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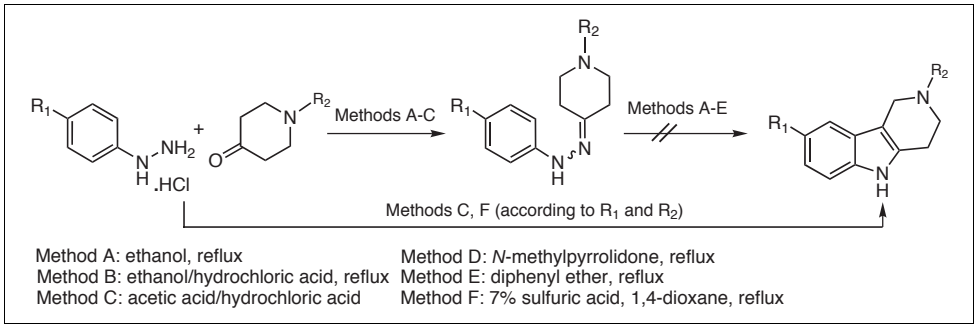
Received July 8, 2005



The Fischer reaction is applied to the synthesis of 8-substituted tetrahydro-γ-carbolines with electron-donating or electron-withdrawing groups, using catalytic or thermal methods. The reaction conditions must be varied according to the nature of the *N* 1 substituent of the piperidone. The best results are observed when a releasing group is present on the arylhydrazine and a benzyl substituent on the nitrogen of piperidone. Formation of carbolines with a withdrawing substituent is observed in soft acidic conditions; in others, reaction ended at the hydrazone level or did not evolve.

J. Heterocyclic Chem., **43**, 571 (2006).

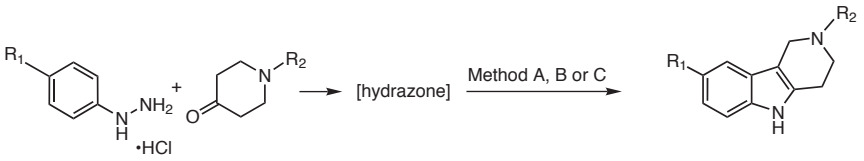
Introduction.

Over the years, a number of reports have shown that γ-carbolines – or pyrido[4,3-*b*]indoles – have various biological activities in antipsychotic [1], antibiotic [2] and antitumor [3] fields, although studies of their chemical activities are limited compared to those of β-carbolines – or pyrido[3,4-*b*]indoles – structurally related to tryptophan and serotonin. γ-Carbolines can be synthesized using various methods like the Graebe-Ullmann procedure [4], Pictet-Spengler cyclization, Fischer annulation [5], ring closure of aldimine [6], Suzuki-type reaction [7], intramolecular Diels-Alder reaction [8] or Pd-catalyzed annulation of alkynes [5]. In the course of our project directed towards the development of new antitumor compounds, we have envisaged the synthesis of new tetrahydro-γ-carbolines *via* the most widely used method, the Fischer reaction [9]. They constitute a scaffold possessing three potential sites of reactivity and of modulation, the carbon atoms of the homocycle and the nitrogen atoms of the pyrrole and of the piperidine. As for indole, the synthesis of tetrahydro-γ-carbolines proceeds through a [3,3] sigmatropic rearrangement followed by cyclization and elimination of ammonia. Regioselectivity is only observed when the intermediate arylhydrazone comes from a symmetrical substituted γ-piperidone. Electron donor groups have previously been investigated as substituents of the benzo cycle [10], but our interest focused on the design of tetrahydro-γ-carbolines possessing electron withdrawing substituents on C 8 and a free reactive site on piperidine nitrogen. The influence of the *N*-protective group of 4-piperidone on the course of cyclization was also studied as well as the conditions required for its feasibility.

Chemistry.

The aim of this work was access to γ-carbolines using, if possible, a limited number of one-pot procedures as well as easily reproducible acidic conditions. The Fischer synthesis of indole [11] is by far the most widely used method to synthesize this condensed heterocycle [1,10-15]. We applied this principle to prepare tetrahydro-carbolines **7**-**11** (Scheme 1) by reacting equimolar quantities of substituted arylhydrazines **1**-**5** with *N*-protected-4-piperidones **6a**,**b**,**d** or 4-piperidone hydrochloride **6c**, in a nitrogen atmosphere, according to different cyclization conditions (methods A, B or C), thereby bypassing isolation of the arylhydrazone intermediate. Carbolines **7b**, **8b**, **8c**, **9b**, **9c**, **11b**, **11c** were obtained thermally according to an unlikely free-radical mechanism (method A: ethanol reflux, 2 hours) in 55-95% yields (Table 1). Cyclization into compounds **7c**, **8a**, **9a**, **10a**, **10b** was best obtained and gave good yields (61-92%) in a saturated hydrochloric acid-ethanol refluxing solution (method B: 3 hours), compared to other Lewis acid catalysts already described such as boron trifluoride, polyphosphoric acid, cuprous or zinc chloride [16]. This acid-catalyzed Fischer reaction is initiated by the

Scheme 1



1-5 **6a-d** **7a-c**, **8a-c**, **9a-c**, **10a**,**b**, **11a-c**

1,**7** R_1 = OMe **a** R_2 = Bn
2,**8** R_1 = F **b** R_2 = COOEt
3,**9** R_1 = Br **c** R_2 = H
4,**10** R_1 = SMe **d** R_2 = Boc
5,**11** R_1 = H

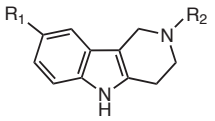
Method A: ethanol, reflux
Method B: ethanol/hydrochloric acid, reflux
Method C: acetic acid/hydrochloric acid

conventional mechanism involving the rupture of the *N-N* bond of low energy and a Cope rearrangement.

