SYNTHESIS AND REACTIVITY OF 2-(1,3-DITHIAN-2-YL)INDOLES II[1]

SYNTHESIS OF 2-ACYLINDOLE DERIVATIVES

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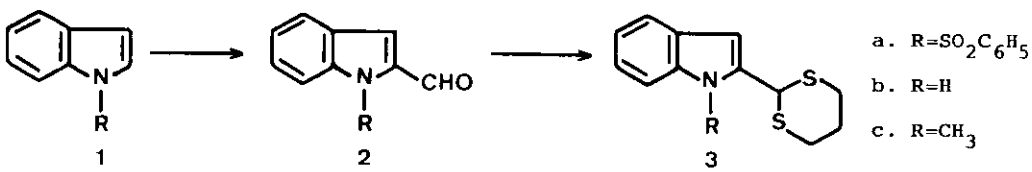
Abstract- Some reactions of the anions (**4b** and **4c**) derived from indole dithianes **3b** and **3c** respectively, towards aldehydes, ketones, α,β-unsaturated ketones, alkyl halides, and epoxides are reported.

In a previous paper[1] we reported a study concerning the reactivity of the anions derived from the indole dithianes **3a** and **3b** towards a series of electrophiles. In this respect, the anion derived from **3a** was ineffective whereas the dianion **4b**, derived from **3b**, gave good yields of C-2 disubstituted dithianes. The required indole dithiane **3b** was prepared by reaction of 2-lithio-1-(phenylsulfonyl)indole with 2-chloro-1,3-dithiane followed by deprotection of the indole nitrogen.

We present here some additional reactions of the dianion **4b** that further illustrate the potential of this indolic synthon and a comparative study of the reactivity of the anions (**4b** and **4c**) derived from **3b** and **3c** respectively, towards electrophiles, especially carbonyl compounds. Some of the products prepared in this way could be further elaborated into indole alkaloids and related systems. Thus, compounds 5, 19, and 20 (see Table I) possess the



Scheme I

2-(4-piperidylmethyl)indole moiety present in uleine and dasycarpidone as well as in Strychnos alkaloids, whereas compounds **6** and **7** have the 2-(3-pyridylethyl)- and 2-(4-pyridylethyl)indole unit characteristic of Aspidosperma alkaloids and ervitsine, respectively.

In this work, the indole dithianes **3a** and **3c** were prepared in 88% and 80% yields, respectively, by thioacetalization of the corresponding aldehydes **2a** and **2c** with 1,3-propanedithiol in the presence of p-toluenesulfonic acid (Scheme I). In turn, aldehyde **2a** was obtained according to the Gribble procedure[2] by reaction of 2-lithio-1-(phenylsulfonyl)indole with DMF. Similarly, aldehyde **2c** was obtained in 66% yield operating from 1-methylindole (**1c**).[3] This classical but effective two-step procedure allows the preparation of **3a** and **3c** from the corresponding 1-substituted indoles **1a** and **1c** in 71% and 53% overall yield, respectively, in a 20-gram scale.

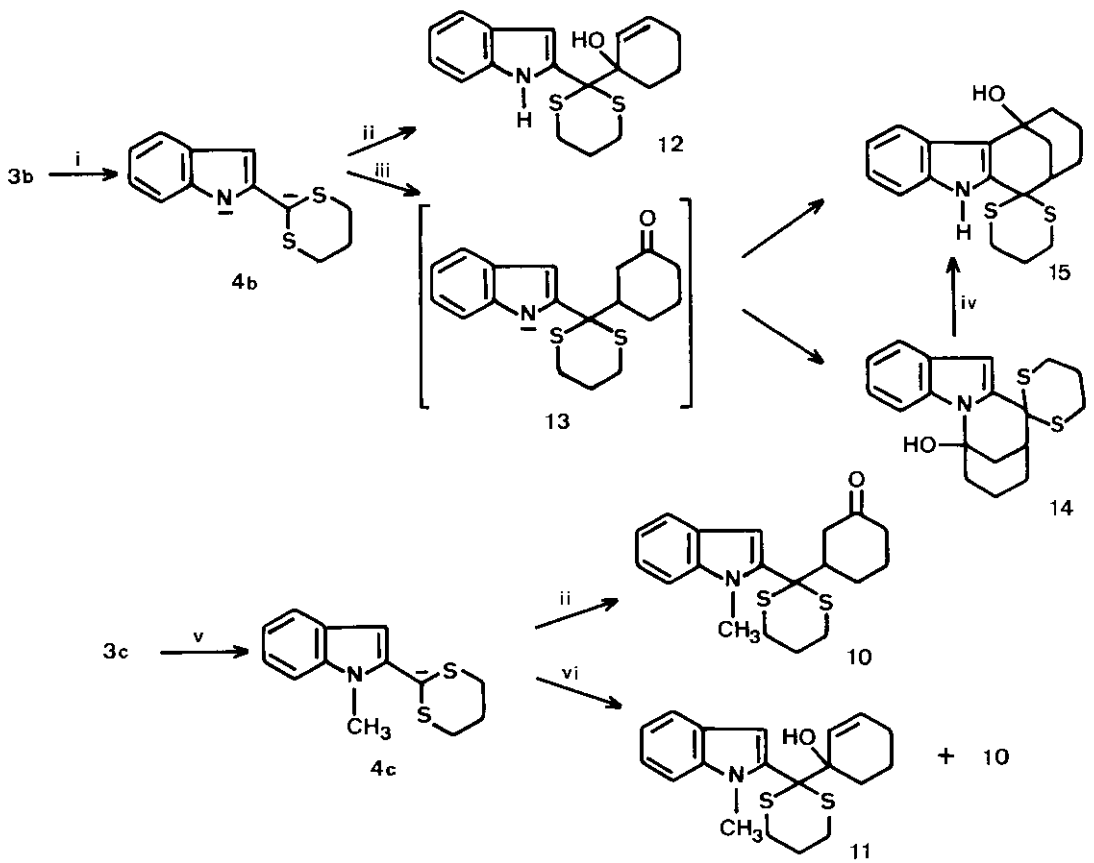
Like the dianion **4b**,[1] the anion **4c**, generated from dithiane **3c** by treatment with n-BuLi in THF at -20°C, smoothly reacts (-20°C to room temp.) with highly electrophilic carbonyl centers such as those present in N-methyl-4-piperidone, nicotinaldehyde, and isonicotinaldehyde to give the corresponding alcohols (**5-7**) in high yields (see Table I). However, each of these anions showed a different behaviour when cyclohexanone was used as electrophile. Thus, **4b** reacted at -70°C[4] to room temperature in THF to give alcohol **8** in 71% yield whereas the same reaction conditions were ineffective for **4c**, the starting materials being recovered unchanged. In the latter case, the desired alcohol **9** was obtained in 78% yield when the addition was carried out at -70°C for a short time and the reaction was quenched at this temperature. The behaviour of **4c** in its reaction with cyclohexanone under the first set of conditions (-70°C to room temp.) reflects the reversibility of the process as a consequence of the greater stability of this anion as compared with the dianion **4b**.

This factor can also explain the different course of the reactions of anions **4b** and **4c** with 2-cyclohexenone (Scheme II). Thus, the anion **4c** reacts with this enone at -20°C to room temperature in THF to give exclusively the more stable (thermodynamic) 1,4-addition product,[5] i.e. ketone **10**, whereas under the same reaction conditions the dianion **4b** gives the 1,2-addition (kinetic) product, i.e. allylic alcohol **12**. As expected, in the first case the regioselectivity of the addition could be partially reversed by lowering both the polarity

of the solvent and the reaction temperature,[5b] conditions that favour the formation of the kinetic product. Thus, when 2-cyclohexenone was added at -78°C to a suspension of the anion **4c** in hexane-THF and the reaction mixture was quenched at this temperature after 10 min, a 2:3 mixture (73% overall yield) of allylic alcohol **11** and ketone **10** was obtained.

