Inhibitors of Monoamine Oxidase II

Syntheses of Some *N*-2(9)-Substituted Tetrahydro-β-carbolines and Evaluation of Their Inhibitory Activities

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Tetrahydro-β-carbolines with alkyl or aralkyl substitution on N-9, alkyl on N-2, and alkyl on both N-2 and N-9 were synthesized and their monoamine oxidase inhibitory activities evaluated. Two different binding conformations were proposed for the 9-methyl and the 9-hydrogen series. The binding of the 9-methyl group hydrophobically to the enzyme would account for the high inhibitory activities of 9-methyl compounds. In the case of 9-hydrogen-2-alkyl series, since there is no methvl group on the indolic nitrogen, hydrophobic bonding would not be possible. Relief of steric hindrance due to the 2-alkyl would probably cause the molecule to assume another binding conformation. Of all the compounds tested, 2,9-dimethyltetrahydro-β-carboline was the most active inhibitor. Its activity was about one-third that of the previously reported 9-methyltetrahydro-β-carboline.

IN A PREVIOUS PAPER (1) on inhibitors of monoamine oxidase, the influence of methyl substitution on the inhibitory activity of β-carbolines was studied. 9-Methyltetrahydro-β-carboline was found to be a competitive inhibitor of the enzyme, being three times more active than iproniazid, a one-time clinically used antidepressant. Initial findings also indicated that the N-2 nitrogen of the tetrahydro-β-carboline could be substituted by alkyl groups as large as propyl without affecting the inhibitory activity.

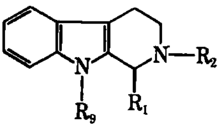
Since a 35-fold increase in inhibitory activity was obtained by the substitution of a methyl group on the N-9 nitrogen of tetrahydro-β-carboline, the synthesis and evaluation of inhibitory effect of some N-9 substituted tetrahydro-β-carbolines has been undertaken, and the studies extended to include some 2,9-disubstituted compounds.

DISCUSSION

A 35-fold increase in inhibitory activity (Table I) was observed when a methyl group was introduced on the N-9 nitrogen of tetrahydro-β-carboline (I). This was attributed to either the increase in the electron density of the indole nucleus of 9-methyltetrahydro-β-carboline (II) thus giving better binding, or the binding of the 9-CH_3 group itself hydrophobically to the enzyme, or both (1). The possibility of the existence of a hydrophobic region on the enzyme in proximity to the 9-CH_3 of II was then explored. Extension of the 9-CH_3 by one carbon resulted in a 50-fold decrease in inhibitory activity of 9-ethyl compound (III). This unexpected decrease in activity was at first thought to be caused by the projection of the terminal CH_3 of the ethyl group into a possible hydrophilic region of the enzyme. In order to investigate this possibility, a hydrophilic group such as hydroxyl was chosen to replace the terminal hydrophobic CH_3 of the ethyl group, anticipating that the binding of OH to the hydrophilic region of the enzyme would result in increased inhibition.

Synthetically, it seemed more appropriate to protect the N-2 nitrogen of the tetrahydro-β-carboline by substitution so that the addition of the hydroxymethyl to the N-9 nitrogen would be exclusive. Alkylation on the N-2 position was assumed not to interfere with studies on the N-9 position, since a previous finding (1) revealed no change in inhibitory activity when alkylating the N-2 nitrogen of 1-methyltetrahydro-β-carboline (XIII) with methyl or *n*-propyl (see XIV and XV). Since

TABLE I—INHIBITION OF MONOAMINE OXIDASE BY TETRAHYDRO-β-CARBOLINES



Compound	R_1	R_2	R_9	I_{50}[a] (m*M*)
I[b]	H	H	H	0.34[c]
II[b]	H	H	CH_3	0.01[c]
III[b]	H	H	C_2H_5	0.46
IV[b]	H	H	n-C_3H_7	0.34
V[b]	H	H	i-C_5H_{11}	0.50
VI[b]	H	H	$CH_2C_6H_5$	0.30
VII[b]	H	H	C_6H_5	0.32
VIII	H	C_2H_5	H	1.40
IX	H	n-C_3H_7	H	1.37
X[b]	H	C_2H_5	CH_3	0.13
XI[b]	H	C_2H_5	CH_2OH	0.74
XII[b]	H	CH_3	CH_3	0.035
XIII	CH_3	H	H	1.50[c]
XIV[b]	CH_3	CH_3	H	1.50[c]
XV[b]	CH_3	n-C_3H_7	H	1.30[c]

[a] Concentration of an inhibitor giving 50% inhibition of the enzyme. [b] Hydrochloride salt. [c] Data from *Reference 1.*

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an N-2 ethyl substituent would be easily obtained by the reduction of the N-2 acetyl compound, 2-ethyl-9-hydroxymethyltetrahydro-β-carboline (XI) was synthesized. For comparison with the 2-hydrogen series, 2-ethyl-9-methyltetrahydro-β-carboline (X) and 2-ethyltetrahydro-β-carboline (VIII) were also prepared.