Whatever the method used (A or B) for preparing tetrahydrocarbolines **7b**-**9c**, yields ranged from good to high whereas **7a** resulted from cyclization in hydrochloric medium only (88% yield) [15] at room temperature (method C), following formation *in situ* of the corresponding phenylhydrazone in glacial acetic acid. More difficulties were encountered for the synthesis of carbolines **10** possessing a SMe substituent. It should be noted that **10a**,**b** and **10c** were synthesized following methods B and C, whereas none of these compounds were obtained according to method A (thermal conditions) and synthesis of **10d** was unsuccessful using any of the three methods. This may be explained by the fact that starting materials **4** and **6d** were insoluble in the reaction medium, even under reflux conditions. Whereas compound **11a** was synthesized by method C (71% yield), **11b** and **11c** were synthesized according to method A in 95 and 80% yields, respectively. The best yields as regards cyclization (Table 1) combine a *p*-releasing group (R_1) and a benzyl group (R_2) which increase the basicity of the piperidone nitrogen; these contradict previous conclusions where an *N*-carbethoxy group was found to favor Fischer cyclization [10].

Table 1

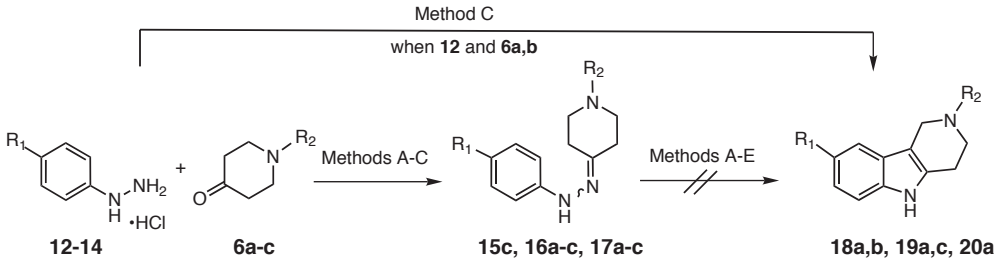
Tetrahydropyrido[4,3-*b*]indoles **7**-**11**, **18**-**20**



Compd	R_1	R_2	Method	Yield (%)
*7a	OMe	Bn	C	88
*7b	OMe	COOEt	A	60
**7c	OMe	H	B	75
**8a	F	Bn	B	82
*8b	F	COOEt	A	55
**8c	F	H	A	88
**9a	Br	Bn	B	92
*9b	Br	COOEt	A	55
**9c	Br	H	A	70
*10a	SMe	Bn	B	88
*10b	SMe	COOEt	B	61
*10c	SMe	H	C	20
10d	SMe	Boc	none	-
*11a	H	Bn	C	71
*11b	H	COOEt	A	95
**11c	H	H	A	80
**18a	NO_2	Bn	C	20
*18b	NO_2	COOEt	C	3
***19a	SO_2Me	Bn	F	65
***19c	SO_2Me	H	F	65
***20a	SO_2NH_2	Bn	F	70

*: base; **: hydrochloride; ***: sulfate; Methods A-C: see Scheme 1; Method F: 7% sulfuric acid, 1,4-dioxane, 80°.

Scheme 2



12-14 **6a-c** **15c, 16a-c, 17a-c** **18a,b, 19a,c, 20a**

12, **15**, **18** R_1 = NO_2 **a** R_2 = Bn
13, **16**, **19** R_1 = SO_2Me **b** R_2 = COOEt
14, **17**, **20** R_1 = SO_2NH_2 **c** R_2 = H

Methods A-C: see Scheme 1
Method D: N-methylpyrrolidone, reflux
Method E: diphenyl ether, reflux
Method F: see Table 1

When R_2 = H, cyclization into **7c**, **8c**, **9c**, **11c** also gave fairly good yields (70-88%) while they have been obtained in a two-step procedure involving hydrolysis of the carbethoxy *N*-protective group [10].

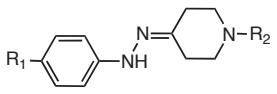
Lastly, we undertook the preparation of tetrahydrocarbolines possessing an electron withdrawing group R_1, such as NO_2, SO_2Me or SO_2NH_2. With the exception of the 8-nitro tetrahydrocarbolines **18a**, **18b** from method C, and whatever the conditions used (methods A-C, method D: refluxing in *N*-methylpyrrolidone or method E: refluxing in diphenyl ether [17], sulfuric acid-hydrochloric acid or polyphosphoric acid) or the nature of substituent R_2, reaction stopped at the hydrazone step to give compounds **15c**, **16**, **17** (Scheme 2, Table 2).

This method has until now been the only way to obtain 8-nitro-1,2,3,4-tetrahydro-γ-carbolines. It offers the best access to **18b**, since nitration (sodium nitrite/ trifluoroacetic acid) [18] failed on tetrahydrocarboline **11b**, while corresponding carbolines were synthesized by electrophilic aromatic nitration [4], and reduction of the pyridine system remain versatile.

Low yields observed for preparation of tetrahydrocarbolines **18a**,**b** or formation of hydrazones **15c**, **16**, **17** can be attributed to the strong withdrawing and deactivating effect of the substituent on carbon 8 conjugated with hydrazine: the tautomeric hydrazone-enehydrazine equilibrium is displaced toward the former in strong acidic medium *via* a *N* 4 – C 3 proton transfer [19] (Scheme 3) or even in thermal conditions and competes with Cope cyclization.

Table 2

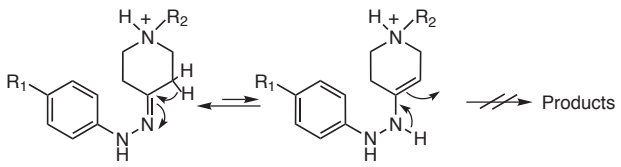
Arylhydrazones **15c**, **16**, **17**



Compd	R_1	R_2	Method	Yield (%)
*15c	NO_2	H	A	85
**16a	SO_2Me	Bn	C	90
**16b	SO_2Me	COOEt	A	90
*16c	SO_2Me	H	A	95
**17a	SO_2NH_2	Bn	C	90
*17b	SO_2NH_2	COOEt	A	72
**17c	SO_2NH_2	H	B	95

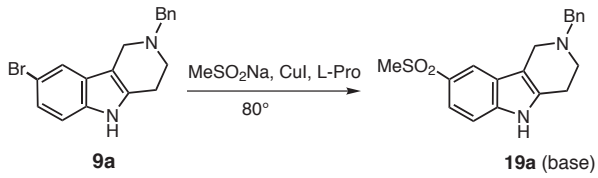
*: hydrochloride; **: base; Methods A, C: see Scheme 1.