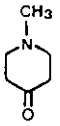
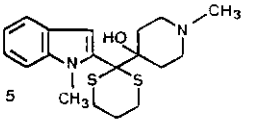
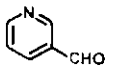
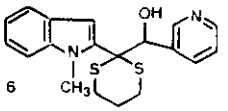
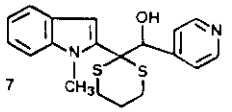
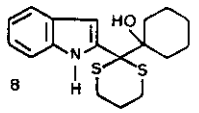
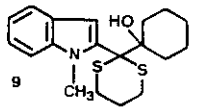
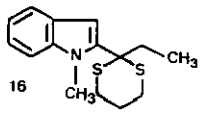
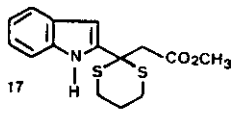
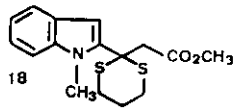
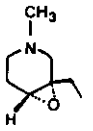
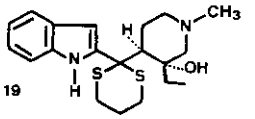
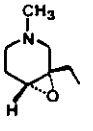
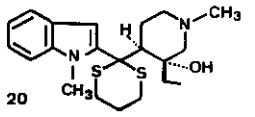
On the other hand, reaction of 2-cyclohexenone with the dianion **4b** in THF-HMPA[6] (4:1 ratio) at -50°C for 30 min, followed by quenching of the reaction mixture at -20°C, gave (62% yield) a mixture of the unexpected pentacycles **14** and **15**. The formation of these compounds can be rationalized by considering that the carbonyl group in the initially formed ketone **13** undergoes intramolecular nucleophilic attack by the ambident indole anion, either by the nitrogen

Scheme II. Reaction of Dithiane Anions **4b** and **4c** with 2-Cyclohexenone



Reagents and Conditions. (i) n-BuLi (2 equiv.), THF, -20°C, 20 min; (ii) 2-Cyclohexenone, THF, -20°C to room temp.; (iii) 2-cyclohexenone, THF-HMPA (4:1), -50°C to -20°C; (iv) EtOH, reflux; (v) n-BuLi, THF, -20°C, 15 min; (vi) 2-cyclohexenone, THF-hexane (1:1.8), -78°C, 10 min.

Table I

Substrate	Electrophile	Product	Yield (%)
3c		 5	75
3c		 6	83
3c		 7	70
3b		 8	71
3c		 9	78
3c	$BrCH_2CH_3$	 16	83
3b	$BrCH_2COOLi$	 17	38[a]
3c	$BrCH_2COOLi$	 18	66[a]
3b		 19	91
3c		 20	73

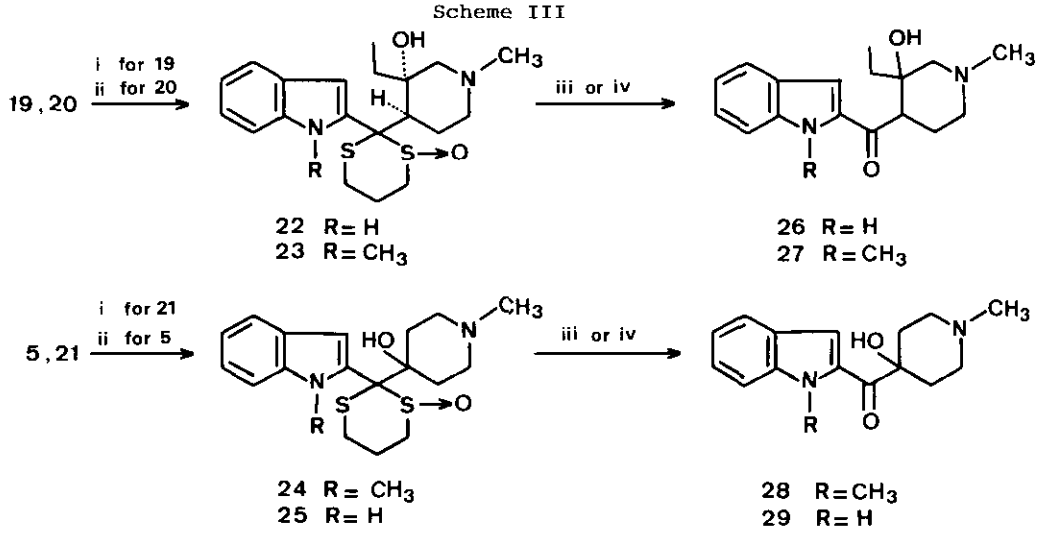
a. Followed by esterification.

or C-3 atom. This result clearly indicated that under the above conditions the 1,4-addition was the only addition mode.[7] Compound **14** was converted into pentacycle **15** during its recrystallization from ethanol. This transformation can be envisaged as involving the heterolysis of the carbon-indole nitrogen bond of the carbinol amine moiety of **14** and the subsequent irreversible cyclization of the resultant ketone carbonyl group upon the indole 3-position.[8]

The structure of compounds **14** and **15** was readily determined from their nmr data. Thus, in the ^{1}H-nmr spectrum of **14** a doublet (J=0.8 Hz) at δ 6.86, absent in **15** and attributable to the indole 3-hydrogen, was observed, whereas the most significant difference in the ^{13}C-nmr spectra was the deshielding of the signal due to C-1 in **14** (δ 85.3) as compared with **15** (δ 70.9).

The reactivity of the anions **4b** and **4c** has also been studied against alkyl halides and epoxides. Like the dianion **4b**,[1] the anion **4c** was alkylated by ethyl bromide (see Table I). In contrast, both anions **4b** and **4c** failed to react under a variety of conditions with methyl bromoacetate, probably due to the acidity of the α-protons of this bromo ester that promotes a proton exchange to give the starting dithiane and the ester enolate. However, ethyl indolepropionates **17** and **18** were prepared in 38% and 66% yields, respectively, by reaction of anions **4b** and **4c** with lithium bromoacetate followed by esterification of the resulting indolepropionic acids.

Scheme III



Reagents and Conditions. (i) MCPBA, CH_2Cl_2-H_2O (80:1), -20°C, 6 h; (ii) 1. EtOH-HCl, 2. $NaIO_4$, EtOH, room temp., 12 h; (iii) THF-HCl (10:1), reflux, 3 h; (iv) 50% CH_3COOH, 80°C, overnight.

Finally, anions **4b** and **4c** reacted at -20°C in THF with 3-ethyl-1-methyl-3,4-epoxypiperidine to give alcohols **19** and **20**, respectively, resulting from the attack to the less substituted epoxide carbon.

As could be expected, deprotection of the dithioacetal function of 2-(1,3-dithian-2-yl)indoles **19**, **20**, **5**, and the corresponding N-demethyl analogue **21**[1] afforded in acceptable yields the corresponding 2-acylindoles **26-29**, respectively.

In conclusion, the method developed in this paper can constitute an useful tool for the synthesis of 2-acylindole derivatives.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-nmr spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Varian XL-200 spectrometer or, when indicated, on a Perkin-Elmer R-24B (60 MHz) instrument, using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. Ir spectra were taken with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Tlc was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm), and the spots were located with uv light or iodoplatinate reagent. Flash column chromatography was carried out on SiO_2 (silica gel 60, 0.040-0.063 mm, Macherey Nagel). Drying of organic extracts during the workup of reactions was performed over anhydrous sodium sulfate. Microanalyses were performed on a Carlo Erba 1106 analyzer by Departamento de Quimica Orgánica Biológica, Barcelona.

1-(Phenylsulfonyl)indole-2-carbaldehyde (**2a**). To a solution of diisopropylamine (21 ml, 0.148 mol) in anhydrous THF (25 ml) cooled at -70°C was added n-butyllithium (1.6 M 100 ml, 0.16 mol). The solution was stirred at -70°C for 30 min, warmed slowly to 0°C, and then 1-(phenylsulfonyl)indole[9] (34.4 g, 0.134 mol) in anhydrous THF (100 ml) was quickly added. The reaction mixture was stirred for 30 min at 0°C and cooled to -70°C. Anhydrous DMF (21 ml, 0.30 mol) in THF (30 ml) was added to the resulting solution. After stirring at room temperature for 5 h, the reaction mixture was poured into aqueous ammonium chloride and extracted with ether. The extracts were dried and evaporated to give **2a** (31 g, 81%) as a yellow solid; mp 110-111°C (dichloromethane-hexane) (lit.[2] mp 111-111.5°C).

