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Synthesis of 1,2,3,4-Tetrahydro-β-carboline Derivatives as Hepatoprotective Agents. II. Alkyl 1,2,3,4-Tetrahydro-β-carboline-2-carbodithioates

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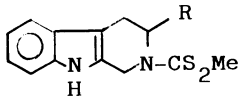
A large number of alkyl 1,2,3,4-tetrahydro-β-carboline-2-carbodithioates (**2** and **5**) with 3-hydroxycarbonyl and 3-hydroxymethyl groups were synthesized and tested for hepatoprotective activity against CCl_4-induced liver damage in mice. Structure–activity relationships were investigated. Lengthening of the alkyl group in **2** and **5** tends to adversely affect the activity. Both enantiomers of the methyl derivatives (**2a** and **5a**), the most potent compounds in this series, were synthesized, and no difference in hepatoprotective activity was observed. Apparent neighboring group participation was observed in the treatment of **5a** with base or acid, giving the cyclized product (**6**) or the rearranged products (**7**, **8**, and **9**).

Keywords——tetrahydro-β-carboline; structure–activity relationship; carbon tetrachloride-induced liver damage; hepatoprotective activity; dithiocarbamate; optical isomer; neighboring group participation

The preceding paper of this series[1] disclosed the synthesis and hepatoprotective activity of *N*-(methylthio)thiocarbonyl derivatives of several α-amino acids. Among them, 1,2,3,4-tetrahydro-2-(methylthio)thiocarbonyl-β-carboline-3-carboxylic acid (**2a**) exhibited the most potent activity as determined in terms of protection against acutely CCl_4-induced liver damage in mice. In view of the novelty of this class of compounds as hepatoprotective agents, we commenced the synthesis of a large number of derivatives in an effort to establish structure–activity relationships (SAR). In the present study, both enantiomers of **2a** and the corresponding 3-hydroxymethyl derivative (**5a**) were synthesized, and their hepatoprotective activity was examined. The effects of varying the alkyl group in the dithiocarbamate moiety of **2** and **5** are also presented.



2a: R = CO_2H
5a: R = CH_2OH

Chart 1

Chemistry

The optical isomers of **2a** were readily synthesized according to the procedure described previously for the racemate[1] (Chart 2). The Pictet–Spengler cyclization of L- and D-tryptophan with formalin according to the method reported by Brossi *et al.*[2] gave (*S*)- and (*R*)-

1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids (**1**), respectively. Reaction of (*S*)- and (*R*)-**1** with carbon disulfide (CS_2) in the presence of potassium hydroxide followed by alkylation with methyl iodide gave the dithiocarbamates [(*S*)- and (*R*)-**2a**], respectively (Table I). The 3-hydroxymethyl derivatives [(*RS*)-, (*S*)-, and (*R*)-**4**][3] were obtained by sodium borohydride reduction[4] of the 3-methoxycarbonyl-β-carbolines[5] [(*RS*)-, (*S*)-, and (*R*)-**3**].

Apparent neighboring group participation was observed in the reaction of **4** with CS_2. When treated with CS_2 and then with methyl iodide in the presence of sodium hydroxide in the usual manner,[1] (*S*)-**4** gave, after chromatographic separation, the dithiocarbamate [(*S*)-**5a**] and the cyclized product (**6**) in 41 and 40% yields, respectively. Replacement of sodium hydroxide with triethylamine in the reaction, however, gave (*S*)-**5a** as a sole product in 90.2% yield. Compounds (*RS*)-**5a** and (*R*)-**5a** were similarly prepared, and their physical properties are listed in Table I.

The cyclized product (**6**) showed the molecular ion peak at *m/z* 244 in its mass spectrum (MS), and no carbonyl band appeared in the infrared (IR) spectrum, in accordance with the fused oxazolidine-2-thione structure. On treatment with aqueous potassium hydroxide in ethanol at room temperature, the dithiocarbamate [(*S*)-**5a**] readily underwent cyclization, apparently *via* intermediate A, giving **6** in 88.9% yield (Chart 3). Heating of (*S*)-**5a** with 10% HCl in ethanol caused precipitation of the hydrochloride (**7**) in 82% yield. Compound **7** was analyzed for $C_{14}H_{16}N_2OS_2 \cdot HCl$ and showed the molecular ion peak at *m/z* 292 in its MS, indicating that **7** is the HCl salt of a compound having a molecular formula identical with that of **5a**. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, **7** showed a singlet

