Synthetic Studies of Indoles and Related Compounds. XXVII.[1] A New Synthesis of Crenatine from Ethyl Indole-2-carboxylate[2]

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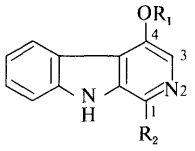
Crenatine (1a), which is a member of a new class of β-carboline alkaloids having an oxygen functionality at the 4-position, was synthesized starting from ethyl 1-benzylindole-2-carboxylate (12a) *via* cyclization of an elaborated C_2-substituent to the 3-position of the indole nucleus and aluminum chloride-catalyzed debenzylation of the protected indolic nitrogen. 1-Ethyl-4-hydroxy-9-methyl-β-carboline (26b), a positional isomer of crenatine with regard to the methyl group, was also synthesized through the same methodology.

Keywords crenatine; ethyl indole-2-carboxylate; indole; β-carboline; cyclization; debenzylation; methylation

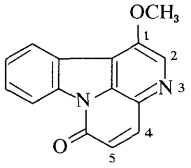
Recently a number of 4-oxygenated β-carboline alkaloids (**1**) have been isolated from Simarubaceae by Ohmoto *et al.*[3a-d] and others.[3e-h] Representative compounds are shown in Table I. Although usual 4-unsubstituted β-carbolines have long been known, the 4-oxygenated ones constitute a new class of β-carbolines. Among them, 4-hydroxy-β-carboline-1-carbaldehyde (**1b**) has been reported[4] to have antitumor and xanthine oxidase-inhibitory activities. However, the biological activities of other compounds have not been examined, probably because of the limited amounts that could be isolated from natural sources. There have been only a few synthetic examples reported by Cook and co-workers, who synthesized crenatine[5] (**1a**) and 1-methoxycanthin-6-one[6] (**1g**) *via* 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation at the 4-position of the β-carboline nucleus as a key step. We now report[2] details of a new synthesis of crenatine (**1a**), which should provide a general synthetic route to these 4-oxygenated β-carboline alkaloids (**1**).

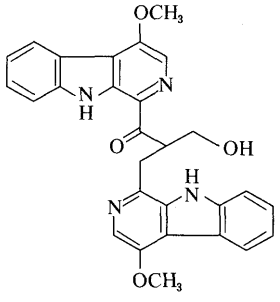
TABLE I. Naturally Occurring 4-Oxygenated-β-carbolines



1a—f

	R_1	R_2
1a	Me	Et (crenatine)
1b	H	CHO
1c	Me	CO_2Me
1d	Me	COMe
1e	Me	$CH(OH)CH_2OH$
1f	Me	$CH=CH_2$

1g: 

1h: 

Trial of Cyclization from the 3- to the 2-Position of the Indole Nucleus for β-Carboline Synthesis At first, we planned to synthesize 4-oxygenated β-carbolines (**1**) *via* the Bischler–Napieralski reaction.[7] However, a direct application of the Bischler–Napieralski reaction to the 3-acylamide (**2**) has been reported[8a,b] to give an oxazole (**4**), but not the desired cyclization product (**3**). As this result shows that the amide part reacted with the 3-acyl part but not with the C_2-position, we tried protection of the 3-acyl group. The conversion of the 3-acylamide (**2**) into the ketal (**5**) was unsuccessful, but the 3-acylamide (**2**) was converted into the thioketal amide (**6**) in reasonable yield. The reaction of the thioketal amide (**6**) with phosphorus oxychloride ($POCl_3$) did not give the expected cyclization product (**7**), but abnormally gave 3-propionylindole (**8**) as a sole product. This compound (**8**) is presumably formed as follows. The amide (**6**) is transformed to the imino phosphate (**9**), which cyclizes toward the C_3-position to yield the spiro intermediate (**10**). In this intermediate (**10**), the older bond of the two at the C_3-position is cleaved to provide a cation (**11**), which is hydrolyzed to 3-propionylindole (**8**). Bischler–Napieralski reaction of indoles was suggested[9] to proceed through a spiro intermediate such as **10** rather than by direct attack at the C_2-position. In the present case, as cleavage of the older bond at the C_3-position in the intermediate (**10**), leading to a more stable cation (**11**), is favored over rearrangement of the newer bond at the C_3-position, a β-carboline skeleton would not be formed. This mechanism has been supported by Cook *et al.*[6a]

Cyclization of the 2-Substituent to the 3-Position to Obtain the β-Carboline Skeleton Thus, we developed a new methodology for construction of 4-oxygenated β-carboline using ethyl indole-2-carboxylates (**12**), on the basis of our studies on the synthetic chemistry of ethyl indole-2-carboxylates.[1,10] The present strategy involves the use of the 2-carboethoxy group of ethyl indole-2-carboxylates (**12**) as a one-carbon unit, and cyclization of the elongated C_2-substituent to the nucleophilic 3-position. It is an advantage that the cyclization also results in the introduction of an oxygen functionality at the 4-position of the β-carboline skeleton. However, this cyclization reaction has a problem as to the direction of cyclization. That is, Johnson *et al.*[11] reported that cyclization of the

