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Synthesis of 1,2,3,4-Tetrahydro-β-carboline Derivatives as Hepatoprotective Agents. IV. Positional Isomers of 1,2,3,4-Tetrahydro-2-methylthiothiocarbonyl-β-carboline-3-carboxylic Acid and Its 1-Alkylated Derivatives

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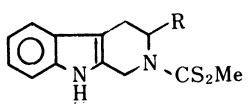
Two tetrahydro-β-carboline-1- and -4-carboxylic acids (**1b, c**) and the corresponding hydroxymethyl derivatives (**2b, c**), which are positional isomers of the 3-carboxylic acid (**1a**) and its 3-hydroxymethyl derivative (**2a**), were synthesized and tested for hepatoprotective activity against carbon tetrachloride (CCl_4)-induced liver damage in mice. The hepatoprotective activity of these positional isomers decreased in the following order; **1a** > **1b** > **1c** > and **2a** > **2b** > **2c**.

The effect of alkyl substitution at the 1 position of **1a** and **2a** was also examined with the *cis* and *trans* isomers (**5a, b**—**14a, b**). Compounds with small alkyl groups such as Me and Et showed potent activity. Lengthening of the alkyl group generally caused a decrease in activity. In a series of the stereoisomers of the 3-carboxylic acids (**5a, b**—**9a, b**), the *cis* isomers tend to be more active than the *trans* counterparts.

Keywords——dithiocarbamate; tetrahydro-β-carboline; hepatoprotective activity; positional isomer; stereoisomer; structure–activity relationship

The synthesis and structure–activity relationships of a series of new 2-alkylthiothiocarbonyl-1,2,3,4-tetrahydro-β-carbolines as hepatoprotective agents were described in our previous papers.[1-3] As a result of an examination of the effects of substitution on the dithiocarbamate group,[2] C_3,[3] the benzene ring,[3] and the indole nitrogen,[3] the 3-carboxylic acid (**1a**) and the 3-hydroxymethyl derivative (**2a**) were found to exhibit the most potent hepatoprotective activity. In those studies, the presence of hydrophilic substituents such as carboxylic acid and hydroxymethyl groups at the 3 position was shown to be the most favorable.[3] Therefore, it became of interest to examine the effect of transposition of these functionalities to the 1 or 4 position of the β-carboline skeleton. This paper describes the synthesis and hepatoprotective activity of the 1- and 4-carboxylic acids (**1b, c**) and the corresponding hydroxymethyl derivatives (**2b, c**), which are positional isomers of **1a** and **2a**. The effect of alkyl substitution at the 1 position of **1a** and **2a** was also examined with the *cis* and *trans* isomers (**5a, b**—**14a, b**).