Scheme 3



Finally, milder acidic conditions [20] (Method F: 7% sulfuric acid, 1,4-dioxane, 80°) led to sulfones **19a**, **19c**, **20a** with similar yields as did methods A-C, without the formation of tetrahydrocarboline **18a**,**b**. A structural proof for **19a** was given (Scheme 4) by a coupling reaction of

Scheme 4



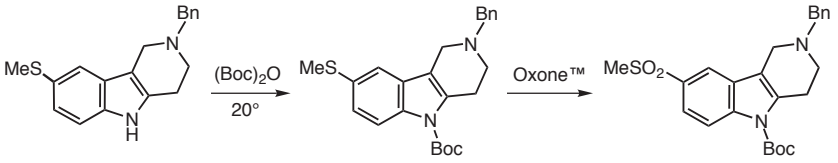
8-bromotetrahydrocarboline **9a** with sodium methanesulfonate catalyzed by a mixture of cuprous iodide/L-Pro [21]. Several attempts at direct sulfide oxidation of the 8-SMe moiety of carboline **10a** using Oxone™ [22], *m*-chloroperbenzoic acid [23], magnesium monoperoxyphtalate [24], potassium permanganate [25], periodic oxide [26] or hydrogen peroxide [27] failed, presumably due to the instability of the electron rich indole part [28]. Previous protection (and deactivation) of the nitrogen indole [29] of **10c** as carbamate (**21**) made it difficult to obtain Oxone™ oxidation of the thioether into the corresponding sulfone **22** (Scheme 5).

Even if the Fischer reaction has been shown to be versatile toward indole or other heterocycles synthesis, its use in γ-carboline formation has given either low yields without forced thermal conditions or activated pyridine use [4], or none. This study has proved, that unlike what has been stated, the formation of tetrahydro-γ-carbolines bearing a strong electron-withdrawing substituent on C 8 is possible, depending on the nature of the piperidone *N*-protective group. These results indicate the scope and the generality of the Fischer reaction in γ-carboline synthesis which greatly depends on the concentration of the acidic catalyst used.

EXPERIMENTAL

Moisture-sensitive reactions were performed in dry nitrogen. Analytical tlc was performed on precoated Kieselgel $60F_{254}$ plates (Merck). Compounds were visualized by uv and/or with iodine. Flash chromatography was performed with silica gel Kieselgel Si 60, 0.040-0.063 mm (Merck). Melting points were determined with a Büchi 535 capillary melting point apparatus and remain uncorrected. The structure of all compounds are supported by ir spectra on a Brucker Vector 22 instrument and ^{1}H nmr spectrum at 300 MHz on a Brucker DPX-300 spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane, J values are in Hertz, and the splitting

Scheme 5



10a **21** **22**

patterns are designed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. APCI$^+$ (atmospheric pressure chemical ionization) mass spectra were obtained on an lc-ms system Thermo Electron Surveyor MSQ. 4-Substituted phenylhydrazines were purchased from commercial suppliers with the exception of the methylthio derivative **4** which was prepared as reported [30].

General Procedures for the Preparation of Tetrahydropyrido[4,3-*b*]-indoles and Arylhydrazones.

Method A.

A mixture of 4-substituted phenylhydrazine hydrochloride (1 mmol) and appropriate 4-piperidone derivative (1 mmol) in ethanol (30 mL) was heated at reflux for 2 hours. The precipitate that formed was collected by filtration and recrystallized.

Method B.

A solution of 4-substituted phenylhydrazine hydrochloride (1 mmol) and appropriate 4-piperidone derivative (1 mmol) was stirred in dry hydrochloric acid–saturated ethanol (30 mL). The reaction mixture was heated at reflux for 3 hours. After standing overnight at room temperature, the solid was collected by filtration or the solution was made basic with 10% aqueous potassium carbonate solution and extracted with ethyl acetate. After concentration, the residue was either filtered or purified on a silica gel column and recrystallized.

Method C.

Appropriate 4-piperidone (1 mmol) was added dropwise to a stirred suspension of 4-substituted phenylhydrazine hydrochloride (1 mmol) in glacial acetic acid (100 mL). The solution was then stirred at room temperature for 2 hours before saturated dry hydrochloric acid–glacial acetic acid was added. The solution was made basic with 10% aqueous potassium carbonate solution. The product that precipitated was filtered or the solution was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. The residual oil was purified by chromatography on silica gel.

Method D.

Appropriate arylhydrazone **16a**,**b** and **17a**,**b** (1 mmol) was dissolved in *N*-methylpyrrolidone (10 mL) and heated at reflux for 24 hours. The solution was diluted in water, stirred for 1 hour and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under vacuum. In every case, the starting product was recovered.

Method E.

Appropriate arylhydrazone **16a**,**b** and **17a**,**b** (1 mmol) was dissolved in diphenyl ether (10 mL) and heated at reflux for 24 hours. Monitoring by tlc indicated a degradation of the starting product or traces of γ-carboline.

Method F.

1-Benzyl-4-piperidone (0.2 mL, 1 mmol) was added dropwise to a stirred suspension of 4-substituted phenylhydrazine hydrochloride (1 mmol) in a solution of 7% concentrated sulfuric acid (20 mL) in 1,4-dioxane (20 mL). The mixture was heated at reflux for 18 hours then cooled to room temperature. The solvent was evaporated and the organic product was filtered and recrystallized.

Ethyl 1,3,4,5-Tetrahydro-8-methoxy-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**7b**).

This compound was obtained at 60% yield according to method A; mp 160° (ethanol 95%) lit [10] 159-160°; R_f = 0.49 (methylene dichloride:methanol+ammonia, 9:1, v/v); orange solid; ir (neat): 3305 (NH), 1670 (C=O) cm^{-1}; uv: λ max 250 nm; ^{1}H nmr (DMSO-d_6): δ 1.22 (t, J = 7.3 Hz, 3H, CH_3), 2.77 (m, 2H, CH_2), 3.72 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 4.10 (q, J = 7.3 Hz, 2H, CH_2), 4.55 (s, 2H, CH_2), 6.67 (dd, J = 2.3, 8.5 Hz, 1H, CH), 6.93 (s, 1H, CH), 7.17 (d, J = 8.5 Hz, 1H, CH), 10.73 (b, 1H, NH); ms: m/z 275 (M+H)$^+$.

