SYNTHETIC APPLICATIONS OF 2-(1,3-DITHIAN-2-YL)INDOLES.[1,2] A NEW SYNTHETIC APPROACH TO STRYCHNOS ALKALOIDS

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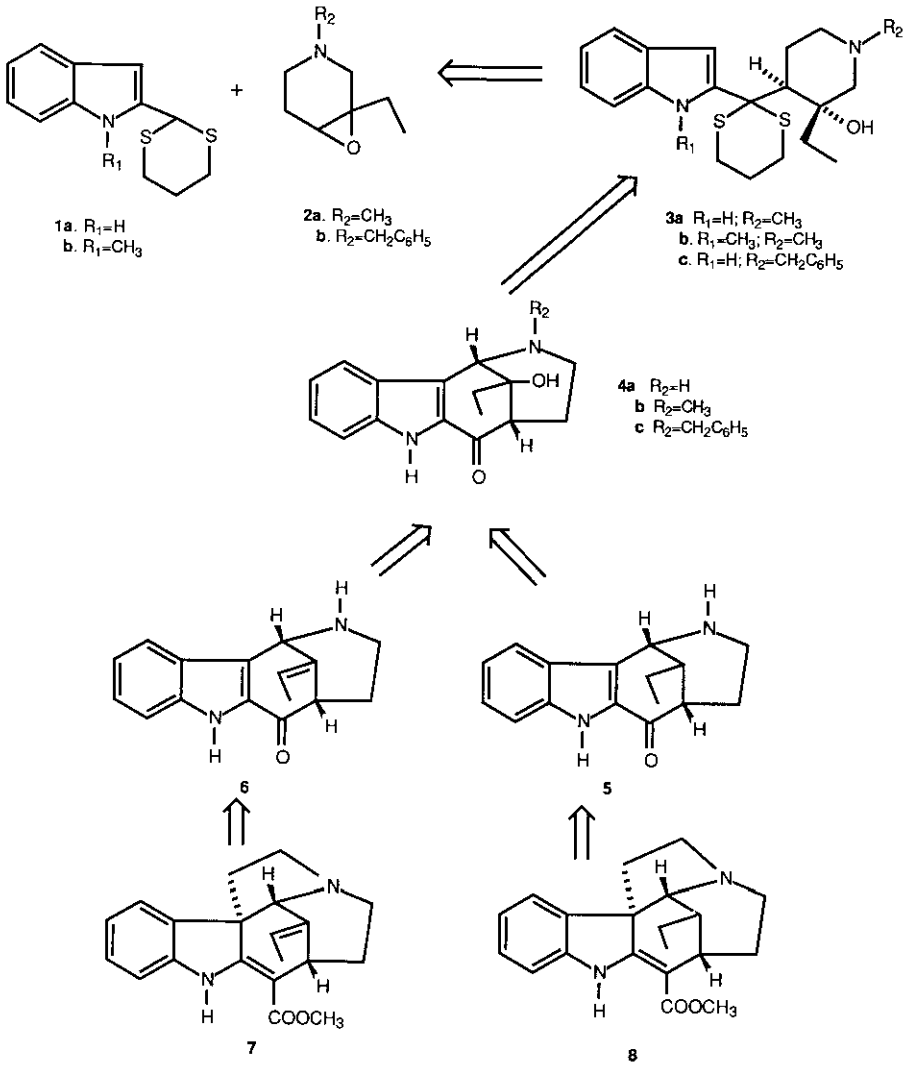
Abstract- The first synthesis of Na-methyl-20-hydroxydasycarpidone **17b** and the tetracyclic systems **16a** and **16b** are reported. The synthesis involves an acid cyclization of an appropriate 4-indolyl - carbonyl-2-piperidinecarbonitrile **15** which in turn is obtained regioselectively from the corresponding piperidinol **9** by a modified Polonovski reaction.

In the retrosynthetic analysis outlined in Scheme 1, aimed at the total synthesis of the pentacyclic Strychnos alkaloids condilocarpine (**7**) and tubotaiwine (**8**),[3] the alkaloid N-demethyldasycarpidone (**5**)[4] and its dehydro derivative **6**, unknow at present, are key intermediates. A variety of methods have been developed to construct the "E-ring" of the target alkaloids from such tetracyclic precursors[5] and the necessary transformation of the C-keto group in both **5** and **6** can in principle be achieved using standard reactions.[6]

In recent studies[1,7] we demonstrated that the indole dithiane **1a** could be prepared both by reaction of the C-2 anion of 1-benzenesulfonylindole with 2-chloro-1,3-dithiane, or by reaction of the precursor 1-phenylsulfonylindole-2-carbaldehyde with 1,3-propanedithiol in acidic medium, followed by treatment of the resultant intermediate with aqueous base. It was further shown that the dianion derived from **1a** reacts with epoxide **2a** to give the trisubstituted piperidine **3a** in high yield.[1] The closely related reaction of the anion of the N-methylindolyldithiane **1b** with epoxide **2a** was also efficient providing access to compound **3b**. In a continuation of our work on the chemistry of 2-(1,3-dithian-2-yl)indoles we describe in this report results on the preparation of the N-methyl derivative **17b** of 20-hydroxydasycarpidone **4b**[12] (Scheme 1), whose