1-Methylindole-2-carbaldehyde (**2c**). To a cooled (0°C) solution of n-butyllithium (1.6 M 63 ml, 0.1 mol) in anhydrous THF (60 ml) was added 1-methylindole (11 g, 84 mmol) in anhydrous THF (30 ml). The solution was refluxed for 2 h and then cooled to -78°C. Anhydrous DMF (12.4 ml, 168 mmol) in THF (15 ml) was added and the resulting solution was stirred at -78°C for 15 min and at room temperature for 2 h. The reaction mixture was poured into aqueous ammonium chloride and extracted with ether. The combined extracts were dried

and evaporated to give **2c** (8.8 g, 66%); mp 72-73°C (ether); ir (KBr) 1665 (CO); ^{1}H-nmr 4.09 (s, 3H, NCH_3), 7.1-7.3 (m, 2H, 5-H and 6-H), 7.40 (d, J=1 Hz, 1H, 3-H), 7.42 (dd, J=6 and 1 Hz, 1H, 7-H), 7.73 (dt, J=8 and 1 Hz, 1H, 4-H), 9.86 (s, 1H, CHO); ^{13}C-nmr 31.5 (NCH_3), 110.3 (C-7), 117.4 (C-3), 120.7 (C-2), 120.8 (C-4), 123.3 (C-5), 126.2 (C-3a), 126.8 (C-6), 135.8 (C-7a), 182.8 (CHO). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.69; N, 8.79. Found: C, 75.53; H, 5.63; N, 8.79.

2-(1,3-Dithian-2-yl)-1-(phenylsulfonyl)indole (**3a**). A stirred solution of aldehyde **2a** (30.4 g, 0.1 mol), p-toluenesulfonic acid (580 mg, 3 mmol), 1,3-propanedithiol (13.8 ml, 0.16 mol), and anhydrous benzene (400 ml) was refluxed for 8 h with removal of water by a Dean-Stark trap. The reaction mixture was poured into 2N aqueous sodium hydroxide and extracted with benzene. The organic extracts were washed several times with water, dried, and evaporated to give dithiane **3a**[1] which was recrystallized from hexane-ether (35g, 88%).

2-(1,3-Dithian-2-yl)-1-methylindole (**3c**). Operating as above, from aldehyde **2c** (12.7 g, 80 mmol), p-toluenesulfonic acid (242 mg, 1.3 mmol), 1,3-propanedithiol (10.4 ml, 0.1 mol), and anhydrous benzene (300 ml), dithiane **3c** (16 g, 80%) was obtained; mp 130-131°C (acetone); ^{1}H-nmr 2.10 (qt, J=11.2 and 4 Hz, 1H, 5-Ha), 2.1-2.3 (m, 1H, 5-He), 2.97 (ddd, J=14.4, 4, and 3.5 Hz, 2H, 4He), 3.10 (ddd, J=14.4, 11.2, and 3.2 Hz, 2H, 4-Ha), 3.83 (s, 3H, NCH_3), 5.43 (s, 1H, 2-Ha), 6.69 (s, 1H, In-3H), 7.12 (td, J=8 and 1 Hz, 1H, In-5H), 7.24 (td, J=8 and 1 Hz, 1H, In-6H), 7.30 (dd, J=8 and 1 Hz, 1H, In-7H), 7.59 (dd, J=8 and 1 Hz, 1H, In-4H); ^{13}C-nmr 25.2 ($SCH_2\underline{C}H_2$), 30.0 (NCH_3), 31.8 (SCH_2), 42.8 (SCHS), 101.6 (In-C3), 109.2 (In-C7), 119.7 (In-C5), 120.8 (In-C4), 122.0 (In-C6), 127.2 (In-C3a), 136.5 (In-C7a), 137.6 (In-C2); ms (m/z,%) 249 (M^+,69), 216 (11), 174 (100), 144 (35), 130 (33), 115 (31), 89 (14), 74 (12), 45 (20). Anal. Calcd for $C_{13}H_{15}NS_2$: C, 62.60; H, 6.06; N, 5.61; S, 25.71. Found: C, 62.90; H, 5.92; N, 5.67; S, 25.74.

3-Ethyl-1-methyl-3,4-epoxypiperidine. Method A. Trifluoroperacetic acid, prepared from 92% hydrogen peroxide (0.5 ml, 14 mmol) and trifluoroacetic anhydride (2.6 ml, 18.6 mmol) in dichloromethane (4 ml) at 0°C for 15 min, was slowly added with a glass pipette to a cooled (-5°C) solution of 3-ethyl-1-methyl-1,2,5,6-tetrahydropyridine[10] (2 g, 16 mmol) and trifluoroacetic acid (1.22 ml, 16 mmol) in dichloromethane (6 ml). After the mixture was stirred at this temperature for 2 h, water (10 ml) was slowly added. The resulting two-phase mixture was poured into aqueous sodium bicarbonate and extracted with dichloromethane. The organic extracts were dried and evaporated and the resulting residue was distilled at reduced pressure to give 3-ethyl-1-methyl-3,4-epoxypiperidine (1.23 g, 55%); bp 125°C (15 mm Hg); ^{1}H-nmr 0.96 (t, J=6 Hz, 3H, CCH_3), 1.5-1.7 (m, 3H), 1.9-2.3 (m, 3H), 2.23 (s, 3H, NCH_3), 2.60 and 2.76 (2d, J_{AB}=12 Hz, 1H each, NCH_2), 3.15 (br s, 1H, 4-H); ^{13}C-nmr 7.76 ($\underline{C}CH_3$), 24.9 ($\underline{C}H_2CH_3$), 27.9 (C-5), 44.9 (NCH_3), 48.0 (C-6), 55.0 (C-4), 56.5 (C-2), 59.4 (C-3). Anal. Calcd for $C_8H_{15}NO.1/2H_2O$: C, 63.96; H, 10.73; N,

9.32). Found: C, 63.63; H, 10.41; N, 9.27. Method B. To a solution of 3-ethyl-1-methyl-1,2,5,6-tetrahydropyridine [10] (14 g, 0.11 mol) and trifluoroacetic acid (8.42 ml, 0.11 mol) in water-dioxane (400 ml, 7:3) was added N-bromosuccinimide (21.5 g, 0.12 mol) portionwise. The mixture was stirred at room temperature for 1.25 h and then cooled to 0°C. Sodium carbonate (23.3 g, 0.22 mol) was added portionwise and the resulting mixture was stirred at room temperature overnight and extracted with ether. Evaporation of the ethereal extracts gave a crude product which was treated with a solution of potassium hydroxide (11.5 g, 0.17 mol) in methanol (300 ml) at room temperature for 1 h. The reaction mixture was diluted with water and extracted with ether. The organic extracts were dried and evaporated to give 3-ethyl-1-methyl-3,4-epoxypiperidine (12.4 g, 78%), which was used without further purification.

General Procedure for the Preparation of Compounds **5-7, 10, 12, 19,** and **20.** n-Butyllithium (1.6 M in hexane, 2.1 or 1.1 eq.) was slowly added via syringe to a cooled (-20°C) solution of **3b** or **3c** (1 eq.) in dry THF (30 ml) under argon atmosphere. The mixture was stirred for 15-20 min and the electrophile (1.1 eq.) was added at -20°C promoting a decolored solution. After stirring for 30 min, the reaction mixture was allowed to warm slowly to room temperature. For compounds **10** and **12** the reaction mixture was quenched with aqueous ammonium chloride and extracted with ether. For compounds **5-7, 19** and **20** the reaction mixture was poured into 5% hydrochloric acid and extracted with ether. The aqueous phase was basified with potassium carbonate and extracted with ether. In all cases the organic extracts were dried and evaporated to dryness in vacuo.