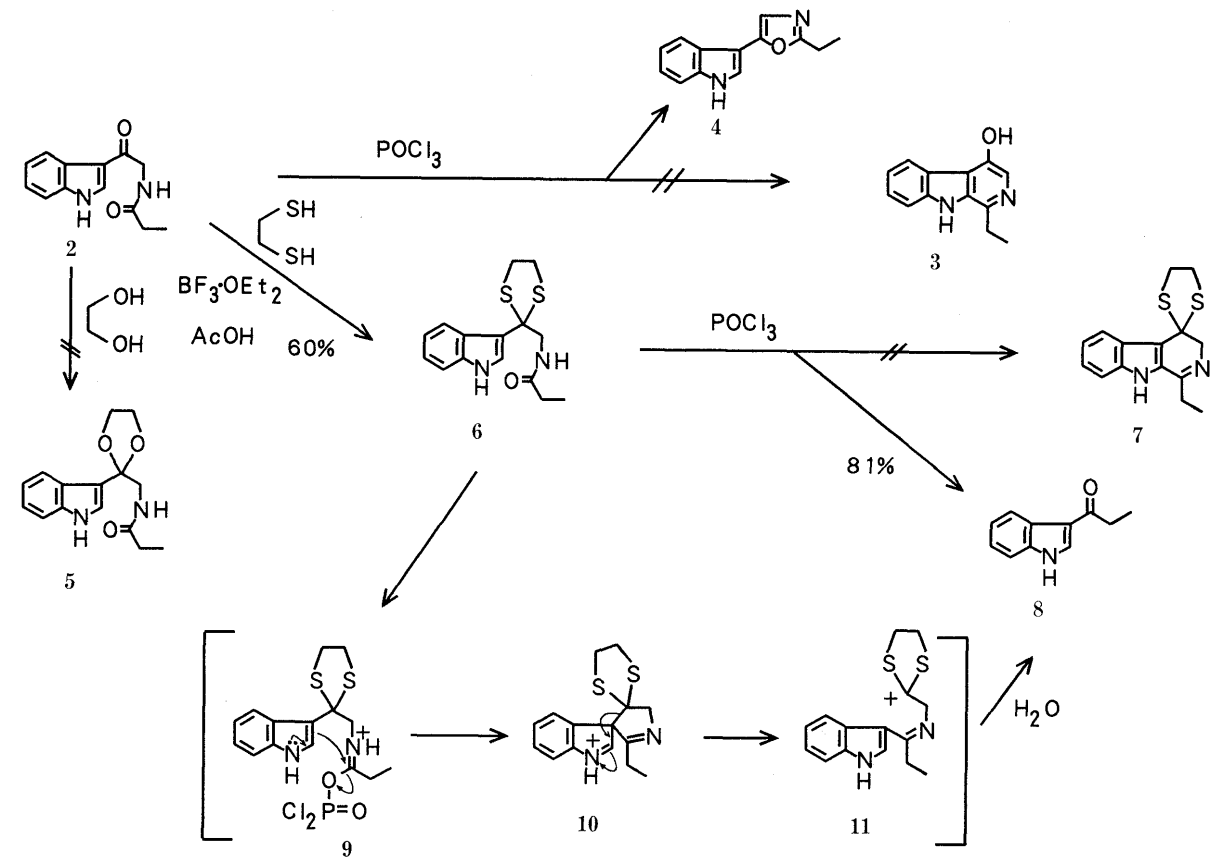


Chart 1

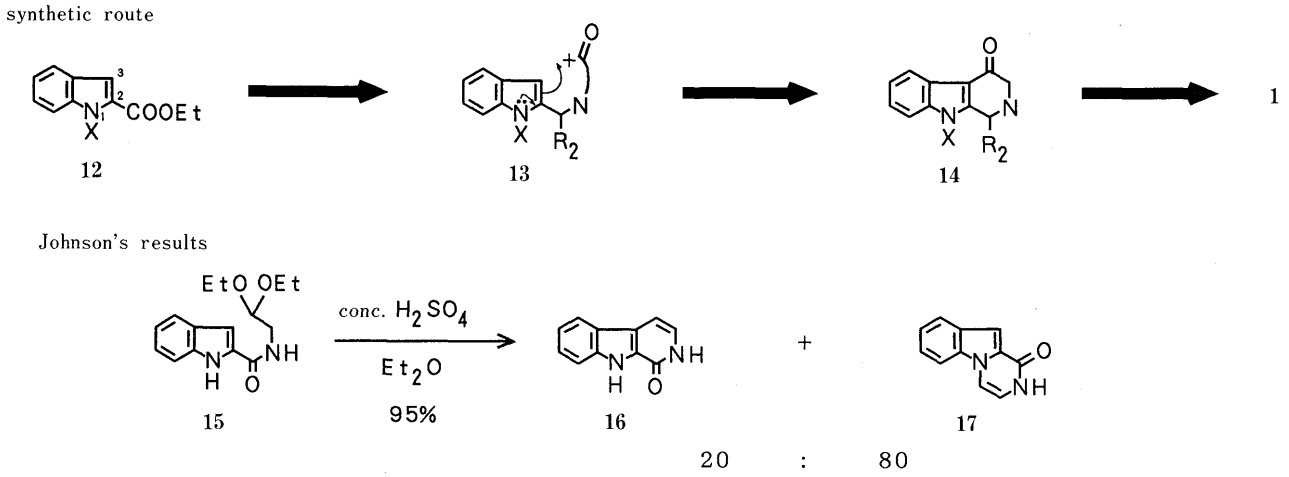


Chart 2

2-acyl compound (**15**) gave the C_3-cyclized product (**16**) as a minor product, and the C_1-cyclized product (**17**) as the major one. Thus, we used ethyl 1-benzyl-1*H*-indole-2-carboxylate (**12a**) as a substrate in order to protect the 1-position. The reason for use of the benzyl group is that the electron-donating 1-benzyl group should make the C_3-position more nucleophilic and that the benzyl group can be removed at any time after cyclization by means of a new and mild method which we had developed for debenzylation of 2-acylindoles.[12]

The 1-benzylindole (**12a**) was allowed to react with ethyl propionate under Claisen condensation conditions to give the keto-ester (**18a**). The keto-ester (**18a**) was, without purification, treated with sulfuric acid to give 1-benzyl-2-propionyl-1*H*-indole (**19a**) (ketone degradation). Conversion of **19a** into the glycinate (**22a**) by treatment with ethyl glycinate *via* formation of the Schiff's base or reductive amination was unsuccessful. The introduction of a nitrogen functionality into the 2-propionylindole (**19a**) to obtain the formamide (**21a**) was achieved by employing the Leuckart reaction under high temperature and pressure, but the yield was variable (8—54%), and the autoclaving procedure was inconvenient. For improvement of this step, the propionylindole (**19a**) was converted to the oxime (**20a**) in a usual manner. The oxime (**20a**) was separable into two geometrical isomers [(*E*)- and (*Z*)-**20a**] but their configuration was not