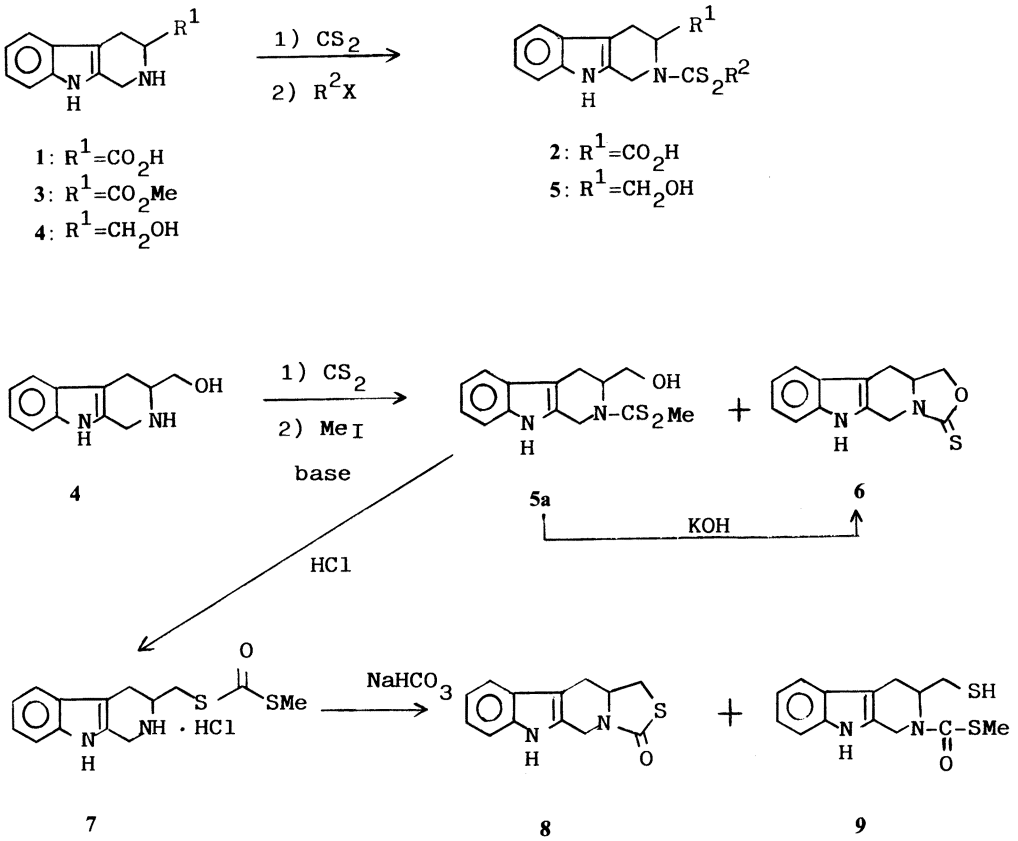


Chart 2

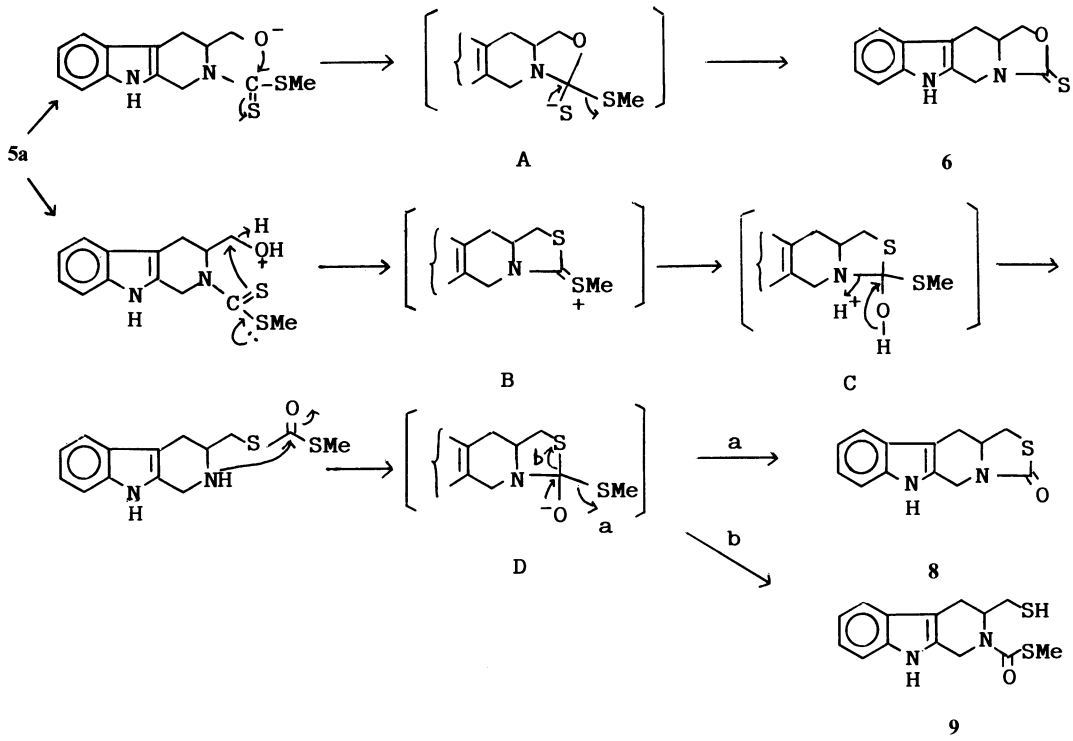


Chart 3

assignable to the SMe group at δ 2.48 ppm. The IR spectrum of **7** exhibited the carbonyl absorption at 1640 cm^{-1} together with NH_2^+ absorption at 2330—2730 cm^{-1}. On the basis of these spectroscopic data, the dithiocarbonate structure (**7**) was assigned for this compound. Upon alkalinization with aqueous sodium bicarbonate, **7** gave, after chromatographic separation, two compounds (**8** and **9**) in 43 and 11.2% yields, respectively. Compound **8** (M^+: *m/z* 244), which is isomeric with the oxazolidine-2-thione (**6**), was assigned the fused 2-thiazolidinone structure based on its carbonyl absorption at 1640 cm^{-1}. On the other hand, the MS of **9** showed the molecular ion peak at *m/z* 292, indicating that this compound is isomeric with **5a** or **7**. The presence of the SH group in **9** was confirmed by an absorption at 2550 cm^{-1}, and the thiol proton resonance at δ 1.47 ppm (t, J = 8 Hz, disappeared on addition of D_2O). The IR and NMR spectra of **9** also showed the presence of a methylthiocarbonyl group (carbonyl absorption at 1640 cm^{-1} and a singlet at δ 2.41 ppm for the SMe group). On the basis of these data, the 3-mercaptomethyl-2-(methylthio)carbonyl structure was assigned for **9**.

Formation of **7**, **8**, and **9** may be rationalized in terms of the sequence of reactions outlined in Chart 3. Protonation at the hydroxyl group of **5a** followed by intramolecular attack of the thiocarbonyl group would give intermediate