1-Methyl-4-[2-(1-methyl-2-indolyl)-1,3-dithian-2-yl]-4-piperidinol (**5**). Operating as above, from **3c** (0.5 g, 2 mmol), anhydrous THF (30 ml), n-butyllithium (1.38 ml, 2.2 mmol), and N-methyl-4-piperidone (0.25 ml, 2.2 mmol), the alcohol **5** (0.54 g, 75%) was obtained after recrystallization from acetone-methanol; mp 186-187°C; ir (KBr) 3100-3500 (OH); ^{1}H-nmr 1.7-1.9 (m, 4H), 2.23 (s, 3H, NCH_3), 2.65-2.84 (m, 10H), 4.19 (s, 3H, NCH_3), 7.12 (s, 1H, In-3H), 7.13 (t, J=8 Hz, 1H, In-5H), 7.24 (t, J=8 Hz, 1H, In-6H), 7.32 (d, J=8 Hz, 1H, In-7H), 7.60 (d, J=8 Hz, 1H, In-4H); ^{13}C-nmr ($CDCl_3$ - DMSO-d_6) 24.6 ($SCH_2\underline{C}H_2$), 28.2 (br, $NCH_2\underline{C}H_2$), 32.4 (In-NCH_3), 33.9 (SCH_2), 45.8 (NCH_3), 51.0 (NCH_2), 66.3 (SCS), 75.1 (CHOH), 109.1 and 110.0 (In-C3 and In-C7), 119.1 and 119.8 (In-C4 and In-C5), 121.7 (In-C6), 126.0 (In-C3a), 136.6 (In-C7a), 139.5 (In-C2); ms (m/z;%) 291 (1), 249 (50), 213 (6), 197 (4), 174 (57), 159 (16), 130 (30), 114 (61), 96 (33), 70 (45), 42 (100). Anal. Calcd for $C_{19}H_{26}N_2OS_2$: C, 62.98; H, 7.17; N, 7.72; S, 17.65. Found: C, 62.65; H, 7.21; N, 8.03; S, 17.53.

α-[2-(1-Methyl-2-indolyl)-1,3-dithian-2-yl]-3-pyridinemethanol (**6**). Operating as above, from **3c** (1.12 g, 4.5 mmol), anhydrous THF (90 ml), n-butyllithium (3.1 ml, 5 mmol), and nicotinaldehyde (0.35 ml, 5 mmol), the alcohol **6** (1.2 g, 83%) was obtained. A sample of **6** was purified by flash chromatography (ether); mp 162-163°C (ether-acetone); ir (KBr) 3100-3300 (OH); ^{1}H-nmr 1.8-2.0

(m, 2H, $SCH_2\underline{CH}_2$), 2.6 -3.0 (m, 4H, SCH_2), 3.87 (s, 3H, NCH_3), 5.23 (s, 1H, C<u>H</u>OH), 6.87 (d, <u>J</u>=0.6 Hz, 1H, In-3H), 7.0-7.3 (m, 4H), 7.32 (dt, <u>J</u>=8 and 1.8 Hz, 1H, In-4H), 7.54 (dt, <u>J</u>=8 and 1.1 Hz, 1H, In-7H), 8.28 (d, <u>J</u>=2.2 Hz, 1H, Py-2H), 8.44 (dd, J=5 and 1.7 Hz, 1H, Py-6H); ^{13}C-nmr 24.4 ($SCH_2\underline{CH}_2$), 27.5 and 27.7 (SCH_2), 33.2 (NCH_3), 61.1 (SCS), 77.4 (CHOH), 109.6 and 109.8 (In-C3 and In-C7), 119.8 and 120.6 (In-C4 and In-C5), 122.3 and 122.5 (In-C6 and Py-C5), 126.2 (In-C3a), 134.9 and 135.8 (In-C2 and In-C7a), 136.1 (Py-C4), 139.7 (Py-C3), 148.4 (Py-C2 and Py-C6); ms (m/z,%) 248 (M^+-PyCHOH, 100), 174 (34), 149 (9), 106 (13), 108 (44), 78 (20), 80 (37), 57 (29), 41 (35). Anal. Calcd for $C_{19}H_{20}N_2OS_2$: C, 64.01; H, 5.65; N, 7.85; S, 17.98. Found: C, 63.78; H, 5.57; N, 7.83; S, 18.04.

<u>α-[2-(1-Methyl-2-indolyl)-1,3-dithian-2-yl]-4-pyridinemethanol</u> (**7**). Operating as above, from **3c** (0.5 g, 2 mmol), anhydrous THF (50 ml), <u>n</u>-butyllithium (1.4 ml, 2.2 mmol), and pyridine-4-carbaldehyde (0.17 ml, 2.2 mmol), the alcohol **7** (0.42 g, 70%) was obtained after purification by flash chromatography (ether); mp 190-192°C (ether-acetone); ir ($CHCl_3$) 3100-3500 (OH); ^{1}H-nmr 1.8-2.0 (m, 2H, $SCH_2\underline{CH}_2$), 2.6-3.0 (m, 4H, SCH_2), 3.88 (s, 3H, NCH_3), 5.17 (s, 1H, C<u>H</u>OH), 6.81 (s, 1H, In-3H), 6.89 (d, <u>J</u>=8 Hz, 2H, Py-β H), 7.12 (ddd, <u>J</u>=8, 7, and 1.8 Hz, 1H, In-5H), 7.25 (td, <u>J</u>=8 and 0.9 Hz, 1H, In-6H), 7.31 (br d, <u>J</u>=7 Hz, 1H, In-4H), 7.53 (dt, <u>J</u>=8 and 0.9 Hz, 1H, In-7H), 8.27 (d, <u>J</u>=8 Hz, 1H, Py-αH); ^{13}C-nmr 24.3 ($SCH_2\underline{CH}_2$), 27.6 and 27.7 (SCH_2), 33.4(NCH_3), 61.8 (SCS), 77.8 (CHOH), 109.6 (In-C3 and In-C7), 119.9 and 120.6 (In-C4 and In-C5), 122.5 (In-C6), 124.4 (Py-C3 and Py-C5), 126.0 (In-C3a), 134.6 (In-C7a), 139.6 (In-C2), 143.6 (Py-C2 and Py-C6), 146.9 (Py-C4); ms (m/z;%) 248 (M^+-CHOH, 100), 174 (31), 127 (9), 99 (15), 78 (6). Anal. Calcd for $C_{19}H_{20}N_2OS_2$: C, 64.01; H, 5.65; N, 7.85. Found: C, 63.87; H, 5.54; N, 7.78.

<u>1-[2-(2-Indolyl)-1,3-dithian-2-yl]cyclohexanol</u> (**8**). To a solution of **3b** (0.15 g, 0.63 mmol) in anhydrous THF (20 ml) cooled at -20°C under argon atmosphere was slowly added <u>n</u>-butyllithium (1.6 M, 0.8 ml, 1.28 mmol). The mixture was stirred for 20 min and then cyclohexanone (0.063 ml, 0.69 mmol) was added at -70°C. The reaction mixture was stirred for 30 min at -70°C, allowed to reach the room temperature, treated with aqueous ammonium chloride, and extracted with ether. The organic extracts were dried, evaporated, and chromatographed (benzene) to give the alcohol **8** (0.15 g, 71%); mp 199-201°C (acetone); ir (KBr) 3445 (NH), 3265 (OH); ^{1}H-nmr 1.4 -2.0 (m, 12H), 2.65-2.85 (m, 4H, SCH_2), 6.81 (dd, <u>J</u>=2.1 and 0.6 Hz, 1H, In-3H), 7.12 (td, <u>J</u>=7.2 and 1.2 Hz, 1H, In-5H), 7.20 (td, <u>J</u>=7.2 and 1.2 Hz, 1H, In-6H), 7.38 (br d, <u>J</u>=7.2 Hz, 1H, In-4H), 7.62 (br d, <u>J</u>=7.2 Hz, 1H, In-7H). Anal. Calcd for $C_{18}H_{23}NOS_2$: C, 64.83; H, 6.95; N, 4.20; S, 19.23. Found: C, 64.90; H, 7.04; N, 4.12; S, 19.12.