1a: R = CO_2H
2a: R = CH_2OH

Chart 1

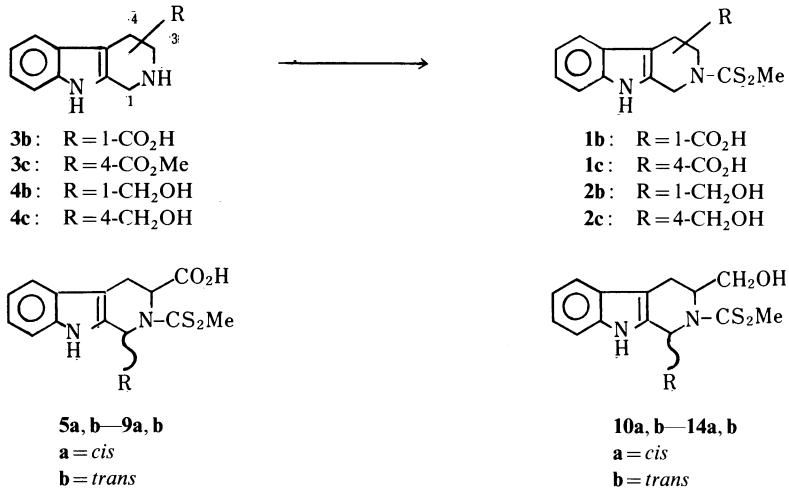


Chart 2

Chemistry

1,2,3,4-Tetrahydro-β-carboline-1-carboxylic acid (**3b**)[4] and the 1-hydroxymethyl derivative (**4b**)[5] were prepared according to the known procedure. The 4-methoxycarbonyl-β-carboline (**3c**) was obtained by Pictet–Spengler cyclization of the β-alanine derivative (**16**)[6] with formaldehyde. Lithium aluminum hydride ($LiAlH_4$) reduction of **3c** readily gave the 4-hydroxymethyl derivative (**4c**). The β-carbolines (**3b** and **4b**, **c**) were converted to the corresponding dithiocarbamates (**1b** and **2b**, **c**) by the reaction with carbon disulfide (CS_2) and methyl iodide (MeI) in the presence of sodium hydroxide (NaOH) or triethylamine (Et_3N). Similar treatment of the ester (**3c**) followed by alkaline hydrolysis gave the 4-carboxylic acid (**1c**).

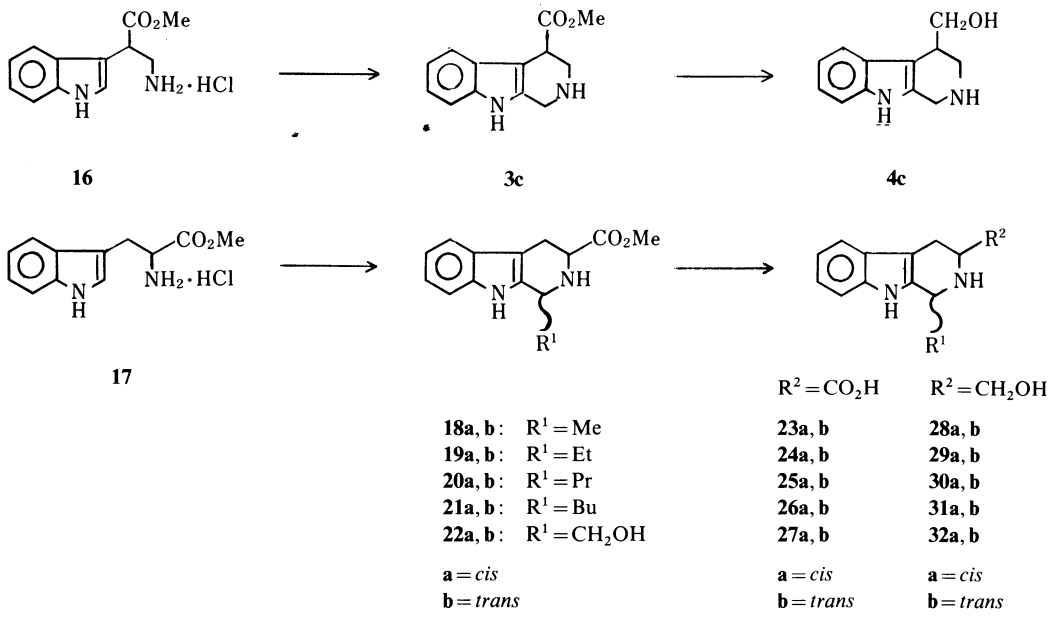


Chart 3

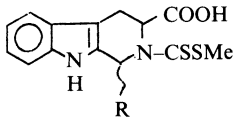
The *cis* and *trans* isomers of the 1-alkyl-β-carboline-3-carboxylic acid (**23**)[7] and the esters (**19**[8] and **22**[9]) were prepared by the reported procedure. The higher homologues (**20** and **21**) were similarly prepared by Pictet–Spengler cyclization of DL-tryptophan methyl ester (**17**) with butanal and pentanal, respectively. The resulting mixtures of the *cis* and *trans* isomers of the esters (**20a**, **b** and **21a**, **b**) were separated by column chromatography. Stereochemical assignment of these isomers was based on the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra. Cook *et al.*[10] reported that the C_1 and C_3 signals of the *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines were clearly upfield from those of the corresponding *cis* isomers. The C_1 and C_3 signals of the *cis*-1-propyl derivative (**20a**) appeared at 52.54 and

