$C_{18}H_{19}N_3O_2$, 238(4) $C_{15}H_{14}N_2O$, 237(26) $C_{15}H_{13}N_2O$, 236(100) $C_{15}H_{12}N_2O$, 224(11) $C_{14}H_{12}N_2O$, 223(39) $C_{14}H_{11}N_2O$, 210(15) $C_{13}H_{10}N_2O$, 209(6) $C_{13}H_9N_2O$, and 195(9) $C_{13}H_9NO$; $m^*$ = 180.2 [309($M^+$) → 236].

*V-ac.*—$\nu^{KBr}$: 3315 (N—H), 3070 (phenyl), 2960 ($CH_3$), 2820 (N—$CH_3$), 1640 (C=O amide), 1592 and 1506 (phenyl), 1478 ($CH_3$ and $CH_2$), 1457 and 1392 ($CH_3$), 1327 (Ar—N), 1250 (N—$CH_3$), 1168 and 1142 (C—N), and 770 (*o*-substituted phenyl) $cm.^{-1}$. *m/e* (relative intensity): 309(66) $C_{18}H_{19}N_3O_2$, 251(12) $C_{16}H_{15}N_2O$, 250(100) $C_{16}H_{14}N_2O$, 238(7) $C_{15}H_{14}N_2O$, 237(34) $C_{15}H_{13}N_2O$, 224(13) $C_{14}H_{12}N_2O$, 210(5) $C_{13}H_{10}N_2O$, and 209(15) $C_{13}H_9N_2O$; $m^*$ = 202.3 [309($M^+$) → 250].

*VI-ac.*—$\nu^{KBr}$: 3295 (N—H), 3060 (phenyl), 2930 ($CH_3$), 1630 (C=O amide), 1597 and 1502 (phenyl), 1475 ($CH_3$ and $CH_2$), 1458 and 1390 ($CH_3$), 1298 (*N*-ring H), 1249 (N—$CH_2$), 1160 (C—N), and 762 (*o*-substituted phenyl) $cm.^{-1}$. *m/e* (relative intensity): 295(74) $C_{17}H_{17}N_3O_2$, 237(19) $C_{15}H_{13}N_2O$, 236(100) $C_{15}H_{12}N_2O$, 224(15) $C_{14}H_{12}N_2O$, 223(63) $C_{14}H_{11}N_2O$, 210(16) $C_{13}H_{10}N_2O$, and 195(12) $C_{13}H_9NO$; $m^*$ = 188.8 [295($M^+$) → 236].

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# Inhibition of MAO by β-Carbolinium Halides


**BENG T. HO▲, PATRICIA M. GARDNER, and K. E. WALKER**



**Abstract** □ In the search for a compound capable of selective inhibition of peripheral MAO, a number of 2,9-disubstituted β-carbolinium compounds were synthesized. With tryptamine as the substrate, these compounds generally exerted greater inhibition of the enzyme from human liver mitochondria than that from bovine liver. An exception to this was 2-propargyl-9-methyl-β-carbolinium bromide (VII), which inhibited the enzyme from both sources to a nearly equal extent. The inhibitory activity of 2,9-dimethyl-β-carbolinium iodide (I) was further studied with mitochondrial MAO of human liver, heart, and brain; rat liver, heart, and brain; mouse liver; and bovine liver; tryptamine and tyramine were used as substrates. Compound I was more effective than pargyline in inhibiting tryptamine oxidation by human MAO from peripheral tissues but was less active than pargyline toward tyramine oxidation. Kinetic studies on the inhibition of tryptamine oxidation indicated I to be a mixed-type inhibitor with MAO from human tissues and rat liver and competitive with MAO from rat heart and brain and bovine liver. The inactivation of tryptamine oxidation by I was reversible in nature, as was VII which bears a propargyl ($CH_2C{\equiv}CH$) group, the same group that endows pargyline with its irreversible binding to MAO. Since the rate of irreversible inactivation of MAO by pargyline was decreased by the presence of I, there exists the possibility of a common binding site for the two compounds.