<u>1-[2-(1-Methyl-2-indolyl)-1,3-dithian-2-yl]cyclohexanol</u> (**9**). To a solution of **3c** (0.4 g, 1.6 mmol) in anhydrous THF (50 ml) cooled at -20°C under argon atmosphere was slowly added <u>n</u>-butyllithium (1.6 M, 1.1 ml, 1.76 mmol). The

mixture was stirred at -20°C for 15 min and then cyclohexanone (0.16 ml, 1.76 mmol) was added at -70°C. The reaction mixture was stirred at -70°C for 15 min, quenched at this temperature with aqueous ammonium chloride, and extracted with ether. The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (1:1 petroleum ether-ether) to give alcohol **9** (0.43 g, 78%); mp 116-118°C (acetone-ether); ir (KBr) 3300-3550 (OH); ^{1}H-nmr 1.45-1.95 (m, 12H), 2.7-2.9 (m, 4H, SCH_2), 4.20 (s, 3H, NCH_3), 7.11 (d, J=0.6 Hz, 1H, In-3H), 7.14 (ddd, J=7.8, 7 and 1.2 Hz, 1H, In-5H), 7.25 (td, J=7.8 and 1.2 Hz, 1H, In-6H), 7.35 (dm, J=7 Hz, 1H, In-4H), 7.61 (dm, J=7.8 Hz, 1H, In-7H); ^{13}C-nmr 21.8 (C-4), 24.9 ($SCH_2\underline{CH_2}$), 25.4 (C-3), 28.7 (C-2), 33.1 (SCH_2), 33.8 (NCH_3), 67.5 (SCS), 77.9 (COH), 109.8 (In-C3), 110.4 (In-C7), 119.8 (In-C4), 120.4 (In-C5), 121.9 (In-C6), 126.3 (In-C3a), 136.1 (In-C7a), 139.7 (In-C2); ms (m/z,%) 347 (M^+,1), 249 (100), 234 (8), 216 (3), 174 (73), 130 (18), 99 (39), 81 (67). Anal. Calcd for $C_{19}H_{25}NOS_2$: C, 65.66; H, 7.25; N, 4.03. Found: C, 65.56; H, 7.08; N, 3.49.

3-[2-(1-Methyl-2-indolyl)-1,3-dithian-2-yl]cyclohexanone (**10**). Operating as in the general procedure, from **3c** (1.1 g, 4.4 mmol), anhydrous THF (90 ml), n-butyllithium (2.9 ml, 4.9 mmol), and 2-cyclohexenone (0.47 ml, 4.9 mmol), the ketone **10** (1.05 g, 69%) was obtained after purification by flash chromatography (ether); mp 188-189°C (hexane-ether); ir (KBr) 1700 (CO); ^{1}H-nmr 1.0-1.6 (m, 3H, 5-H and 6-Ha), 1.72 (td, J=12 and 4 Hz, 1H, 3-Ha), 1.92 (dd, J=12 and 4 Hz, 1H), 1.85-2.22 (m, 4H, 4-H and $SCH_2\underline{CH_2}$), 2.30 (br d, J=12 Hz, 1H, 6-He), 2.48 (ddd, J=12, 3 and 2 Hz, 1H, 2-He), 2.64-2.84 (m, 2H, SCHe), 2.99 (ddd, J=15, 12 and 3 Hz, 1H, SCHa), 3.0-3.1 (m, 1H), 3.19 (ddd, J=15, 12 and 3 Hz, 1H, SCHa), 4.21 (s, 3H, NCH_3), 7.08 (ddd, J=8, 6.6 and 1.4 Hz, 1H, In-5H), 7.22 (ddd, J=8, 6.6 and 1.4 Hz, 1H, In-6H), 7.25 (s, 1H, In-3H), 7.32 (ddd, J=8, 1.4 and 0.8 Hz, 1H, In-4H), 7.92 (ddd, J=8, 1.4 and 0.8 Hz, 1H, In-7H); ms (m/z,%) 345 (M^+, 48), 271 (100), 238 (46), 210 (27), 106 (27), 45 (46), 41 (99). Anal. Calcd for $C_{19}H_{23}NOS_2$: C, 66.04; H, 6.71; N, 4.05; S, 18.56. Found: C, 66.31; H, 6.84; N, 4.15; S, 18.62.

1-[2-(1-Methyl-2-indolyl)-1,3-dithian-2-yl]-2-cyclohexenol (**11**). To a solution of **3c** (0.65 g, 2.61 mmol) in anhydrous THF (50 ml) cooled at -20°C under argon atmosphere was slowly added n-butyllithium (1.6 M, 1.8 ml, 2.87 mmol). The mixture was stirred for 15 min, cooled at -78°C, and diluted with hexane (90 ml). 2-Cyclohexenone (0.28 ml, 2.87 mmol) was added at -78°C and the reaction mixture was stirred for 10 min, quenched at -78°C with aqueous ammonium chloride, and extracted with ether. The organic extracts were dried and evaporated to give a crude 3:2 mixture of the ketone **10** and the alcohol **11** (overall yield 73%) which was separated by flash chromatography (4:1 petroleum ether-ether). Alcohol **11** (0.27 g, 30%): ir (KBr) 3540 (NH), 3120-3340 (OH); ^{1}H-nmr 1.5-2.1 (m, 8H), 2.6-2.9 (m, 4H, SCH_2), 4.18 (s, 3H, NCH_3), 6.00 (dt, J=10 and 3 Hz, 1H, =CH), 6.15 (br d, J=10 Hz, 1H, =CH), 7.09 (s, 1H, In-3H), 7.12 (td, J=8 and 1.2 Hz, 1H, In-5H), 7.25 (td, J=8 and 1.2 Hz, 1H, In-6H), 7.34 (br d, J=8 Hz, 1H, In-4H), 7.60 (br d, J=8 Hz, 1H, In-7H); ^{13}C-nmr 18.7 (C-5), 24.9 ($SCH_2\underline{CH_2}$), 25.2 (C-4), 28.3 (C-6), 32.4 (SCH_2), 34.1 (NCH_3), 65.5 (SCS), 75.6

(COH), 109.9 (In-C3), 110.3 (In-C7), 119.6 (In-C4), 120.3 (In-C5), 121.8 (In-C6), 126.4 (In-C3), 128.8 (In-C3a), 132.6 (C-2), 136 (In-C7a), 139.9 (In-C2); ms (m/z,%) 345 (M^+, 1), 248 (100), 174 (42), 97 (54), 41 (94). Anal. Calcd for $C_{19}H_{23}NOS_2$: C, 66.04; H, 6.71; N, 4.05; S, 18.56. Found: C, 66.27; H, 6.66; N, 3.96; S, 18.46.

1-[2-(2-Indolyl)-1,3-dithian-2-yl]-2-cyclohexanol (12). Operating as in general procedure, from **3b** (0.47 g, 2 mmol), anhydrous THF (50 ml), n-butyllithium (2.5 ml, 4 mmol), and 2-cyclohexenone (0.2 ml, 2.1 mmol), the alcohol **12** (0.45 g, 68%) was obtained after purification by flash chromatography (dichloromethane); mp 164-166°C (ethanol); ir (KBr) 3520 (OH), 3300 (NH); ^{1}H-nmr 1.5-2.1 (m, 8H), 2.6-2.9 (m, 4H, SCH_2), 6.02 (m, 1H, =CH), 6.12 (br d, J=10 Hz, 1H, =CH), 6.84 (dd, J=2.1 and 0.8 Hz, 1H, In-3H), 7.12 (td, J=7 and 1.2 Hz, 1H, In-5H), 7.20 (td, J=7 and 1.2 Hz, 1H, In-6H), 7.45 (br d, J=7 Hz, 1H, In-4H), 7.64 (br d, J=7 Hz, 1H, In-7H); ms (m/z,%) 331 (M^+, 1), 234 (100), 160 (51), 117 (9), 97 (8), 89 (9). Anal. Calcd for $C_{18}H_{21}NOS_2$: C, 65.12; H, 6.40; N, 4.23; S, 19.34. Found: C, 64.85; H, 6.44; N, 4.53; S, 19.07.

