal drug delivery enhancement effect.[12] In addition to the pharmacological potential they also are synthetic intermediates[13] and are important for various functional resins.[14]

MATERIALS AND METHODS

Analytical Methods and Reagents

NMR spectra were recorded either on a Varian EM-390 90 MHz or on a Varian XL-400 400 MHz spectrometer. Chemical shifts are reported as δ values in parts per million downfield from Me_4Si as the internal standard in $CDCl_3$. Thin-layer chromatography was performed on EM/UV silica gel plates with a UV indicator. Melting points were obtained with a Fisher–Johns melting point apparatus and are uncorrected. Elemental combustion analyses were performed by G.D. Searle Laboratories, Skokie, IL. Mass spectra were recorded on a VG Instruments VG70-250SE high resolution spectrometer. Column chromatography was performed with Merck silica gel (230–400 mesh). All chemicals were purchased from Aldrich Chemical Co. and were used without further purification. Dichloromethane was dried by passing through an alumina column. DMF and triethylamine were distilled from BaO before use. Glassware was dried in the oven overnight when dry conditions were required. All reactions were carried out in an atmosphere of inert gas (nitrogen or argon) except hydrogenations.

Chemistry

5-Oxo-1-phenylpyrrolidine-3-carboxylic acid (**6a**) Aniline (22 ml, 0.3 mol) was added to a solution if itaconic acid (39 g, 0.3 mol) in 300 ml of water then the resulting

mixture was heated at reflux for 2 h. The crystalline colorless solid (42 g, 68%) that was produced was collected by filtration and washed twice with cold water. Additional product (17 g, 28%) was obtained by concentration of the mother liquors. Further purification can be done by recrystallization from water to give colorless crystals; mp 197–200°C; ^{1}H NMR (90 MHz, $CDCl_3$/DMSO) δ 7.05–7.60 (m, 5H), 4.00 (d, 2H), 3.27 (m, 1H), 2.80 (d, 2H); IR 3025 (broad, s), 1725 (s), and 1644 cm^{-1} (s); HRMS (EI) Calc. for $C_{11}H_{11}NO_3$, 205.0739, found 205.0742. Anal. Calc. for $C_{11}H_{11}NO_3$: C, 64.49; H, 5.37; N, 6.83%. Found: C, 64.39; H, 5.43; N, 6.82%.

1-(4-Methoxyphenyl)-5-oxo-pyrrolidine-3-carboxylic acid (**6b**) The same procedure for preparation of **6a** was employed, except the product was harvested upon cooling the reaction mixture to room temperature. The title compound was obtained as a pinkish crystalline solid in up to 97% yield; mp 168–170°C; ^{1}H NMR (90 MHz, $CDCl_3$/DMSO) δ 7.45 (d, 2H), 6.87 (d, 2H), 6.05 (b.s), 4.00 (d, 2H), 3.78 (s, 3H), 3.32 (m, 1H), and 2.80 ppm (dd, 2H); IR (KBr pellet) 3020 (broad, s), 1725 (s), and 1646 cm^{-1} (s); HRMS (EI) calc. for $C_{12}H_{13}NO_4$, 235.0844, found 235.0840.

Methyl 5-oxo-1-phenylpyrrolidine-3-carboxylate (**7a**) To a solution of **6a** (10.7 g, 0.1 mol) in 150 ml of methanol at 0°C, thionyl chloride (9.1 ml, 0.12 mol) was added. The resulting mixture was stirred at 0°C for 1 h and then the temperature was allowed to rise to room temperature. The mixture was kept stirring for 3 h at room temperature then the methanol was removed *in vacuo*, and the residual oil was distilled at 160–165°C/2 mmHg. A colorless oil was obtained, which solidified upon standing (18.5 g, 85%); mp 73–75°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.10–7.68 (m, 5H), 4.05 (dd, 2H), 3.75 (s, 3H), 3.35 (m, 1H), 2.85 (dd, 2H); IR (KBr pellet) 1735 (s), and 1690 cm^{-1} (s); HRMS (EI), calc. for $C_{11}H_{11}NO_3$, 205.0739, found 205.0743.