B. Cleavage of the C–N bond by protonation at the nitrogen in intermediate C would lead to **7**. Upon alkalinization, **7** would give intermediate D, from which **8** or **9** could be formed by expulsion of the SMe group or by cleavage of the C–S bond in the thiazolidine ring, respectively.

To examine the effect of varying the alkyl group in the dithiocarbamate moiety on hepatoprotective activity, a number of derivatives (**2b—p** and **5b—l**) listed in Tables II and III were synthesized. Since no difference of activity between the optical isomers (**2a** and **5a**) was observed (see below), the choice of the chirality of starting materials (*S*, *R*, or *RS*) was

TABLE I. Optical Isomers of Tetrahydro-2-methylthiothiocarbonyl-β-carboline Derivatives (**2a** and **5a**)

Compd. No.	mp (°C) (Recryst. solvent)	Yield (%)	$[\alpha]_D^{20}$ (°), $c=1.0$ (Solvent)	Formula	Analysis (%) Calcd (Found)				Hepatoprotective activity[b]	
					C	H	N	S	100 mg/kg	10 mg/kg
(*S*)-**2a**	103—105 (dec.) (aq. EtOH)	73	+196.4 ($CHCl_3$)	$C_{14}H_{14}N_2O_2S \cdot 1/2H_2O$	53.31 (53.25	4.79 4.63	8.88 8.63	20.33 20.12)	AA	AA
(*R*)-**2a**	103—106 (dec.) (aq. EtOH)	60	−196.0 ($CHCl_3$)	$C_{14}H_{14}N_2O_2S_2 \cdot 1/2H_2O$	(53.18	4.76	8.76	20.19)	AA	AA
(*RS*)-**2a**[a]									AA	AA
(*S*)-**5a**	114—116 (aq. EtOH)	90	+159.0 (MeOH)	$C_{14}H_{16}N_2OS_2$	57.50 (57.44	5.52 5.49	9.58 9.60	21.93 21.80)	AA	AA
(*R*)-**5a**	106—108 (aq. EtOH)	88	−158.6 (MeOH)	$C_{14}H_{16}N_2OS_2$	(57.21	5.75	9.53	21.89)	AA	AA
(*RS*)-**5a**	172—173 (aq. EtOH)	90	—	$C_{14}H_{16}N_2OS_2$	(57.58	5.46	9.61	21.99)	AA	AA