TABLE I. Hepatoprotective Activities of the Positional Isomers (**1a, b, c** and **2a, b, c**)

Compd. No.	Hepatoprotective activity 100 mg/kg	10 mg/kg
1a[a]	AA	AA
1b	AA	D
1c	A	
2a[a]	AA	AA
2b	AA	C
2c	AA	D

a) The (*R*), (*S*), and (*RS*) isomers of these compounds proved to be equipotent. See reference 2.

TABLE II. Dithiocarbamate Derivatives of 1-Substituted Tetrahydro-β-carboline-3-carboxylic Acids



Compd. No.	R	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Hepatoprotective activity 100 mg/kg	10 mg/kg
5a	Me	134—137 ($CHCl_3$)	50	$C_{15}H_{16}N_2O_2S_2 \cdot 1/2\,CHCl_3$	48.98 (48.74)	4.38 4.26	7.37 7.32	16.87 17.01)	AA	AA
5b	Me	173—176 (EtOH–H_2O)	71	$C_{15}H_{16}N_2O_2S_2 \cdot 1/2\,C_2H_5OH$	55.95 (55.91	5.58 5.66	8.16 8.16	18.67 18.84)	AA	A
6a	Et	198—200 (EtOH–H_2O)	53	$C_{16}H_{18}N_2O_2S_2$	57.46 (57.34	5.42 5.66	8.38 8.32	19.17 19.00)	AA	AA
6b	Et	155—157 (EtOH–H_2O)	70	$C_{16}H_{18}N_2O_2S_2$	57.46 (57.69	5.42 5.74	8.38 8.33	19.17 18.82)	AA	D
7a	Pr	Powder	59	$C_{17}H_{20}N_2O_2S_2$	58.59 (58.63	5.78 5.75	8.04 8.02	18.40 18.23)	AA	B
7b	Pr	Powder	41	$C_{17}H_{20}N_2O_2S_2 \cdot 1/2\,C_2H_5OH$	58.19 (57.94	6.24 6.06	7.54 7.75	17.26 17.36)	AA	A
8a	Bu	100—105 (EtOH–H_2O)	71	$C_{18}H_{22}N_2O_2S_2$	59.64 (59.43	6.12 6.11	7.73 7.54	17.69 17.42)	A	
8b	Bu	99—102 (EtOH–H_2O)	75	$C_{18}H_{22}N_2O_2S_2 \cdot C_2H_5OH \cdot 1/4\,H_2O$	58.15 (58.09	6.95 6.70	6.78 6.88	15.52 15.24)	A	
9a	$-CH_2OH$	Powder	54	$C_{15}H_{16}N_2O_3S_2 \cdot 1/2\,C_2H_5OH$	53.46 (53.28	5.33 5.30	7.79 7.65	17.84 17.61)	AA	AA
9b	$-CH_2OH$	187—188 (EtOH–H_2O)	34	$C_{15}H_{16}N_2O_3S_2$	53.55 (53.68	4.79 4.80	8.33 8.25	19.06 19.00)	A	

56.54 ppm, respectively, while those of the *trans* counterpart (**20b**) appeared at 50.17 and 52.51 ppm. The corresponding 1-butyl derivatives (**21a, b**) behaved similarly (see Experimental). These upfield shifts in the *trans*-isomers are quite similar to those reported for the corresponding 1-ethyl-3-methoxycarbonyl derivatives (**19a, b**).[10] The esters (**20a, b** and **21a, b**) were hydrolyzed to the corresponding acids (**25a, b** and **26a, b**) without epimerization. The 3-hydroxymethyl derivatives (**28a, b—32a, b**) were obtained by sodium borohydride ($NaBH_4$) reduction[11] of **18a, b—22a, b** (Table IV). The β-carbolines (**23a, b—32a, b**) were converted to the *N*-methylthiothiocarbonyl derivatives (**5a, b—14a, b**) listed in Tables II and III in the usual manner.