Ethyl 8-Fluoro-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**8b**).

This compound was obtained at 55% yield according to method A; mp 169° (ethanol) lit [10] 169-170°; R_f = 0.74 (methylene dichloride:methanol+ammonia, 9:1, v/v); orange solid; ir (neat): 3278 (NH), 1672 (C=O) cm^{-1}; uv: λ max 255 nm; ^{1}H nmr (DMSO-d_6): δ 1.21 (t, J = 7.0 Hz, 3H, CH_3), 2.78 (t, J = 5.2 Hz, 2H, CH_2), 3.73 (t, J = 5.6 Hz, 2H, CH_2), 4.09 (q, J = 7.0 Hz, 2H, CH_2), 4.55 (s, 2H, CH_2), 6.85 (td, J = 2.1, 9.3 Hz, 1H, CH), 7.19 (dd, J = 2.1, 9.3 Hz, 1H, CH), 7.27 (dd, J = 4.7, 8.8 Hz, 2H, CH), 7.36 (b, 1H, NH); ms: m/z 263 (M+H)$^+$.

8-Fluoro-2,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole Monohydrochloride (**8c**).

This compound was obtained at 88% yield according to method A; mp > 230° (ethanol) lit [1] 259-261°; R_f = 0.05 (methylene dichloride:methanol+ammonia, 9:1, v/v); bordeaux solid; ir (neat): 3208 (NH$^+$) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.03 (s, 2H, CH_2), 3.44 (s, 2H, CH_2), 4.25 (s, 2H, CH_2), 7.11 (m, 3H, CH), 9.47 (b, 1H, NH), 11.34 (b, 1H, NH$^+$); ms: m/z 191 (M-HCl+H)$^+$.

Ethyl 8-Bromo-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**9b**).

This compound was obtained at 55% yield according to method A; mp 193° (ethanol 95%) lit [10] 192-193°; R_f = 0.86 (methylene dichloride:methanol+ammonia, 9:1, v/v); brown

solid; ir (neat): 3284 (NH), 1665 (C=O) cm^{-1}; uv: λ max 245 nm; ^1H nmr (DMSO-d_6): δ 1.21 (t, J = 7.3 Hz, 3H, CH_3), 2.79 (t, J = 5.5 Hz, 2H, CH_2), 3.73 (t, J = 5.5 Hz, 2H, CH_2), 4.41 (q, J = 7.3 Hz, 2H, CH_2), 4.55 (s, 2H, CH_2), 7.13 (dd, J = 1.7, 8.5 Hz, 2H, CH), 7.25 (d, J = 8.5 Hz, 1H, CH), 7.62 (d, J = 1.5 Hz, 1H, CH), 11.15 (b, 1H, NH); ms: m/z 323 $(M)^+$, 325 $(M+2)^+$.

8-Bromo-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole Monohydrochloride (**9c**).

This compound was obtained at 70% yield according to method A; mp > 230° (ethanol) lit [31] 282-284°; R_f = 0.63 (methylene dichloride:methanol+ammonia, 9:1, v/v); brown solid; ir (neat): 3222 (NH^+) cm^{-1}; uv: λ max 240 nm; ^1H nmr (DMSO-d_6): δ 3.03 (t, J = 5.2 Hz, 2H, CH_2), 3.42 (t, J = 5.2 Hz, 2H, CH_2), 4.24 (s, 2H, CH_2), 7.32 (m, 2H, CH), 7.68 (s, 1H, CH), 9.79 (b, 2H, NH), 11.55 (b, 1H, NH^+); ms: m/z 250 $(M-HCl-H)^+$, 252 $(M-HCl+H)^+$.

Anal. Calcd. for $C_{11}H_{11}BrN_2$•HCl: C, 45.94; H, 4.21; N, 9.74. Found: C, 46.02; H, 4.45; N, 9.51.

Ethyl 1,3,4,5-Tetrahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**11b**).

This compound was obtained at 95% yield according to method A; mp 121° (ethanol 95%) lit [10] 121-123°; R_f = 0.68 (methylene dichloride:methanol, 9:1, v/v); orange solid; ir (neat): 3300 (NH), 1667 (C=O) cm^{-1}; uv: λ max 265 nm; ^1H nmr (deuteriochloroform): δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 2.86 (t, J = 5.8 Hz, 2H, CH_2), 3.87 (t, J = 5.8 Hz, 2H, CH_2), 4.21 (q, J = 7.1 Hz, 2H, CH_2), 4.71 (s, 2H, CH_2), 7.15 (m, 2H, CH), 7.32 (d, J = 7.8 Hz, 1H, CH), 7.47 (d, J = 7.1 Hz, 1H, CH), 7.88 (b, 1H, NH); ms: m/z 245 $(M+H)^+$.

2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indole Monohydrochloride (**11c**).

This compound was obtained at 80% yield according to method A; mp > 230° (ethanol); R_f = 0.34 (ethyl acetate:ethanol, 9:1, v/v); white solid; ir (neat): 3293 (NH^+) cm^{-1}; uv: λ max 275 nm; ^1H nmr (deuteriochloroform): δ 2.47 (m, 2H, CH_2), 2.94 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 6.67 (m, 2H, CH), 6.97 (m, 2H, CH), 9.69 (b, 1H, NH^+); ms: m/z 214 $(M-HCl+CH_3CN+H)^+$.

Anal. Calcd. for $C_{11}H_{12}N_2$•HCl: C, 63.31; H, 6.28; N, 13.42. Found: C, 63.50; H, 6.14; N, 13.12.

4-Piperidinone 4-Nitrophenylhydrazone Monohydrochloride (**15c**).