**Keyphrases** □ MAO inhibitors, potential—synthesis of 2,9-disubstituted β-carbolinium halides □ β-Carbolinium halides, 2,9-disubstituted—synthesis, inhibition of MAO


Accumulated evidence for multiple forms of MAO in various tissues suggests differences in the metabolism of biogenic amines in the central and peripheral nervous systems (1–8). Many compounds, including those of the potent irreversible type such as iproniazid, pargyline, and tranylcypromine, do not exert selective inhibition of MAO of either the central or peripheral nervous system. An inhibitor whose action is specific for MAO of peripheral tissues may be useful in determining the origin of hypertension and the mechanism of reserpine action and would prove valuable in the therapy of angina pectoris because of the absence of central behavioral effects. In addition, selective inhibition of centrally localized MAO could be achieved with the combination of a nonspecific irreversible inhibitor and a specific peripheral reversible inhibitor; this would involve pretreatment with the latter to saturate the peripheral enzyme binding site, thus allowing exposure of only central MAO to the irreversible inactivation by the former. The effects of peripheral inhibition would be short lived, while the central effects from the irreversible inhibitor would be manifested until the enzyme could be regenerated (9).

One approach to designing an inhibitor with these characteristics involves exploiting the impermeability of cerebral tissue to highly polar compounds. Quater-

Table I—Physical Constants of 2,9-Disubstituted β-Carbolinium Halides

| Compound | Melting Point | Yield, % | Empirical Formula | Analysis, % Calc. | Found |
|---|---|---|---|---|---|
| I | 270–274° | 66 | $C_{13}H_{13}IN_2$ | C 48.17 | 48.03 |
| | | | | H 4.04 | 4.07 |
| | | | | N 8.64 | 8.64 |
| II | 281–284° | 70 | $C_{13}H_{13}ClN_2 \cdot {}^1/_2H_2O$ | C 64.59 | 64.67 |
| | | | | H 5.84 | 5.96 |
| | | | | N 11.59 | 11.48 |
| III | 279–279.5° | 75 | $C_{14}H_{15}IN_2$ | C 49.72 | 49.50 |
| | | | | H 4.47 | 4.41 |
| | | | | N 8.29 | 8.43 |
| IV | 256–257° | 50 | $C_{15}H_{17}IN_2$ | C 51.15 | 51.02 |
| | | | | H 4.87 | 4.83 |
| | | | | N 7.95 | 7.74 |
| V | 265–266° | 60 | $C_{14}H_{17}IN_2O$ | C 47.47 | 47.37 |
| | | | | H 4.27 | 4.13 |
| | | | | N 7.91 | 7.73 |
| VI | 237–238° | 70 | $C_{13}H_{13}IN_2O$ | C 45.90 | 45.78 |
| | | | | H 3.85 | 3.68 |
| | | | | N 8.24 | 8.21 |
| VII | 219–220° | 53 | $C_{15}H_{13}BrN_2$ | C 59.82 | 59.70 |
| | | | | H 4.35 | 4.78 |
| | | | | N 9.30 | 9.40 |

nary ammonium compounds, for instance, are well documented as exhibiting difficulty in penetrating the brain (10). In this laboratory, a number of 2,9-disubstituted β-carbolinium compounds (Table I) were synthesized with this potential.

## EXPERIMENTAL[1]

**2,9-Dimethyl-β-carbolinium Iodide (I)**—To a solution of 0.7 g. (3.8 mmoles) of 9-methyl-β-carboline (11) in 5 ml. of ethanol was added 0.56 g. (4.0 mmoles) of methyl iodide. After standing at room temperature for 48 hr., the product was filtered, yielding 0.8 g. (66%), m.p. 274–276°. Compounds III–VI were prepared by this procedure. See Table I for their physical constants.

**2-Propynyl-9-methyl-β-carbolinium Bromide (VII)**—To a solution of 0.88 g. (5 mmoles) of 9-methyl-β-carboline in 3 ml. of ethanol was added gradually 0.66 g. (5.5 mmoles) of propargyl bromide. After standing at room temperature for 24 hr., the product was filtered and twice recrystallized from isopropanol–water, yielding 0.80 g. (53.4%), m.p. 219–220° dec. See Table I for its physical constants.

**2,9-Dimethyl-β-carbolinium Chloride (II)**—A mixture of 1.8 g. (10 mmoles) of 9-methyl-β-carboline, 2 g. (20 mmoles) of methyl chloride, and 15 ml. of ethanol was heated in a Parr bomb at 50° for 8 hr. After cooling, the product was filtered to yield 1.6 g. (70%), m.p. 281–284° dec. See Table I for its physical constants.

**Tissues**—Human heart, liver, and brain were obtained at autopsy, within 12 hr. after death, from individuals devoid of pathological factors; these organs were stored at −25°. Bovine liver was obtained from a commercial source[2]. Rat heart, liver, and brain were taken from male Sprague-Dawley rats, 200–250 g., and mouse liver was taken from male Yale Swiss mice, 25–30 g.