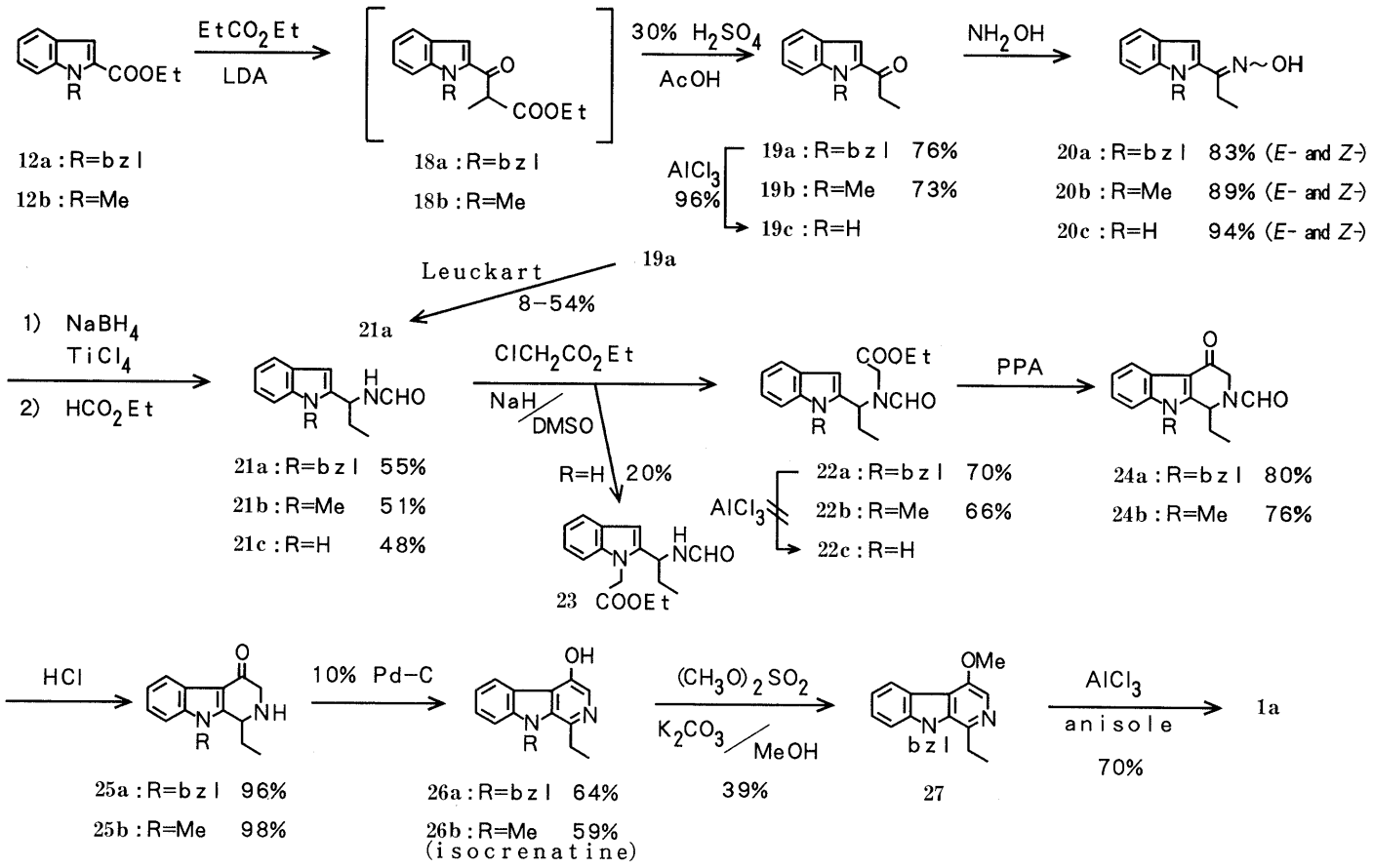


Chart 3

determined. The oxime [**20a**, a mixture of (*E*)- and (*Z*)-] was reduced with sodium borohydride–titanium tetrachloride and the resulting amine was formylated with ethyl formate to give the same formamide (**21a**). This reaction was better than the above-mentioned Leuckart reaction from the viewpoints of easy handling and average yield. The *N*-alkylation of the formamide (**21a**) with ethyl chloroacetate under basic conditions smoothly gave the glycinate (**22a**). Although the glycinate (**22a**) showed a clear single spot on thin layer chromatography (TLC) and a sharp melting point, ^{1}H-nuclear magnetic resonance (^{1}H-NMR) of **22a** showed apparently an equimolar mixture of two isomers (see the experimental section). This can be explained in terms of rotational isomerism due to the formamide moiety. The glycinate (**22a**) was then cyclized with polyphosphoric acid (PPA) to give the cyclic ketone (**24a**).

The cyclization toward the 3-position is inevitable, as the 1-position is blocked by the benzyl group in the glycinate (**22a**). In the case of the cyclization of the 1-unsubstituted substrate (**15**), a mixture of two cyclized products (**16** and **17**) has been obtained.[11] Thus, we were interested in the cyclization direction for the corresponding NH-compound (**22c**) in comparison with that of **15**. Debenzylation of the *N*-benzyl glycinate (**22a**) to prepare the NH-glycinate (**22c**) was unsuccessful. Thus, 1-benzyl-2-propionyl-1*H*-indole (**19a**) was debenzylated to the corresponding NH-compound (**19c**). The reductive amination of **19c** with ethyl glycinate was also unsuccessful. Then 2-propionylindole (**19c**) was treated in the same way as the corresponding 1-benzyl derivative (**19a**) to give the NH-formamide (**21c**). The next alkylation of **21c** with ethyl chloroacetate, however, gave only the 1-alkylated compound (**23**) with recovered starting material (**21c**) (40%), but not the desired glycinate (**22c**). These unsuccessful results show that the protection of indolic NH is appropriate for the present route. The problem of cyclization in the NH-indole series remains to be solved.

The hydrolysis of the cyclic ketone (**24a**) with hydrochloric acid gave the NH-compound (**25a**), which was in turn aromatized with 10% palladium on carbon to give the 4-hydroxy-β-carboline (**26a**) in a reasonable yield. The methylation of the 4-hydroxy-β-carboline (**26a**) was carried out with diazomethane or dimethyl sulfate–base to give the desired methyl ether (**27**). But the best yield was only 39%, although various conditions were examined. The final debenzylation process to obtain crenatine (**1a**) was achieved[13] by application of our method[12] using aluminum chloride in anisole. This synthetic crenatine was identical with the natural one[3b,g] as judged from the ^{1}H-NMR and infrared (IR) spectra, and mixed melting point determination.

Although the ^{1}H-NMR spectrum of our synthetic sample is identical with that of the natural product, Cook's spectrum[5] seems to be slightly different, as shown in Table II. Although the melting point of their sample was the same as that of the natural product, we considered that their sample might be 1-ethyl-4-hydroxy-9-methyl-β-carboline (isocrenatine) (**26b**), which might be formed by unexpected *N*-methylation of 4-demethyl crenatine (**28**) in place of the

TABLE II. Comparison of ^{1}H-NMR Data for Three Kinds of Crenatine (in $CDCl_3$)

^{1}H-NMR ($CDCl_3$) δ (ppm)	Natural **1a** (Sánchez and Comin)[3g]	Synthetic **1a** (Ours)	Synthetic **1a** (Cook *et al.*)[5]	Isocrenatine (**26b**)
OMe	4.10 (3H, s)	4.08 (3H, s)	4.42 (3H, s)	—
N-Me	—	—	—	4.12 (3H, s)
$CH_2\underline{CH}_3$	1.40 (3H, t, J=7 Hz)	1.42 (3H, t, J=7.0 Hz)	1.50 (3H, t, J=8 Hz)	1.47 (3H, t, J=7.6 Hz)
$C\underline{H}_2CH_3$	3.13 (2H, q, J=7 Hz)	3.06 (2H, q, J=7.0 Hz)	3.35 (2H, q, J=8 Hz)	3.42 (2H, q, J=7.6 Hz)
C_3-H	8.00 (1H, s)	7.93 (1H, s)	8.55 (1H, s)	8.18 (1H, s)
C_5-H	8.37 (1H, d, J=7.5 Hz)	8.27 (1H, d, J=8.0 Hz)	8.95 (1H, d, J=8.0 Hz)	8.52 (1H, d, J=8.2 Hz)
mp (°C)	177—179	180—182	174	276—282 (dec.)

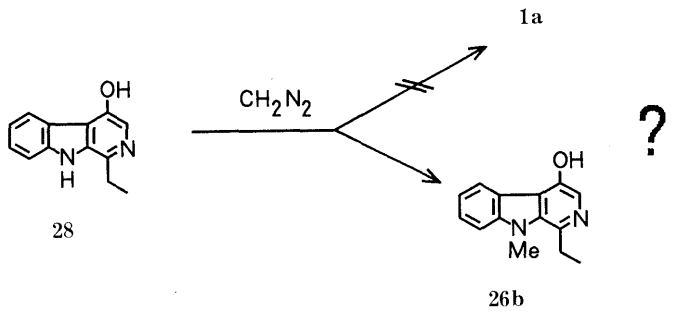


Chart 4

expected *O*-methylation at their final methylation step with diazomethane[5] (Chart 4). This would be consistent with the facts that our 4-hydroxy compound (**26a**) had unexpectedly low reactivity for *O*-methylation and that an *N*- and *O*-bifunctionalized compound[14] was reported to react with diazomethane preferentially at the *N*-position.