The 2-ethyl compound (VIII) was first found to be a weak inhibitor, being four times less active than I. The corresponding 9-methyl compound (X) was 13-fold less active than II. Thus, it seemed that the steric hindrance by the 2-ethyl group could account for the decrease in inhibitory activity of 2-ethyl compounds when compared with the 2-hydrogen series. Of greater interest was to determine whether or not the enzyme could tolerate a smaller N-2 substituent like the methyl group. The 2,9-dimethyltetrahydro-β-carboline (XII) was indeed a very good inhibitor, being about one-third as active as II and about four times more active than X. This phenomenon was, however, not observed in the 9-hydrogen series. Here, the activity remained the same when the 2-alkyl chain was reduced from propyl to ethyl (IX → VIII). This, along with the previous finding that in the 1-methyl series XIV was equally as active as XV, suggested that it was not at all impossible to have two different modes of binding for substituted tetrahydro-β-carbolines on monoamine oxidase.

Judging from the similarity in inhibitory activities between XIV and XV, and VIII and IX, it was postulated that the 2-ethyl and 2-propyl groups of the above two series might have projected into a "noncontact" area away from the binding site. The conformation A (Fig. 1) proposed for the four compounds was different from conformation B (Fig. 2) proposed for all the 9-methyltetrahydro-β-carbolines. That a class of compounds can assume different conformations of binding to an enzyme has been presented (2). The assumption for the mode of binding of different series of substituted tetrahydro-β-carbolines is as follows.

(*a*) Since a compound always assumes a binding position giving a maximum inhibitory effect, the increase in inhibitory activity of all 9-methyl compounds was thought to be due to the hydrophobic bonding of their 9-methyl group to the enzyme (conformation B). In this conformation, any substituent on the N-2 position larger than hydrogen would cause a decrease in activity. This decrease was observed in inhibitory activity as the length of the 2-alkyl side chain was increased, therefore resulting in increased steric hindrance. This was true for XII and X.

(*b*) When there is no methyl group on the indolic nitrogen, hydrophobic bonding would not be possible, therefore relief of steric hindrance due to the 2-alkyl groups (see conformation B) became an important factor. The preferable binding conformation for both VIII and IX more likely was the conformation A, where the 2-alkyl groups could be projected to the noncontact area and away from the binding site. This could account for the unchanged activity from 2-ethyl to 2-propyl. A similar rationalization could be applied to the 1-methyl series. Apparently, in the conformation B the enzyme would not tolerate a 1-methyl group, and a "twist" to the conformation A not only relieved this steric hindrance, but also allowed substituents on N-2 nitrogen to be projected to the noncontact area. Note that the inhibitory activities of the 1-methyl-2-alkyl series (XIII–XV) were the same as those of the 1-hydrogen-2-alkyl series (VIII and IX).

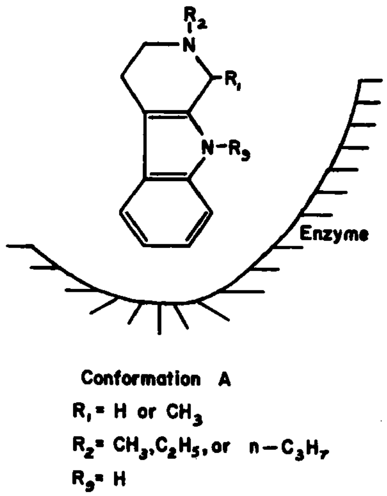


Fig. 1—Proposed conformation of 2-alkyl tetrahydro-β-carbolines.

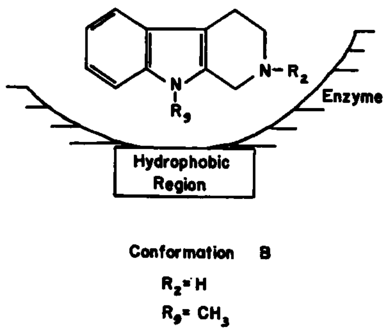
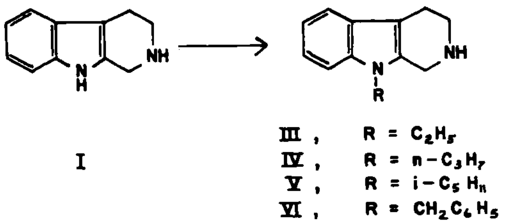


Fig. 2—Proposed conformation of 9-methyltetrahydro-β-carbolines.

