Pergamon

Tetrahedron, Vol. 52, No. 10, pp. 3563-3574, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00033-6

Synthetic Applications of 2-(1,3-Dithian-2-yl)indoles VI.[1] Synthesis of 20-Epidasycarpidone

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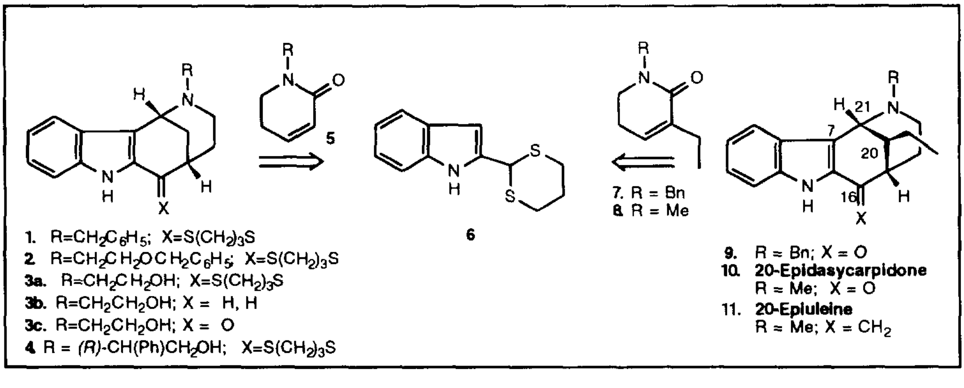
Abstract– 20-Epidasycarpidone (**10**) and its *N*-benzyl analogue **9** have been synthesized *via* a conjugate addition of 2-(1,3-dithian-2-yl)indole (**6**) and 3-ethyl-Δ^3-piperidein-2-ones **7** and **8**, respectively. The transformation of 20-epidasycarpidone to 20-epiuleine (**11**) has been carried out as described in the literature in order to corroborate the structural assignments.

Introduction

In the context of our studies on the synthesis of *Strychnos* alkaloids using 2-(1,3-dithian-2-yl)indoles as "umpoled" synthetic equivalents of 2-acylindoles, we recently reported the synthesis of dasycarpidone derivatives **1-4**.[1,2] Our approach to building the tetracyclic dasycarpidone framework was based on the conjugate addition of the dianion of dithianylindole **6** on Δ^3-piperidein-2-ones **5**, partial reduction of the amide moiety of the resulting adduct, and final acid treatment to close the C7-C21 bond.[3,4] Our subsequent aim has been the introduction of the C-20 ethyl chain, characteristic of the Aspidospermatan biogenetic subtype alkaloids. The closure of ring C by cyclization of an iminium salt upon the indole 3-position has been shown to



1. $R=CH_2C_6H_5$; $X=S(CH_2)_3S$
2. $R=CH_2CH_2OCH_2C_6H_5$; $X=S(CH_2)_3S$
3a. $R=CH_2CH_2OH$; $X=S(CH_2)_3S$
3b. $R=CH_2CH_2OH$; X = H, H
3c. $R=CH_2CH_2OH$; X = O
4. R = (*R*)-$CH(Ph)CH_2OH$; $X=S(CH_2)_3S$

6

7. R = Bn
8. R = Me

9. R = Bn; X = O
10. **20-Epidasycarpidone** R = Me; X = O
11. **20-Epiuleine** R = Me; X = CH_2

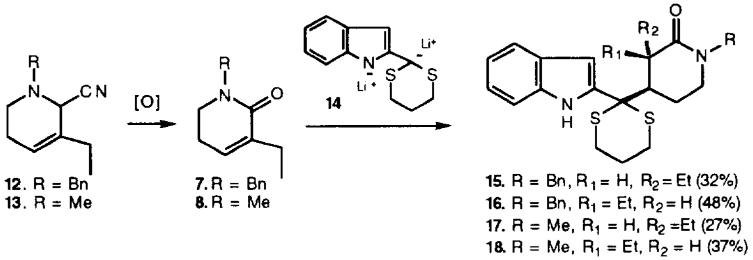
Scheme 1

yield predominantly 20-epidasycarpidone,[5] in which the ethyl chain is axial with respect to the piperidine ring (Scheme 1). However, the major isomer formed by an acid treatment of tetracyclic epianalogues lacking the C-16 ketone function is that with the ethyl substituent in an equatorial disposition.[5d] Accordingly, we had observed in previous work that the treatment of 2-cyano-3-ethyl-4-[2-(2-indolyl)-2-(1,3-dithianyl]piperidines with hot 50% aqueous AcOH yielded the (propylenedisulfanyl)dasycarpidone derivative with an equatorial configuration of the ethyl substituent.[2]