In order to clarify this question, we planned a synthesis of isocrenatine (**26b**). The synthesis was carried out in the same way as that of crenatine (**1a**), starting from ethyl 1-methyl-1*H*-indole-2-carboxylate (**12b**), as shown in Chart 3 (b-series). The sequence of reactions from **12b** to **26b** could be carried out in a similar manner to that of the a-series (from **12a** to **26a**). A special feature of the b-series is that the ketone degradation of **18b** to 1-methyl-2-propionyl-1*H*-indole (**19b**) by refluxing of **18b** in a mixture of H_2SO_4 and acetic acid gave a mixture of the desired **19b** and 1-methyl-3-propionyl-1*H*-indole, formed by rearrangement of the 2-propionylindole (**19b**). Milder conditions gave the desired 2-acyl one (**19b**) as the major product. The melting point [mp 276—282 °C (dec.)] and ^{1}H-NMR data of thus prepared isocrenatine (**26b**), shown in Table II, and its solubility in organic solvents are very different from those of crenatine (**1a**). This result clearly shows that Cook's sample was crenatine (**1a**), not isocrenatine (**26b**).

Conclusion

In this paper we present a synthesis of crenatine by a new methodology which involves the use of ethyl 1-benzyl-1*H*-indole-2-carboxylate (**12a**) as the starting material and cyclization from the 2- to the 3-position of the indole nucleus. This type of cyclization has not been much employed for β-carboline synthesis[11] and thus represents a useful supplement to known methods (cyclization from the 3- to the 2-position). During the above sequence, we found that the aluminum chloride-catalyzed debenzylation[12] method for 2-acylindoles developed by us was also effective for β-carboline. We are now investigating the application of this methodology to general synthesis of 1-substituted 4-oxygenated β-carbolines (**1**) and will report the results in the near future.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a Shimadzu IR-400 spectrometer (in Nujol, unless otherwise stated). ^{1}H-NMR spectra were measured on Hitachi R-24B (60 MHz), Hitachi-R 900 (90 MHz), JEOL-4H-100 (100 MHz), and JEOL GX-400 (400 MHz) spectrometers in deuteriochloroform unless otherwise stated, with tetramethylsilane as an internal reference. The data at 60 MHz were recorded, unless otherwise stated. The assignments of NH signals of indoles were confirmed by disappearance of the signals after addition of deuterium oxide, and the protons of the 3-position were identified at the same time, by observing that the broad singlet or doublet signal changed to a sharp singlet signal. Mass spectra (MS) were measured on JEOL JMS-01-SG-2 and JEOL JMS-D 300 spectrometers with a direct inlet system. Column chromatography was carried out over silica gel. For column chromatography, Silica gel 60 (70—230 mesh ASTM, Merck, unless otherwise stated), and for TLC, Silica gel 60 F_{254} (Merck) were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; dif, diffused; Ar: aromatic; BP, base peak.

***N*-[2,2-Ethylenedithio-2-(1*H*-indol-3-yl)ethyl]propionamide (6)** Ethanedithiol (1.7 ml, 20.3 mmol) and boron trifluoride etherate (2.5 ml, 20.3 mmol) were added to a solution of *N*-[2-oxo-2-(1*H*-indol-3-yl)-ethyl]propionamide[8a,b] (**2**) (0.800 g, 3.47 mmol) in acetic acid (15 ml). The mixture was stirred at room temperature for 44 h, then poured into water and extracted with ethyl acetate. The organic layer was washed with 5% NaOH, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography using benzene–ethyl acetate (10 : 1) as a solvent to give the title compound (**6**) (640 mg, 60%). Recrystallization from ethyl acetate–hexane gave colorless needles, mp 153—154 °C. *Anal.* Calcd for $C_{15}H_{18}N_2OS_2$: C, 58.79; H, 5.92; N, 9.14. Found: C, 58.60; H, 5.95; N, 8.96. IR ν_{max} cm^{-1}: 3270 (NH), 1650 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.97 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 2.13 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.45 (4H, s, $SC\underline{H}_2C\underline{H}_2S$), 3.97 (2H, d, J=6.0 Hz, $CC\underline{H}_2N$), 6.9—8.0 (6H, m, Ar-H and NH), 10.9 (1H, br s, NH). MS *m/z*: 306 (M^+, 3%), 220 (BP).

1-(1*H*-Indol-3-yl)-1-propanone (8) $POCl_3$ (0.077 ml, 0.8 mmol) was added to a solution of the thioketal (**6**) (50 mg, 0.16 mmol) in acetonitrile (0.5 ml), and the mixture was stirred at room temperature for 3 h and then at 50 °C for 1.3 h under an argon atmosphere. The reaction mixture was then poured into water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (36 mg) was purified by column chromatography using benzene–ethyl acetate (10 : 1) to give the title compound (**8**) (23 mg, 81%). Recrystallization from benzene gave colorless prisms, mp 173—174 °C. This compound was identical with an authentic sample, (lit.[15] mp 171—173 °C). IR ν_{max} cm^{-1}: 3150 (NH), 1630 (C=O). ^{1}H-NMR δ: 1.26 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 2.92 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 7.2—7.6 (3H, m, $C_{5,6,7}$-H), 7.86 (1H, dif d, J=3.0 Hz, C_2-H), 8.3—8.5 (1H, m, C_4-H), 9.0 (1H, br s, NH). MS *m/z*: 173 (M^+, 31%), 144 (BP).

1-(1-Benzyl-1*H*-indol-2-yl)-1-propanone (19a) A 1.6 M solution of *n*-butyllithium (67 ml, 0.11 mol) in hexane and a solution of hexamethylphosphoramide (HMPA) (18.9 ml, 0.11 mol) in dry tetrahydrofuran

(THF) (10 ml) were added to a solution of diisopropylamine (15.2 ml, 0.11 mol) in dry THF (15 ml) at −78 °C under an argon atmosphere. Ethyl propionate (12.7 ml, 0.11 mol) was added portionwise to the above solution, and the resulting solution was stirred at the same temperature for 10 min. To this solution, a solution of ethyl 1-benzyl-1*H*-indole-2-carboxylate (**12a**) (10.0 g, 35.8 mmol) in dry THF (20 ml) was added portionwise. The mixture was allowed to reach room temperature and stirred for 20 min, then poured into H_2O, neutralized with aqueous NH_4Cl, and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (37.2 g) was column-chromatographed using hexane–ethyl acetate (40 : 1) to give the starting material (**12a**) (3.65 g) and ethyl 2-methyl-3-oxo-3-(1-benzyl-1*H*-indol-2-yl)propionate (**18a**) (12.5 g, contaminated with HMPA) as an oil. ^{1}H-NMR δ: 1.12 (3H, t, J=7.0 Hz, CH_2CH_3), 1.45 (3H, d, J=7.0 Hz, $CHCH_3$), 4.10 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.35 (1H, q, J=7.0 Hz, $COCHCH_3$), 5.84 (2H, s, NCH_2Ph), 6.9—7.5 (9H, m, Ar-H), 7.6—7.9 (1H, m, C_4-H). MS *m/z*: 335 (M^+, 60%), 91 (BP).

This β-keto ester (**18a**) (12.5 g) was, without further purification, added to a solution of concentrated H_2SO_4 (8.8 ml) in a mixture of water (44 ml) and acetic acid (66 ml), and the mixture was refluxed for 1.6 h. The reaction mixture was poured into water and extracted with methylene chloride. The organic layer was washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crystalline residue (7.11 g, 76%) was recrystallized from benzene–hexane to give colorless prisms (6.84 g, 73%), mp 64—66 °C. Further recrystallization from the same solvent gave an analytical sample as colorless prisms, mp 65.5—66 °C. *Anal.* Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.79; H, 6.49; N, 5.33. IR ν_{max} cm^{-1}: 1670 (C=O). ^{1}H-NMR δ: 1.16 (3H, t, J=7.0 Hz, CH_2CH_3), 2.96 (2H, q, J=7.0 Hz, CH_2CH_3), 5.81 (2H, s, NCH_2Ph), 6.9—7.5 (9H, m, Ar-H), 7.6—7.8 (1H, m, C_4-H). MS *m/z*: 263 (M^+, 40%), 91 (BP).