a) See reference 1. *b*) AA = significantly effective; A, B, and C = effective; D = ineffective. For criteria, see reference 1.

arbitrary.

Pharmacology and Structure–Activity Relationships

The dithiocarbamates (**2** and **5**) prepared in the present study were tested for hepatoprotective activity against 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 included in Tables I—III.

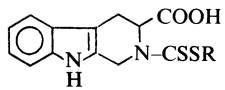
As can be seen in Table I, no difference of hepatoprotective activity between optical isomers of **2a** was observed. This is also the case for the corresponding 3-hydroxymethyl derivative (**5a**), which exhibited potent activity comparable to that of **2a**.

The effect of varying the alkyl group in the dithiocarbamate moiety was examined next for a series of the carboxylic acids (**2b—p**) and the hydroxymethyl derivatives (**5b—l**) (Tables II and III). Lengthening of the alkyl group (R) in **2** tends to adversely affect the activity. Thus, a change from methyl (**2a**) to decyl (**2f**) resulted in a gradual decrease in hepatoprotective activity. This is also the case for the corresponding 3-hydroxymethyl derivatives (**5a—f**) (Table III). These results suggest that the hepatoprotective activity of a series of the alkyl dithiocarbamates (**2** and **5**) decreases with increasing hydrophobicity of the alkyl group. The presence of a secondary alkyl group caused a marked fall in activity, as exemplified by the isopropyl derivative (**2d**).

Since some of the benzyl dithiocarbamates were significantly active, the activity of several aralkyl derivatives (**2g—p** and **5g—l**) was examined. In a series of substituted benzyl derivatives (**2g—l**), activity increased with increasing electron-donating ability of the substituent, as shown by the 4-NH_2 (**21**), 4-OMe (**2i**), and 4-Me (**2k**) derivatives. In contrast, the presence of electron-withdrawing groups such as 4-NO_2 (**2j**) and 4-Cl (**2h**) caused a marked decrease in activity (Table II). In a series of the corresponding 3-hydroxymethyl derivatives (**5g—k**), however, no clear SAR could be deduced with respect to the effect of substituents on the benzene ring (Table III). Thienyl dithiocarbamates exhibited potent activity both in the carboxylic acid (**2m**) and in the 3-hydroxymethyl (**5l**) series.

Further studies on the SAR of new dithiocarbamates of β-carboline as hepatoprotective agents are being continued.

TABLE II. Various Dithiocarbamate Derivatives of Tetrahydro-β-carboline-3-carboxylic Acid