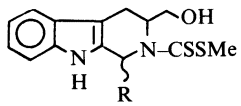
Pharmacology and Structure–Activity Relationships

The dithiocarbamates prepared in the present study were tested for hepatoprotective activity against acutely CCl_4-induced liver damage in mice after oral administration by the method reported previously.[1] The results were evaluated according to the criteria defined previously[1] and are listed in Tables I—III.

With regard to the activity of the positional isomers (Table I), the hepatoprotective activity of the carboxylic acids decreased in the following order: **1a** > **1b** > **1c**. This is also the case for the corresponding hydroxymethyl derivatives (**2a—c**). This observation and the favorable effect of the presence of hydrophilic substituents at the 3 position appear to suggest that some neighboring group participation of the 3-substituent with the dithiocarbamate group is important for the manifestation of activity.

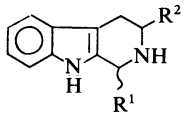
The effects of introduction of various alkyl groups at C_1 of **1a** and **2a** are summarized in

TABLE III. Dithiocarbamate Derivatives of 1-Substituted Tetrahydro-3-hydroxymethyl-β-carbolines



Compd. No.	R	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)				Hepatoprotective activity	
					C	H	N	S	100 mg/kg	10 mg/kg
10a	Me	164—166 (EtOH–H_2O)	90	$C_{15}H_{18}N_2OS_2$	58.79 (58.69	5.92 5.80	9.14 9.19	20.93 20.94)	AA	AA
10b	Me	153—156 (EtOH–H_2O)	80	$C_{15}H_{18}N_2OS_2$	58.79 (58.67	5.92 5.97	9.14 9.20	20.93 21.03)	AA	A
11a	Et	177—180 (Et_2O)	65	$C_{16}H_{20}N_2OS_2$	59.96 (60.23	6.29 6.30	8.74 8.79	20.01 19.84)	AA	D
11b	Et	170—172 (EtOH–H_2O)	77	$C_{16}H_{20}N_2OS_2$	59.96 (60.00	6.29 6.29	8.74 8.63	20.01 19.78)	AA	D
12a	Pr	Powder	80	$C_{17}H_{22}N_2OS_2$	61.04 (60.83	6.63 6.55	8.37 8.32	19.17 19.31)	C	
12b	Pr	Powder	74	$C_{17}H_{22}N_2OS_2$	61.04 (60.87	6.63 6.78	8.37 8.33	19.17 19.20)	A	
13a	Bu	Powder	61	$C_{18}H_{24}N_2OS_2$	62.03 (62.15	6.94 6.87	8.04 7.92	18.40 18.16)	D	
13b	Bu	Powder	70	$C_{18}H_{24}N_2OS_2$	62.03 (62.28	6.94 6.90	8.04 7.87	18.40 18.21)	C	
14a	$-CH_2OH$	Powder	38	$C_{15}H_{18}N_2O_2S_2$ $1/2\,C_2H_5OH$	55.63 (55.45	6.13 6.01	8.11 8.20	18.56 18.78)	AA	B
14b	$-CH_2OH$	179—180 (EtOH–H_2O)	39	$C_{15}H_{18}N_2O_2S_2$	55.87 (55.81	5.63 5.64	8.69 8.53	19.89 19.87)	AA	B