1-(1-Methyl-1*H*-indol-2-yl)-1-propanone (19b) Ethyl 1-methyl-1*H*-indole-2-carboxylate (**12b**) (4.07 g) was allowed to react under the same reaction conditions as used for the benzyl compound (**12a**). Ethyl 2-methyl-3-oxo-3-(1-methyl-1*H*-indol-2-yl)propionate (**18b**) (4.58 g, 88%) was obtained as a yellow oil. IR ν_{max} cm^{-1}: 1735, 1663 (C=O). ^{1}H-NMR δ: 1.18 (3H, t, J=7.0 Hz, CH_2CH_3), 1.49 (3H, d, J=7.0 Hz, $CHCH_3$), 4.01 (3H, s, NCH_3), 4.12 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.19 (1H, q, J=7.0 Hz, $CHCH_3$), 6.9—7.8 (5H, m, Ar-H). The β-keto ester (**18b**) was used for the following reaction without further purification.

The β-keto ester (**18b**) was stirred in a mixture of 30% aqueous H_2SO_4 and acetic acid (2 : 1 v/v) at 80 °C for 6 h.[16] The same work-up gave a crude mixture of products as a yellow oil. Column chromatography using hexane–ethyl acetate (20 : 1 v/v) gave the title compound (**19b**) (3.04 g, 81% from **12b**). Recrystallization from hexane gave pale yellow plates, mp 52—53 °C. *Anal.* Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.07; H, 7.08; N, 7.45. IR ν_{max} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 1.20 (3H, t, J=7.5 Hz, CH_2CH_3), 2.94 (2H, q, J=7.5 Hz, CH_2CH_3), 3.99 (3H, s, NCH_3), 6.9—7.4 (4H, m, Ar-H), 7.5—7.7 (1H, m, C_4-H). MS *m/z*: 187 (M^+, 65%), 158 (BP).

Further elution with the same solvent after obtaining **19b** gave 1-(1-methyl-1*H*-indol-3-yl)-1-propanone (70 mg, 1.9% from **12b**). Recrystallization from hexane gave pale yellow plates, mp 82—83 °C. *Anal.* Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.02; H, 7.00; N, 7.52. IR ν_{max} cm^{-1}: 1640 (C=O). ^{1}H-NMR δ: 1.25 (3H, t, J=7.0 Hz, CH_2CH_3), 2.83 (2H, q, J=7.0 Hz, CH_2CH_3), 3.75 (3H, s, NCH_3), 7.1—7.4 (3H, m, Ar-H), 7.58 (1H, s, C_2-H), 8.1—8.5 (1H, m, C_5-H). MS *m/z*: 187 (M^+, 33%), 158 (BP).

1-(1*H*-Indol-2-yl)-1-propanone (19c) A solution of 1-(1-benzyl-1*H*-indol-2-yl)-1-propanone (**19a**) (2.640 g, 10.0 mmol) in benzene (30 ml) was added to anhydrous $AlCl_3$ (5.350 g, 40.1 mmol) in benzene (20 ml) under an argon atmosphere, and the mixture was stirred at room temperature for 20 min, then added to 5% aqueous $NaHCO_3$ (100 ml). The reaction mixture was stirred for 30 min, and extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residual oil (3.234 g) was column-chromatographed using benzene to give the title compound (**19c**) (1.661 g, 96%). Recrystallization from benzene gave colorless plates, mp 153—154.5 °C. *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.29; H, 6.38; N, 8.07. IR ν_{max} cm^{-1}: 3305 (NH), 1650 (C=O). ^{1}H-NMR δ: 1.29 (3H, t, J=7.5 Hz, CH_2CH_3), 3.00 (2H, q, J=7.5 Hz, $COCH_2CH_3$), 7.0—7.9 (5H, m, Ar-H), 9.2—9.7 (1H, br s, NH). MS *m/z*: 173 (M^+, 50%), 144 (BP).

1-(1-Benzyl-1*H*-indol-2-yl)-1-propanone Oximes [(*E*)- and (*Z*)-20a] 1-(1-Benzyl-1*H*-indol-2-yl)-1-propanone (**19a**) (2.630 g, 10 mmol) was added to a solution of hydroxylamine hydrochloride (1.463 g, 21 mmol) and AcONa (1.666 g, 20 mmol) in water (10 ml) and ethanol (40 ml). The mixture was refluxed for 3 h, then poured into water extracted with benzene, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a yellow oil (3.01 g) which was separated into two oximes, (*E*)- or (*Z*)-**20a** (1.415 g, 51%) and (*Z*)- or (*E*)-**20a** (0.345 g, 12%), by column chromatography using hexane–ethyl acetate (10 : 1 v/v).

The first oxime [(*E*)- or (*Z*)-**20a**] was recrystallized from benzene–hexane to give colorless prisms, mp 129—131 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.89; H, 6.55; N, 9.96. IR ν_{max} cm^{-1}: 3300 (OH). ^{1}H-NMR δ: 1.08 (3H, t, J=7.0 Hz, CH_2CH_3), 2.75 (2H, q, J=7.0 Hz, CH_2CH_3), 5.68 (2H, s, NCH_2Ph), 6.7—7.4 (9H, m, Ar-H and NOH), 6.80 (1H, s, C_3-H), 7.4—7.7 (1H, m, C_4-H). MS *m/z*: 278 (M^+, 44%), 91 (BP).

The second oxime [(*Z*)- or (*E*)-**20a**] was recrystallized from benzene–hexane to give colorless prisms, mp 165—166.5 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.70; H, 6.57; N, 10.06. IR ν_{max} cm^{-1}: 3250 (OH). ^{1}H-NMR δ: 0.91 (3H, t, J=7.0 Hz, CH_2CH_3), 2.36 (2H, q, J=7.0 Hz, CH_2CH_3), 5.30 (2H, s, NCH_2Ph), 6.51 (1H, s, C_3-H), 6.8—7.4 (8H, m, Ar-H), 7.50—7.75 (1H, m, C_4-H), 9.16 (1H, s, NOH). MS *m/z*: 278 (M^+, 44%), 261 and 91 (BP).

A separate experiment gave the oximes [(*E*)- and (*Z*)-**20a**] as a mixture in 83% yield.

1-(1-Methyl-1*H*-indol-2-yl)-1-propanone Oximes [(*E*)- and (*Z*)-20b] 1-(1-Methyl-1*H*-indol-2-yl)-1-propanone (**19b**) (936 mg, 5 mmol) was treated with hydroxylamine hydrochloride (702 mg, 10 mmol) in the same manner as described for the reaction of the benzyl compound (**19a**). The same work-up procedure gave the two oximes, (*E*)- or (*Z*)-**20b** (787 mg, 78%) and (*Z*)- or (*E*)-**20b** (114 mg, 11%).