Reaction of Dianion **4b** with 2-Cyclohexenone in THF-HMPA. n-Butyllithium (1.6 M, 2.5 ml, 4 mmol) was slowly added to a solution of **3b** (0.47 g, 2 mmol) in dry THF (20 ml) and HMPA (5 ml) cooled at -50°C under argon atmosphere. After stirring for 10 min, 2-cyclohexenone (0.19 ml, 2 mmol) was added at -50°C. The reaction mixture was stirred at this temperature for 30 min, allowed to reach -20°C, quenched with aqueous ammonium chloride, and extracted with ether. The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (dichloromethane) to give a mixture (0.41 g, 62%) of tetracycles **14** and **15**. When the above mixture was recrystallized from methanol, pure **15** was obtained. Compound **14**: ir (KBr) 3100-3600 (OH); ^{1}H-nmr 1.4-1.6 (m, 2H, 3-H), 1.72 (td, J=13 and 4 Hz, 1H, 2-Ha), 1.8-2.4 (m, 5H, SCH_2CH_2, 4-H, and 12-Ha), 2.12 (dd, J=12 and 4 Hz, 1H, 12-He), 2.6-2.8 (m, 2H, 2-H and 5-H), 2.98 (dm, J=12 Hz, 2H, SCHe), 3.16 (ddd, J=14, 12, and 4 Hz, 2H, SCHa), 6.86 (d, J=0.8 Hz, 1H, In-7H), 7.0-7.2 (m, 2H, In-9H and In-10H), 7.56 (br d, J=8 Hz, 1H, In-8 H), 7.92 (br d, J=8 Hz, 1H, In-11H); ^{13}C-nmr 19.5 (C-3), 24.4 (SCH_2CH_2), 27.5 and 28.0 (SCH_2), 29.6 (C-4), 35.7 (C-12), 36.7 (C-5), 39.5(C-2), 51.4 (C-6), 85.3 (C-1), 102.4 (C-7), 114.0 (C-11), 119.7 and 120.7 (C-8 and C-9), 121.8 (C-10), 128.7 (C-7a), 134.7 (C-6a), 139.5 (C-11a). Compound **15**: mp 251-253°C (acetone); ir (KBr) 3100-3600 (OH); ^{1}H-nmr ($CDCl_3$-CD_3OD) 1.5-1.7 (m, 2H, 3-H), 1.70 (td, J=12 and 4 Hz, 1H, 2-Ha), 1.89 (dd, J=12 and 4 Hz, 1H, 12-He), 1.9-2.3 (m, 5H, SCH_2CH_2, 4-H and 12-Ha), 2.59 (dq, J=12 and 2.6 Hz, 1H, 2-He), 2.76 (dt, J=14 and 4 Hz, 2H, SCHe), 3.00 (br s, 1H, 5-He), 3.20 (ddd, J=14, 12 and 4 Hz, 2H, SCHa), 7.04 (td, J=7 and 1.3 Hz, 1H, 10-H), 7.16 (td, J=7 and 1.3 Hz, 1H, 9-H), 7.34 (dd, J=1 and 0.5 Hz, 1H, 11-H), 7.80 (dd, J=1 and 0.5 Hz, 1H, 8-H); ^{13}C-nmr ($CDCl_3$-CD_3OD) 20.6 (C-3), 24.4 (SCH_2CH_2), 26.8 and 28.5 (SCH_2), 29.5 (C-4), 36.5 (C-12), 39.1 (C-5), 40.3 (C-2), 51.6 (C-6), 70.9 (C-1), 110.9 (C-8), 116.8 (C-11b), 119.2 and 120.5 (C-10 and C-11), 122.1 (C-9), 124.1 (C-11a), 133.2 (C-6a), 136.0 (C-7a); ms (m/z,%) 331 (M^+, 31), 298 (7), 257 (100), 224 (50), 195 (36), 167 (18), 153 (20), 130 (8), 115 (7),

85 (32), 83 (47). Anal. Calcd for $C_{18}H_{21}NOS_2$: C, 65.22; H, 6.39; N, 4.23; S, 19.34. Found: C, 65.17; H, 6.36; N, 3.92; S, 18.97.

2-(2-Ethyl-1,3-dithian-2-yl)-1-methylindole (**16**). To a solution of **3c** (0.4 g, 1.6 mmol) in anhydrous THF (50 ml) cooled at -20°C under argon atmosphere was slowly added n-butyllithium (1.6 M, 1.1 ml, 1.76 mmol). After the mixture was stirred for 15 min, ethyl bromide (0.13 ml, 1.76 mmol) was added at -70°C. The reaction mixture was stirred at -70°C for 15 min, quenched at this temperature with aqueous ammonium chloride, and extracted with ether. The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (1:1 petroleum ether-ether) to give **16** (0.37 g, 83%); mp 195-196°C (ether); ^{1}H-nmr (60 MHz) 0.83 (t, J=7 Hz, 3H, CH_2CH_3), 1.6-2.0 (m, 2H, SCH_2CH_2), 2.20 (q, J=7 Hz, 2H, CH_2CH_3), 2.5-3.0 (m, 4H, SCH_2), 3.80 (s, 3H, NCH_3), 6.66 (s, 1H, In-3H), 6.7-7.1 (m, 3H, In-H), 7.33 (br d, J=7 Hz, 1H, In-7H). Anal. Calcd for $C_{15}H_{19}NS_2.H_2O$: C, 60.98; H, 7.15; N, 4.73; S, 21.70. Found: C, 61.18; H, 6.83; N, 4.68; S, 21.36.

Methyl [2-(2-Indolyl)-1,3-dithian-2-yl]acetate (**17**). n-Butyllithium (1.6 M, 11.7 ml, 18.7 mmol) was slowly added under argon atmosphere to a cooled (-20°C) solution of **3b** (2 g, 8.5 mmol) in anhydrous THF (100 ml). After the mixture was stirred at -20°C for 20 min, a solution of lithium bromoacetate, prepared from bromoacetic acid (1.41 g, 10.2 mmol), n-butyllithium (1.6 M, 7.1 ml, 11.2 mmol), and anhydrous THF (50 ml), was slowly added. The resulting mixture was stirred at -20°C for 1 h 30 min, allowed to reach the room temperature, stirred for additional 30 min, poured into aqueous sodium carbonate, and washed with ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The organic extract was dried and evaporated to give a solid which was dissolved in methanol (200 ml) and 0.5 N hydrogen chloride-methanol (70 ml). The resulting solution was stirred at room temperature for 15 h. The solvent was removed and the residue was dissolved in water, basified with solid sodium carbonate, and extracted with ether. Evaporation of ethereal extracts afforded a residue which was purified by flash chromatography (dichloromethane) to give ester **17** (1 g, 38%); mp 173-174°C (methanol); ir (KBr) 3330 (NH), 1720 (CO); ^{1}H-nmr 1.95 (m, 2H, SCH_2CH_2), 2.80 (m, 4H, SCH_2), 3.09 (s, 2H, $COCH_2$), 3.56 (s, 3H, OCH_3), 6.78 (dd, J=2 and 0.8 Hz, 1H, In-3H), 7.05-7.40 (m, 3H, In-H), 7.60 (dm, J=7.6 Hz, 1H, In-7H). Anal. Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.60; H, 5.57; N, 4.55; S, 20.85. Found: C, 58.66; H, 5.29; N, 4.41; S, 20.90.

Methyl [2-(1-Methyl-2-indolyl)-1,3-dithian-2-yl]acetate (**18**). Operating as above, except for the reaction time which was prolonged to 5 h at room temperature, a solution of dithiane **3c** (4.1 g, 16.4 mmol) in anhydrous THF (240 ml) was treated with n-butyllithium (1.6 M, 10.8 ml, 17.3 mmol) and then with lithium bromoacetate (19.7 mmol). The resulting crude acid was esterified as above to give ester **18** (3.5 g, 66%). An analytical sample was obtained by flash chromatography (1:1 petroleum ether-ethyl acetate); ir (NaCl) 1730 (CO); ^{1}H-nmr (60 MHz) 1.85 (m, 2H, SCH_2CH_2), 2.70 (m, 4H, SCH_2), 3.20 (s, 2H, $COCH_2$), 3.30

(s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 6.70 (s, 1H, In-3H), 6.8-7.2 (m, 3H, In-H), 7.4 (m, 1H, In-7H). Anal. Calcd for $C_{16}H_{19}NO_2S_2$: C, 59.78; H, 5.96; N, 4.36; S, 19.95. Found: C, 59.83; H, 5.95; N, 4.18; S, 20.05.