In the light of these precedents we considered that it should be possible to prepare dasycarpidone-type alkaloids by our methodology using 3-ethyl-Δ^3-piperideinones **7** and **8** as the piperidine synthons. We report here the synthesis of 20-epidasycarpidone (**10**), its *N*-benzyl analogue **9**, and 20-epiuleine (**11**).[5b]

Results and discussion

The starting 3-ethyl-Δ^3-piperideinones **7** and **8** were prepared by MCPBA or dioxirane[6] oxidation of the corresponding 2-cyano-3-ethyl-Δ^3-piperideines **12** and **13** (Scheme 2), which constitutes an alternative methodology to the classical oxidation of 2-piperidones.[7] Treatment of indolyldithiane **6**[8] with 2 equivalents of *n*-BuLi, followed by condensation of the resulting dianion **14** with *N*-benzyl-Δ^3-piperidein-2-one **7** yielded a 1:1.5 mixture of diastereoisomeric lactams *trans*-**15** and *cis*-**16**, in 80% yield (Scheme 2). Similarly, the condensation of dianion **14** with *N*-methyl-Δ^3-piperidein-2-one **8** gave a 1:1.4 mixture of epimeric lactams *trans*-**17** and *cis*-**18** in 64% yield. In both cases the epimers were isolated by flash chromatography to allow independent study of each in the subsequent reduction-cyclization step.

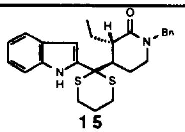
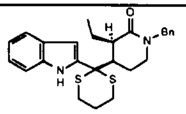
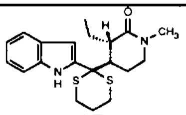
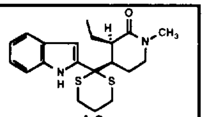


Scheme 2

The relative stereochemistry of compounds **15**-**18** was inferred from the spectral data. Thus, in the ^{13}C NMR spectra of the major isomers *cis*-**16** and *cis*-**18**, in which the ethyl substituent is in an axial disposition, the ethyl methylene carbon and C-5 appeared more shielded than in compounds *trans*-**15** and *trans*-**17** as a consequence of the γ-gauche effect (Table 1). A significant upfield shift of the 3-H protons in the major isomers **16** and **18**, observed in the ^1H NMR spectra ($\Delta\delta \sim -0.8$ ppm), corroborated the assignments (Table 2).

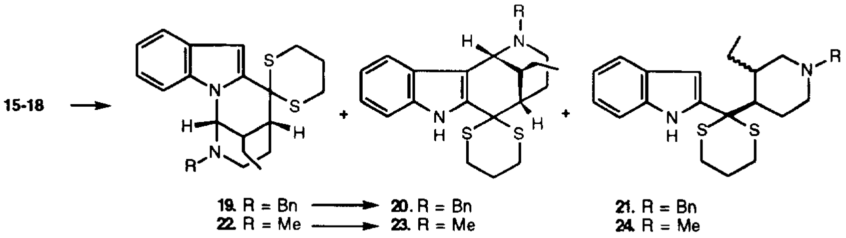
The next step was the partial reduction of lactams **15**-**18** to the corresponding iminium salts, which were expected to react spontaneously with the indole nucleus. We anticipated that more of the cyclization would occur on the indole nitrogen atom than on the indole 3-position,[1,2,9] and that the major *cis*-isomers would cyclize with less difficulty than the corresponding *trans*-isomers, since the C-2 position in the intermediate iminium salt is *a priori* less hindered. However, it was difficult to predict the stereochemical fate of the ethyl substituent as a function of the starting isomer used.