Scheme 1

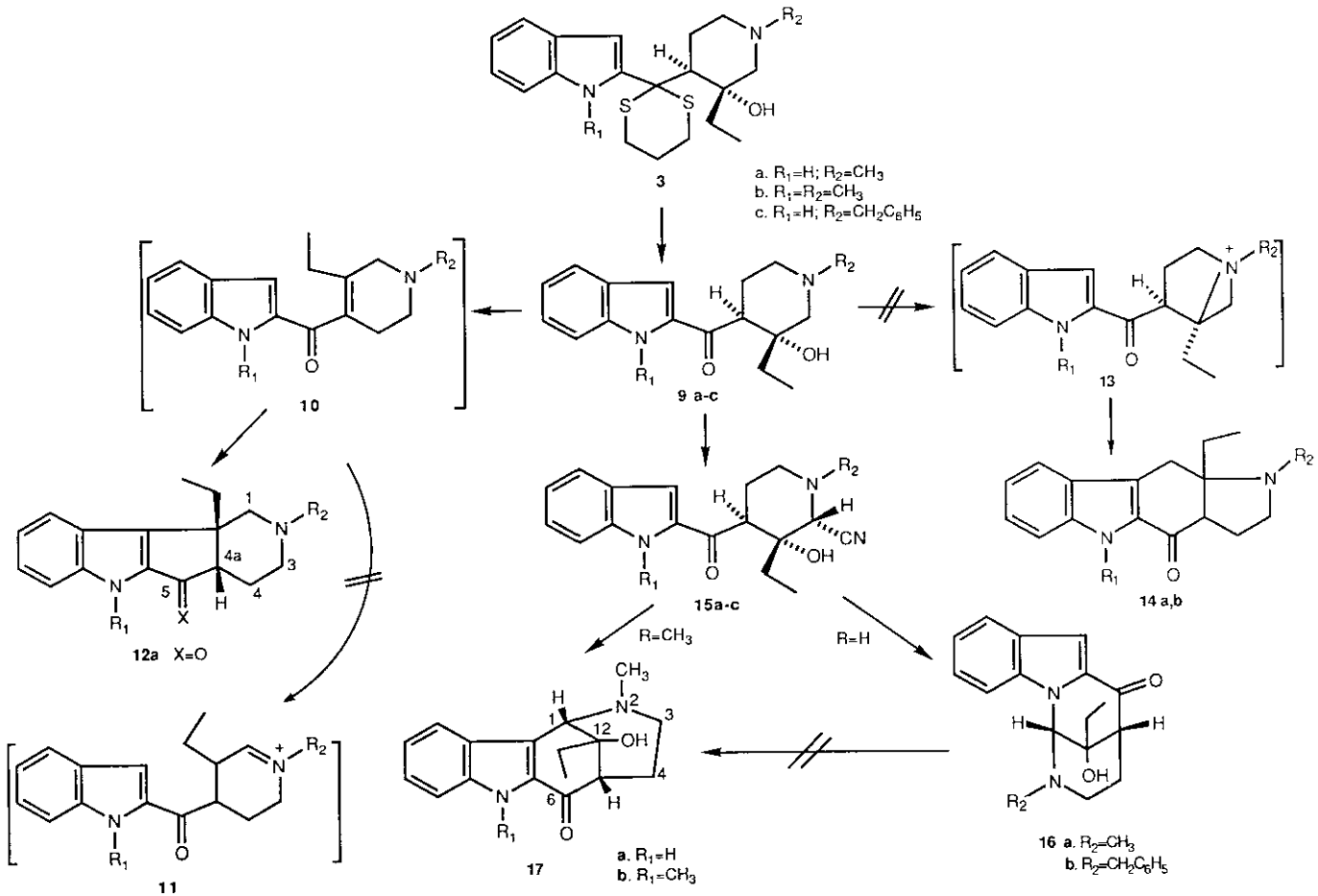
N-demethyl analogue constitutes the projected precursor to indoles **5** and **6**.

Compounds **3a** and **3b** were obtained from the anions of dithianes **1a** and **1b** with epoxide **2a** in THF at -20 °C [1] in 91% and 73% yield, respectively. Compound **3c,** with a benzyl group upon the piperidine nitrogen atom, was similarly obtained in 65% yield from reaction of the anion of dithiane **1a** with epoxide **2b**. The large coupling constant (J~11 Hz) observed for the C-4 proton in the ^{1}H-nmr spectra of these compounds revealed that the bulky C-4 dithianylindole substituent was equatorial in the preferred piperidine ring conformation (Table 1). Assuming that the attack on the

epoxide by the dithiane anion occurs at C-4 from the axial direction it follows that the relative C_4(dithianyl)-C_3(ethyl) stereochemistry is cis. Conversion of dithianes **3a-c** to the corresponding ketones **9a-c** was achieved in two steps involving oxidation of sulphur and then hydrolysis of the resultant sulfoxide. From the small coupling constant ($W_{1/2}$~10 Hz) for the C-4 proton of the products and from the observed "γ-gauche" effect on carbon-2 (Δδ~2 ppm) and in particular on carbon-6 absorptions (Δδ~4 ppm) in their ^{13}C-nmr spectra it was determined that hydrolysis of the ketone was accompanied by a change in the piperidine ring conformation so as to place the keto substituent axial (Table 1).

Initial attempts to activate the piperidine C-2 position with respect to cyclization with the indole moiety were directed toward elimination of a molecule of water to give the α,β-unsaturated ketone **10**,[13,14] as under the acid conditions of the reaction it is conceivable that isomerization of the carbon-carbon double bond[15] would occur generating iminium ion intermediate **11**. However, refluxing of compound **9a** in 6N hydrochloric acid gave a single product (yield 65%) whose nmr data did not correlate with the dasycarpidone skeleton. Two structures **12a** and **14a** were considered for this product. Compound **12a** would be obtained if the initially formed α,β-unsaturated ketone **10** underwent a Nazarov-type electrocyclization[16] before double bond shift occurred, or by a Friedel-Crafts type reaction[17], and compound **14a** is viewed as being formed via ring opening of an aziridinium ion intermediate **13**.[18] Differentiation between these two possibilities was made on the basis of the chemical shifts of aliphatic carbons in the ^{13}C-nmr spectrum. In particular the relatively downfield chemical shift of the C-1 at δ 67.4 is only consistent with structure **12a**.[19] The similar conversion of dithiane **3a** to the tetracyclic indole **12** (X=$SCH_2CH_2CH_2S$) seems to support the Frieldel-Crafts hypothesis.