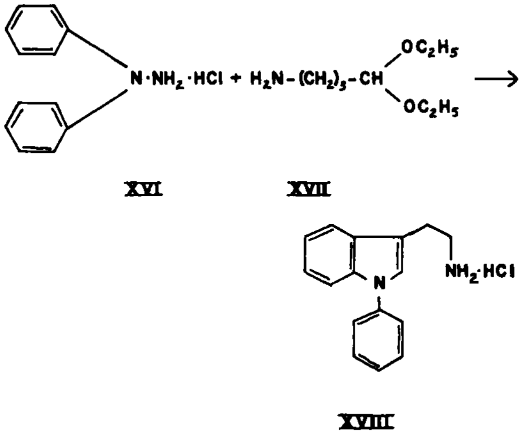
The data on the inhibitory activities of 9-alkyl and 9-aralkyl series indicated that the 9-ethyl compound (III) was 45-fold less active than the 9-methyl compound (II). Since further increase in the length of alkyl chain did not result in large decreases in inhibitory activities, it was assumed that for tetrahydro-β-carbolines any 9-alkyl or 9-aralkyl group larger than methyl would not bind in the conformation B. However, whether the binding conformation of 9-alkyl- or 9-aralkyl-tetrahydro-β-carbolines assumed the conformation A or whether there was a third conformation for the binding of these 9-substituted compounds remains to be determined. The observation that the 9-hydroxymethyl-2-ethyl compound (XI) was not as active as 9-methyl-2-ethyl compound (X) was then not to be unexpected, in view of the apparent steric requirements for conformation B. Apparently, the steric hindrance due to the terminal OH group caused XI to assume a binding conformation which was similar to that for tetrahydro-β-carbolines with N-9 substitutions larger than methyl.

CHEMISTRY

9-Alkyltetrahydro-β-carbolines were prepared by treating the sodium salt of the tetrahydro-β-



Scheme I



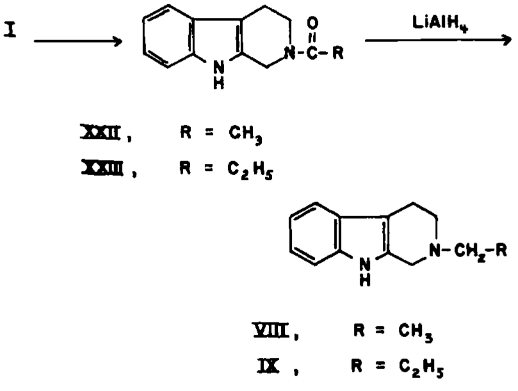
Scheme II

carboline (I) with the appropriate alkyl halides (Scheme I). Alkylation in liquid ammonia gave 9-ethyltetrahydro-β-carboline (III), 9-propyltetrahydro-β-carboline (IV), and 9-isoamyltetrahydro-β-carboline (V) in 56, 20, and 30% yields, respectively. It was found that the reaction of 1-iodo-3-methylbutane with I required longer time than with the lower alkyl halides. In a previous run, when the reaction was allowed to proceed for only 20 min. after the addition of the alkyl halide, as in the preparation of III and IV, a mixture of product and starting material was isolated.

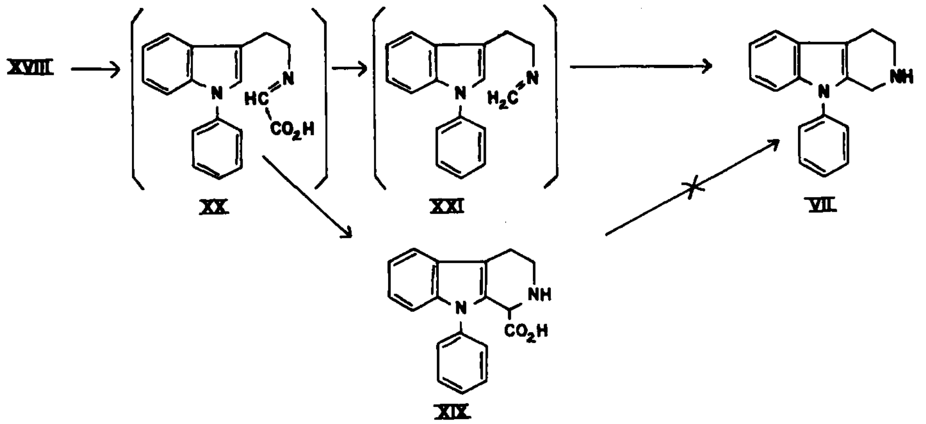
The preparation of 9-benzyltetrahydro-β-carboline (VI) was carried out by the reaction of I with benzyl chloride in dimethylformamide in the presence of sodium hydride.