TABLE IV. 1,3-Disubstituted 1,2,3,4-Tetrahydro-β-carbolines



Compd. No.	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
24a	236—237 (EtOH–H_2O)	72	$C_{14}H_{16}N_2O_2 \cdot C_2H_5OH$	66.19 (66.01)	7.64 7.70	9.65 9.51)
24b	242—243 (EtOH–H_2O)	67	$C_{14}H_{16}N_2O_2 \cdot C_2H_5OH$	66.19 (66.12)	7.64 7.50	9.65 9.58)
25a	225—226 (EtOH–H_2O)	81	$C_{15}H_{18}N_2O_2 \cdot H_2O$	65.20 (65.01)	7.29 7.05	10.14 10.00)
25b	210—211 (EtOH–H_2O)	78	$C_{15}H_{18}N_2O_2 \cdot 1/2\,H_2O$	67.39 (67.53)	7.16 6.98	10.48 10.45)
26a	215—216 (MeOH)	78	$C_{16}H_{20}N_2O_2 \cdot H_2O$	66.19 (66.12)	7.63 7.62	9.65 9.62)
26b	204—205 (MeOH)	79	$C_{16}H_{20}N_2O_2 \cdot H_2O$	66.19 (66.40)	7.63 7.39	9.65 9.88)
27a	241—242 (MeOH)	90	$C_{13}H_{14}N_2O_3 \cdot H_2O$	59.08 (59.34)	6.10 6.01	10.60 10.39)
27b	231—233 (MeOH)	65	$C_{13}H_{14}N_2O_3 \cdot 1/2\,H_2O$	61.17 (61.01)	5.92 5.81	10.97 10.82)
28a	176—178 (EtOH)	69	$C_{13}H_{16}N_2O$	72.19 (71.98)	7.46 7.53	12.95 12.67)
28b	197—198 (MeOH)	81	$C_{13}H_{16}N_2O$	72.19 (72.10)	7.46 7.50	12.95 12.79)
29a	205—206 (MeOH)	84	$C_{14}H_{18}N_2O$	73.01 (73.06)	7.87 7.85	12.16 12.22)
29b	170.5—171 (MeOH)	85	$C_{14}H_{18}N_2O$	73.01 (73.17)	7.87 7.88	12.16 12.20)
30a	218—219 (MeOH–H_2O)	75	$C_{15}H_{20}N_2O$	73.74 (73.86)	8.25 8.18	11.46 11.52)
30b	170.5—171 (MeOH–H_2O)	64	$C_{15}H_{20}N_2O$	73.74 (73.62)	8.25 8.26	11.46 11.48)
31a	222—223 (EtOH)	86	$C_{16}H_{22}N_2O$	74.38 (74.25)	8.58 8.58	10.84 10.78)
31b	175—176 (EtOH)	80	$C_{16}H_{22}N_2O$	74.38 (74.55)	8.58 8.48	10.84 10.89)
32a	Powder	63	$C_{13}H_{16}N_2O_2 \cdot H_2O$	62.38 (62.19)	7.25 7.04	11.19 11.23)
32b	Powder	75	$C_{13}H_{16}N_2O_2 \cdot H_2O$	62.38 (62.15)	7.25 7.18	11.19 11.12)

Tables II and III. As regards the size of alkyl groups, the compounds with small alkyl groups such as Me and Et showed potent activity. The activity of **5a**, **6a**, or **10a** is comparable to that of **1a** or **2a**. Lengthening of the alkyl group generally caused a decrease in activity. Introduction of a hydroxymethyl group at C_1 gave a favorable effect, as exemplified by the 1,3-*cis*-hydroxymethyl derivative (**9a**).

In a series of the stereoisomers of the 3-carboxylic acids (**5a**, **b**—**9a**, **b**), *cis* isomers tend to be more active than the *trans* counterparts (**5a** *vs.* **5b** and **6a** *vs.* **6b**). On the other hand, this tendency is not apparent in the stereoisomers of the 3-hydroxymethyl derivatives (**10a**, **b**—

14a, b).