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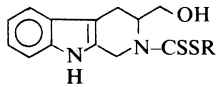
Compd. No.	R	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)					Hepatoprotective activity[b]	
					C	H	Cl	N	S	100 mg/kg	10 mg/kg
(*RS*)-**2b**	Et	177—178 (aq. EtOH)	69	$C_{15}H_{16}N_2O_2S_2 \cdot 1/5\,C_2H_5OH$	56.11 (55.97	5.25 5.09		8.50 8.59	19.45 19.72)	AA	A
(*RS*)-**2c**	Pr	180—182 (dec.) (EtOH)	69	$C_{16}H_{18}N_2O_2S_2$	57.46 (57.30	5.42 5.43		8.38 8.22	19.17 18.98)	A	
(*RS*)-**2d**	iso-Pr	188—190 (EtOH)	31	$C_{16}H_{18}N_2O_2S_2 \cdot C_2H_5OH$	56.82 (56.70	6.36 6.37		7.36 7.37	16.85 16.92)	D	
(*RS*)-**2e**	Bu	163—164 ($CHCl_3$)	36	$C_{17}H_{20}N_2O_2S_2$	58.59 (58.31	5.78 5.63		8.04 7.82	18.40 18.17)	B	
(*RS*)-**2f**	Decyl	152—154 (dec.) (hexane)	55	$C_{23}H_{32}N_2O_2S_2$	63.85 (64.17	7.46 7.48		6.47 6.52	14.82 14.67)	B	
(*RS*)-**2g**	$-CH_2-C_6H_5$	Powder	50	$C_{20}H_{18}N_2O_2S_2$	62.80 (62.63	4.74 4.72		7.32 7.18	16.77 16.54)	B	
(*RS*)-**2h**	$-CH_2-C_6H_4-Cl$	Powder	65	$C_{20}H_{17}ClN_2O_2S_2$	57.61 (57.79	4.11 4.26	8.50 8.70	6.72 6.71	15.38 15.08)	D	
(*RS*)-**2i**	$-CH_2-C_6H_4-OMe$	195—196 (iso-Pr_2O)	79	$C_{21}H_{20}N_2O_3S_2$	61.14 (61.05	4.89 4.82		6.79 6.83	15.55 15.34)	A	
(*RS*)-**2j**	$-CH_2-C_6H_4-NO_2$	Powder	54	$C_{20}H_{17}N_3O_4S_2 \cdot 1/4\,CH_3CO_2C_2H_5$	56.11 (56.41	4.26 4.16		9.35 9.27	14.27 14.40)	C	
(*RS*)-**2k**	$-CH_2-C_6H_4-Me$	188—190 (dec.) (aq. EtOH)	39	$C_{21}H_{20}N_2O_2S_2 \cdot 1/2\,C_2H_5OH$	63.29 (63.26	5.31 5.11		6.87 6.87	15.72 15.72)	A	
(*R*)-**2l**[a]	$-CH_2-C_6H_4-NH_2$	Powder	36	$C_{20}H_{19}N_3O_2S_2 \cdot 1/2\,CH_3CO_2C_2H_5$	60.01 (59.75	5.12 5.06		9.84 9.82	15.02 15.46)	AA	B
(*RS*)-**2m**	$-CH_2-C_4H_3S$	172—173 (dec.) (EtOH)	40	$C_{18}H_{16}N_2O_2S_3 \cdot 1/5\,C_2H_5OH$	55.56 (55.52	4.35 4.19		7.04 7.03	24.18 24.34)	AA	A
(*R*)-**2n**[a]	$-CH_2-C_4H_3O$	Powder	14	$C_{18}H_{16}N_2O_3S_2 \cdot 1/2\,CH_3CO_2C_2H_5$	58.80 (58.55	4.93 4.91		6.86 6.60	15.70 15.57)	B	
(*RS*)-**2o**	$-CH_2-C_4H_3N$	Powder	36	$C_{19}H_{17}N_3O_2S_2$	59.51 (59.29	4.47 4.63		10.96 10.76	16.72 16.51)	D	
(*RS*)-**2p**	$-CH_2CH_2-C_6H_5$	Powder	47	$C_{21}H_{20}N_2O_2S_2$	63.61 (63.39	5.08 5.05		7.06 6.93	16.17 16.30)	C	

a) (*R*)-**21**, $[\alpha]_D^{20}$ −118.0° (*c*=0.5, EtOH); (*R*)-**2n**, $[\alpha]_D^{20}$ −151.2° (*c*=1.0, MeOH). *b*) See footnote *b* in Table I.

TABLE III. Various Dithiocarbamate Derivatives of Tetrahydro-3-hydroxymethyl-β-carboline