This compound was obtained at 85% yield according to method A; mp > 230° (ethanol 95%); R_f = 0.10 (methanol); yellow solid; ir (neat): 3221 (NH^+), 1305 (NO_2) cm^{-1}; uv: λ max 395 nm; ^1H nmr (DMSO-d_6): δ 2.64 (t, J = 6.1 Hz, 2H, CH_2), 2.84 (t, J = 6.1 Hz, 2H, CH_2), 3.25 (m, 4H, CH_2), 7.20 (d, J = 9.4 Hz, 2H, CH_2), 8.10 (d, J = 9.4 Hz, 2H, CH), 9.31 (b, 2H, NH), 10.37 (b, 1H, NH^+); ms: m/z 235 $(M-HCl+H)^+$, 276 $(M-HCl+CH_3CN+H)^+$.

Anal. Calcd. for $C_{11}H_{14}N_4O_2$•HCl: C, 48.80; H, 5.58; N, 20.70. Found: C, 48.65; H, 5.68; N, 20.81.

1-Ethoxycarbonylpiperidinone 4-Methanesulfonylphenylhydrazone (**16b**).

This compound was obtained at 90% yield according to method A; mp 166° (methanol); R_f = 0.69 (methylene dichloride:methanol, 9:1, v/v); yellow solid; ir (neat): 3325 (NH), 1690 (C=O), 1296 (SO_2CH_3), 1140 (SO_2CH_3) cm^{-1}; uv: λ max 265 nm; ^1H nmr (DMSO-d_6): δ 1.21 (t, J = 7.1 Hz, 3H, CH_3), 2.43 (t, J = 6.1 Hz, 2H, CH_2), 2.57 (t, J = 6.1 Hz, 2H, CH_2), 3.08 (s, 3H, CH_3), 4.07 (q, J = 7.1 Hz, 2H, CH_2), 7.66 (d, J = 8.7 Hz, 2H, CH), 7.81 (d, J = 8.7 Hz, 2H, CH); ms: m/z 340 $(M+H)^+$, 381 $(M+CH_3CN+H)^+$.

Anal. Calcd. for $C_{15}H_{21}N_3O_4S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 52.73; H, 6.12; N,. 12.56.

4-Piperidinone 4-Methanesulfonylphenylhydrazone Monohydrochloride (**16c**).

This compound was obtained at 95% yield according to method A; mp 189° (methanol); R_f = 0.10 (methanol); yellow solid; ir (neat): 3328 (NH^+), 1292 (SO_2CH_3), 1143 (SO_2CH_3) cm^{-1}; uv: λ max 300 nm; ^1H nmr (DMSO-d_6): δ 2.63 (t, J = 5.9 Hz, 2H, CH_2), 2.83 (t, J = 5.9 Hz, 2H, CH_2), 3.09 (s, 3H, CH_3), 3.23 (m, 4H, CH_2), 7.23 (d, J = 8.8 Hz, 2H, CH), 7.68 (d, J = 8.8 Hz, 2H, CH), 9.44 (b, 2H, NH), 9.99 (b, 1H, NH^+); ms: m/z 268 $(M-HCl+H)^+$.

Anal. Calcd. for $C_{12}H_{17}N_3O_2S$•HCl•0.5H_2O: C, 46.03; H, 6.07; N, 13.43. Found: C, 46.27; H, 5.96; N, 13.59.

1-Ethoxycarbonylpiperidinone 4-Sulfamoylphenylhydrazone Monohydrochloride (**17b**).

This compound was obtained at 72% yield according to method A; mp 187° (ethanol); R_f = 0.84 (methylene dichloride: ethyl acetate, 1:1, v/v); yellow solid; ir (neat): 3663 (NH^+), 1713 (C=O), 1322 (SO_2NH_2), 1155 (SO_2NH_2) cm^{-1}; uv: λ max 290 nm; ^1H nmr (DMSO-d_6): δ 1.19 (t, J = 6.6 Hz, 3H, CH_3), 2.42 (t, J = 6.0 Hz, 2H, CH_2), 2.53 (t, J = 5.9 Hz, 2H, CH_2), 3.50 (m, 4H, CH_2), 4.06 (q, J = 6.6 Hz, 2H, CH_2), 7.11 (d, J = 8.8 Hz, 2H, CH), 7.59 (d, J = 8.8 Hz, 2H, CH); ms: m/z 341 $(M-HCl+H)^+$.

Anal. Calcd. for $C_{14}H_{20}N_4O_4S$•HCl: C, 44.62; H, 5.62; N, 14.87. Found: C, 44.77; H, 5.75; N, 14.82.

4-Piperidinone 4-Sulfamoylphenylhydrazone (**17c**).

This compound was obtained at 95% yield according to method B; mp 200° (isopropyl alcohol); R_f = 0.50 (methylene dichloride:methanol, 9:1, v/v); yellow solid; ir (neat): 3191 (NH), 3072 (NH), 1713 (C=O), 1322 (SO_2NH_2), 1155 (SO_2NH_2) cm^{-1}; uv: λ max 290 nm; ^1H nmr (DMSO-d_6): δ 1.89 (s, 4H, CH_2), 1.96 (s, 4H, CH_2), 7.02 (b, 2H, NH_2), 7.12 (d, J = 8.5 Hz, 2H, CH), 7.60 (d, J = 8.5 Hz, 2H, CH), 9.16 (b, 1H, NH); ms: m/z 269 $(M+H)^+$.

Anal. Calcd. for $C_{11}H_{16}N_4O_2S$•0.25H_2O: C, 48.38; H, 6.05; Found: C, 48.70; H, 6.02.

2,3,4,5-Tetrahydro-8-methoxy-1*H*-pyrido[4,3-*b*]indole Monohydrochloride (**7c**).

This compound was obtained at 75% yield according to method B; mp > 230° (ethanol) lit [31] > 250°; R_f = 0.49 (methylene dichloride:methanol+ammonia, 9:1, v/v); white solid; ir (neat): 3302 (NH^+) cm^{-1}; uv: λ max 230 nm; ^1H nmr (DMSO-d_6): δ 3.00 (m, 2H, CH_2), 3.39 (m, 2H, CH_2), 3.73 (s, 3H, CH_3), 4.21 (s, 2H, CH_2), 6.70 (d, J = 8.6 Hz, 1H, CH), 6.98 (s, 1H, CH), 7.22 (d, J = 8.6 Hz, 1H, CH), 9.82 (b, 2H, NH), 11.14 (b, 1H, NH^+); ms: m/z 203 $(M-HCl+H)^+$.