After pharmacological evalution of the most potent compounds of this series,[1-3] the (*S*)-3-hydroxymethyl-2-methylthiothiocarbonyl derivative [(*S*)-**2a**] was selected for further study as a candidate for a clinically useful hepatoprotective agent. Compound (*S*)-**2a** exhibits potent hepatoprotective activity against liver damage acutely induced by galactosamine, bromobenzene, and α-naphthyl isothiocyanate in rats. It also exhibits a therapeutic effect on chronic liver damage induced by CCl_4 in rats. Further studies on (*S*)-**2a** as a possible hepatoprotective agent are in progress and will be reported in a separate paper.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a JEOL PMS-60 instrument and ^{13}C-NMR spectra were recorded with a JEOL FX-100S spectrometer at 25 MHz. Chemical shifts are given as δ values from tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, and q=quartet. Mass spectra (MS) were measured with a Hitachi RMU-6M instrument.

1,2,3,4-Tetrahydro-2-methylthiothiocarbonyl-β-carboline-1-carboxylic Acid (1b)——CS_2 (912 mg, 12 mmol) was added to a solution of **3b**[4] (2.16 g, 10 mmol) and 10 N NaOH (2 ml, 20 mmol) in dimethyl sulfoxide (DMSO) (6 ml), and the whole was stirred at room temperature for 10 min. After addition of MeI (1.7 g, 12 mmol), the mixture was stirred for 10 min, poured into water, and extracted with AcOEt. The aqueous layer was acidified with 10% HCl and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from aq. EtOH to give **1b** (1.24 g, 41%), mp 146—147 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1705. MS *m/z*: 306 (M^+), 258, 215. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.69 (3H, s). *Anal.* Calcd for $C_{14}H_{14}N_2O_2S_2$: C, 54.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 54.73; H, 4.66; N, 9.08; S, 20.67.

1,2,3,4-Tetrahydro-2-methylthiothiocarbonyl-β-carboline-4-carboxylic Acid (1c)——A solution of **3c**·HCl (110 mg, 0.41 mmol), Et_3N (0.12 ml, 0.82 mmol), and CS_2 (0.03 ml, 0.5 mmol) in DMSO (1 ml) was stirred at room temperature for 1 h. MeI (0.03 ml, 0.5 mmol) was added, and the whole was stirred for 3 h. The mixture was diluted with water, extracted with AcOEt, and the extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was dissolved in MeOH (3 ml), and 1 N NaOH (0.52 ml) was added. The mixture was stirred at room temperature overnight and evaporated. The residue was acidified with 10% HCl, extracted with AcOEt, and the extract was washed with water and dried over $MgSO_4$. The solvent was evaporated off to give an oil, which was crystallized from aq. EtOH to provide **1c** (101 mg, 80%), mp 202—204 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1700. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.68 (3H, s). MS *m/z*: 306 (M^+), 259, 215, 169. *Anal.* Calcd for $C_{14}H_{14}N_2O_2S_2$: C, 54.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 54.97; H, 4.60; N, 9.06; S, 20.60.

The carboxylic acids (**5**—**9**) were synthesized in a manner similar to that described for **1b** and their physical properties are listed in Table II.

Methyl 1,2,3,4-Tetrahydro-1-hydroxymethyl-β-carboline-2-carbodithioate (2b)——A solution of **4b**[5] (380 mg, 1.9 mmol), CS_2 (0.13 ml, 2 mmol), and Et_3N (0.28 ml, 2 mmol) in MeOH (12 ml)–H_2O (4 ml) was stirred at room temperature for 30 min, and then MeI (0.1 ml, 2 mmol) was added. The mixture was stirred for 2.5 h, and the solvent was evaporated off under reduced pressure. The residue was dissolved in AcOEt, and this solution was washed with water, 5% HCl, and water, and then dried over Na_2SO_4. After removal of the solvent, the residue was triturated with aq. EtOH to give **2b** (400 mg, 73%) as a powder. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (3H, s). MS *m/z*: 292 (M^+), 274, 261, 259, 244. *Anal.* Calcd for $C_{14}H_{16}N_2OS_2$: C, 57.50; H, 5.52; N, 9.58; S, 21.93. Found: C, 57.30; H, 5.67; N, 9.38; S, 21.67.