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Compd. No.	R	mp (°C) (Recryst. solvent)	Yield (%)	$[\alpha]_D^{20}$ (°), $c=1.0$ (Solvent)	Formula	Analysis (%) Calcd (Found)					Hepatoprotective activity[a]	
						C	H	Cl	N	S	100 mg/kg	10 mg/kg
(*S*)-**5b**	Et	74—76 (EtOH)	65	+146.0 (MeOH)	$C_{15}H_{18}N_2OS_2$	58.79 (58.54	5.92 6.05		9.14 8.90	20.93 21.00)	AA	A
(*S*)-**5c**	Pr	130—131 (aq. EtOH)	78	+141.8 (MeOH)	$C_{16}H_{20}N_2OS_2$	59.97 (60.11	6.29 6.30		8.74 8.72	20.01 20.30)	AA	A
(*S*)-**5d**	Bu	60—63 (EtOH)	60	+133.6 (MeOH)	$C_{17}H_{22}N_2OS_2$	61.04 (60.96	6.63 6.71		8.31 8.25	19.17 19.07)	D	
(*S*)-**5e**	Hexyl	102—106 (Et_2O–hexane)	73	+130.0 (MeOH)	$C_{19}H_{26}N_2OS_2$	62.94 (62.73	7.23 7.21		7.72 7.63	17.69 17.54)	A	
(*S*)-**5f**	Decyl	115—118 (Et_2O–hexane)	59	+113.0 (MeOH)	$C_{23}H_{34}N_2OS_2$	65.98 (66.14	8.18 8.20		6.69 6.71	15.32 15.47)	B	
(*S*)-**5g**	–CH_2–C$_6$H$_5$	Powder	70	+117.3 (MeOH)	$C_{20}H_{20}N_2OS_2$	65.19 (64.97	5.47 5.46		7.60 7.50	17.40 17.39)	AA	D
(*S*)-**5h**	–CH_2–C$_6$H$_4$–Cl	175—176 (dec.) (AcOEt–hexane)	67	+94.4 (MeOH)	$C_{20}H_{19}ClN_2OS_2$	59.61 (59.64	4.75 4.81	8.80 8.91	6.95 6.76	15.91 16.09)	AA	D
(*RS*)-**5i**	–CH_2–C$_6$H$_4$–OMe	Powder	71	—	$C_{21}H_{22}N_2O_2S_2$	63.29 (63.11	5.56 5.50		7.03 6.92	16.09 15.65)	AA	A
(*RS*)-**5j**	–CH_2–C$_6$H$_4$–NO_2	193—194 (MeOH)	71	—	$C_{20}H_{19}N_3O_3S_2$	58.09 (57.82	4.63 4.69		10.16 10.33	15.51 15.61)	C	
(*S*)-**5k**	–CH_2–C$_6$H$_4$–NH_2	Powder	50	+123.6 (DMF)	$C_{20}H_{21}N_3OS_2$	59.82 (60.04	5.77 5.76		10.46 10.75	15.97 15.88)	B	
(*S*)-**5l**	–CH_2–C$_4$H$_3$S	Powder	55	+108.4 (MeOH)	$C_{18}H_{18}N_2OS_3$	57.72 (57.48	4.84 4.81		7.48 7.64	25.68 25.40)	AA	C

a) See footnote *b* in Table I.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi IR-215 spectrometer. ^{1}H-NMR spectra were taken on a JEOL-60 instrument. Chemical shifts are given as δ values from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. MS were measured with a Hitachi RMU-6M instrument. Optical rotations were determined on a Union PM-201 automatic digital polarimeter.

(3*S*), (3*R*), and (3*RS*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid (1)——These compounds were synthesized from L-, D-, and DL-tryptophan according to the method reported by Brossi *et al.*[2]

(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid[2] **[(*S*)-1]**——mp 291—294 °C (dec.), $[\alpha]_D^{20}$ −63.3° (*c* = 1.0, 1 N HCl : MeOH = 1 : 1) [*lit.*[2] mp 315 °C, $[\alpha]_D^{25}$ −49.6° (*c* = 1.0, 1 N HCl : MeOH = 1 : 1)].

(3*R*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid [(*R*)-1]——mp 290—293 °C (dec.), $[\alpha]_D^{20}$ +62.4° (*c* = 1.0, 1 N HCl : MeOH = 1 : 1).

(3*RS*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid [(*RS*)-1]——mp 286—288 °C (dec.).

Methyl (3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylate [(*S*)-3] Hydrochloride[4]——L-Tryptophan methyl ester hydrochloride (5.09 g, 20 mmol) was dissolved in MeOH (60 ml), and formalin (35%, 1.89 g, 22 mmol) was added to the solution. The mixture was stirred at room temperarture overnight, and the solvent was evaporated off. The residual solid was crystallized from MeOH to yield (*S*)-**3**·HCl (4.42 g, 82.9%), mp 250—253 °C, $[\alpha]_D^{20}$ −67.2° (*c* = 1.0, MeOH). Compounds (*R*)-**3** and (*RS*)-**3** were prepared in a similar manner [lit.[4] mp 284—285 °C, $[\alpha]_D^{20}$ −62.5° (*c* = 0.4, EtOH)].

Methyl (3*R*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylate [(*R*)-3] Hydrochloride——mp 247—249 °C (MeOH), 79%, $[\alpha]_D^{20}$ +69.6° (*c* = 1.0, MeOH).