The first oxime [(*E*)- or (*Z*)-**20b**] was recrystallized from benzene–hexane to give colorless prisms, mp 147—149.5 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.47; H, 6.97; N, 13.63. IR ν_{max} cm^{-1}: 3250 (OH), 1665 (C=N). ^{1}H-NMR δ: 1.21 (3H, t, J=7.0 Hz, CH_2CH_3), 2.82 (2H, q, J=7.0 Hz, CH_2CH_3), 3.88 (3H, s, NCH_3), 6.70 (1H, s, C_3-H), 6.9—7.9 (5H, m, Ar-H and NOH). MS *m/z*: 202 (M^+, 98%), 130 (BP).

The second oxime [(*Z*)- or (*E*)-**20b**] was recrystallized from benzene–hexane to give colorless prisms, mp 158—161 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.46; H, 6.98; N, 13.70. IR ν_{max} cm^{-1}: 3200 (OH), 1645 (C=N). ^{1}H-NMR δ: 1.10 (3H, t, J=7.0 Hz, CH_2CH_3), 2.59 (2H, q, J=7.0 Hz, CH_2CH_3), 3.61 (3H, s, N-CH_3), 6.41 (1H, s, C_3-H), 6.9—7.7 (4H, m, Ar-H), 8.9 (1H, br s, NOH). MS *m/z*: 202 (M^+, 96%), 130 (BP).

1-(1*H*-Indol-2-yl)-1-propanone Oxime (20c) 1-(1*H*-Indol-2-yl)-1-propanone (**19c**) (341 mg, 1.97 mmol) was treated with hydroxylamine hydrochloride (292 mg, 4 mmol) in the same manner as described for the reaction of the benzyl compound (**19a**). The same work-up procedure gave a mixture of two oximes (348 mg, 94%). As it was hard to separate the mixture, the oxime was characterized as the (*E*)- and (*Z*)-mixture.

Recrystallization from benzene gave colorless prisms, mp 102.5—111.5 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.16; H, 6.38; N, 14.53. IR ν_{max} cm^{-1}: 3425 (NH), 1610 (C=N). ^{1}H-NMR δ: 1.27 and 1.31 (totally 3H, t, J=8.0 Hz, CH_2CH_3), 2.79 and 2.81 (totally 2H, q, J=8.0 Hz, CH_2CH_3), 6.74 and 6.77 (totally 1H, s, C_3-H), 6.9—7.8 (totally 4H, m, Ar-H), 8.5 and 8.9 (totally 2H, br s, NH and OH). MS *m/z*: 188 (M^+, BP).

***N*-[1-(1-Benzyl-1*H*-indol-2-yl)propyl]formamide (21a)** a) From the Oxime (**20a**): A solution of 1-(1-benzyl-1*H*-indol-2-yl)-1-propanone oxime [**20a**, a mixture of (*E*)- and (*Z*)-form] (278 mg, 1.0 mmol) in 1,2-dimethoxyethane (2 ml) was added to a solution of $NaBH_4$ (158 mg, 4.2 mmol) and $TiCl_4$[17] (0.23 ml, 2.1 mmol) in 1,2-dimethoxyethane (3 ml) under an argon atmosphere. The mixture was stirred at 50—60 °C for 1.5 h, then the reaction was quenched by adding water (10 ml), and the whole was made alkaline with concentrated NH_4OH, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residual yellow oil (254 mg) of the corresponding amine was treated with ethyl formate (2.5 ml), and the mixture was refluxed for 2 h. After the reaction was complete, the excess ethyl formate was evaporated off *in vacuo* to leave a pale orange oil (254 mg). The oil was purified by column chromatography using hexane–ethyl acetate (2 : 1) to give the title compound (**21a**) as a solid (122 mg, 42%). Recrystallization from benzene gave colorless prisms, mp 148.5—150.5 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.31; H, 6.93; N, 9.30. IR ν_{max} cm^{-1}: 3300 (NH), 1650 (C=O). ^{1}H-NMR δ: 0.87 (3H, t, J=7.0 Hz, CH_2CH_3), 1.6—2.2 (2H, m, $CHCH_2CH_3$), 4.9—5.7 (2H, m, CHNH and NH), 5.32 (2H, s, NCH_2Ph), 6.45 (1H, s,

C_3-H), 6.7—7.4 (8H, m, Ar-H), 7.4—7.8 (1H, m, C_4-H), 7.80 (1H, s, CHO). MS *m/z*: 292 (M^+, 48%), 91 (BP).

b) By Leuckart Reaction: 1-(1-Benzyl-1*H*-indol-2-yl)-1-propanone (**19a**) (3.00 g, 11 mmol) was mixed with formic acid (10 ml), formamide (20 ml), and $(NH_4)_2SO_4$ (600 mg) in an autoclave. The mixture was stirred at 190 °C for 7 h, then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (3.0 g) was purified by column chromatography using ethyl acetate–hexane (1 : 4) to give the title compound (**21a**) (1.82 g, 55%). Recrystallization from benzene gave colorless needles, mp 149—150.5 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.65; H, 6.86; N, 9.33.

***N*-[1-(1-Methyl-1*H*-indol-2-yl)propyl]formamide (21b)** 1-(1-Methyl-1*H*-indol-2-yl)-1-propanone oxime [**20b**, a mixture of (*E*)- and (*Z*)-form] (1.013 g, 5 mmol) was treated with $NaBH_4$ (764 mg, 20 mmol) and $TiCl_4$ (1.1 ml, 10 mmol) in 1,2-dimethoxyethane in the same way as described for the reaction of the benzyl compound (**20a**). Subsequent treatment of the corresponding amine (752 mg) with ethyl formate (12.5 ml) gave the title compound (**21b**) (550 mg, 51% from **21b**). Recrystallization from benzene gave colorless prisms, mp 128—130.5 °C. *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.21; H, 7.46; N, 12.66. IR ν_{max} cm^{-1}: 3240 (NH), 1675, 1650 (C=O). ^{1}H-NMR δ: 1.01 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.7—2.2 (2H, m, $CHC\underline{H}_2CH_3$), 3.61 (3H, s, NCH_3), 5.0—5.5 (1H, m, $C\underline{H}NHCHO$), 5.6—6.0 (1H, m, NH), 6.33 (1H, s, C_3-H), 6.8—7.6 (4H, m, Ar-H), 8.01 (1H, s, CHO). MS *m/z*: 216 (M^+, 81%), 187 (BP).

***N*-[1-(1*H*-Indol-2-yl)propyl]formamide (21c)** 1-(1*H*-Indol-2-yl)-1-propanone oxime (**20c**) (380 mg, 2.0 mmol) was treated with $NaBH_4$ (432 mg, 11.4 mmol) and $TiCl_4$ (0.92 ml, 8.4 mmol) in 1,2-dimethoxyethane in the same way as described for the reaction of the benzyl compound (**20a**). Subsequent treatment of the corresponding amine (277 mg) with ethyl formate (12 ml) gave the title compound (**21c**) (197 mg, 48% from **20c**) as a solid. Recrystallization from benzene–hexane gave colorless prisms, mp 112—114 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.52; H, 7.00; N, 13.70. IR ν_{max} cm^{-1}: 3350, 3300 (NH), 1640 (C=O). ^{1}H-NMR δ: 0.99 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.7—2.3 (2H, m, $CHC\underline{H}_2CH_3$), 4.8—5.3 (1H, m, $CH_2C\underline{H}NH$), 5.8—6.2 (1H, br, NH), 6.29 (1H, brs, C_3-H), 6.9—7.7 (4H, m, Ar-H), 8.1 (1H, brs, CHO), 8.8—9.3 (1H, br, NH). MS *m/z*: 202 (M^+, 97%), 173 and 118 (BP).