**Purification of Enzyme**—Mitochondrial MAO from human and rat liver was prepared by the method of Sordahl *et al.* (12) with the following modifications: (*a*) the tissue was homogenized in 10 volumes of 0.25 *M* sucrose; and (*b*) the mitochondrial pellet was suspended in 1.6 times the original tissue weight of 0.01 *N* sodium phosphate buffer, pH 7.6, and sonified for 30 min. while being maintained at 4°. The suspension was then centrifuged at 100,000×*g* for 1 hr., and the resulting supernate was stored at −25° until assay.

In the preparation of mitochondrial MAO from human and rat heart, to ensure complete homogenization the heart tissue was ground through a small chilled tissue press before homogenization in 12 volumes of 0.25 *M* sucrose. The procedure described for liver MAO was then followed, and the sonified suspension was used in the assay without further centrifugation.

Since purification of mitochondrial MAO from human and rat brain using the procedure for liver and heart yielded preparations of low specific activity, a modified method of Nagatsu *et al.* (13) was used. The mitochondrial pellet obtained from the whole rat brain or occipital cortex of human brain was suspended in five times the original tissue weight of 0.01 *M* potassium phosphate buffer, pH 7.4. The suspension was heated at 40° for 10 min. and then rapidly cooled in an ice bath. To solubilize the mitochondrial enzyme, a nonionic detergent[3] was added to a final concentration of 1% with constant stirring. The mixture was stored overnight at 0° and then centrifuged for 1 hr. at 107,000×*g*. The supernate was stored at −25° until assay.

Mitochondrial MAO from bovine and mouse liver was isolated and purified according to a published procedure (11). This procedure was similar to that used for human and rat liver.

**Enzyme Assay**—All stock solutions of the compounds were prepared in water, except IV which was dissolved in 50% aqueous dimethyl sulfoxide. Incubation using tryptamine-2-$^{14}$C hydrochloride as the substrate was carried out as previously described (11). When tyramine-1-$^{14}$C was used as the substrate, the product of the enzyme reaction was extracted with ethyl acetate from a highly acidic medium. In the case of IV, an equal amount of dimethyl sulfoxide was present in both the controls and the samples containing varying concentrations of the inhibitor. From a plot of the percent inhibition *versus* the molar concentration of the inhibitor, the concentration of the compound producing 50% inhibition ($I_{50}$) was then determined.

**$K_i$ and $K_m$ Determination**—The approximate concentration of I producing 50% inhibition was used in experiments in which tryptamine-2-$^{14}$C concentration was varied from 6 to 60 μ*M*. Plots of the reciprocal of the substrate concentration *versus* the reciprocal of the reaction velocity were constructed using the method of least squares. The $K_i$ value, where competitive inhibition was encountered, was calculated according to the method of Dixon and Webb (14). When mixed-type inhibition was encountered, the method of Krupka (15) was used to calculate $K_i$ values.

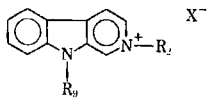
**Determination of Reversible and Irreversible Inhibition**—Using the $I_{50}$ concentrations of I, VII, or pargyline hydrochloride found with tryptamine deamination by human liver MAO, the inhibitors were preincubated with the corresponding enzyme preparations in the reaction mixture (without substrate) as described previously. After designated time intervals, tryptamine-2-$^{14}$C was added and the residual MAO activity was determined after an additional 30 min. of incubation. In another experiment with human liver MAO, I and pargyline were combined in the same concentrations as when they were preincubated separately. A control was prepared by

[1] Melting points were taken on a Mel-Temp apparatus and are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. IR spectra were taken with a Perkin-Elmer spectrophotometer, model 237B, and were compatible with the assigned structures.

[2] Burton Brothers, Houston, Tex.

[3] Triton X-100.

**Table II**—Inhibition of Human and Bovine Liver MAO by 2,9-Disubstituted β-Carbolinium Halides



| Compound | $R_2$ | $R_9$ | X | $I_{50}$, $\mu M$[a,b,c] Human | Bovine |
|---|---|---|---|---|---|
| I | $CH_3$ | $CH_3$ | I | 3.0 | 16.0 |
| II | $CH_3$ | $CH_3$ | Cl | 2.0 | 19.0 |
| III | $C_2H_5$ | $CH_3$ | I | 21.0 | 100.0 |
| IV | $C_3H_7$ | $CH_3$ | I | 23.5 | 112.0 |
| V | $CH_3$ | $CH_2OCH_3$ | I | 18.0 | 180.0 |
| VI | $CH_3$ | $CH_2OH$ | I | 5.5 | 178.0 |
| VII | $CH_2C{\equiv}CH$ | $CH_3$ | Br | 4.0 | 3.5 |

[a] Concentration of an inhibitor required to produce 50% inhibition of the enzyme. [b] Each value represents the mean obtained from at least two experiments. [c] Substrate: tryptamine-2-$^{14}$C hydrochloride.

preincubating the enzyme alone for the same time intervals before the addition of substrate. From a semilog plot of nanomoles of product formed *versus* time of preincubation, reversibility or irreversibility of the inhibitors was estimated according to the method of Zeller *et al.* (16).