Anal. Calcd. for $C_{12}H_{14}N_2O$•HCl: C, 60.38; H, 6.33; N, 11.73. Found: C, 60.11; H, 5.95; N, 11.86.

8-Fluoro-2,3,4,5-tetrahydro-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]-indole Monohydrochloride (**8a**).

This compound was obtained at 82% yield according to method B; mp > 230° (methanol) lit [32] 245.5-246.5°; R_f = 0.47

(methylene dichloride:methanol+ammonia, 9:1, v/v); white solid; ir (neat): 3150 (NH^+) cm^{-1}; uv: λ max 255 nm; ^1H nmr (DMSO-d_6): δ 3.16 (m, 2H, CH_2), 3.38 (m, 2H, CH_2), 3.69 (m, 1H, NH), 4.28 (m, 2H, CH_2), 4.49 (m, 2H, CH_2), 6.91 (td, J = 2.3, 9.3 Hz, 1H, CH), 7.21 (dd, J = 2.0, 9.3 Hz, 1H, CH), 7.33 (dd, J = 2.0, 2.3 Hz, 1H, CH), 7.48 (m, 3H, CH), 7.70 (m, 2H, CH), 11.42 (b, 1H, NH), 11.47 (b, 1H, NH^+); ms: m/z 281 $(M-HCl+H)^+$.

8-Bromo-2,3,4,5-tetrahydro-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]-indole Monohydrochloride (**9a**).

This compound was obtained at 92% yield according to method B; mp > 230° (ethanol); R_f = 0.53 (methylene dichloride:methanol, 9:1, v/v); brown solid; ir (neat): 3207 (NH^+) cm^{-1}; uv: λ max 235 nm; ^1H nmr (methanol-d_4): δ 3.41 (t, J = 6.1 Hz, 2H, CH_2), 3.50 (s, 2H, CH_2), 3.87 (t, J = 6.1 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 7.43 (m, 2H, CH), 7.75 (m, 6H, CH); ms: m/z 341 $(M-HCl)^+$, 343 $(M-HCl+2)^+$.

2,3,4,5-Tetrahydro-8-methylthio-2-(phenylmethyl)-1*H*-pyrido-[4,3-*b*]indole (**10a**).

This compound was obtained at 88% yield according to method B; chromatography eluent: cyclohexane:ethyl acetate (4:1, v/v); mp 187° (ethanol 95%); R_f = 0.68 (methylene dichloride:methanol, 9:1, v/v); brown solid; ir (neat): 3144 (NH) cm^{-1}; uv: λ max 240 nm; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 2.78 (m, 2H, CH_2), 2.89 (t, J = 5.2 Hz, 2H, CH_2), 3.71 (s, 2H, CH_2), 3.82 (s, 2H, CH_2), 7.15 (s, 1H, CH), 7.37 (m, 7H, CH), 8.04 (b, 1H, NH); ms: m/z 309 $(M+H)^+$.

Anal. Calcd. for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.39; N,8.87.

Ethyl 2,3,4,5-Tetrahydro-8-methylthio-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**10b**).

This compound was obtained at 61% yield according to method B; chromatography eluent: cyclohexane:ethyl acetate (4:1, v/v); R_f = 0.57 (methylene dichloride:ethyl acetate, 1:1, v/v); oil; ir (neat): 3291 (NH), 1668 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.32 (t, J = 7.0 Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.83 (t, J = 5.1 Hz, 2H, CH_2), 3.86 (m, 2H, CH_2), 4.22 (q, J = 7.0 Hz, 2H, CH_2), 4.68 (s, 2H, CH_2), 7.22 (m, 2H, CH), 7.45 (s, 1H, CH), 8.02 (b, 1H, NH); ms: m/z 291 $(M+H)^+$.

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.85; H, 6.16; N, 9.48.

2,3,4,5-Tetrahydro-8-methoxy-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]-indole (**7a**).

This compound was obtained at 88% yield according to method C; mp 120° (ethanol 95%) lit [15] 119-120°; R_f = 0.56 (methylene dichloride:methanol, 9:1, v/v); brown solid; ir (neat): 3387 (NH) cm^{-1}; uv: λ max 270 nm; ^1H nmr (deuteriochloroform): δ 2.82 (d, J = 5.1 Hz, 2H, CH_2), 2.90 (t, J = 5.1 Hz, 2H, CH_2), 3.72 (s, 2H, CH_2), 3.82 (s, 2H, CH_2), 3.84 (s, 3H, CH_3), 6.77 (dd, J = 2.2, 8.7 Hz, 1H, CH), 6.84 (s, 1H, CH), 7.15 (d, J = 8.7 Hz, 1H, CH), 7.39 (m, 5H, CH), 7.77 (b, 1H, NH); ms: m/z 293 $(M+H)^+$.

2,3,4,5-Tetrahydro-8-methylthio-1*H*-pyrido[4,3-*b*]indole (**10c**).

This compound was obtained at 20% yield according to method C; R_f = 0.11 (methylene dichloride:methanol, 4:1, v/v); brown oil; ir (neat): 3670 (NH) cm^{-1}; uv: λ max 235 nm; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 2.79 (m, 2H, CH_2), 3.24 (b, 2H, CH_2), 4.07 (s, 1H, CH_2), 7.20 (m, 2H, CH), 7.41 (s, 1H, CH), 8.08 (b, 1H, NH); ms: m/z 219 $(M+H)^+$, 260 $(M+CH_3CN+H)^+$.

Anal. Calcd. for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.98; H, 6.24; N, 12.97.

2,3,4,5-Tetrahydro-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]indole (**11a**).

This compound was obtained at 71% yield according to method C; mp 159° (ethanol 95%) lit [15] 158-159°; R_f = 0.43 (methylene dichloride:methanol, 9:1, v/v); white solid; ir (neat): 3377 (NH) cm^{-1}; uv: λ max 265 nm; ^1H nmr (deuteriochloroform): δ 2.80 (m, 4H, CH_2), 3.71 (s, 2H, CH_2), 3.83 (s, 2H, CH_2), 7.30 (m, 8H, CH), 7.73 (b, 1H, NH); ms: m/z 263 $(M+H)^+$.