Ethyl *N*-[1-(1-Benzyl-1*H*-indol-2-yl)propyl]-*N*-formylaminoacetate (22a) A solution of *N*-[1-(1-benzyl-1*H*-indol-2-yl)propyl]formamide (**21a**) (500 mg, 1.7 mmol) in dimethyl sulfoxide (DMSO) (4 ml) was added slowly to a suspension of 60% NaH (84 mg, 2.1 mmol) under an argon atmosphere. The mixture was stirred at 50 °C for 3 h. To this solution, ethyl chloroacetate (0.552 ml, 5.2 mmol) was added. The reaction mixture was stirred at 90 °C for 4 h, poured into ice-water and extracted with ether. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was column-chromatographed using hexane–ethyl acetate (4 : 1) to give the title compound (**22a**) (450 mg, 70%) after recovery of the starting material (**21a**) (140 mg, 28%). Recrystallization of **22a** from benzene gave colorless prisms, mp 114.5—116 °C. *Anal.* Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.71; H, 7.00; N, 7.38. IR ν_{max} cm^{-1}: 1735; 1680 (C=O). ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 0.71 and 0.88 (totally 6H, each t, J=7.5 Hz, 2×$CH_2C\underline{H}_3$), 1.7—2.1 (2H, m, $CHC\underline{H}_2CH_3$), 3.3—4.0 (4H, m, $OC\underline{H}_2CH_3$ and $COCH_2N$), 4.7—5.1 (1H, m, $NC\underline{H}CH_2$), 5.1—5.6 (2H, m, NCH_2Ph), 6.60 and 6.65 (totally 1H, each s, C_3-H), 6.8—7.3 (8H, m, Ar-H), 7.3—7.6 (1H, m, C_4-H), 8.03 and 8.25 (totally 1H, each s, CHO). MS *m/z*: 378 (M^+, BP).

Ethyl *N*-Formyl-*N*-[1-(1-methyl-1*H*-indol-2-yl)propyl]aminoacetate (22b) *N*-[1-(1-Methyl-1*H*-indol-2-yl)propyl]formamide (**21b**) (216 mg, 1.0 mmol) was treated with 50% NaH (72 mg, 1.5 mmol) and ethyl chloroacetate (0.324 ml, 3 mmol) in the same manner as described for the reaction of the corresponding benzyl compound (**21a**). After work-up, the glycinate (**22b**) (199 mg, 66%) was obtained as a pale yellow oil, with recovery of the starting material (**21b**) (40 mg, 19%). IR ν_{max} cm^{-1}: 1740, 1660 (C=O). ^{1}H-NMR δ: 0.6—1.5 (6H, m, 2×$CH_2C\underline{H}_3$), 1.7—2.3 (2H, m, $CHC\underline{H}_2CH_3$), 3.4—4.4 (7H, m, $OC\underline{H}_2CH_3$, $NC\underline{H}_2CO$, NCH_3), 4.68 and 5.71 (totally 1H, each dif t, J=7.5 Hz, $NC\underline{H}CH_2$), 6.44 and 6.48 (toally 1H, each s, C_3-H), 6.9—7.7 (4H, m, Ar-H), 8.13 and 8.34 (totally 1H, each s, CHO). MS *m/z*: 302 (M^+, BP). High-resolution MS: Calcd for $C_{17}H_{22}N_2O_3$: 302.1625. Found: 302.1644.

***N*-{1-[1-(Ethoxycarbonylmethyl)-1*H*-indol-2-yl]propyl}formamide (23)** A solution of *N*-[1-(1*H*-indol-2-yl)propyl]formamide (**21c**) (79 mg, 0.39 mmol) in dimethylformamide (DMF) (2 ml) was added to a suspension of 60% NaH (24 mg, 0.6 mmol) in DMF (1 ml) under an argon atmosphere. The mixture was stirred at 50 °C for 3.5 h, and, after cooling, ethyl bromoacetate (0.135 ml, 1.2 mmol) was added. The mixture was stirred at room temperature for 50 min and at 50 °C for 30 min, poured into ice-water and extracted with ether. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (134 mg) was column-chromatographed using hexane–ethyl acetate (3 : 1 v/v) to give the title compound (**23**) (22 mg, 20%) and the starting material (**21c**) (32 mg, 40%). Recrystallization of **23** from benzene–hexane gave pale yellow prisms, mp 131—135 °C. IR ν_{max} cm^{-1}: 3280 (NH), 1740, 1640 (C=O). ^{1}H-NMR δ: 1.03 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.26 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.6—2.4 (2H, m, $CHC\underline{H}_2CH_3$), 4.16 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.88 (2H, s, $NC\underline{H}_2CO$), 5.1—5.4 (1H, m, $NC\underline{H}CH_2$), 5.5—6.0 (1H, br, NH), 6.45 (1H, s, C_3-H), 6.9—7.7 (4H, m, Ar-H), 8.01 (1H, dif s, CHO). MS *m/z*: 288 (M^+, 96%), 259 (BP). High-resolution MS: Calcd for $C_{16}H_{20}N_2O_3$: 288.1475. Found: 288.1435.

9-Benzyl-1-ethyl-2-formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (24a) A mixture of ethyl *N*-[1-(1-benzyl-1*H*-indol-2-yl)propyl]-*N*-formylaminoacetate (**22a**) (300 mg, 0.79 mmol) and PPA (10 g) was stirred at 70 °C for 5 h. After cooling, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (326 mg) was separated into each component by column chromatography using hexane–ethyl acetate (2 : 1), the starting material (**22a**) (32 mg, 11%) and the title compound (**24a**) (210 mg, 80%). Recrystallization of **24a** from methanol gave colorless prisms, mp 107—113 °C. *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75;88; H, 6.06; N, 8.43. Found: C, 75.86; H, 6.08; N, 8.50. IR ν_{max} cm^{-1}: 1660, 1640 (C=O). ^{1}H-NMR δ: 1.00 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.5—2.1 (2H, m, $CHC\underline{H}_2CH_3$), 4.18 (2H, s, C_3-H), 5.40 (2H, s, $C\underline{H}_2Ph$), 5.7—6.1 (1H, m, C_1-H), 6.9—7.5 (8H, m, Ar-H), 8.1—8.4 (1H, m, C_5-H), 8.23 (1H, s, CHO). MS *m/z*: 332 (M^+, 47%), 303 (BP).

1-Ethyl-2-formyl-9-methyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (24b) A mixture of ethyl *N*-formyl-*N*-[1-(1-methyl-1*H*-indol-2-yl)propyl]aminoacetate (**22b**) (330 mg, 1.09 mmol) and PPA (4.0 g) was stirred at 75 °C for 40 min. The same work-up procedure as described for the reaction of the benzyl compound (**22a**) gave the title compound (**24b**) (214 mg, 76%). Recrystallization from ethyl acetate gave colorless needles, mp 180—181.5 °C. *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.21; H, 6.32; N, 10.96. IR ν_{max} cm^{-1}: 1675, 1665, 1650 (C=O). ^{1}H-NMR δ: 1.18 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.7—2.2 (2H, m, $CHC\underline{H}_2CH_3$), 3.81 (3H, s, NCH_3), 4.20 (2H, s, C_3-H), 5.88 (1H, t, J=8.0 Hz, C_1-H), 7.2—7.5 (3H, m, Ar-H), 8.1—8.4 (1H, m, C_5-H), 8.25 (1H, s, CHO). MS *m/z*: 256 (M^+, 40%), 227 (BP).