Methyl 1-(4-methoxyphenyl)-5-oxo-pyrrolidine-3-carboxylate (**7b**) The same procedure as for the preparation of **7a** was followed. The title compound was obtained as a white solid in 93% yield; mp 86–88°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.46 (d, 2H), 6.90 (d, 2H), 4.03 (dd, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.35 (m, 1H), and 2.85 ppm (dd, 2H); IR (KBr pellet) 1733 (s), 1691 (s), and 1513 cm^{-1} (s); HRMS (EI), calc. for $C_{13}H_{15}NO_4$, 249.1001, found, 249.1001. Anal. Calc. for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62%. Found: C, 62.26; H, 6.04; N, 6.22%.

4-Hydroxymethyl-1-phenyl-2-pyrrolidinone (**8a**) To a stirred solution of **7a** (1.1 g, 5.0 mmol) in 15 ml of methanol under nitrogen at room temperature, sodium borohydride (380 mg, 10 mmol) was added portionwise. The resulting cloudy solution was heated at reflux for 2 h, more sodium borohydride (190 mg, 5.0 mmol) was added, and refluxing was continued overnight. TLC analysis (silica gel, ethyl acetate) of the mixture indicated disappearance of starting material (R_f = 0.70). The resulting mixture was cooled to 0°C, the residual sodium borohydride was destroyed by successive addition of water (5 ml) and 10% HCl (5 ml), then the methanol was removed *in vacuo*. The aqueous residue was extracted with ethyl acetate (3 × 25 ml). The combined organic extracts were extracted with saturated sodium bicarbonate and dried over magnesium sulfate. Following removal of the ethyl acetate and silica gel column chromatography (20 g of silica gel, ethyl acetate) a viscous oil (R_f = 0.20) was obtained which solidified upon standing (0.90 g, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2H), 7.40 (t, 2H), 7.15 (t, 1H), 3.95 (dd, 1H), 3.75

(dd, 2H), 3.65 (dd, 1H), 2.70 (m, 2H), and 2.43 ppm (dd, 1H); IR (KBr pellet) 3360 (broad, s), and 1646 cm^{-1} (s).

4-Hydroxymethyl-1-(4-methoxyphenyl-2-pyrrolidinone (**8b**) The same procedure used for the preparation of **8a** was employed. The title compound was obtained in 86% as a white crystalline solid; mp 111–113°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2H), 6.90 (d, 2H), 3.92 (dd, 1H), 3.80 (s, 3H), 3.71 (m, 2H), 2.70 (m, 2H), 2.41 (d, 1H), 1.89 (m, 1H), and 1.64 ppm (s, 1H); IR (KBr pellet) 3361 (broad, s), 1647 (s), and 1515 cm^{-1} (s); HRMS (EI), calc. for $C_{12}H_{15}NO_3$, 221.1052, found 221.1051. Anal Calc. for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33%. Found: C, 65.14; 6.80; N, 6.25%.

4-Methanesulfonyloxymethyl-1-phenyl-2-pyrrolidinone (**9a**) To a stirred solution of **8a** (0.8 g, 4.2 mmol) in 20 ml of anhydrous methylene chloride at 0°C under nitrogen was added triethylamine via syringe followed by methanesulfonyl chloride (0.39 ml, 5.0 mmol). The reaction was complete within 30 min after stirring at 0°C as evidence by TLC analysis (ethyl acetate, $R_f = 0.20$). The resulting mixture was extracted successively with 10 ml each of water, 10% HCl, and saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate; removal of the solvent *in vacuo* gave a viscous oil (0.98 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2H), 7.35 (t, 2H), 7.13 (t, 1H), 4.30 (dd, 1 H), 4.20 (dd, 1H), 4.02 (dd, 1H), 3.70 (dd, 1H), 3.00 (s, 3H), 2.90 (m, 1H), 2.75 (dd, 1H), and 2.40 ppm (dd, 1H); IR (neat) 1695 (s), 1594 (s), 1495 (s), 1410 (s), and 1250 cm^{-1} (s); HRMS (EI) calc. for $C_{12}H_{15}NO_4S$, 269.0722, found 269.0719.