2,3,4,5-Tetrahydro-8-nitro-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]-indole Monohydrochloride (**18a**).

This compound was obtained at 20% yield from hydrazine **12** (base), according to method C; the precipitate obtained after reaction with hydrochloric acid-glacial acetic acid was directly recrystallized; mp > 230° (ethanol:water, 1:1, v/v); R_f = 0.61 (methylene dichloride:methanol+ammonia, 9:1, v/v); yellow solid; ir (neat): 3088 (NH^+), 1336 (NO_2) cm^{-1}; uv: λ max 255 nm; ^1H nmr (DMSO-d_6): δ 2.89-3.27 (m, 2H, CH_2), 3.55 (m, 2H, CH_2), 4.40 (m, 2H, CH_2), 4.53 (m, 2H, CH_2), 7.51 (m, 4H, CH), 7.69 (m, 2H, CH), 8.02 (m, 1H, CH), 8.53 (s, 1H, CH), 11.25 (b, 1H, NH), 12.10 (s, 1H, NH^+); ms: m/z 308 $(M-HCl+H)^+$.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$•HCl: C, 62.88; H, 5.28; N, 12.22. Found: C, 62.63; H, 5.33; N, 12.21.

Ethyl 1,3,4,5-Tetrahydro-8-nitro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**18b**).

This compound was obtained at 3% yield from hydrazine **12** (base), according to method C; chromatography eluent: methylene dichloride:ethyl acetate (9:1, v/v); the oil was diluted in chloroform and precipitated from a mixture isopropyl alcohol-ethyl ether; mp 200° (ethanol); R_f = 0.52 (methylene dichloride: ethyl acetate, 1:1, v/v); yellow solid; ir (neat): 3249 (NH), 1658 (C=O) cm^{-1}; uv: λ max 255 nm; ^1H nmr (deuteriochloroform): δ 1.36 (t, J = 7.3 Hz, 3H, CH_3), 2.92 (m, 2H, CH_2), 3.92 (m, 2H, CH_2), 4.23 (q, J = 7.3 Hz, 2H, CH_2), 4.75 (s, 2H, CH_2), 7.35 (d, J = 8.8 Hz, 1H, CH), 8.11 (dd, J = 2.3, 9.0 Hz, 1H, CH), 8.28 (b, 1H, NH), 8.45 (d, J = 2.3 Hz, 1H, CH); ms: m/z 290 $(M+H)^+$, 331 $(M+CH_3CN+H)^+$.

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.03; H, 5.36; N, 14.41.

1-(Phenylmethyl)-4-piperidinone 4-Methanesulfonylphenyl-hydrazone (**16a**).

This compound was obtained at 90% yield according to method C; mp 169° (ethanol 95%); R_f = 0.34 (methylene dichloride:methanol, 9:1, v/v); yellow solid; ir (neat): 3331 (NH), 1299 (SO_2CH_3), 1133 (SO_2CH_3) cm^{-1}; uv: λ max 290 nm; ^1H nmr (deuteriochloroform): δ 2.57 (m, 8H, CH_2), 3.02 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 7.11 (d, J = 8.7 Hz, 2H, CH), 7.33 (m, 5H, CH), 7.52 (b, 1H, NH), 7.74 (d, J = 8.7 Hz, 2H, CH); ms: m/z 358 $(M+H)^+$.

Anal. Calcd. for $C_{19}H_{23}N_3O_2S$: C, 63.84; H, 6.49; N, 11.75. Found: C, 63.58; H, 6.54; N, 11.82.

1-(Phenylmethyl)-4-piperidinone 4-Sulfamoylphenylhydrazone (**17a**).

This compound was obtained at 90% yield according to method C; mp 199° (ethanol 95%); R_f = 0.17 (methylene dichloride:methanol, 9:1, v/v); orange solid; ir (neat): 3262 (NH), 1315 (SO_2NH_2), 1158 (SO_2NH_2) cm^{-1}; uv: λ max 270 nm; ^1H nmr (DMSO-d_6): δ 2.35 (m, 4H, CH_2), 2.50 (m, 4H, CH_2), 3.53 (m, 2H, CH_2), 7.02 (b, 2H, NH_2), 7.08 (d, J = 8.8 Hz, 2H, CH), 7.33 (m, 5H, CH), 7.58 (d, J = 8.8 Hz, 2H, CH), 9.45 (b, 1H, NH); ms: m/z 359 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_{22}N_4O_2S$: C, 60.31; H, 6.19; N, 15.63 Found: C, 60.70; H, 6.45; N, 15.29.

2,3,4,5-Tetrahydro-8-methanesulfonyl-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]indole Monosulfate (**19a**).

This compound was obtained at 65% yield according to method F; mp > 230°; R_f = 0.61 (methylene dichloride: methanol, 9:1, v/v); brown solid; ir (neat): 3346 (NH^+), 1294 (SO_2CH_3), 1141 (SO_2CH_3) cm^{-1}; uv: λ max 240 nm; ^1H nmr (DMSO-d_6): δ 2.91 (m, 4H, CH_2), 3.21 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.02 (s, 2H, CH_2), 7.29-7.61 (m, 6H, CH), 7.63 (dd, J = 1.5, 7.5 Hz, 1H, CH), 8.00 (d, J = 1.2 Hz, 1H, CH), 8.53 (b, 1H, NH); ms: m/z 341 $(M+H)^+$.

The Preparation of 2,3,4,5-Tetrahydro-8-methanesulfonyl-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]indole (**19a**, base).