Table 1. ^{13}C NMR Data of 3-ethyl-2-piperidones **15-18**^{a,b}

Compound **Carbon**	 **15**	 **16**	 **17**	 **18**
C-2	172.4	171.8	172.5	172.0
C-3	45.1	46.1	44.7	46.0
C-4	48.8	49.5	48.3	49.1
C-5	27.7	22.2	27.6	22.0
C-6	44.2	49.0	47.2	48.8
SCH_2	27.9 and 28.3	27.8 and 28.6	27.8 and 28.1	27.7 and 28.5
SCH_2CH_2	24.6	24.6	24.6	24.7
SCS	59.6	57.3	59.0	57.3
NCH_3	-	-	34.7	34.1
$NCH_2C_6H_5$	50.0	49.2	-	-
$\mathit{CH_2}CH_3$	24.0	20.8	22.6	20.8
$CH_2\mathit{CH_3}$	11.5	12.9	11.5	12.7

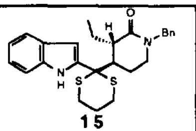
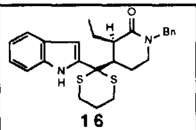
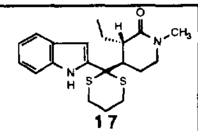
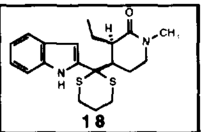
a. Aromatic carbons are equivalent in the four compounds (± 0.2 ppm): 137.2 (In-C2), 105.3, (In-C3), 128.4 (In-C3a), 120.3 (In-C4), 119.7 (In-C5), 122.0 (In-C6), 110.0 (In-C7), 136.2 (In-C7a).
b. Assignments were confirmed by COSY (H,C) experiments.

The results obtained in the reduction-cyclization (Scheme 3) of compounds **15-18** are summarized in Table 3. Thus, treatment of piperidone *cis*-**16** with an excess of Red-Al® in THF (entry 3) yielded a 3:1 mixture of hexahydro-1,5-methanodiazocino[4,3-*a*]indole **19** and the 20-epidasycarpidone precursor **20** in an excellent total yield. No traces of piperidine **21** were detected in this case. Under identical experimental conditions, lactam *cis*-**18** (entry 5) yielded the cyclized compound **22** as the major product, together with small amounts of methanoazocinoindole **23** and piperidine **24**.



Scheme 3

Table 2. ^{1}H NMR Data of 3-ethyl-2-piperidones **15-18**.^{a}

Compound Proton	 **15**	 **16**	 **17**	 **18**
3-H	3.12 m	2.22 m	2.99 ddd (8, 6, 3)	2.25 m
4-H	2.30 td (8, 3)	2.35 br d (10)	2.31 ddd (6, 2)	2.35 dt (12, 4)
5-H	1.78 m	2.22 m	1.80-1.90	2.25 m
6-Hax	3.12 m	3.08 ddd (12, 6)	3.34 ddd (13, 8, 6)	3.14 ddd (12, 10, 6)
6-Heq	3.12 m	3.25 ddd (12, 6, 2)	3.13 dd (13, 6)	3.31 ddd (12, 6, 2)
SCHa	2.83 td (14, 4)	2.89 td (14, 3)	2.85 m	2.88 m
SCHe	2.66 dt (14, 4)	2.65 dt (14, 3)	2.65 dt (14, 4)	2.64 dt (14, 4)
SCH_2CH_2	1.88 m	1.87 dt (12, 3)	1.80-1.90 m	1.84 m
$CH_3C\mathit{H}_2$	1.63 q (8)	1.52 m 2.22 m	1.50-1.70 m	1.46 m 2.25 m
$C\mathit{H}_3CH_2$	0.91 t (8)	0.99 t (8)	0.89 t (8)	0.93 t (8)
NCH_3	–	–	2.79 s	2.82 s
$NCH_2C_6H_5$	4.30 d (14) 4.70 d (14)	4.26 d (14) 4.71 d (14)	–	–
In-3H	6.80 d (1)	6.80 d (1)	6.80 d (1)	6.78 d (1)
In-4H	7.58 d (7)		7.60 d (7)	7.60 d (7)
In-5H	7.10-7.30 m	7.10-7.30 m	7.11 t (7)	7.11 t (7)
In-6H	7.10-7.30 m	7.10-7.30 m	7.19 t (7)	7.18 t (7)
In-7H	7.35 d (7)	7.10-7.30 m	7.38 d (7)	7.35 d (7)
In-NH	8.65 sa	8.25 s	8.70 sa	8.62 sa
C_6H_5	7.20-7.30 m	7.20-7.40 m	–	–

a. Coupling constants are given in brackets (Hz).