1-(4-Methoxyphenyl)-4-methylsulfonyloxymethyl-2-pyrrolidinone (**9b**) The same procedure for preparation of **9a** was employed. The title compound was isolated as white crystals (92%); mp 105–107°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 2H), 6.85 (d, 2H), 4.27 (dd, 1H), 4.22 (dd, 1H), 3.93 (dd, 1H), 3.73 (s, 3H), 3.65 (dd, 1H), 3.00 (s, 3H), 2.89 (m, 1H), 2.73 (dd, 1H), and 2.38 ppm (dd, 1H); IR (KBr pellet) 1694 (s), 1516 (s), 1357 (s), 1350 (s), 1250 (s), 1250 (s), and 1162 cm^{-1} (s); HRMS (EI), calc. for $C_{13}H_{17}NO_5S$, 299.0827, found 299.0818. Anal. Calc. for $C_{13}H_{17}NO_5S$: C, 52.17; H, 5.73; N, 4.68%. Found: C, 51.67; H, 5.69; N, 4.69%.

4-Azidomethyl-1-phenyl-2-pyrrolidinone (**10a**) To a stirred solution of mesylate **9a** (400 mg, 1.5 mmol) in 10 ml of anhydrous DMF, sodium azide (483 mg, 7.43 mmol) was added at 40°C under N_2. The mixture was allowed to stir overnight then it was diluted with diethyl ether, and extracted with water (2 × 25 ml). The organic layer was dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a colorless oil (280 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 2H), 7.41 (t, 2H), 7.20 (t, 1H), 4.05 (dd, 1H), 3.70 (dd. 1H), 3.58 (dd, 1H), 3.50 (dd, 1H), 2.78 (m, 2H), and 2.46 ppm (dd, 1H); IR (neat) 2105 (m), and 1690 cm^{-1} (s); HRMS (EI) calc. for $C_{11}H_{12}N_4O$, 216.1011, found 216.1010.

4-Azidomethyl-1-(4-methoxyphenyl)-2-pyrrolidinone (**10b**) The same procedure for preparation of **10a** was employed. The title compound was obtained as a colourless oil in 91% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H), 6.95 (d, 2H), 3.97 (dd, 1H), 3.80 (s, 3H), 3.67 (dd, 1H), 3.57 (dd, 1H), 3.47 (dd, 1H), 2.76 (m, 2H),

and 2.44 ppm (dd, 1H); IR (neat) 2104 (m), and 1691 cm^{-1} (s); HRMS (EI) calc. for $C_{12}H_{14}N_4O_2$, 246.1117, found 246.1122.

4-Aminomethyl-1-phenyl-2-pyrrolidinone hydrochloride (**4a**) A stirred mixture of azide **10a** (250 mg, 1.15 mol), and 80 mg of 10% Pd/C in 10 ml of absolute ethanol was hydrogenated at room temperature for 5 h. The solid was removed by filtration and the filtrate was saturated with gaseous HCl. The solvent was removed *in vacuo*, and the solid residue was recrystallized from ethanol/diethyl ether to give a white solid (210 mg, 81%); mp 182–184°C; ^1H NMR (400 MHz, D_2O) δ 7.52 (m, 4H), 7.40 (t, 1H), 4.17 (dd, 1H), 3.83 (dd, 1H), 3.28 (m, 2H), 3.00 (m, 2H), and 2.60 ppm (dd, 1H); IR (KBr pellet) 3415 (s, broad), 2974 (s, broad), 1660 (s), 1598 (s); HRMS (EI) calc. for $C_{11}H_{15}N_2OCl$ (−HCl), 190.1106, found 190.1104. Anal. Calc. for $C_{11}H_{15}N_2OCl$: C, 58.28; H, 6.67; N, 12.36%. Found: C, 57.95, H, 6.85, N, 12.44%.

4-Aminomethyl-1-(4-methoxyphenyl-2-pyrrolidinone hydrochloride (**4b**) The same procedure for preparation of **4a** was employed. The title product was obtained as a white solid in 89% yield; mp 184–187°C; ^1H NMR (400 MHz, D_2O) δ 7.42 (d, 2H), 7.12 (d, 2H), 4.15 (m, 1H), s, 3.90 (s, 3H), 3.80 (m, 1H), 3.42 (m, 1H), 3.29 (m, 1H), 2.95 (m, 2H), and 2.60 ppm (m, 1H); HRMS (EI) calc. for $C_{12}H_{17}N_2O_2Cl$ (−HCl), 220.1211, found 220.1211; Anal. calc. for $C_{12}H_{17}N_2O_2Cl$: C, 56.14; H, 6.67; N, 10.91%. Found: C, 56.32; H, 6.74; N, 11.13%.