Bromo derivative **9a** (0.3 g, 1 mmol), sodium methanesulfonate (0.3 g, 1.2 mmol), copper iodide (0.05 g, 0.1 mmol), L-proline (0.06 g, 0.5 mmol) and sodium hydroxide (0.01 g, 0.2 mmol) were heated in dimethylsulfoxide at 80°. After 48 hours, the cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residual oil was purified by column chromatography (ethyl acetate:ethanol, 9:1, v/v) and carboline was obtained at 60% yield; mp = 186° (methanol); R_f = 0.43 (methylene dichloride:methanol, 9:1, v/v); yellow solid; ir (neat): 3346 (NH), 1340 (SO_2CH_3), 1149 (SO_2CH_3) cm^{-1}; uv: λ max 240 nm; ^1H nmr (deuteriochloroform): δ 2.92 (m, 4H, CH_2), 3.06 (s, 3H, CH_3), 3.72 (s, 2H, CH_2), 3.82 (s, 2H, CH_2), 7.46 (m, 6H, CH), 7.64 (dd, J = 1.5, 7.5 Hz, 1H, CH), 8.00 (d, J = 1.2 Hz, 1H, CH), 8.38 (b, 1H, NH); ms: m/z 341 $(M+H)^+$.

Anal. Calcd. for $C_{19}H_{20}N_2O_2S•0.25H_2O$: C, 66.16; H, 5.95; N, 8.12. Found: C, 66.08; H, 6.06; N, 8.20.

2,3,4,5-Tetrahydro-8-methanesulfonyl-1*H*-pyrido[4,3-*b*]indole Monosulfate (**19c**).

This compound was obtained at 65% yield according to method F; mp 182° (methanol); yellow solid; R_f = 0.56 (methylene dichloride:methanol, 9:1, v/v); ir (neat): 3207 (NH^+), 1279 (SO_2CH_3), 1124 (SO_2CH_3) cm^{-1}; uv: λ max 240 nm; ^1H nmr (DMSO-d_6): δ 3.07 (m, 2H, CH_2), 3.15 (s, 3H, CH_3), 3.50 (m, 2H, CH_2), 4.41 (m, 2H, CH_2), 7.59 (m, 2H, CH), 8.12 (s, 1H, CH), 9.10 (b, 1H, NH^+); ms: m/z 251 $(M+H)^+$, 292 $(M+CH_3CN+H)^+$.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S•0.5H_2SO_4$: C, 48.15; H, 5.03; N, 9.36. Found: C, 48.44; H, 4.98; N, 9.02.

2,3,4,5-Tetrahydro-2-(phenylmethyl)-8-sulfamoyl-1*H*-pyrido-[4,3-*b*]indole Monosulfate (**20a**).

This compound was obtained at 70% yield according to method F; mp > 230° (acetonitrile:water, 1:1); R_f = 0.32 (methylene dichloride:ethyl acetate+ammonia, 1:9, v/v); white solid; ir (neat): 3251 (NH^+), 1320 (SO_2NH_2), 1152 (SO_2NH_2) cm^{-1}; uv: λ max 235 nm; ^1H nmr (DMSO-d_6): δ 2.97 (m, 2H, CH_2), 3.23 (m, 2H, CH_2), 3.97 (s, 2H, CH_2), 4.07 (b, 2H, NH_2), 4.13 (s, 2H, CH_2), 7.08 (s, 2H, CH), 7.46 (m, 5H, CH), 7.81 (s, 1H, CH), 9.96 (s, 1H, NH), 11.49 (b, 1H, NH^+); ms: m/z 342 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_{19}N_3O_2S•0.5H_2SO_4•1.5H_2O$: C, 51.78; H, 5.15; N, 10.07. Found: C, 51.48; H, 5.39; N, 10.02.

The Preparation of 5-*tert*-Butoxycarbonyl-2,3,4,5-tetrahydro-8-methylthio-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]indole (**21**).

DMAP (0.46 g, 3.8 mmols) was added dropwise to carboline **10a** (1.2 g, 3.8 mmols) dissolved in acetonitrile (25 mL). After stirring for 2 hours, di-*tert*-butyl dicarbonate (0.83 g, 3.8 mmols) was added portionwise. After 2 more hours, the suspension was filtered, the solvent was removed and the residual oil was chromatographed on silical gel (methylene dichloride:ethyl acetate, 9:1, v/v) to give a white solid at 32% yield; mp 181°; R_f = 0.56 (methylene dichloride:ethyl acetate, 9:1, v/v); ir (neat): 1731 (C=O) cm^{-1}; uv: λ max 255 nm; ^1H nmr (deuteriochloroform): δ 1.68 (m, 9H, CH_3), 2.99 (t, J = 5.3 Hz, 2H, CH_2), 3.09 (s, 3H, CH_3), 3.87 (m, 2H, CH_2), 4.21 (q, J = 7.1 Hz, 2H, CH_2), 4.71 (m, 2H, CH_2), 7.20 (m, 1H, CH), 7.24 (m, 1H, CH), 8.04 (m, 1H, CH); ms: m/z 409 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{28}N_2O_2S$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.81; H, 6.80; N, 6.95.

The Preparation of 5-*tert*-Butoxycarbonyl-2,3,4,5-tetrahydro-8-methanesulfonyl-2-(phenylmethyl)-1*H*-pyrido[4,3-*b*]indole (**22**).

Oxone™ (potassium peroxymonosulfate) (1.5 g, 2.5 mmols) in water (10 mL) was added dropwise to a well stirred cooled solution (0°) of carboline **21** in methanol (10 mL). After 30 min, the solution was extracted with chloroform, dried over magnesium sulfate before the solvent was evaporated. The residual oil was chromatographed on silica gel (ethyl acetate:ethanol, 9:1, v/v) to give a white solid at 10% yield; mp 190°; R_f = 0.54 (methylene dichloride:methanol, 9:1, v/v); ir (neat): 1734 (C=O), 1291 (SO_2CH_3), 1141 (SO_2CH_3) cm^{-1}; uv: λ max 235 nm; ^1H nmr (deuteriochloroform): δ 1.67 (s, 9H, CH_3), 2.90 (t, J = 5.5 Hz, 2H, CH_2), 3.07 (s, 3H, CH_3), 3.16 (m, 2H, CH_2), 3.65 (s, 2H, CH_2), 3.81 (s, 2H, CH_2), 7.36 (m, 5H, CH), 7.79 (dd, J = 1.8, 8.8 Hz, 1H, CH), 7.91 (d, J = 1.8 Hz, 1H, CH), 8.34 (d, J = 8.8 Hz, 1H, CH); ms: m/z 441 $(M+H)^+$.

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.01; H, 5.36; N, 14.64.

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