3-Ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]-1-methyl-3-piperidinol (**19**). Operating as indicated in the general procedure, from **3b** (0.75 g, 3.2 mmol), anhydrous THF (70 ml), n-butyllithium (4 ml, 6.4 mmol), and 3-ethyl-1-methyl-3,4-epoxypiperidine (0.5 g, 3.5 mmol), the alcohol **19** (1.1 g, 91%) was obtained after purification by flash chromatography (99:1 dichloromethane-methanol); mp 183-184°C (ether-acetone); ir (KBr) 3290 (OH); 3480 (NH); ^{1}H-nmr 0.85 (t, 3H, CCH_3), 1.46 (d, J=11 Hz, 1H, 2-Ha), 1.7-2.2 (m, 7H), 2.20 (s, 3H, NCH_3), 2.66 (br d, J=14 Hz, 1H, 6-He), 2.7-2.9 (m, 5H, SCH_2 and 4-H), 2.93 (br d, J=11 Hz, 1H, 2-He), 6.90 (s, 1H, In-3H), 7.20 (t, J=7 Hz, 1H, In-5H), 7.30 (t, J=7 Hz, 1H, In-6H), 7.43 (d, J=7 Hz, 1H, In-4H), 7.66 (d, J=7 Hz, 1H, In-7H), 8.86 (s, 1H, NH); ^{13}C-nmr 7.2 ($C\underline{C}H_3$), 24.7 ($SCH_2\underline{C}H_2$), 26.8 and 27.1 (C-5 and $\underline{C}H_2CH_3$), 28.2 and 28.5 (SCH_2), 46.0 (NCH_3), 56.7 (C-6), 58.0 (SCS), 59.7 (C-4), 64.0 (C-2), 75.7 (C-3), 105.5 (In-C3), 111.4 (In-C7), 120.2 and 120.7 (In-C4 and In-C5), 122.6 (In-C6), 128.2 (In-C3a), 136.2 (In-C2), 138.2 (In-C7a); ms (m/z,%) 376 (M^+, 40), 301 (12), 234 (26), 160 (20), 142 (100), 114 (81), 99 (16), 57 (29), 44 (34), 42 (16). Anal. Calcd for $C_{20}H_{28}N_2OS_2$: C, 63.79; H, 7.49; N, 7.44. Found: C, 63.58; H, 7.15; N, 7.72.

3-Ethyl-1-methyl-4-[2-(1-methyl-2-indolyl)-1,3-dithian-2-yl]-3-piperidinol (**20**). *Operating as indicated in the general procedure, from* ***3c*** (0.6 g, 2.4 mmol), anhydrous THF (50 ml), n-butyllithium (1.6M, 1.67 ml, 2.7 mmol), and 3-ethyl-1-methyl-3,4-epoxypiperidine (0.38 g, 2.7 mmol), the alcohol **20** (0.68 g, 73%) was obtained after flash chromatography (97:3 ether-diethylamine); mp 174-175°C (acetone-methanol); ir (KBr) 3520-3445 (OH); ^{1}H-nmr 0.75 (br t, 3H, CCH_3), 1.51 (d, J=11 Hz, 1H, 2-Ha), 1.7-2.3 (m, 7H), 2.21 (s, 3H, NCH_3), 2.4-2.8 (m, 5H, SCH_2 and 4-H), 2.95 (br d, J=11 Hz, 1H, 2-He), 3.35 (br, 1H, OH), 4.01 (s, 3H, In-NCH_3), 7.05 (s, 1H, In-3H), 7.11 (t, J=8 Hz, 1H, In-5H), 7.21 (t, J=8 Hz, 1H, In-C6), 7.31 (d, J=8 Hz, 1H, In-4H), 7.59 (d, J=8 Hz, 1H, In-7H); ^{13}C-nmr 7.1 ($C\underline{C}H_3$), 24.5 ($SCH_2\underline{C}H_2$), 27.5 (C-5), 28.9 ($\underline{C}H_2CH_3$), 31.8 (SCH_2), 33.3 (In-NCH_3), 45.9 (NCH_3), 56.7 (C-4 and C-6), 63.4 (C-2), 77.2 (C-3), 108.4 and 109.8 (In-C3 and In-C7), 119.9 and 120.4 (In-C4 and In-C5), 122.4 (In-C6), 126.0 (In-C3a), 135.9 (In-C7a), 139.5 (In-C2); ms (m/z,%) 390 (M^+, 12), 248 (45), 182 (27), 174 (51), 167 (23), 142 (54), 114 (38), 57 (100), 42 (74). Anal. Calcd for $C_{21}H_{30}N_2OS_2$: C, 64.57; H, 7.74; N, 7.17; S, 16.41. Found: C, 64.93; H, 7.80; N, 7.46; S, 16.30.

3-Ethyl-3-hydroxy-1-methyl-4-piperidyl 2-Indolyl Ketone (**26**). A solution of dithiane **19** (1 g, 2.65 mmol) and 85% MCPBA (0.46 g, 2.78 mmol) in dichloromethane (80 ml) and water (1 ml) was stirred at -20°C under argon atmosphere for 6 h. The reaction mixture was poured into aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated to give a solid which was purified by flash chromatography. On elution with dichloromethane-methanol (99:1), a diastereoisomeric mixture

of sulfoxides **22** (1 g, 96%) was obtained; mp 154-156°C (ethanol); ir (KBr) 3100-3500 (OH); ^{1}H-nmr 0.76 and 1.05 (2 t, J=7 Hz, 3H each, CCH_3), 2.18 and 2.20 (2 s, 3H each, NCH_3), 6.76 and 6.83 (2 s, 1H each, In-3H), 7.1-7.4 (m, 3H, In-H), 7.63 (d, J=7 Hz, 1H, In-7H), 10.50 (br s, 1H, NH); ^{13}C-nmr (major isomer) 7.5 ($C\underline{C}H_3$), 25.2 and 26.6 ($\underline{C}H_2CH_3$ and $SCH_2\underline{C}H_2$), 27.8 and 29.5 (SCH_2 and $NCH_2\underline{C}H_2$), 45.8 (NCH_3), 47.7 ($SOCH_2$), 54.5 (C-4), 56.2 (NCH_2), 65.7 (C-2), 74.6 and 75.0 (C-3 and SCS), 107.5 (In-C3), 112.0 (In-C7), 120.4 , 120.5 and 120.7 (In-C4, In-C5 and In-C6), 126.0 (In-C3a), 134.7 (In-C2), 136.6 (In-C7a); ms (m/z,%) 392 (M^+, 1), 391 (6), 168 (6), 140 (6), 114 (100), 57 (12).

Method A. A solution of **22** (0.6 g, 1.5 mmol), THF (40 ml), and concentrated hydrochloric acid (4 ml) was refluxed for 3 h under argon atmosphere. The cooled mixture was poured into aqueous potassium carbonate and extracted with ether. The organic layer was washed with water, dried, and evaporated. The resulting oil was purified by flash chromatography (97:3, dichloromethane-methanol) to give **26** (0.3 g, 66%); mp 162-163°C (ethanol); ir ($CHCl_3$) 3100-3500 (OH), 3450 (NH), 1630 (CO); ^{1}H-nmr 0.93 (t, J=7 Hz, 3H, $C\underline{C}H_3$), 1.65 (m, 2H, $C\underline{H}_2CH_3$), 1.85 (br d, J=13 Hz, 1H, 5-He), 2.35 (s, 3H, NCH_3), 2.45 and 2.90 (br d and d, J_{AB}=13 Hz, 1H each, 2-H), 3.60 (m, $W_{1/2}$=10.5 Hz, 1H, 4-H), 7.14 (ddd, J=8, 7 and 1.2 Hz, 1H, In-5H), 7.24 (br s, $W_{1/2}$=5 Hz, 1H, In-3H), 7.35 (td, J=7 and 1.2 Hz, 1H, In-6H), 7.44 (br d, J=8 Hz, 1H, In-4H), 7.72 (d, J=8 Hz, 1H, In-7H), 9.60 (br s, 1H, NH); ^{13}C-nmr 6.9 ($C\underline{C}H_3$), 24.8 ($\underline{C}H_2CH_3$), 30.0 (C-5), 45.3 (C-4), 46.3 (NCH_3), 51.1 (C-6), 60.7 (C-2), 71.2 (C-3), 110.8 (In-C3), 112.4 (In-C7), 121.3 (In-C4), 123.6 (In-C5), 127.0 (In-C6), 127.7 (In-C3a), 135.2 (In-C2), 138.0 (In-C7a), 194.4 (C=O); ms (m/z,%) 286 (M^+, 11), 268 (15), 229 (81), 186 (100), 144 (42), 130 (23), 124 (27), 114 (46), 89 (15), 71 (23), 58 (15). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.91; H, 8.02; N, 9.56.

Method B. A solution of **22** (1.9 g, 4.83 mmol) and 50% acetic acid (80 ml) was heated at 80°C overnight. The reaction mixture was poured into aqueous potassium carbonate and extracted with ether. Drying and evaporation of the organic extracts followed by flash chromatography (98:2, ether-diethylamine) afforded ketone **26** (1 g, 70%).