Methyl 1,2,3,4-Tetrahydro-4-hydroxymethyl-β-carboline-2-carbodithioate (2c)——This compound was prepared in 58% yield as a powder from **4c** under conditions analogous to those described above. ^{1}H-NMR ($CDCl_3$) δ: 2.69 (3H, s). MS *m/z*: 292 (M^+), 274, 259, 244. *Anal.* Calcd for $C_{14}H_{16}N_2OS_2 \cdot 1/3H_2O$: C, 56.36; H, 5.63; N, 9.39; S, 21.49. Found: C, 56.53; H, 5.38; N, 9.28; S, 21.56.

The hydroxymethyl compounds (**10**—**14**) were prepared in a manner similar to that described for **2b**. Their physical data are listed in Table III.

Methyl 1,2,3,4-Tetrahydro-β-carboline-4-carboxylate (3c) Hydrochloride——A solution of **16**[6] (2.04 g, 8 mmol) and 35% formalin (828 mg, 9.6 mmol) in MeOH (160 ml) was stirred at room temperature for 18 h. The mixture was diluted with ether, and the resulting crystals were collected by filtration and dried to give **3c** (2.04 g, 95%) as colorless needles, mp 223—225 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3160, 3100, 1730. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 3.73 (3H, s), 4.40 (2H, s). MS *m/z*: 230 (M^+), 215, 213, 201, 196. *Anal.* Calcd for $C_{13}H_{14}N_2O_2 \cdot HCl$: C, 58.54; H, 5.67; Cl, 13.29; N, 10.50. Found: C, 58.47; H, 5.48; Cl, 13.31; N, 10.46. The free base had mp 172—174 °C (AcOEt).

1,2,3,4-Tetrahydro-4-hydroxymethyl-β-carboline (4c) Oxalate——A solution of **3c** (1.115 g, 4.84 mmol) in tetrahydrofuran (THF) (34 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (365 mg) in THF, and the whole was stirred at room temperature for 2.5 h. An excess of the hydride was decomposed by addition of water, and the

insoluble material was filtered off. The filtrate was concentrated to give an oil, which was converted to the oxalate to give **4c**·oxalate (1.17 g, 83%), mp 227—228 °C (H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3410, 3230, 1610. MS *m/z*: 202 (M^+), 184, 144. *Anal.* Calcd for $C_{12}H_{14}N_2O \cdot C_2H_2O_4$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.56; H, 5.40; N, 9.55.

Methyl *cis*-1,2,3,4-Tetrahydro-1-methyl-β-carboline-3-carboxylate (18a) Hydrochloride——$SOCl_2$ (71.6 ml, 0.99 mol) was added dropwise to a suspension of **23a**[7] (188 g, 0.82 mol) at −10 °C, and the mixture was refluxed for 4 h. After removal of the solvent, the residue was recrystallized from MeOH to give **18a**·HCl (218 g, 95%), mp 226—230 °C (dec.) (lit.[7] mp 228—230 °C).

Methyl *trans*-1,2,3,4-Tetrahydro-1-methyl-β-carboline-3-carboxylate (18b)——This compound was similarly prepared from **23b**[7] in 85% yield. mp 154—156 °C (MeOH–iso-Pr_2O). IR ν_{max}^{Nujol} cm^{-1}: 3340, 1730. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, *J*=6.7 Hz), 3.7 (3H, s). MS *m/z*: 244 (M^+), 229, 185, 169. *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.81; H, 6.61; N, 11.49.