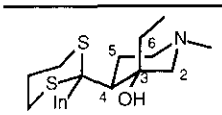
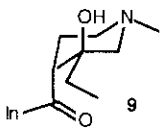
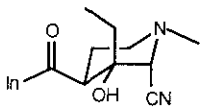
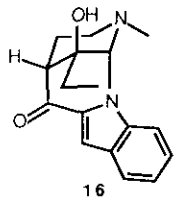
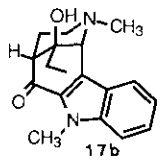
In view of this result an alternative approach was followed for the activation of the piperidine C-2 center which involved conversion of compounds **9a-c** to the corresponding α-aminonitriles **15a-c** by modified Polonovski reaction[20] of their N-oxides followed by trapping the intermediate iminium ions with cyanide ion.[21] Although the formation of the two regioisomeric α-aminonitriles might be expected in these Polonovski reactions, a single regioisomer was observed (tlc and nmr examination).[22] It was readily evident from the appearance of the α-aminonitrile methine proton as a sharp singlet (δ~3.9) that introduction of cyanide only occurred at C-2 . The origin of this remarkable regioselectivity is unknown at present; however, an analogous result was obtained from the reaction of epipandoline N-oxide with trifluoroacetic anhydride and potassium cyanide.[23]


3
a. R1=H; R2=CH3
b. R1=R2=CH3
c. R1=H; R2=CH2C6H5
9 a-c
10
13
14 a,b
12a X=O
15a-c
R=CH3
R=H
11
17
a. R1=H
b. R1=CH3
16 a. R2=CH3
b. R2=CH2C6H5

Scheme 2

It was also clear from the occurrence of the C-4 hydrogen (δ~3.8) as a doublet of doublets (J~12 and 4 Hz) that the piperidine ring prefers the conformation in which the ketone substituent is equatorial and the C-3 ethyl group is axial (Table 1). The axial orientation of the cyano

Table 1. General Nmr Data of Compounds **3**, **9**, **15**,**16**, and **17**

	^{13}C-nmr(δ)					^{1}H-nmr(δ)	
	C-2	C-3	C-4	C-5	C-6	4-H	CH_2-CH_3
 **3**	64	76	60	27	57	2.69 br d J=12 Hz	1.70-2.20 masked
 **9**	61	71	49	29	51	3.60 br s $W_{1/2}$ 11 Hz	1.40-1.70 m
 **15**	63	72	49	25	49	3.80 dd J~11 and 5 Hz	1.56 m 1H 2.12 m 1H
 **16**	73	71	50	25	45	2.80 br s $W_{1/2}$ 9 Hz	1.43 m 1H 1.36 m 1H
 **17b**	61	74	53	25	45	2.64 br s $W_{1/2}$ 8.5 Hz	1.43 m 1H 1.52 m 1H

group follows from stereoelectronic arguments[24] and was confirmed by measurement of the $J_{C\text{-}H}$ coupling constant of the C-2 position . A value of 149 Hz for the aminonitrile **15b** indicates

that the C-2 hydrogen is equatorial. In the 2D nOe spectrum a strong nOe effect was observed between the ethyl protons and the equatorial proton of 2-position.[25] Comparison of the ^{1}H-nmr spectrum of indolylcarbonylpiperidines **9** with α–aminonitriles **15** permits to observe different chemical shift values for the axial and equatorial orientations of the ethyl group. Thus, in **9** the methylene protons of ethyl group appear at δ~1.4-1.7 whereas in α-aminonitrile **15** the axial disposition of the ethyl chain provides two more deshielded signals for the non equivalent protons (δ 1.56 and 2.12; Δδ=0.56 ppm) . The change of piperidine ring conformation between **9** and **15** can be explained by considering the $A^{(1,2)}$ strain[26] between the equatorial ethyl chain and the C-2 proton in the intermediate piperidinium salt .

As anticipated, cyclization of **15a** under acidic conditions led to formation of compound **16a** and not **17a**, since an analogous ring closure was observed by Joule[13] in their synthesis of dasycarpidone and deethyldasycarpidone. However, these workers described that an acidic isomerization (50% AcOH, 95°C, 4 h; 60%) of the N-indole cyclized product to the C3-indole cyclized isomer could be effected. Unfortunately, a similar isomerization of **16a** to **17a** could not be achieved under the same conditions. Identical problems were encountered in the reaction of the N-benzyl substituted α-aminonitrile **15c** with acid which gave **16b** exclusively.

The configuration of C-12 in the tetracyclic compounds **16** was inferred from 2D-nOe spectrum. Thus, the equatorial disposition of the ethyl group was deduced from the absence of a nOe effect with the axial C-4 proton but its existence with the equatorial C-1 methine proton as well as the C-7 and C-8 indolyl protons. Moreover, the chemical shifts of two methylene non-equivalent protons (δ~1.36 and 1.43; Δδ~0.07 ppm) are indicative of this equatorial disposition.

This regiochemical problem was circumvented in the reaction of aminonitrile **15b**. In this case, where the indole nitrogen is substituted by a methyl group, clear conversion to Na-methyl-20-hydroxydasycarpidone **17b** was observed. Compound **17b** was obtained in 42% yield after purification on column chromatography. The tetracyclic compound **17b** shows in the ^{1}H-nmr spectrum characteristic signals at δ 4.05 and 2.64 for the methine C-1 and C-5 protons, respectively. The ethyl group adopts, also in this case, an equatorial disposition as was confirmed by the chemical shifts (δ 1.43 and 1.52) and the lower Δδ between the two methylene protons of ethyl groups. To our knowledge 20-hydroxydasycarpidone has not yet been isolated from plant extracts. The transformation of compound **17b** to key intermediates **5** and **6** is presently being studied.

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 using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. The 2D-nmr spectra of homo- and heteronuclear correlation, and 2D-nOe spectra, were recorded on a Bruker 200 by Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette. 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 0.0063-0.200 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 Departament de Química Orgànica Biològica, Barcelona.