## RESULTS AND DISCUSSION

The inhibitory activities of several 2,9-disubstituted β-carbolinium halides with MAO from human and bovine liver mitochondria are shown in Table II. With the exception of VII, these β-carbolines exhibited greater inhibition with the enzyme from human liver than that from bovine liver. While MAO from both sources was equally inhibited by VII, VI was 30 times more active with the human MAO. Further differentiation could be made by comparing V and VI; Compound VI inhibited human MAO three times more than V, but its ability to inhibit bovine MAO did not differ from that of V. It is possible that a group on the human enzyme capable of forming hydrogen bonding with the hydrogen of the 9-$CH_2OH$ group on VI is lacking in the bovine enzyme. The six- and 11-fold losses of activity when comparing the $I_{50}$ values of I with V observed for human and bovine MAO, respectively, could indicate the lack of tolerance of the enzyme for the bulk of the $OCH_3$ group.

The degree of inhibition decreased by six- to eightfold when the alkyl chain at the N-2 position of β-carbolines was lengthened beyond the methyl. This decrease in the inhibitory activities of III and IV does not appear to be due to the steric interaction between the 2-ethyl or 2-propyl group and the enzyme, since VII with a 2-propargyl group comparable in size to the propyl was six times more active than IV. Compound VII was 4.5 times more active than I with bovine MAO. It is most likely that the 2-propargyl group further facilitated the binding of VII to the enzyme, although the nature of binding of this group is yet to be determined.

The inhibition of I was further studied with additional sources of MAO and in the presence of an additional substrate, tyramine (Table III). Unlike pargyline, which exhibited greater inhibitory action toward tyramine oxidation than toward tryptamine oxidation, selective inhibition of tyramine oxidation by I was limited only to the enzyme from rat heart and liver as well as human brain and liver. Tissue selectivity was observed for I with human MAO, where it was 20–70 times more effective in inhibiting the heart and liver enzyme than MAO from the brain. A similar pattern was detected with rat MAO, but only when tyramine was used as substrate. Pargyline, on the other hand, was found to be more active with human brain MAO than with the heart and liver enzyme; with rat MAO, the liver enzyme was affected to a greater extent than that from the heart and brain. The selective inhibition of the deamination of tyramine, as opposed to tryptamine, by mouse and bovine liver MAO agreed with data reported by Gorkin *et al.* (17) and Fuller (18). The inhibitory activity of I with mouse or bovine liver MAO was not substrate dependent.

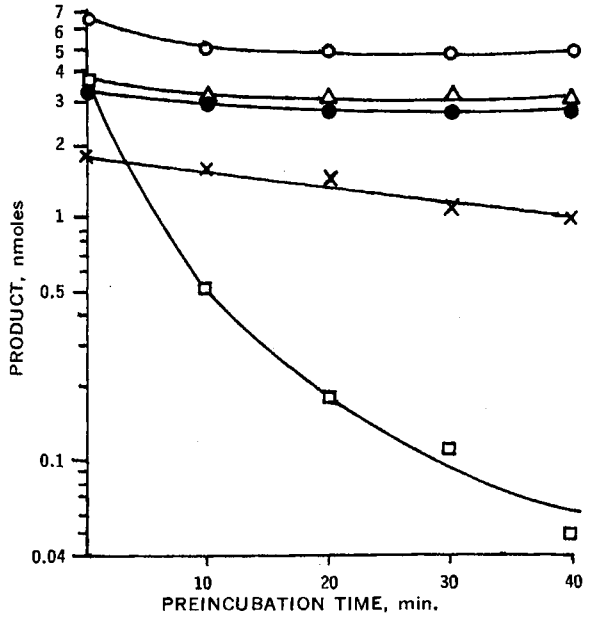



**Figure 1**—*Effect of I, VII, and pargyline preincubation on tryptamine oxidation catalyzed by human liver MAO. Key:* ○, *enzyme control;* △, *3 μM I;* ●, *5 μM VII;* ×, *3 μM I and 10 μM pargyline; and* □, *10 μM pargyline.*

When the activities of both inhibitors were compared, pargyline was found to be more potent than I in inhibiting tyramine oxidation by MAO from human tissues; I, on the other hand, was more effective than pargyline in inhibiting tryptamine oxidation by human MAO, with the exception of the brain enzyme. With mouse and bovine enzyme, I was a less effective inhibitor than pargyline regardless of the substrate. The comparative effects of the two inhibitors with rat MAO varied with the source of the enzyme and the substrate used.