Condensation of 1,1-diphenylhydrazine hydrochloride (XVI) and α-aminobutyraldehyde diethyl acetal (XVII) at 95° in the presence of hydrochloric acid according to the patent procedure (3) gave 1-phenyltryptamine hydrochloride (XVIII) (Scheme II).

For the preparation of some tetrahydro-β-carbolines the corresponding tryptamine derivatives have been previously treated with glyoxylic acid to form the 1-carboxytetrahydro-β-carbolines which were then decarboxylated yielding the desired products (1). When the same method was employed in the preparation of VII, the intermediate 1-carboxyl-9-phenyl-tetrahydro-β-carboline (XIX) failed to decarboxylate. A final solution to this was to carry out the reaction of XVIII and glyoxylic acid in refluxing aqueous solution instead of at room temperature. At the elevated temperature 1-phenyltryptamine most likely first condensed with glyoxylic acid to give the Schiff base, XX, which then decarboxylated and subsequently cyclized to 9-phenyltetrahydro-β-carboline (VII) (Scheme III). This mechanism has been proposed for the reaction of tryptamine with α-keto acids at elevated temperature (4). Since from the reaction mixture a product that had identical infrared spectrum with 1-carboxy-9-phenyl compound (XIX) formed at pH 4, it was assumed that the cyclization of XX to



Scheme IV

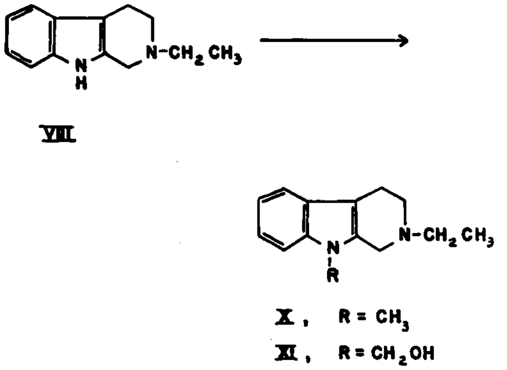


Scheme III

XIX competed with the decarboxylation of XX to give XXI and then VIII. Compound VII had been prepared *via* the condensation of 1-phenyltryptamine with formaldehyde (3).

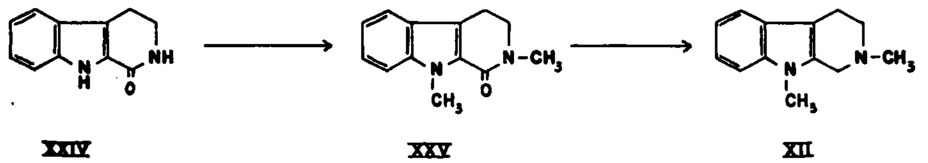
Acylation of I without application of heat gave 2-acetyltetrahydro-β-carboline (XXII), and 2-propionyltetrahydro-β-carboline (XXIII) in 87.6 and 88.2%, respectively. These two 2-acyltetrahydro-β-carbolines were then reduced with lithium aluminum hydride to give a 66.3% yield of 2-ethyltetrahydro-β-carboline (VIII) and 71.4% of 2-propyltetrahydro-β-carboline (IX) (Scheme IV).

2-Ethyl-9-methyltetrahydro-β-carboline (X) was obtained in a 60% yield by the methylation of VIII with methyl iodide and sodium amide in liquid ammonia. Hydroxymethylation of VIII was performed in aqueous solution with formaldehyde at pH 5.5–6.0. Four days at room temperature gave 9-hydroxymethyl-2-ethyltetrahydro-β-carboline (XI) in 36% yield (Scheme V).



Scheme V

An incomplete methylation of 1-oxotetrahydro-β-carboline (XXIV) resulted when the reaction was carried out in liquid ammonia in the presence of sodium amide. Treatment of XXIV in boiling tetrahydrofuran with methyl iodide and sodium hydride, however, gave the desired product (XXV) in 72% yield. XXV was reduced by lithium aluminum hydride to 2,9-dimethyltetrahydro-β-carboline (XII) in 54% yield (Scheme VI).



Scheme VI

EXPERIMENTAL

Melting points are corrected and were taken on a Fisher-Johns apparatus. Infrared spectra were obtained with a Perkin-Elmer spectrophotometer model 237 B. For qualitative ultraviolet spectra a Beckman spectrophotometer model DB-G was used.