1-Benzyl-3-ethyl-3,4-epoxypiperidine (**2b**). To a solution of 1-benzyl-3-ethyl-1,2,5,6-tetrahydropyridine[27] (10.4 g, 51.7 mmol) and trifluoroacetic acid (1.85 ml, 24.8 mmol) in 7:3 water-dioxane (150 ml), was added N-bromosuccinimide (4.88 g, 27.4 mmol) portionwise. The mixture was stirred at room temperature for 1.25 h and then cooled to 0°C. Sodium carbonate (5.3 g, 49.7 mmol) 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 (2.1 g, 37.3 mmol) in methanol (100 ml) at room temperature for 2 h. The reaction mixture was diluted with water and extracted with ether. The organic extracts were dried, evaporated, and chromatographed (1:1 hexane-ether) to give 1-benzyl-3-ethyl-3,4-epoxypiperidine as an oil (4 g, 74%); ^{1}H-nmr 0.91 (t, J=7 Hz, 3H, CH_2CH_3), 1.40-1.65 (m, 2H, CH_2CH_3), 1.90-2.00 (m, 3H, 5-H and 6-Ha), 2.15-2.35 (m, 3H, 2-H and 6-He), 2.61 (d, J=13 Hz, 1H, CH_A-Ar), 2.84 (dd, J=13 and 1.2 Hz, 1H, CH_B-Ar), 3.06 (t, J= 2.4 Hz, 1H, 4-H), 7.20-7.30 (m, 5H, Ar-H); ^{13}C-nmr 8.4 (CH_3), 25.7 (C-5), 28.9 (CH_2CH_3), 45.8 (C-6), 55.3 (C-2), 56.5 (C-4), 60.3 (C-3), 62.3 (CH_2-Ar), 127.0 (C-para), 128.2 (C-meta), 128.9 (C-ortho), 138.0 (C-ipso); ms (m/z, %) 217 (M^+, 6), 200 (9), 134 (8), 126 (11), 91 (100), 65 (15), 42 (15). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 76.99; H, 8.80; N, 6.32.

1-Benzyl-3-ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]-3-piperidinol (**3c**). n-Butyllithium (1.6 M, 20 ml, 32 mmol) was slowly added via syringe to a cooled (-20°C) solution of dithiane **1a** (3.43 g, 14.6 mmol) in anhydrous THF (150 ml) under argon atmosphere. The mixture was stirred for 20 min and the epoxide **2b** (3.8 g, 17.5 mmol) was added at -20°C . After stirring for 30 min, the reaction mixture was quenched at -20°C with aqueous ammonium chloride and extracted with ether. The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (ether) to give alcohol **3c** (4.3 g, 65%); mp 221-223°C (ether-acetone); ir (KBr) 3420 (OH), 3500 (NH); ^{1}H-nmr ($CDCl_3$+CD_3OD) 0.64 (t, J= 7 Hz, 3H, CH_2CH_3), 1.47 (d, J=11 Hz, 1H, 2-Ha), 1.80-2.30 (m, 7H), 2.62 (dt, J=14.3 and 4.4 Hz, 1H, 6-He), 2.69 (dd, J=11 and 1.2 Hz, 1H, 4-Ha), 2.50-3.00 (m, 5H, SCH_2 and 2-He), 3.31 (d, J=13.2 Hz, 1H, CH_A-Ar), 3.52 (d, J=13.2 Hz, 1H, CH_B-Ar), 6.80 (s, 1H, In-3H), 7.09 (t, J=7 Hz, 1H, In-5H), 7.18 (t, J=7 Hz, 1H, In-6H),

7.37 (d, J=7 Hz, 1H, In-4H), 7.58 (d, J=7 Hz, 1H, In-7H), 9.30 (br s, 1H, NH); ms (m/z, %) 452 (M^+, 1), 235 (7), 199 (3), 160 (9), 133 (2), 91 (100), 43 (22). Anal. Calcd for $C_{26}H_{30}N_2OS_2$: C, 69.00 ; H, 7.13; N, 6.19; S, 14.16. Found: C, 69.18; H, 7.11; N, 6.08; S, 14.10.

1-Benzyl-3-ethyl-3-hydroxy-4-piperidyl 2-Indolyl Ketone (**9c**). A solution of dithiane **3c** (1.5 g, 3.32 mmol) and 85% MCPBA (0.72 g, 3.98 mmol) in dichloromethane (120 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 3:7 diastereomeric mixture of 1-benzyl-3-ethyl-4-[2-(2-indolyl)-1-oxide-1,3-dithian-2-yl]-3-piperidinol (1 g, 67%) which was separated by flash chromatography (98:2 ether-diethylamine). Lower Rf (equatorial sulfoxide) : mp 182-185°C (ether-acetone); ir ($CHCl_3$) 3320 (OH), 3525 (NH); ^{1}H-nmr 0.80 (t, J=7 Hz, 3H, CH_2CH_3), 3.30 (d, J=11 Hz, 1H, CH_A-Ar), 3.50 (d, J=11 Hz, 1H, CH_B-Ar), 6.75 (s, 1H, In-3H), 7.13 (t, J=6 Hz, 1H, In-5H), 7.25 (t, J=6 Hz, 1H, In-6H), 7.37 (d, J=6 Hz, 1H, In-4-H), 7.62 (d, J=6 Hz, 1H, In-7H), 10.45 (br, 1H, NH); ^{13}C-nmr 6.8 (CH_3), 24.9 (SCH_2CH_2), 26.0 (C-5), 27.5 (CH_2CH_3), 29.2 (SCH_2), 47.4 ($SOCH_2$), 53.9 (C-6), 54.7 (C-4), 62.3 (C-2), 63.0 (NCH_2Ar) ,68.7 (SCS), 75.3 (C-3), 107.0 (In-C3), 107.0 (In-C7), 119.9 and 120.3 (In-C4 and In-C5), 122.5 (In-C6), 126.0 (In-C3a), 127.2 (C-para), 128.2 and 129.2 (C-ortho and C-meta), 134.7 (In-C2), 136.5 (In-C7a), 138.2 (C-ipso); ms (m/z, %) 468 (M^+, 0.3), 216 (1), 199 (3), 189 (17), 159 (2), 91 (100), 89 (7), 65 (6), 57 (9), 42 (4). Higher Rf (axial sulfoxide) : ir ($CHCl_3$): 3540 (NH), 3200-3400 (OH); ^{1}H-nmr 0.61 (t, J=7 Hz, 3H, CH_2CH_3), 3.35 (d, J=11 Hz, 1H, CH_A-Ar), 3.50 (d, J=11 Hz, 1H, CH_B-Ar), 6.80 (s, 1H, In-3H), 7.14 (t, J=7 Hz, 1H, In-5H), 7.21 (t, J=7 Hz, 1H, In-6H), 7.42 (d, J=7 Hz, 1H, In-4H), 7.64 (d, J=7 Hz, 1H, In-7H), 10.4 (br, 1H, NH); ^{13}C-nmr 6.6 (CH_3), 25.1 (SCH_2CH_2), 26.2 (C-5), 29.3 (SCH_2), 46.4 ($SOCH_2$), 52.5 (C-6), 53.9 (C-4), 61.1 (C-2), 62.4 (NCH_2Ar), 68.4 (SCS), 74.8 (C-3), 105.8 (In-C3), 112.3 (In-C7), 120.4 (In-C4), 120.5 (In-C5), 123.0 (In-C6), 126.0 (In-C3a), 127.1 (C-para) , 128.2 and 129.2 (C-ortho and C-meta), 134.0 (In-C2), 136.2 (In-C7a), 138.4 (C-ipso); ms (m/z, %) 468 (M^+, 6), 362 (1), 305 (1), 216 (3), 190 (54), 130 (7), 91 (100), 65 (6), 57 (10), 42 (5). Anal. calcd for $C_{26}H_{31}N_2O_2S_2Cl$: C, 61.82; H, 6.59, N. 5.55, S, 12.69. Found: C, 61.80; H, 6.61; N, 5.45, S, 13.05.