Methyl *cis*-1,2,3,4-Tetrahydro-1-propyl-β-carboline-3-carboxylate (20a) and Methyl *trans*-1,2,3,4-Tetrahydro-1-propyl-β-carboline-3-carboxylate (20b)——A solution of **17** (33 g, 0.13 mol) and butanal (21.0 g, 0.29 mol) in MeOH (450 ml) was refluxed for 48 h and concentrated to one half of the initial volume. The resulting solid was collected by filtration to give **20a**·HCl (15.4 g, 38%, mp 205—207 °C from MeOH). The mother liquor was evaporated to dryness, and the residue was basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated to give an oil, which was chromatographed on silica gel using $CHCl_3$ as the eluent. The first eluate gave an additional amount of **20a** (2.5 g, mp 98—100 °C from iso-PrOH–iso-Pr_2O. Total yield 45%). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3200, 1740. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 52.54 (C_1), 56.54 (C_3). MS *m/z*: 272 (M^+), 229. *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.30; H, 7.36; N, 10.41. From the second eluate, **20b** (8.2 g, 23%, mp 116—118 °C from iso-Pr_2O) was obtained. IR ν_{max}^{Nujol} cm^{-1}: 3420, 1718. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 50.17 (C_1), 52.51 (C_3). MS *m/z*: 272 (M^+), 229. *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.72; H, 7.39; N, 10.25.

Methyl *cis*-1-Butyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (21a) and Methyl *trans*-1-Butyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (21b)——These compounds were prepared from **17** in a manner similar to that described above. The *cis* compound (**21a**); 53%, mp 85—87 °C (iso-Pr_2O–iso-PrOH). IR ν_{max}^{Nujol} cm^{-1}: 3340, 3240, 1740. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 52.80 (C_1), 56.60 (C_3). MS *m/z*: 286 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.26; H, 7.68; N, 9.75. The *trans* compound (**21b**); 25%, mp 102—103 °C (iso-Pr_2O–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3320, 3150—3050, 1720. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 50.46 (C_1), 52.51 (C_3). MS *m/z*: 286 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.32; H, 7.73; N, 9.77.

***cis*-1-Ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (24a)**——A solution of **19a**[8] (5.0 g, 19.3 mmol) and 1 N NaOH (30 ml) in MeOH (30 ml) was stirred at room temperature for 1.5 h, and the solvent was evaporated off under reduced pressure. Then 5% HCl was added to the residue and the resulting solid was collected by filtration washed with water, and then dried. Recrystallization from aq. EtOH gave **24a** (3.4 g, 72%), mp 236—237 °C. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3250, 1650. ^{1}H-NMR (DMSO-d_6–CF_3CO_2H) δ: 1.07 (3H, t, *J*=7.0 Hz), 3.47 (2H, q, *J*=7.0 Hz). MS *m/z*: 244 (M^+), 215, 169.

The carboxylic acids (**24b**, **25a**, **b**, **26a**, **b**, and **27a**, **b**) were similarly prepared and are listed in Table IV.

***cis*-1,2,3,4-Tetrahydro-3-hydroxymethyl-1-methyl-β-carboline (28a)**——$NaBH_4$ (7.0 g, 0.185 mol) was added to **18a**·HCl (13.2 g, 0.047 mol) in 85% aq. EtOH (150 ml) at 15—17 °C, and the mixture was stirred at room temperature for 10 h and then refluxed for 2 h. Insoluble material was filtered off, and the filtrate was concentrated. The residue was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. The solvent was evaporated off to give a solid, which was recrystallized from EtOH to afford **28a** (7.0 g, 69%), mp 176—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.40 (3H, d, *J*=6.4 Hz). MS *m/z*: 216 (M^+), 201, 185, 183, 157.

The hydroxymethyl compounds (**28b**, **29a**, **b**, **30a**, **b**, **31a**, **b**, and **32a**, **b**) were prepared in a similar manner and are listed in Table IV.

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