9-*n*-Propyl-1,2,3,4-tetrahydro-β-carboline (IV)—1,2,3,4-Tetrahydro-β-carboline (5.16 g., 0.03 mole) was added slowly with stirring to a sodamide solution, prepared by reacting 0.92 g. (0.04 g. atom) of sodium with 60–70 ml. of liquid ammonia in the presence of a catalytic amount of ferric nitrate. After all the amine had dissolved, 6.8 g. (0.04 mole) of 1-iodopropane was added slowly over a period of 30 min. Stirring was continued for an additional 20 min. The mixture was evaporated to dryness by a stream of helium while the flask was immersed in hot water. Water (15 ml.) was added to the residue and the product was extracted with toluene (2 × 200 ml.). After filtration of the combined toluene extracts with anhydrous sodium sulfate, the solvent was evaporated *in vacuo* leaving 6.3 g. of orange oil. The product was dissolved in 30 ml. of benzene, and after removal of suspended solid by filtration, the solvent was again evaporated *in vacuo* giving 6.0 g. (93.7%) of orange oil. The extraction process was repeated with 70 ml. of boiling heptane to yield a colorless oil, which was converted to 3.8 g. (50%) of yellow hydrochloride by the addition of ether–HCl to an ethereal solution of the oil. One recrystallization from ethanol gave 1.5 g. (20%), m.p. 231–232°; $\lambda_{\max.}$ (KBr) 3.30, 3.88, 3.43, 3.50, 3.60, 3.70, 3.80, 3.85, 3.94, 4.10–4.15 (CH, NH_2^+); 6.20, 6.35 (C═C); 13.45 μ (indole CH); $\lambda_{\max.}$ (EtOH) 204, 224, 277, 282, 292 (s) mμ.

Anal.—Calcd. for $C_{14}H_{19}ClN_2$: C, 67.0; H, 7.63; N, 11.2. Found: C, 67.2; H, 7.64; N, 11.3.

9-Isoamyl-1,2,3,4-tetrahydro-β-carboline (V)—1,-2,3,4-Tetrahydro-β-carboline (6.88 g., 0.04 mole) was treated with a mixture of 1.04 g. (0.045 g. atom) of sodium in liquid ammonia and 8.91 g. (0.045 mole) of 1-iodo-3-methylbutane as in the preparation of 9-*n*-propyltetrahydro-β-carboline, except after the addition of the alkyl halide the reaction was allowed to proceed for 1 hr. After the evaporation of liquid ammonia, about 50 ml. of water was added to the residue, and the product was extracted with ether (2 × 150 ml.). The ethereal solution was shaken with 150 ml. of 15% hydrochloric acid and the aqueous layer was separated. During an extraction of the aqueous solution with about 100 ml. of ether, the hydrochloride salt precipitated. When the hydrochloride salt was neutralized by sodium hydroxide, the solid free amine was liberated, which became an oil upon drying *in vacuo*. Conversion of the free amine again into the hydrochloride gave 3.5 g. (31.2%) of yellow solid. The hydrochloride salt was recrystallized from ethanol–ether to give 2.5 g. (22.3%) of white solid. A second recrystallization from the same solvent mixture yielded 1.5 g., m.p. 229–230°; $\lambda_{\max.}$ (KBr) 3.28, 3.38, 3.43, 3.49, 3.60, 3.65, 3.70, 3.77, 3.83, 3.91, 4.08 (CH, NH_2^+); 6.20, 6.35, 6.80, 6.85 (C═C, CH); 7.20, 7.22 [$C-(CH_3)_2$]; 13.60 μ (indole CH).

Anal.—Calcd. for $C_{16}H_{23}ClN_2$: C, 68.9; H, 8.31; N, 10.0. Found: C, 68.9; H, 8.56; N, 10.1.

9-Ethyl-1,2,3,4-tetrahydro-β-carboline (III)—In a similar manner as in the preparation of 9-*n*-propyltetrahydro-β-carboline, 9-ethyltetrahydro-β-carboline was obtained as a yellow oil. It was converted into the hydrochloride salt, m.p. 233.5–235° (ethanol). On the silica gel chromatogram in *n*-propanol–ammonium hydroxide (95:5) this hydrochloride traveled as a single spot which was different from the starting material. A portion of the yellow oil was converted into its picrate salt. The melting point (225–226° dec.) of the picrate agreed with that reported (224–225°) by Leonard and Elderfield prepared from 1-ethyltryptamine and formaldehyde (5).