A solution of a mixture of sulfoxides (3.8 g, 8.11 mmol) and 50% acetic acid (300 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 (99:1 ether-diethylamine) afforded ketone **9c** (2 g, 70%): mp 247-250 °C (acetone); ir (KBr) 1640 (C=O), 3100-3500 (OH); ^{1}H-nmr 0.84 (t, J=7 Hz, 3H, CH_2CH_3), 1.45-1.60 (m, 2H, CH_2CH_3), 1.80 (br d, J=13 Hz, 1H, 5-He), 2.20-2.40 (m, 1H, 5-Ha), 2.50-2.70 (m, 3H, 2-Ha and 6-H), 3.00 (d, J= 10.4 Hz, 1H, 2-He), 3.58 (d, J=13 Hz, 1H, CH_A-Ar), 3.60 (masked, 1H, 4H), 3.67 (d, J=13 Hz, 1H, CH_B-Ar), 7.18 (t, J=6 Hz, 1H, In-5-H), 7.25 (s, 1H, In-3H), 7.35 (t, J=7 Hz, 1H, In-6H), 7.42 (d, J=7 Hz, 1H, In-6H), 7.71 (d, J=7 Hz, 1H, In-7H), 9.20 (br s, 1H, NH); ^{13}C-nmr 6.9 (CH_2CH_3), 26.1 (CH_2CH_3), 29.3 (C-5), 49.0 (C-4), 49.3 (C-6), 59.6 , (C-2), 62.5 (CH_2Ar), 71.4 (C-3), 109.7 (In-C3), 112.1 (In-C7), 121.0 (C-4), 123.2 (In-C5), 126.5 (In-C6), 127.2 (Ar-para), 127.6 (In-C3a), 128.3 (C-ortho), 129.0 (C-meta), 135.5 (In-C2), 137.5 (In-C7a), 137.5 (C-ipso), 194.7 (C=O); ms (m/z, %) 361 (M^+, 7), 343 (2), 305 (7), 199 (11), 185 (18), 143 (17), 91 (100), 65

(12), 57 (11), 42 (9). Anal. Calcd for $C_{23}H_{25}N_2O_2Cl$: C, 69.25; H, 6.82; N, 7.02. Found: C, 69.56; H, 6.76, N, 7.02.

cis-1-Ethyl-3-methyl-7-oxo-1,2,3,4,5,6-hexahydro-1,6-methanoazonino[5,4-b]indole (**12a**). A solution of ketone **9a** (1.0 g, 3.49 mmol) in 6N hydrochloric acid (80 ml) was refluxed for 5 h. The reaction mixture was basified with solid sodium carbonate and extracted with ether. The organic extracts were dried and evaporated , and the residue was purified by flash chromatography (99:1 ether-diethylamine) to give tetracyclic ketone **12a** as an oil (0.61 g, 65%) ; ir ($CHCl_3$) 1640 (CO), 3460 (NH) ; ms (m/z, %) 268 (M^+, 18) , 223 (7), 197 (32), 58 (100); ^{1}H-nmr 0.91 (t, J=7 Hz, 3H, CH_2CH_3), 1.90-2.10 (m, 1H, 3-Ha), 2.02 (br d, J= 8 Hz, 1H, 4-He), 2.14 (d, J=11.7 Hz, 1H, 1-Ha), 2.10-2.20 (masked, 2H, CH_2CH_3), 2.16 (s, 3H, NCH_3), 2.32 (dddd, J=8, 6.5, 2.5, and 2 Hz, 1H, 4-Ha), 2.55-2.65 (m, 1H, 3-He), 2.89 (dd, J=8 and 2 Hz, 1H, 4a-H), 2.94 (br d, J=11.7 Hz, 1H, 1-He), 7.17 (ddd, J= 8, 7, and 1.2 Hz, 1H, In-9H), 7.36 (ddd, J=8, 7, and 1.2 Hz, 1H, In-8H), 7.48 (dt, J=8 and 1.2 Hz, 1H, In-7H), 7.69 (br d, J=8 Hz, 1H, In-10H), 9.00 (br, 1H, NH); ^{13}C-nmr 9.6 (CH_2CH_3), 22.3 (C-4), 29.2 (CH_2CH_3), 45.0 (C-10c), 46.4 (NCH_3),53.0 (C-4a), 53.5 (C-3), 67.3 (C-1), 113.9 (C-7), 120.5 (C-9), 121.7 (C-10), 122.6 (C-10a), 126.7 (C-8), 137.4 (C-10b), 143.6 (C-5a), 150.0 (C-6a), 195.9 (C-5). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.04; H, 7.55; N, 10.52.