Enzyme and Assays

Bovine liver MAO-B was isolated according to the method of Salach.[15] MAO activity was assayed in Tris buffer (100 mM, pH 9.0) at 25°C with cinnamylamine as the substrate as previously described.[3]

Time-dependent Inactivation Experiments (*General methods*) Solutions (180 μl each) of 4-aminomethyl-1-aryl-2-pyrrolidinone hydrochloride (22.22, 11.11, 6.67, 5.56, 0.00 mM) in potassium phosphate buffer (500 mM, pH 7.40) containing 10% DMSO as cosolvent were pre-incubated at 25°C. To these solutions, was added MAO-B (20 μl buffer). After being mixed, the samples were incubated at 25°C. They were periodically agitated and assayed for MAO activity by removing 10 μl of the mixture and adding it to 490 μl of the cinnamylamine solution in Tris buffer (1.02 mM, pH 9.0) as described above, The enzyme activity thus determined was corrected against a control containing no inactivator. Kinetic constants (K_I and k_{inact}) were determined as described by Kitz and Wilson.[20]

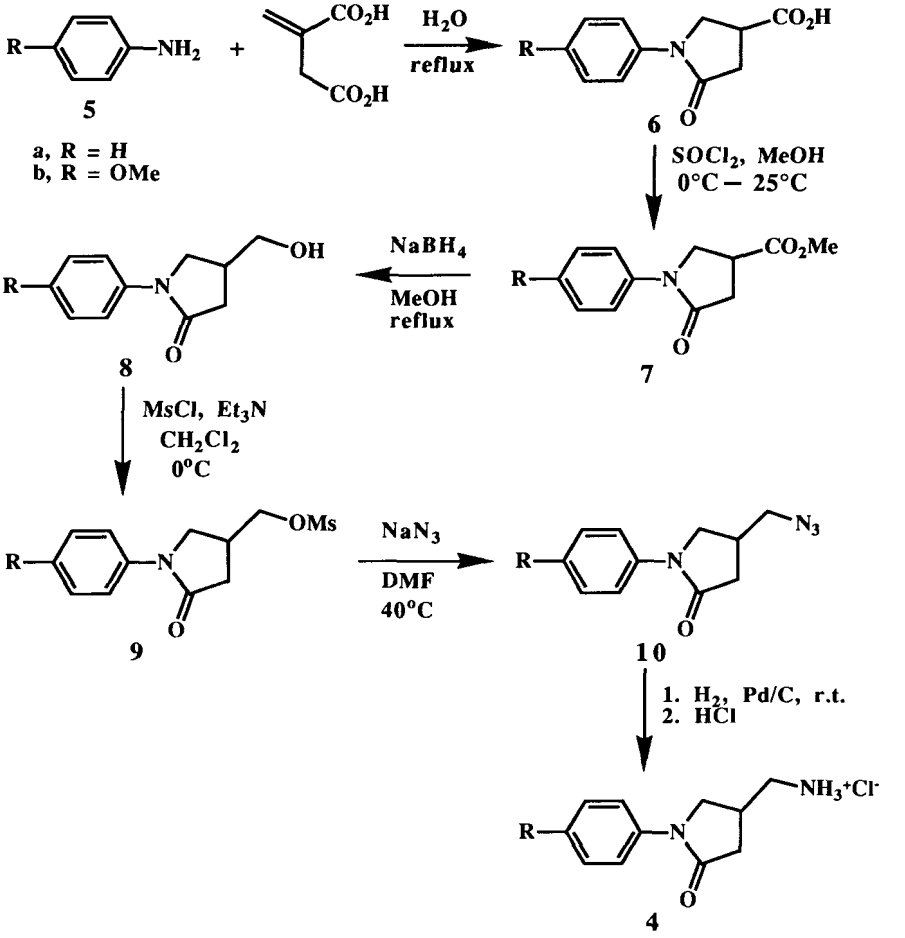
Effects of β-Mercaptoethanol and Benzylamine on the Rate of Inactivation of MAO-B by 4-Aminomethyl-1-aryl-2-pyrrolidinone Hydrochloride The following four solutions (180 μl each) were prepared in potassium phosphate buffer (500 mM, pH 7.40) and pre-incubated at 25°C; 4-aminomethyl-1-aryl-2-pyrrolidinone hydrochloride (27.7 mM), β-mercaptoethanol (0.28 mM), 4-aminomethyl-1-aryl-2-pyrrolidinone hydrochloride (27.7 mM) containing β-mercaptoethanol (0.28 mM), and a control with only the buffer. To these solutions, was added MAO-B (120 μg in 20 μl buffer). The mixtures were incubated at 25°C, and the MAO activity was assayed as described above. The same experiment was repeated except that benzylamine (277 mM) was substituted for β-mercaptoethanol.