Methyl (3*RS*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylate [(*RS*)-3] Hydrochloride[4]——mp 218—222 °C (MeOH), 75% (lit.[4] mp 228—230 °C).

(3*S*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-β-carboline [(*S*)-4]——$NaBH_4$ (10 g, 0.264 mol) was added to a mixture of (*S*)-**3**·HCl (21.0 g, 0.079 mol), EtOH (400 ml), and water (40 ml) under ice-cooling. The mixture was stirred at room temperature for 2 h and then refluxed for 3 h. Insoluble material was filtered off, and washed with hot EtOH, and the filtrate and the washing were concentrated. Water was added to the residue, and a solid was collected, washed with water, and dried. Recrystallization from EtOH gave (*S*)-**4** (12.1 g, 76%), mp 192—193 °C, $[\alpha]_D^{20}$ −83.0° (*c* = 1.0, MeOH). Compounds (*R*)-**4** and (*RS*)-**4** were prepared in a similar manner.

(3*R*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-β-carboline [(*R*)-4]——mp 192—194 °C (EtOH–hexane), 63% $[\alpha]_D^{20}$ +81.9° (*c* = 1.0, MeOH).

(3*RS*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-β-carboline[5] **[(*RS*)-4]**——mp 187—188 °C (iso-PrOH), 64% (lit.[5] mp 168 °C).

(3*R*)-1,2,3,4-Tetrahydro-2-(methylthio)thiocarbonyl-β-carboline-3-carboxylic Acid [(*R*)-2a]——CS_2 (1.82 ml, 30 mmol) was added to a solution of (*R*)-**1** (6.49 g, 30 mmol) and KOH (3.5 g, 60 mmol) in 50% aqueous EtOH (110 ml) under cooling in an ice-bath, and the whole was stirred at room temperature for 1 h. MeI (5.11 g, 36 mmol) was added to the mixture, and the whole was stirred at room temperature for 4 h. After removal of the solvent, the residue was dissolved in H_2O and extracted with ether. The aqueous layer was acidified with 10% HCl and extracted with AcOEt. The extracts were washed with H_2O and dried over $MgSO_4$. The solvent was removed and the residue was purified by chromatography on silica gel using $CHCl_3$–MeOH (97 : 3) as the eluent to give (*R*)-**2a** (5.5 g, 60%), mp 103—106 °C (dec.) (aq. EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1713. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s). MS *m/z*: 306 (M^+), 258 (M^+ − MeSH). The corresponding enantiomer [(*S*)-**2a**] was similarly prepared and its properties are listed in Table I. Various derivatives (**2b**—**p**) listed in Table II were also synthesized in the same manner.

Methyl (3*S*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-β-carboline-2-carbodithioate [(*S*)-5a]——CS_2 (11.65 g, 0.15 mol) was added to a solution of (*S*)-**4** (30.3 g, 0.15 mol) and Et_3N (15.5 g, 0.15 mol) in MeOH (300 ml)–H_2O (80 ml), and the whole was stirred at room temperature for 30 min. MeI (21.73 g, 0.15 mol) was added, and the mixture was stirred at room temperature for 1.5 h. After removal of the solvent, the residue was dissolved in AcOEt, washed with 5% HCl and H_2O, and dried over Na_2SO_4. The solvent was evaporated off to give a solid, which was recrystallized from aqueous EtOH to yield (*S*)-**5a** (42.0 g, 90.2%), mp 114—116 °C. IR ν_{max}^{Nujol} cm^{-1}: 3370, 1630. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s). MS *m/z*: 292 (M^+), 244 (M^+ − MeSH). The corresponding (*R*) and (*RS*) isomers were similarly prepared and their physical properties are listed in Table I. Various derivatives (**5b**—**l**) listed in Table III were also synthesized in essentially the same manner.

Methyl (3*S*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-β-carboline-2-carbodithioate [(*S*)-5a] and (11a*S*)-5,5a,11,11a-Tetrahydro-1*H*,3*H*-oxazolo[4′,3′ : 6,1]pyrido[3,4-*b*]indole-3-thione (6)——A solution of (*S*)-**4** (2.02 g, 10 mmol), 2 N NaOH (15 ml, 30 mmol), and CS_2 (2.33 g, 30 mmol) in 80% EtOH (50 ml) was stirred at 0 °C for 30 min, and then MeI (4.26 g, 30 mmol) was added. After being stirred at 0 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in AcOEt, and this solution was washed with water, and then dried over Na_2SO_4. The solvent was evaporated off to leave an oil, which was chromatographed on silica gel with $CHCl_3$–AcOEt (19 : 1) as the eluent. The oxazolidine (**6**) was eluted first, (980 mg, 40%), mp 236—237 °C (dec.) (AcOEt). IR ν_{max}^{KBr} cm^{-1}: 3400, 3320.