cis-1-Ethyl-3-methyl-7,7-propylenedithio-2,3,4,5,6,7-hexahydro-(1H)-1,6-methanoazonino[5,4-b] indole (**12a**; X=$SCH_2CH_2CH_2S$). Operating as above from dithiane **3a** (1.0 g, 2.56 mmol) and 6N hydrochloric acid (80 ml), the tetracyclic compound **12a** (X=$SCH_2CH_2CH_2S$) was obtained (0.63 g, 70%): mp 88-89 °C (hexane); ir (KBr) 3240 (NH); ^{1}H-nmr 0.88 (t, J=7 Hz, 3H, CH_2CH_3), 2.34 (s, 3H, NCH_3), 3.25 (dd, J= 10 and 5 Hz, 1H, 4a-H), 7.10 (t, J=7 Hz, 1H, In-9H), 7.20 (t, J=7 Hz, 1H, In-8H), 7.35 (d, J=7 Hz, 1H, In-7H), 7.50 (d, J=7 Hz, 1H, In-10H), 8.15 (br, 1H, NH); ^{13}C-nmr 9.4 (CH_2CH_3), 22.9 (C-4), 23.9 (SCH_2CH_2), 27.6 (SCH_2), 28.9 (CH_2CH_3),45.6 (C-10c), 46.2 (NCH_3), 53.7 (C-4a), 54.6 (C-3), 55.9 (C-5), 64.3 (C-1), 112.0 (C-7), 118.5 and 119.6 (C-10 and C-9), 121.1 (C-10a), 122.6 (C-8), 136.1 (C-10b), 140.4 (C-5a), 145.5 (C-6a); ms (m/z, %) 358 (M^+, 14), 251 (18), 223 (59), 180 (39), 58 (100) . A sample of tetracyclic product was precipitated as hydrochloride: mp 222-223 °C (acetone). Anal. Calcd for $C_{20}H_{27}N_2S_2Cl$: C, 60.81; H, 6.89; N, 7.09. Found: C, 60.55; H, 7.05; N, 6.95.

2-Cyano-3-ethyl-3-hydroxy-1-methyl-4-piperidyl 2-Indolyl Ketone (**15a**). To a solution of ketone **9a** (1.5 g, 5.24 mmol) in dichloromethane (70 ml) stirred under nitrogen atmosphere at 0 °C, MCPBA (85% Merck, 1.17 g, 5.77 mmol) in dichloromethane (10 ml) was added. The reaction mixture was stirred at 0 °C for 1 h, cooled at -15 °C, and the trifluoroacetic anhydride (2.65 ml, 18.34 mmol) was added via syringe. The resulting reaction mixture was stirred at -15 °C for 1 h, and allowed to stir for 30 min at 0 °C. Following this period, a solution of potassium cyanide (10.2 g, 75.72 mmol) in water (8 ml) was added to the reaction mixture and the aqueous layer was quickly adjusted to pH 5.0 by the addition of solid sodium acetate. The resultant two-phase reaction mixture was stirred rapidly for 30 min, basified with 10% aqueous sodium carbonate, and extracted with dichloromethane. The combined organic layers were washed with water, dried and evaporated to give compound **15a** (0.68 g, 42%) after purification on flash chromatography (1:1

petroleum ether-ether) : mp 161-162 °C (ether); ir ($CHCl_3$) 1630 (CO), 2225 (CN), 3400 (NH), 3200-3350 (OH); ^{1}H-nmr 0.86 (t, J=7.6 Hz, 3H, CH_2CH_3), 1.56 (m, 1H, CH_ACH_3), 1.76-1.90 (m, 1H, 5-He), 2.13 (m, 1H, CH_BCH_3), 2.45(s, 3H, NCH_3), 2.55 (td, J=11.7 and 3.6 Hz, 1H, 6-Ha), 2.85 (dt, J=11.7 and 4.6 Hz, 1H, 6-He), 3.77 (dd, J=12 and 4 Hz, 1H, 4-Ha), 3.92 (s, 1H, 2-He), 7.17 (t, J=7 Hz, 1H, In-5H), 7.30-7.50 (m, 2H, In-4H and In-6H), 7.41 (s, 1H, In-3H), 7.72 (d, J=7 Hz, 1H, In-7H), 9.20 (br, 1H, NH); ^{13}C-nmr 6.6 (CH_2CH_3), 24.8 and 25.6 (C-5 and CH_2CH_3), 44.0 (NCH_3), 49.4 (C-6), 49.5 (C-4), 63.0 (C-2), 72.7 (C-3), 112.0 and 112.2 (In-C3 and In-C7),115.6 (CN), 121.1 (In-C4), 123.5 (In-C5), 127.0 (In-C6), 127.4 (In-C3a), 135.9 (In-C2), 137.9 (In-C7a), 192.4 (C=O); ms (m/z, %) 293 (M^+-18, 8), 215 (20), 144 (34), 89 (56), 83 (55), 69 (44), 57 (100). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.60; H, 6.74; N, 13.43.