Reactivation Studies (General) MAO-B (300 μg) was incubated with a 10 mM solution of an inactivator in potassium phosphate buffer (500 mM, pH 7.4) containing 10% DMSO as cosolvent at 25°C for 3 h. The incubation mixture and a control (1000 μl each) were transferred to dialysis bags (Spectrum®, 12,000 MW cut off) and dialyzed against 3 l of potassium phosphate buffer (100 mM, pH 7.0) at room temperature. The MAO-B activity was assayed periodically by removing 20 μl of the mixture and adding it to 480 μl of the cinnamyl amine solution in Tris buffer (1.02 mM, pH 9.0) described above.

RESULTS AND DISCUSSION

Chemistry

The synthetic route to the 4-(aminomethyl)-1-aryl-2-pyrrolidinones (**4**) is shown in Scheme 1. Our approach starts with cyclocondensation of itaconic acid with either



SCHEME 1 Synthetic route to 4-(Aminomethyl)-1-aryl-2-pyrrolidinones.

aniline (**5a**) or anisidine (**5b**) in boiling water[14] or in toluene under Dean–Stark conditions to give 5-oxo-1-phenylpyrrolidinecarboxylic acid (**6a**) or 1-(4-methoxyphenyl)-5-oxo-pyrrolidinecarboxylic acid (**6b**), respectively. It was found, however, that heating the mixture neat caused isomerization of itaconic acid to mesaconic acid, contrary to what was reported for other systems.[11b] Esterification of the acids was done in methanol by treatment with thionyl chloride to give the methyl esters **7a, b.**[16] The ester function was selectively reduced to an alcohol (**8a, b**) with sodium borohydride in refluxing methanol.[17] The alcohols (**8a, b**) were transformed to methylsulfonyl esters (**9a, b**) by treatment with methylsulfonyl chloride in the presence of triethyl amine in dichloromethane at 0°C under an atmosphere of nitrogen.[18] Upon treatment with sodium azide in DMF at 40°C, the mesylates were substituted to azide to furnish **10a** and **10b**. Hydrogenation of the azides in the presence of a catalytic amount of Pd/C in ethanol gave the amines, which were subsequently acidified to produce **4a** and **4b**.[19] All of the steps of the synthesis proceeded in high yields.

Enzymology

Incubation of MAO B with **4a** and **4b** resulted in time-dependent inactivation of the enzyme (see Figure 1 for the time-dependent inactivation of **4b**; **4a** gave a similar plot). The inactivation is biphasic; initially there is a relatively rapid pseudo first-order loss of enzyme activity which is followed by a slower pseudo first-order rate of inactivation. The kinetic constants were determined from a replot of the half-lives of inactivation at a given concentration of inactivator (Figure 2).[20] The K_I and k_{inact} values were 6.9 mM and 0.00074 min^{-1} for **4a** and 6.7 mM and 0.00067 min^{-1} for **4b**. Dialysis of MAO B inactivated by **4b** over a period of 3 hours resulted in complete return of enzyme activity. The half life for reactivation was 22 minutes. As a comparison, dialysis of MAO B inactivated by **1b** (the corresponding oxazolidinone)