^{1}H-NMR (DMSO-d_6) δ: 2.66 (1H, dd, J=15.0, 9.7 Hz), 3.11 (1H, dd, J=15.0, 3.7 Hz), 4.12 (1H, d, J=17.0 Hz), 5.55 (1H, d, J=17.0 Hz). MS m/z: 244 (M^+), 211, 184. $[\alpha]_D^{20}$ −210.8° (c=1.0, tetrahydrofuran (THF)). *Anal.* Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.69; H, 4.89; N, 11.47; S, 12.95. The next fraction gave (*S*)-**5a** (1.20 g, 41%), mp 114—116 °C (aq. EtOH).

Treatment of (*S*)-5a with KOH——A suspension of (*S*)-**5a** (2.92 g, 10 mmol), 10% KOH (20 ml, 36 mmol), and 80% aqueous EtOH (100 ml) was stirred at room temperature for 3 h. The solvent was evaporated off under reduced pressure, and water was added to the residue. A solid was collected by filtration, washed with water, dried, and recrystallized from AcOEt to give **6** (2.17 g, 88.9%), mp 236—238 °C (dec.). Its spectral data were identical with those of **6** obtained from (*S*)-**4**.

***S*-Methyl *S*-((3*S*)-1,2,3,4-Tetrahydro-β-carbolin-3-yl)-methyl Dithiocarbonate Hydrochloride (7)**——A mixture of (*S*)-**5a** (10.0 g, 34 mmol), 10% HCl (500 ml) and EtOH (300 ml) was refluxed for 3 h and concentrated under reduced pressure. The residual solid was washed with water, dried, and recrystallized from EtOH to give **7** (8.72 g, 82%), mp 221—223 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3230, 2330—2730, 1640. NMR ($CDCl_3$–DMSO-d_6) δ: 2.48 (3H, s), 4.42 (2H, s), 10.79 (1H, s). MS m/z: 292 (M^+), 244, 143. *Anal.* Calcd for $C_{14}H_{16}N_2OS_2 \cdot HCl$: C, 51.13; H, 5.21; Cl, 10.78; N, 8.52; S, 19.50. Found: C, 51.47; H, 5.21; Cl, 11.08; N, 8.69; S, 19.78.

(11a*S*)-5,5a,11,11a-Tetrahydro-1*H*,3*H*-thiazolo[4′,3′:6,1]pyrido[3,4-*b*]indol-3-one (8) and *S*-Methyl (3*S*)-1,2,3,4-Tetrahydro-3-mercaptomethyl-β-carboline-2-carbothioate (9)——A mixture of **7** (2.0 g, 6.4 mmol), sat. aqueous $NaHCO_3$ solution (40 ml), and $CHCl_3$ (30 ml) was stirred at room temperature for 10 min. The $CHCl_3$ layer was separated, washed with water, and dried over $MgSO_4$. The solvent was evaporated off to leave an oil, which was purified by chromatography on silica gel with $CHCl_3$ as the eluent. The thiazolidinone (**8**) was eluted first (0.68 g, 43.3%), mp 228—231 °C (dec.) (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3300 (br), 1640. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 4.10 (1H, m), 4.26 (1H, d, J=17.0 Hz), 5.03 (1H, d, J=17.0 Hz). MS m/z: 244 (M^+), 143. *Anal.* Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.73; H, 4.89; N, 11.57; S, 12.97. The next fraction afforded **9** (0.21 g, 11.2%), mp 157—159 °C (AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3370, 2550, 1640. NMR ($CDCl_3$–DMSO-d_6) δ: 1.47 (1H, t, J=8.0 Hz), 2.41 (3H, s) 3.03 (2H, br s). MS m/z: 292 (M^+), 244, 143. *Anal.* Calcd for $C_{14}H_{16}N_2OS_2$: C, 57.50; H, 5.52; N, 9.58; S, 21.93. Found: C, 57.32; H, 5.42; N, 9.54; S, 22.21.

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