2-Cyano-3-ethyl-3-hydroxy-1-methyl-4-piperidyl 1-Methyl-2-indolyl Ketone (**15b**). Operating as above from ketone **9b** (730 mg, 2.43 mmol), MCPBA (85%, Merck, 563 mg, 2.67 mmol), trifluoroacetic anhydride (1.2 ml, 8.51 mmol) and potassium cyanide (478 mg, 7.29 mmol) in water (4 ml), α-aminonitrile **15b** (180 mg, 23%) was obtained after flash chromatography (dichloromethane): mp 146-148 °C (methanol); ir ($CHCl_3$) 1640 (CO), 3560 (OH), 2210 (CN); ^{1}H-nmr 0.87 (t, J=7.5 Hz, 3H, CH_2CH_3), 1.56 (m, 1H, CH_ACH_3), 1.75-1.90 (m, 1H, 5-He), 2.12 (m, 1H, CH_BCH_3), 2.46 (s, 3H, NCH_3), 2.57 (td, J=10.5 and 4 Hz, 1H, 6-Ha), 2.80 (dt, J=12 and 4.5 Hz, 1H, 6-He), 3.80 (dd, J=11 and 5 Hz, 1H, 4-Ha), 3.95 (s, 1H, 2-He), 4.06 (s, 3H, NCH3), 7.17 (ddd, J=7.8, 5.8 and 2 Hz, 1H, In-5H), 7.36-7.45 (m, 2H, In-4H and In-6H), 7.48 (s, 1H, In-3H), 7.73 (dt, J=7.8 and 1.2 Hz, 1H, In-7H); ^{13}C-nmr 6.7 (CH_2CH_3), 25.0 and 25.9 (C-5 and CH_2CH_3), 32.3 (NCH_3), 43.9 (NCH_3), 49.5 (J_{C-H}=134 Hz, C-6), 50.1 (J_{C-H}=133.9 Hz, C-4), 63.2 (J_{C-H}=149 Hz, C-2), 72.8 (C-3), 110.3 (In-C3), 113.4 (In-C7), 115.5 (CN), 121.0 (In-C4), 123.4 (In-C5), 125.7 (In-C3a), 126.6 (In-C6), 135.7 (In-C2), 140.9 (In-C7a), 193.3 (C=O). *Anal. Calcd for* $C_{19}H_{23}N_3O_2.CH_3OH$: C, 67.39; H,7.35; N, 11.79. Found: C, 67.55; H, 7.63; N, 11.83.

12-Ethyl-12-hydroxy-2-methyl-6-oxo-1,2,3,4,5,6-hexahydro-2,6-methano-1,3-diazocino[1,8-a]indole (**16a**). A stirred mixture of nitrile **15a** (0.5 g, 1.6 mmol) and anhydrous p-toluenesulfonic acid (0.7 g, 3.68 mmol) in toluene (80 ml) was refluxed with a Dean-Stark trap under an atmosphere of nitrogen for 16 h. The cooled mixture was basified with 20% aqueous sodium carbonate and extracted with ether. The combined organic layers were dried and evaporated to give the tetracyclic compound **16a** after flash chromatography (dichloromethane) (380 mg, 84%): mp 155-157 °C (acetone); ir ($CHCl_3$) 1670 (CO), 1350-1500 (OH); ^{1}H-nmr 0.87 (t, J=7 Hz, 3H, CH_2CH_3), 1.36 (m, 1H, CH_ACH_3), 1.43 (m, 1H, CH_BCH_3), 1.78-1.94 (m, 1H, 4-Ha), 2.00-2.20 (m, 1H, 3-Ha), 2.36-2.48 (m, 1H, 4-He), 2.48 (s, 3H, NCH_3), 2.53 (ddd, J=13, 6, and 0.9 Hz, 1H, 3-He), 2.78 (br s, $W_{1/2}$=9 Hz, 1H, 5-H), 5.14 (s, 1H, 1-H), 7.19 (ddd, J=7.7, 7, and 1.1 Hz, 1H, 9-H), 7.34 (br s, 1H, 7-H), 7.41 (ddd, J=7.7, 7, and 1.1 Hz, 1H, 10-H), 7.50 (dq, J=7.7 and 1.1 Hz, 1H, 11-H), 7.75 (dt, J=7.7 and 1.1 Hz, 1H, 8-H); ^{13}C-nmr 6.8 (CH_2CH_3), 25.0 (C-4), 29.3 (CH_2CH_3), 43.9 (NCH_3), 45.0 (C-3), 50.0 (C-5), 73.1 (C-1), 71.4 (C-12), 105.5 (C-7), 110.8 (C-11), 121.0 (C-9), 123.5 (C-8), 126.3 (C-10), 127.2 (C-7a), 134.4 (C-6a), 138.6 (C-11a), 192.8 (C-6); ms (m/z, %) 284 (M^+, 37), 227 (29), 144 (30), 110 (38), 69 (65), 57 (100). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C,74.97; H, 7.40; N, 10.28. Found: C, 74.68; H, 7.28; N, 10.11.

12-Ethyl-12-hydroxy-6-oxo-2,7-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (**17b**). Operating as above from α-cyanopiperidine **15b** (165 mg, 0.5 mmol), p-toluenesulfonic acid (230 mg, 1.21 mmol) in toluene (30 ml), compound **17b** (65 mg, 42%) was obtained after flash chromatography (1:1 hexane-ether): mp 145-146 °C (acetone-ether); ir ($CHCl_3$) 1655 (C=O), 3300-3500 (OH); ^{1}H-nmr 0.86 (t, J=7 Hz, 3H, CH_2CH_3), 1.43 (m, 1H, CH_ACH_3), 1.52 (m, 1H, CH_BCH_3), 1.60-1.80 (m, 1H, 4-Ha), 1.84-2.10 (m, 1H, 3-Ha), 2.37 (s, 3H, NCH_3), 2.42 (dd, J=12.6 and 5 Hz, 1H, 3-He), 2.32 (ddd, J=12, 8 and 1.5 Hz, 1H, 4-He), 2.64 (br, $W_{1/2}$=8.5 Hz, 1H, 5-H), 4.05 (d, J=1.1 Hz, 1H, 1-H), 4.13 (s, 3H, NCH_3), 7.19 (t, J=7.5 Hz, 1H, 9-H), 7.41 (t, J=7.5 Hz, 1H, 10-H), 7.42 (d, J=7.5 Hz, 1H, 8-H), 7.67 (d, J=7.5 Hz, 1H, 11-H); ^{13}C-nmr 7.1 (CH_2CH_3), 25.0 (C-4), 29.9 (CH_2CH_3), 31.6 (NCH_3), 43.9 (NCH_3), 45.1 (C-3), 53.1 (C-5), 60.7 (C-1), 73.8 (C-12), 110.6 (C-8), 119.1 (C-11b), 121.1 (C-10), 121.7 (C-11), 126.3 (C-11a), 126.7 (C-9), 132.6 (C-6a), 140.4 (C-7a), 193.6 (C=O); ms (m/z, %) 298 (M^+, 9), 264 (1), 241 (16), 144 (15), 181 (5), 168 (6), 57 (100). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.24; H, 7.51; N, 9.26.