9-Benzyl-1,2,3,4-tetrahydro-β-carboline (VI)—To a stirred suspension of 0.576 g. (24 mmoles) of sodium hydride (50% suspension in mineral oil) in 30 ml. of dimethylformamide (DMF) was added over a period of 20 min. a solution of 3.78 g. (22 mmoles) of tetrahydro-β-carboline in 60 ml. of DMF. After stirring for 1 hr., the resulting solution was cooled in ice while a solution of 2.9 g. (23 mmoles) of benzyl chloride was added dropwise over 10 min. At the end of the addition the mixture was stirred for 1 hr. at ice temperature. Water (150 ml.) was added and the mixture was extracted with chloroform (4 × 75 ml.). The combined chloroform extracts were washed with water (4 × 150 ml.), dried with anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was extracted with 50 ml. of heptane. After the removal of insoluble solid by filtration, the heptane extract was evaporated *in vacuo* leaving an oil that was converted into 3.5 g. (53%) of hydrochloride salt, m.p. 252–258°. The hydrochloride was dissolved in 100 ml. of hot water, and after cooling the gummy insoluble substance extracted with ether (3 × 100 ml.). During the last extraction the hydrochloride precipitated from the aqueous solution and was collected on a filter; yield, 0.462 g. (7%), m.p. 277–279°; $\lambda_{\text{max.}}$ (KBr) 3.28, 3.31, 3.40, 3.45, 3.60, 3.67, 3.70, 3.77, 3.83, 3.90, 3.92, 4.09, 4.15 (CH, NH_2^+); 6.20, 6.25, 6.30, 6.35, 6.69, 6.72, 6.88 (C=C, CH); 13.45, 14.25 μ (indole and phenyl CH). $\lambda_{\text{max.}}$ (EtOH) 207, 223, 275, 282, 295 mμ. No attempt has been made to recover more product from the aqueous solution.

The m.p. of this hydrochloride agreed with that reported (276°) in a patent (3) prepared from the condensation of 1-benzyltryptamine with formaldehyde.

9-Phenyl-1,2,3,4-tetrahydro-β-carboline (VII)—To a refluxed solution of 1.2 g. (4.4 mmoles) of 1-phenyltryptamine hydrochloride (3) in 30 ml. of water was added dropwise a solution of 0.524 g. (6 mmoles) of glyoxylic acid monohydrate in 10 ml. of water. After being refluxed for an additional 1 hr., the mixture was cooled in ice and the solid (XIX) was removed by filtration. The filtrate was first made basic with 30% aqueous potassium hydroxide and the gummy precipitate was extracted with ether (2 × 30 ml.). The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and mixed with ethereal HCl. The hydrochloride was collected on a filter; yield, 0.41 g. (32.5%), m.p. 230–240°. One recrystallization from ethanol gave 0.175 g. (13.8%). The melting point (260–261°) of the pure product agreed with that reported (260–262°) in the literature (3) prepared from the reaction of 1-phenyltryptamine with formaldehyde.

9-Phenyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylic Acid (XIX)—To a solution of 0.898 g. (3.3 mmoles) of XVIII·HCl in 80 ml. of water was added 0.304 g. (3.3 mmoles) of glyoxylic acid monohydrate. After being adjusted to pH 4 with 5% aqueous potassium hydroxide, the mixture was stirred at room temperature for 17 hr. Concentrated hydrochloric acid (5 ml.) was added and the stirring was continued for an additional 1 hour. The resulting "jell-like" mixture was centrifuged. The precipitate washed with ethanol (2 × 40 ml.), and again centrifuged. The precipitate was finally suspended in 80 ml. of ether and collected on a filter; yield, 0.30 g. (27.7%), m.p. 225–226° (with evolution of CO_2). $\lambda_{\text{max.}}$ (KBr) 3.29, 3.38, 3.42, 3.50, 3.65, 3.85 (CH, NH_2^+), 6.16 (COO^-), 6.26, 6.66 (C=C), 13.50 μ (indole CH).

Anal.—Calcd. for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.51; N, 9.6. Found: C, 73.7; H, 5.64; N, 9.6.

2-Propionyl-1,2,3,4-tetrahydro-β-carboline (XXIII)—Tetrahydro-β-carboline (5.16 g., 0.03 mole) and 15 ml. of propionyl anhydride was thoroughly mixed, then allowed to stand at room temperature for 10 min. After cooling briefly in ice, the mixture was poured with stirring into 100 ml. of water, and the solid was collected after 30 min.; yield, 6.0 g. (88.2%), m.p. 204–206°; $\lambda_{\text{max.}}$ (KBr) 3.08 (NH); 6.13, 6.18, 6.30 (C=O, C=C); and 13.40 μ (indole CH).