The $K_i$ values of I obtained with various enzyme preparations in the presence of tryptamine-2-$^{14}$C are shown in Table IV. Mixed-type inhibition (combination of competitive and noncompetitive) was observed with all sources of human MAO; in all cases the $K_i$ value for competitive inhibition was smaller than that for noncompetitive inhibition, indicating a preference of the compound to bind more competitively. In view of recent evidence of MAO isozymes in human and rat liver (3) and human brain (8), it is possible that at least two forms of MAO are present in a given tissue, one being susceptible to competitive inhibition by I and the other being noncompetitively inhibited. In the rat, mixed-type inhibition was observed with only liver MAO and was also of a more competitive nature. The enzyme from rat heart, rat brain, and bovine liver was

**Table III**—Concentrations of I and Pargyline Required to Produce 50% Inhibition of MAO from Various Tissues ($I_{50}$)

| Inhibitor | Substrate | $I_{50}$, $\mu M$[a] Human Liver | Human Heart | Human Brain | Rat Liver | Rat Heart | Rat Brain | Mouse Liver | Bovine Liver |
|---|---|---|---|---|---|---|---|---|---|
| I | Tryptamine | 3.0 | 2.3 | 143.0 | 7.0 | 1.4 | 4.0 | 24.0 | 16.0 |
| | Tyramine | 1.7 | 3.5 | 75.0 | 0.60 | 0.15 | 9.8 | 23.0 | 11.0 |
| Pargyline | Tryptamine | 13.0 | 9.8 | 0.87 | 7.5 | 27.2 | 23.0 | 0.20 | 0.10 |
| | Tyramine | 0.66 | 0.69 | 0.15 | 0.83 | 1.40 | 0.95 | 0.059 | 0.070 |

[a] Each value represents the mean obtained from at least two experiments.

**Table IV**—Inhibition Constants for I with MAO from Various Sources

| Enzyme Source | $K_i$, $\mu M$[a,b] Competitive | $K_i$, $\mu M$[a,b] Noncompetitive | $K_m$, $\mu M$[a,b] |
|---|---|---|---|
| Human | | | |
| Liver | 0.83 | 3.2 | 12.0 |
| Heart | 0.92 | 4.8 | 20.3 |
| Brain | 66.7 | 125.0 | 31.3 |
| Rat | | | |
| Liver | 2.3 | 8.8 | 23.6 |
| Heart | 0.21 | — | 13.8 |
| Brain | 3.4 | — | 62.9 |
| Bovine | | | |
| Liver | 8.5 | — | 83.4 |

[a] Each value represents the mean obtained with two separate preparations of the enzyme. [b] Substrate: tryptamine-2-$^{14}$C hydrochloride.

competitively inhibited by I. This finding does not preclude the possible presence of isozymes in these tissues; several forms of the enzyme have been reported in the rat brain (5).

The larger $K_m$ value for tryptamine with the bovine liver MAO indicated a lesser affinity of this enzyme for the substrate as compared with the liver MAO from both humans and rats (Table IV). Tryptamine also demonstrated a weaker affinity for brain MAO than for the enzyme from all other tissues.

The nature of binding of I and VII, in terms of reversibility or irreversibility, was studied during tryptamine oxidation. Although the structure of VII bears a propargyl ($CH_2C{\equiv}CH$) group, this compound, unlike pargyline, did not exert irreversible inhibition of human liver MAO, since preincubation of VII (and also I) with the enzyme preparation followed by titration of residual enzyme with the substrate did not show progressive inactivation with time (Fig. 1). In another experiment, when the combined effect of pargyline and I preincubation on MAO from human liver was studied, the rate of irreversible inactivation of MAO by pargyline was decreased by the presence of I (Fig. 1). This suggests either a common binding site for the two compounds or, alternatively, the binding of I and/or the conformational changes it produced in the enzyme sterically hindered the binding of pargyline.

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