2-Benzyl-12-ethyl-12-hydroxy-6-oxo-1,2,3,4,5,6-hexahydro-2,6-methano-1,3-diazocino[1,8-a]indole (**16b**). To a solution of ketone **9c** (0.85 g, 235 mmol) in dichloromethane (120 ml) stirred under nitrogen atmosphere at 0 °C, MCPBA (85% Merck, 469 mg, 2.58 mmol) in dichloromethane (40 ml) was added. The reaction mixture was stirred at 0 °C for 1 h and then was basified with 10% aqueous sodium carbonate and extracted with dichloromethane. The combined organic layers were dried and evaporated to give 1-benzyl-3-ethyl-3-hydroxy-1-oxide-4-piperidyl 2-indolyl ketone (0.7 g, 75%); ir ($CHCl_3$) 1640 (C=O), 3100-3300 (OH), 3440 (NH); ^{1}H-nmr ($CDCl_3$) 0.89 (t, J=7 Hz, 3H, CH_2CH_3), 1.36 (m, 1H, CH_ACH_3), 1.44 (m, 1H, CH_BCH_3), 1.73 (br d, J=13.6 Hz, 1H, 5-He), 3.54 (d, J=10 Hz, 1H, 2-Ha), 3.58 (t, J=10 Hz, 1H, 6-Ha), 3.75 (d, J=2 Hz, 1H, 4-Ha), 3.87 (d, J=10.2 Hz, 1H, 2-He), 4.38 (d, J=12 Hz, 1H, CH_A-Ar), 4.48 (d, J=12 Hz, 1H, CH_B-Ar), 7.17 (ddd, J=8, 6 and 2 Hz, 1H, In-5H), 7.25-7.60 (m, 2H, In-6H), 7.29 (d, J=2 Hz, 1H, In-3H), 7.73 (dd, J=8 and 1 Hz, 1H, In-7H), 9.20 (br s, 1H, NH); ^{13}C-nmr 6.4 (CH_2CH_3), 21.1 (CH_2CH_3), 30.7 (C-5), 47.0 (C-4), 59.4 (C-6), 65.1 (NCH_2Ar), 76.5 (C-2), 111.3 (In-C3), 112.8 (In-C7), 121.5 (In-C4), 123.7 (In-C5), 127.4 (In-C6), 127.7 (In-C3a), 128.9 (C-para), 129.3 (C-meta), 133.1 (C-ortho), 135.1 (In-C2), 138.7 (In-C7a), 138.8 (C-ipso) , 195.3 (C=O).

To a solution of the N-oxide (0.7 g, 1.85 mmol) in dichloromethane (50 ml) stirred under an atmosphere of nitrogen at -15 °C, trifluoroacetic anhydride (1.15 ml, 8.23 mmol) was added via syringe. The resulting mixture was stirred 1 h at -15 °C and then 15 min at room temperature. Following this period, a solution of potassium cyanide (459 mg, 7.05 mmol) in water (2 ml) was added to the reaction mixture and the aqueous layer was quickly adjusted to pH 5.0 by the addition of solid sodium acetate. The resultant two-phase reaction mixture was stirred rapidly for 30 min, basified with 10% aqueous sodium carbonate, and extracted with dichloromethane. The combined organic layers were washed with water, dried and evaporated to give α-aminonitrile (0.55 g, 60 %); ir ($CHCl_3$) 3440 (NH), 2260 (CN), 1640 (C=O).

A stirred mixture of α-aminonitrile (0.43 g, 1.1 mmol) and anhydrous p-toluenesulfonic acid (0.7 g, 3.68 mmol) in anhydrous toluene (80 ml) was refluxed with a Dean-Stark trap under an atmosphere of nitrogen for 16 h. The cooled mixture was basified with 20% aqueous sodium carbonate and extracted with ether. The combined organic layers were dried and evaporated to

give the tetracyclic compound **16b** (after flash chromatography, 130 mg, 32%): mp 217-219 °C (acetone); ir ($CHCl_3$) 3150-3400 (OH), 1650 (C=O); ^{1}H-nmr 0.87 (t, J=7 Hz, 3H, CH_2CH_3), 1.20-1.80 (m, 3H, 4-Ha and CH_2CH_3), 2.00-2.60 (m, 3H, 3-He and 4-He), 2.83 (br s, $W_{1/2}$= 9 Hz, 1H, 5-H), 3.42 (d, J=13 Hz, 1H, CH_A-Ar), 4.10 (d, J=13 Hz, 1H, CH_B-Ar), 5.32 (s, 1H, 1-H), 7.10-7.70 (m, 10H, Ar-H); ^{13}C-nmr 6.7 (CH_2CH_3), 25.4 (C-4), 29.2 (CH_2CH_3), 42.1 (C-3), 51.3 (C-5), 59.7 (CH_2Ar), 71.6 (C-12), 72.4 (C-1), 105.6 (C-7), 110.7 (C-11), 121.1 (C-9), 123.5 (C-8), 126.3 (C-10), 127.1 (C-7a), 127.7, 128.4, and 128.6 (phenyl), 135.0 (C-6a), 138.4 (C-11a), 193.5 (C=O). Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 77.01; H, 6.81; N, 7.79.

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