Anal.—Calcd. for $C_{14}H_{16}N_2O$: C, 73.6; H, 7.06; N, 12.3. Found: C, 73.4; H, 7.09; N, 12.3.

2-Acetyl-1,2,3,4-tetrahydro-β-carboline (XXII)—In a similar manner as in the preparation of 2-propionyltetrahydro-β-carboline, acetylation of tetrahydro-β-carboline gave 2-acetyl product in a 87.6% yield, m.p. 238–239° [lit. m.p. 237–238° (6)].

2-*n*-Propyl-1,2,3,4-tetrahydro-β-carboline (IX)—A suspension of 1.52 g. (0.04 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran was refluxed with stirring while 4.56 g. (0.02 mole) of 2-propionyltetrahydro-β-carboline was extracted from a Soxhlet thimble. After 14 hr. of heating the cooled mixture was decomposed with water and filtered. The filtered cake was washed with tetrahydrofuran (3 × 50 ml.), and the combined tetrahydrofuran solution was concentrated under reduced pressure almost to dryness. Addition of about 100 ml. of water caused the precipitation of product; yield, 4.1 g. (97.6%), m.p. 132–136°. This crude product was dissolved in 100 ml. of 10% hydrochloric acid. After clarification by filtration through diatomaceous earth,[1] the free base was liberated by the addition of excess 10% potassium hydroxide. The free amine was recrystallized from aqueous ethanol to give 3.0 g. (71.4%) of needles, m.p. 136.5–137.5°. For analysis a hydrochloride salt was prepared; m.p. 242–243° dec. $\lambda_{\text{max.}}$ (KBr) 3.10 (NH), 3.70, 3.76, 3.80, 3.82, 3.88, 4.00, 4.10 (NH^+); 6.15, 6.25 (C=C); 13.35 μ (indole CH).

Anal.—Calcd. for $C_{14}H_{19}ClN_2$: C, 67.0; H, 7.64; N, 11.2. Found: C, 67.2; H, 7.70; N, 11.1.

2-Ethyl-1,2,3,4-tetrahydro-β-carboline (VIII)—In a similar manner as described above, a mixture of 10.6 g. (0.049 mole) of 2-acetyltetrahydro-β-carboline and 4.0 g. (0.1 mole) of lithium aluminum hydride in 550 ml. of tetrahydrofuran was refluxed for 3.5 hr. to yield 8.0 g. (81.6%) of 2-ethyltetrahydro-β-carboline. One recrystallization from aqueous ethanol gave 6.5 g. (66.3%), m.p. 153–154° [lit. m.p. 137–138° (6)]. The hydrochloride salt of the

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[1] Celite, Johns-Manville Corp., New York, N. Y.

β-carboline melted at 229–230° [lit. m.p. 227–229° (6)].

2 - Ethyl - 9 - methyl - 1,2,3,4 - tetrahydro - β-carboline (X)—In a similar manner as in the preparation of IV, 2 g. (0.01 mole) of 2-ethyltetrahydro-β-carboline was treated with a mixture of 0.345 g. (0.015 g. atom) of sodium in liquid ammonia and 2.13 g. (0.015 mole) of methyl iodide. After evaporation, the residue was dissolved in 50 ml. of water, and extracted first with 100 ml. then 50 ml. of ether. The combined ethereal extracts were dried with anhydrous sodium sulfate, decolorized with charcoal, filtered, then evaporated *in vacuo*. The oily residue was dissolved in 25 ml. of heptane, filtered, and mixed with ethereal HCl to precipitate the hydrochloride salt. Recrystallization of this crude hydrochloride with ethanol–ether gave 1.5 g. (60%) of white solid, m.p. 234–235°; $\lambda_{\max.}$ (KBr) 3.28, 3.32, 3.40, 3.44, 3.47, 3.51 (CH); 3.65, 4.01, 4.12, 4.31 (NH^+); 6.20 (C=C); 13.35 μ (indole CH). $\lambda_{\max.}$ (EtOH) 225, 275, 282, 293 mμ.

Anal.—Calcd. for $C_{14}H_{19}ClN_2$: C, 67.0; H, 7.63; N, 11.2. Found: C, 67.2; H, 7.82; N, 11.2.