9-Benzyl-1-ethyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (25a) Concentrated HCl (0.5 ml) was added to a solution of 9-benzyl-1-ethyl-2-formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**24a**) (460 mg, 1.38 mmol) in methanol (2.5 ml). The reaction mixture was stirred at 60 °C for 2.5 h, poured into water, made alkaline with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give pale yellow prisms (403 mg, 96%), mp 156—160 °C. Recrystallization from methanol gave colorless needles, mp 165.5—167.5 °C. *Anal.* Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.86; H, 6.69; N, 9.17. IR ν_{max} cm^{-1}: 3335 (NH), 1655 (C=O). ^{1}H-NMR δ: 1.10 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.4—1.9 (2H, m, $CHC\underline{H}_2CH_3$), 2.41 (1H, s, NH), 3.35 and 3.72 (each 1H, d, J=18.0 Hz, C_3-H), 3.96 (1H, dd, J=9.5 and 4.0 Hz, C_1-H), 5.27 (2H, s, $C\underline{H}_2Ph$), 6.9—7.5 (8H, m, Ar-H), 8.1—8.4 (1H, m, C_5-H). MS *m/z*: 304 (M^+, 7%), 91 (BP).

1-Ethyl-9-methyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (25b) Concentrated HCl (0.14 ml) was added to a solution of 1-ethyl-2-formyl-9-methyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**24b**) (100 mg, 0.39 mmol) in methanol (1.0 ml), and the mixture was stirred at 60 °C for 3.5 h. The same work-up procedure as described for the reaction of the benzyl compound (**24b**) gave the title compound (**25b**) as pale brown crystals (87 mg, 98%), mp 179—190 °C. Recrystallization from ethyl acetate gave colorless prisms, mp 198—200 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.66; H, 7.10; N, 12.21. IR ν_{max} cm^{-1}: 3305 (NH), 1635 (C=O). ^{1}H-NMR δ: 1.20 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.5—2.1 (2H, m, $CHC\underline{H}_2CH_3$), 2.38 (1H, s, NH), 3.32 and 3.70 (each 1H, d, J=17.0 Hz, C_3-H), 3.60 (3H, s, NCH_3), 3.8—4.2 (1H, m, $C\underline{H}CH_2CH_3$), 7.2—7.5 (3H, m, Ar-H), 8.1—8.4 (1H, m, C_5-H). MS *m/z*: 228 (M^+, 13%), 199 (BP).

9-Benzyl-1-ethyl-4-hydroxy-β-carboline (26a) A 10% Pd–C catalyst (130 mg) was added to a solution of 9-benzyl-1-ethyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**25b**) (380 mg, 1.25 mmol) in decalin (3 ml), and the mixture was stirred at 140 °C for 8 h. After the reaction was complete, the mixture was filtered under suction, and the residue was washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue (241 mg, 64%) was recrystallized from methanol to give pale brown prisms, mp 230—240 °C. IR ν_{max} cm^{-1}: *ca.* 2500 (br, OH). ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.03 (2H, q, J=7.5 Hz, $CHC\underline{H}_2CH_3$), 5.84 (2H, s, $C\underline{H}_2Ph$), 6.8—7.7 (8H, m, Ar-H), 7.97 (1H, s, C_3-H), 8.38 (1H, d, J=8.0 Hz, C_5-H), 10.1 (1H, br s, OH). MS *m/z*: 302 (M^+, 51%), 91 (BP). High-resolution MS: Calcd for $C_{20}H_{18}N_2O$: 302.1420. Found: 302.1435.

1-Ethyl-4-hydroxy-9-methyl-β-carboline(Isocrenatine) (26b) A mixture of 1-ethyl-9-methyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**25b**) (105 mg, 0.46 mmol) and 10% Pd–C (35 mg) in decalin (2 ml) was stirred at 140 °C for 4 h and at 180 °C for 2 h. After cooling, the reaction mixture was directly column-chromatographed using methylene chloride–methanol (20 : 1 v/v) to give pale brown crystals (61 mg, 59%), mp 260—270 °C (dec.). Recrystallization from methanol gave pale brown prisms, mp 276—282 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.13; H, 6.32; N, 12.24. IR ν_{max}^{KBr} cm^{-1}: 3600—3300 (OH). ^{1}H-NMR (400 MHz) δ: shown in Table II. MS *m/z*: 226 (M^+, BP).

9-Benzyl-1-ethyl-4-methoxy-β-carboline (27) Powdered K_2CO_3 (237 mg, 1.71 mmol) and dimethyl sulfate (0.132 ml, 1.40 mmol) were added to a solution of 9-benzyl-1-ethyl-4-hydroxy-β-carboline (**26a**) (100 mg, 0.33 mmol) in methanol (2.5 ml), and the mixture was stirred at 64 °C for 10 min. After cooling, the reaction mixture was made alkaline with concentrated NH_4OH and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was column-chromatographed using hexane–ethyl acetate (2 : 1 v/v) to give the title compound (**27**) as a solid (41 mg, 39%). Recrystallization from methanol gave colorless prisms, mp 107—115 °C. IR: no characteristic band. ^{1}H-NMR (90 MHz) δ: 1.31 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.08 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 4.14 (3H, s, OCH_3), 5.73 (2H, s, $C\underline{H}_2Ph$), 6.8—7.5 (8H, m, Ar-H), 8.02 (1H, s, C_3-H), 8.37 (1H, d, J=8.0 Hz, C_5-H). MS *m/z*: 316 (M^+, BP). High-resolution MS: Calcd for $C_{21}H_{20}N_2O$: 316.1577. Found: 316.1602.

The 4-hydroxy compound (**26a**) was methylated to **27** with diazomethane in a mixed solvent of ethyl acetate and ether in 30% yield.

1-Ethyl-4-methoxy-β-carboline (Crenatine) (1a) A solution of 9-benzyl-1-ethyl-4-methoxy-β-carboline (**27**) (26 mg, 0.082 mmol) in anisole (2 ml) was added to $AlCl_3$ (250 mg, 1.87 mmol) under ice-cooling in an argon atmosphere. The reaction mixture was stirred at room temperature for 23 h, poured into ice-water and extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. Removal of the solvent *in vacuo* left the residue, which was purified by column-chromatography using hexane–ethyl acetate (1 : 1 v/v) to give crenatine as crystals (13 mg, 70%). Recrystallization from ethanol gave colorless leaflets, mp 180—182 °C. *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.34; H, 6.32; N, 12.38. IR ν_{max}^{KBr} cm^{-1}: 3420 (br, NH). ^{1}H-NMR (90 MHz): shown in Table II. MS *m/z*: 226 (M^+, BP). High resolution MS: Calcd for $C_{14}H_{14}N_2O$: 226.1107. Found: 226.1103.

The synthetic crenatine was identical with the natural product[3a] in all respects including mixed melting point experiment.

References and Notes

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