4-Hydroxy-1-methyl-4-piperidyl 2-Indolyl Ketone (**29**). Method A. Operating as above, from dithiane **21** (1.16 g, 3.3 mmol) and 85% MCPBA (0.57 g, 3.3 mmol) in dichloromethane (80 ml) and water (1 ml), sulfoxide **25** (0.76 g, 63%) was obtained; ir (KBr) 3000-3600 (OH); ^{1}H-nmr 2.23 (s, 3H, NCH_3), 6.85 (s, 1H, In-3H), 7.1-7.3 (m, 2H, In-5H and In-6H), 7.46 (d, J=7 Hz, 1H, In-4H), 7.73 (d, J=7 Hz, 1H, In-7H), 10.45 (br s, 1H, NH); ^{13}C-nmr 27.8 and 29.7 (C-5 and $SCH_2\underline{C}H_2$), 32.9 and 33.7 (SCH_2 and C-3), 45.9 (NCH_3), 48.8 ($SOCH_2$), 50.8 and 51.1 (NCH_2), 73.5 (SCS), 76.7 (C-4), 107.3 (In-C3), 111.7 (In-C7), 120.0 and 120.4 (In-C4 and In-C5), 122.5 (In-C6), 126.2 (In-C3a), 131.7 (In-C2), 136.3 (C-7a); ms (m/z,%) 364 (M^+, 17), 251 (35), 214 (24), 161 (45), 160 (44), 15 (24), 140 (35), 130 (33), 114 (30), 70 (63), 43 (100), 42 (67). Operating as in the preparation of **26**, from sulfoxide **25** (3 g, 8.2 mmol), THF (400 ml), and concentrated hydrochloric acid (40 ml), ketone **29** was obtained (1.72 g, 81%) after purification by flash chromatography (85:15, chloroform-diethylamine);

mp 210-211°C (ethanol); ir ($CHCl_3$) 3100-3500 (OH), 3450 (NH), 1630 (CO); ^{1}H-nmr (CD_3OD) 1.90 (dd, J=14 and 2 Hz, 2H, 3-He), 2.33 (td, J=14 and 4 Hz, 2H, 3-Ha), 2.46 (s, 3H, NCH_3), 2.76 (td, J=14 and 2 Hz, 2H, 2-Ha), 2.93 (br d, J=14 Hz, 2H, 2-He), 7.13 (td, J=7 and 1 Hz, 1H, In-5H), 7.33 (td, J=7 and 1 Hz, 1H, In-6H), 7.50 (d, J=7 Hz, 1H, In-4H), 7.72 (s, 1H, In-3H), 7.73 (d, J=7 Hz, 1H, In-7H); ^{13}C-nmr (CD_3OD) 34.7 ($NCH_2\underline{C}H_2$), 44.9 (NCH_3), 51.4 (NCH_2), 75.3 (COH), 112.7 and 113.2 (In-C3 and In-C7), 121.4 (In-C4), 123.9 (In-C5), 127.0 (In-C6), 128.7 (In-C3a), 133.0 (In-C2), 138.7 (In-C7a), 197.0 (C=O); ms (m/z,%) 258 (M^+, 62), 241 (14), 240 (24), 201 (22), 144 (16), 114 (22), 89 (29), 71 (47), 70 (100), 44 (27), 42 (25). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.03; N, 10.89. Found: C, 69.42; H, 7.05; N, 10.55.

Method B. A solution of dithiane **21** (0.1 g, 0.28 mmol) in THF (1 ml) was added via syringe under argon atmosphere to a stirred mixture of red mercury (II) oxide (0.12 g, 0.56 mmol), boron trifluoride etherate (0.15 ml, 0.56 mmol), and 15% aqueous THF (3 ml) maintained at room temperature. The resulting mixture was stirred for 20 min. When a white precipitate was observed, ether (5 ml) was added and the precipitate salts were filtered. The organic layer was washed with aqueous sodium carbonate and brine, dried, and evaporated to give ketone **29** (25 mg, 35%).

3-Ethyl-3-hydroxy-1-methyl-4-piperidyl 1-Methyl-2-indolyl Ketone (**27**). To a solution of **20** hydrochloride (5.4 g, 12.8 mmol) in ethanol (200 ml) cooled at 0°C was added sodium perchlorate (3.0 g, 14 mmol) in water (10 ml). The mixture was stirred at room temperature for 12 h and then evaporated. The residue was dissolved in aqueous sodium carbonate and extracted with ether. The extract was dried and evaporated to give crude sulfoxide **23** (4.6 g, 88%). This sulfoxide was dissolved in 50% aqueous acetic acid (100 ml) and heated at 50-60°C overnight. The mixture was basified with solid sodium carbonate and extracted with ether. The organic extracts were dried and evaporated to give ketone **27** (1.8 g, 53%); mp 168-169°C (acetone-ether); ir ($CHCl_3$) 3200-3600 (OH), 1645 (CO); ^{1}H-nmr 0.90 (t, 3H, $CH_2\underline{C}H_3$), 1.4-1.7 (m, 2H, $C\underline{H}_2CH_3$), 2.39 (s, 3H, NCH_3), 2.2-2.7 (m, 4H, NCH_2CH_2), 2.50 and 2.95 (br d and d, J=11 Hz, 1H each, 2-H), 3.63 (m, $W_{1/2}$=11 Hz, 1H, 4-H), 4.05 (s, 3H, In-NCH_3), 7.1-7.2 (m, 2H, In-H), 7.3 -7.4 (m, 1H, In-6H), 7.69 (dt, J=7.7 and 1.1 Hz, 1H, In-7H); ^{13}C-nmr 7.1 ($CH_2\underline{C}H_3$), 26.3 ($\underline{C}H_2CH_3$), 29.3 (C-5), 32.4 (NCH_3), 46.1 (NCH_3), 49.4 (C-4), 51.6 (C-6), 61.8 (C-2), 71.6 (C-3), 110.3 (In-C3), 111.8 (In-C7), 120.8 (In-C4), 123.1 (In-C5), 125.7 (In-C6), 126.0 (In-C3a), 135.4 (In-C2), 140.4 (In-C7a), 196.0 (C=O); ms (m/z,%) 300 (M^+, 6), 283 (23), 243 (16), 200 (33), 158 (40), 144 (30), 124 (100), 114 (25), 89 (27). Anal. Calcd for $C_{18}H_{24}N_2O_2$ C, 71.97; H, 8.05; N, 9.33. Found: C, 71.86; H, 7.95; N, 9.12.

4-Hydroxy-1-methyl-4-piperidyl 1-Methyl-2-indolyl Ketone (**28**). Operating as above, from **5** hydrochloride (0.82 g, 2.07 mmol), ethanol (100 ml), sodium perchlorate (0.48 g, 2.27 mmol), and water (5 ml), crude sulfoxide **24** (0.75 g) was obtained. A solution of **24** (0.75 g), THF (100 ml), and concentrated hydrochloric acid (10 ml) was refluxed for 6 h under argon atmosphere. The cooled mixture was poured into aqueous potassium carbonate and extracted with

ether. Evaporation of the dried extracts, followed by flash chromatography (9:1,ether-diethylamine) gave ketone **28** (0.3 g, 54%); mp 156-157°C (ether-acetone) ir (KBr) 1650 (CO); ^{1}H-nmr 1.75 (br d, J=11 Hz, 2H, 3-He), 2.36 (s, 3H, NCH_3), 2.50 (td, J=11 and 1.5 Hz, 2H, 2-Ha), 2.63 (td, J=11 and 2.5 Hz, 2H, 3-Ha), 2.85 (br d, J=11 Hz, 2H, 2-He), 4.05 (s, 3H, In-3Ha), 7.1-7.2 (m, 2H, In-H), 7.38-7.42 (m, 1H, In-6H), 7.68 (dt, J=8 and 1Hz, In-7H), 7.80 (s, 1H, In-3H); ^{13}C-nmr 32.7 (In-NCH_3), 36.4 (C-3), 46.2 (NCH_3), 51.4 (C-2), 110.3 (In-C3), 113.8 (In-C7), 120.8 (In-C4), 123.2 (In-C5), 125.9 (In-C6), 126.3 (In-C3a), 130.9 (In-C2), 139.7 (In-C7a), 197.7 (C=O); ms (m/z,%) 272 (M^+, 29), 254 (100), 215 (69), 158 (30), 131 (10), 114 (17), 89 (68), 70 (71). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.28. Found: C, 70.22; H, 7.50; N, 10.07.

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