2 - Ethyl - 9 - hydroxymethyl - 1,2,3,4 - tetrahydro-β-carboline (XI)—To a suspension of 1.0 g. (5 mmoles) of 2-ethyltetrahydro-β-carboline in 10 ml. of water was added dropwise concentrated hydrochloric acid until a solution was obtained (about 0.1 ml.). The pH of the solution was adjusted to 5.5–6.0 with aqueous sodium acetate and 5 ml. of 38% (60 mmoles) of formaldehyde was added. The mixture was allowed to stand at room temperature for 4 days. When the solution was made basic with 10% potassium hydroxide, an oil separated. The oil was extracted into 50 ml. of ether, and evaporation of ether gave a gummy product which was then dissolved in ether and converted into 0.5 g. (36%) of hydrochloride salt by mixing with ethereal HCl. The hydrochloride was hygroscopic; it decomposed when heated to 180°. $\lambda_{\max.}$ (KBr) 3.10 (OH); 3.20, 3.25, 3.35, 3.45 (NH^+); 6.18 (C=C); 9.60–9.70 (C–O); 13.40 μ (indole CH); $\lambda_{\max.}$ (EtOH) 204, 224, 272, 279, 289 mμ.

Anal.—Calcd. for $C_{14}H_{19}ClN_2O$: C, 63.0; H, 7.17; N, 10.5. Found: C, 62.8; H, 7.20; N, 10.5.

2,9 - Dimethyl - 1 - oxo - 1,2,3,4 - tetrahydo - β-carboline (XXV)—To a suspension of 1.44 g. (0.06 mole) of sodium hydride (50% suspension in mineral oil) in 25 ml. of tetrahydrofuran was added dropwise a solution of 3.72 g. (0.02 mole) of 1-oxotetrahydro-β-carboline in 50 ml. of tetrahydrofuran over a period of 1 hr. After being refluxed for 45 min., the mixture was cooled in an ice bath while 14.2 g. (0.1 mole) of methyl iodide was added dropwise over a period of 15 min. The resulting mixture was allowed to stand overnight at room temperature, then refluxed for 30 min. After the addition of 3 ml. of water, the mixture was heated under a stream of helium until the volume reduced to about 25 ml. A large amount of water was added and an oil separated. The oil was extracted into 150 ml. of ether and the aqueous layer was again extracted with 100 ml. of ether. The combined ethereal extracts were dried with anhydrous sodium sulfate and evaporated *in vacuo* leaving an oily residue. When the oil was boiled with 15 ml. of heptane for 10 min. then allowed to cool, it solidified to give 3.1 g. (72%), m.p. 77.5–79°; $\lambda_{\max.}$ (KBr) 6.10 (C=O); 6.20, 6.47, 6.70 (C=C); 13.55 μ (indole CH), $\lambda_{\max.}$ (EtOH) 207, 230, 242 (s), 303, 330 (s) mμ.

Anal.—Calcd. for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.58; N, 13.1. Found: C, 73.1; H, 6.63; N, 13.0.

2,9-Dimethyl-1,2,3,4-tetrahydro-β-carboline (XII)—To a stirred suspension of 0.76 g. (0.02 mole) of lithium aluminum hydride in 30 ml. of ether was added dropwise a solution of 2.14 g. (0.01 mole) of 2,9-dimethyl-1-oxo-tetrahydro-β-carboline in 30 ml. of ether. After being stirred at room temperature for 2 hr., the mixture was decomposed with water, filtered, and the filtered cake was washed with ether (3 × 20 ml.). The combined ether solution was dried with anhydrous sodium sulfate and evaporated *in vacuo* leaving a white solid. The solid product was dissolved in ether, filtered to remove small amounts of undissolved product, then mixed with ethereal HCl. The hydrochloride salt, m.p. 242–244°, weighed 2 g. (83.3%). One recrystallization from ethanol gave 1.3 g. (54.1%), m.p. 246–247°; $\lambda_{\max.}$ (KBr) 3.74, 3.83, 3.89, 3.98, 4.03, 4.12, 4.20 (NH^+); 6.20 (C=C); 13.18, 13.30 μ (indole CH), $\lambda_{\max.}$ (EtOH) 204, 227, 276, 282, 292 mμ.

Anal.—Calcd. for $C_{13}H_{17}ClN_2$: C, 65.9; H, 7.23; N, 11.8. Found: C, 66.1; H, 7.30; N, 12.0.

Assay

Mitochondrial monoamine oxidase from beef liver was isolated and purified as previously described (1). All the stock solutions of the hydrochloride salts of inhibitors were prepared in water. Compound VIII was dissolved in 0.01 *N* HCl and compound IX in propylene glycol. Incubation was carried out with tryptamine-2-^{14}C hydrochloride according to the previously described procedure (1).

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Keyphrases

Monoamine oxidase inhibitors
Tetrahydro-β-carbolines, *N*-2(9)-substituted—synthesis
Inhibition, MAO—screening
TLC—separation, identity
IR spectrophotometry—structure