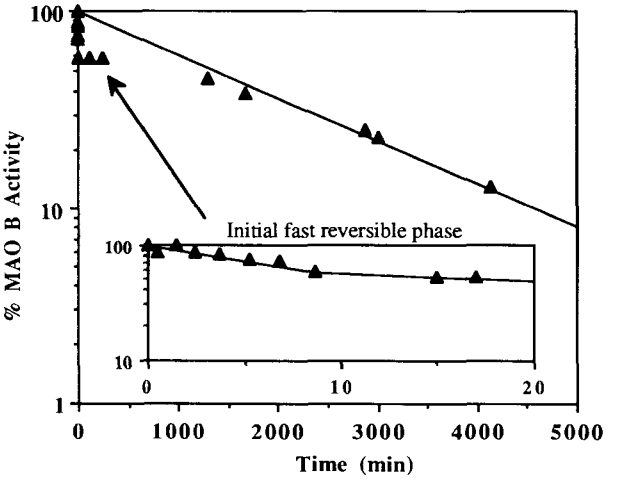


FIGURE 1 Biphasic time-dependent inactivation of MAO B by 4-aminomethyl-1-(4-methoxyphenyl)-2-pyrrolidinone hydrochloride. The insert shows the time course for the first 17 min.

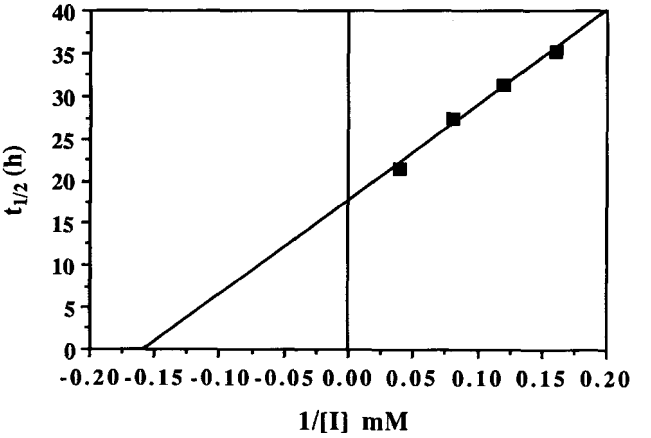


FIGURE 2 Kitz and Wilson[20] replot of the kinetic data obtained in Figure 1.

also brought about full return of enzyme activity but with a half life of 160 minutes. Therefore, the enzyme adduct formed with the 2-pyrrolidinones is less stable than that formed from the oxazolidinones. If incubation of MAO B with **4a** or **4b** is continued overnight, however, exhaustive dialysis does not result in return of the enzyme activity. This also was observed for the corresponding lactone analogues (**3**), but not with the oxazolidinones (**1**), where full return of enzyme activity occurs even after prolonged incubation of MAO B with these compounds. Biphasic kinetics is observed for the inactivation process with the lactam and lactone inactivators, but monophasic kinetics is observed with the oxazolidinones. It is believed that initially there is an unstable adduct formed with the lactams and lactones (e.g., an adduct related to **2**), but this adduct then rearranges to a more stable adduct whose structure is not yet known.

The rate of inactivation of MAO-B by these compounds was not altered by the addition of β-mercaptoethanol to the buffer, suggesting that inactivation is not the result of attachment of some enzyme-generated species that had escaped the active site prior to its attachment (or noncovalent interactions, whichever is the case) with MAO. The rate of inactivation, however, was slowed down by the presence of the substrate benzylamine, indicating that the inactivation is an active site-directed process.

It was found earlier[5] that the most potent compound in the oxazolidinone series was the *N*-methyl analogue of **1** (R = *m*-chlorobenzyloxy). We have determined the kinetic constants for the corresponding primary amine compound (**1**, R = *m*-chlorobenzyloxy; $K_I = 0.067$ mM and $k_{inact} = 0.14\ min^{-1}$) and for **1**, R = OMe ($K_I = 12.5$ mM and $k_{inact} = 0.0008\ min^{-1}$). The kinetic constant for **4b** is comparable to that for **1** (R = OMe), and therefore, when the optimal substituent (*m*-chlorobenzyloxy) is substituted for OMe, it is likely that **4** will be as potent an inactivator of MAO B as is the oxazolidinone analogue.

Inactivation of MAO by **4** indicates that 4-(aminomethyl)-1-aryl-2-pyrrolidinones are useful new structures to be added to the known classes of MAO inactivators. The results with these compounds and with the corresponding oxazolidinones (**1**)

and lactones (**3**) support the hypothesis that an electron-withdrawing group placed near to the amino functionality that is oxidized is important to the stabilization of the proposed enzyme adduct (**2** and related adducts).

Acknowledgements

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