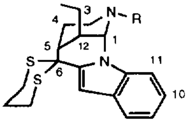
Surprisingly, treatment of *trans*-2-piperidone **15** with Red-Al® (entry 1) gave no reaction, and the starting material was fully recovered. This failure was attributed to the major steric hindrance of the carbonyl group in *trans*-isomers, which is enough to impede the access of the voluminous Red-Al®. The use of $LiAlH_4$/HCl on compound **15** (entry 2) led to piperidine **21** as the sole product in 64% yield. Finally, the reduction of lactam *trans*-**17** was carried out with DIBAH (entry 4), leading to a 4:2:1 mixture of **22**, **23** and **24** in 95% combined isolated yields. Since the total yield of transformation obtained with DIBAH and the proportion of cyclization *versus* total reduction was better than in entry 5, we also assayed the reaction of *cis*-**18** with DIBAH (entry 6), but with no improvement.

The structural assignment of compounds **19-24** was accomplished by 2D NMR experiments and by comparison with described analogues.[2,10] The most characteristic ^{1}H NMR data for 1,5-methanodiazocino[4,3-*a*]indoles **19** and **22** (Table 4) are a singlet at δ~6.90 corresponding to 7-H and a deshielded singlet at δ~5.20 for the angular 1-H. Similarly, the presence of a signal at δ~69.5 (C-1) in the ^{13}C

Table 3. Reduction-cyclization reactions of compounds **15-18**

Entry	Substrate	Reagent	Products (% yield)		
1	**15**	Red-Al®	**19** (0)	**20** (0)	**21** (0)
2	**15**	$LiAlH_4$/HCl	**19** (0)	**20** (0)	**21** (64)
3	**16**	Red-Al®	**19** (70)	**20** (23)	**21** (0)
4	**17**	DIBAH	**22** (62)	**23** (23)	**24** (10)
5	**18**	Red-Al®	**22** (51)	**23** (5)	**24** (5)
6	**18**	DIBAH	**22** (35)	**23** (10)	**24** (10)

Table 4. NMR Data of hexahydro-1,5-methano-2,11b-diazocino[4,3-*a*]indoles **19** and **22**.[a,b]



H-Atom	19 (R=Bn)	22 (R=Me)	C-Atom	19 (R = Bn)	22 (R=Me)
1-Heq	5.30 br s	5.13 d (3)	C-1	69.1	69.8
3-Heq	2.37 m	2.38 ddd (12,4,2)	C-3	42.6	45.4
3-Hax	2.00-2.25 m	2.21 br t (12)	C-4	24.5	24.5
4-Heq	2.00-2.25 m	2.00-2.15 m	C-5	35.0	34.6
4-Hax	2.00-2.25 m	2.00-2.15 m	C-6	52.8	52.7
5-Heq	2.62 br s	2.60 m	C-6a	139.2	138.9
7-H	6.92 s	6.90 s	C-7	101.9	102.0
8-H	7.65 d (7)	7.60 d (7)	C-7a	139.1	136.7
9-H	7.10 t (7)	7.05 t (7)	C-8	119.7	119.7
10-H	7.15 t (7)	7.12 t (7)	C-9	120.6	120.7
11-H	7.40 d (7)	7.40 d (7)	C-10	121.5	121.6
12-He	2.60-2.62 m	2.60 m	C-11	110.4	110.5
SCHax SCHax'	3.00 ddd (14,12,3) 3.15 ddd (14,12,3)	3.15 ddd (15,12,3) 2.98 ddd (15,12,3)	C-11a	126.3	128.6
SCHeq SCHeq'	2.76 dt (14, 3) 2.60-2.70 m	2.76 dt (15,3) 2.69 dt (15,3)	C-12	40.2	39.9
$SCH_2C\mathit{H}_2$	2.00-2.25 m	2.00-2.15 m	$SCH_2\mathit{C}H_2$	23.1	23.1
$CH_3C\mathit{H}_A$ $CH_3C\mathit{H}_B$	1.80-1.95 m 1.95- 2.10 m	1.65-1.80 m 1.95-2.15 m	SCH_2	27.9 29.7	28.0 29.8
$C\mathit{H}_3CH_2$	1.12 t (7)	1.06 t (7)	$CH_3\mathit{C}H_2$	24.4	24.3
NCH_3	–	2.30 s	$\mathit{C}H_3CH_2$	11.8	11.8
NCH_APh NCH_BPh	4.00 d (14) 3.25 d (14)	–	$N\mathit{C}H_3$ $N\mathit{C}H_2Ph$	– 60.3	45.0 –

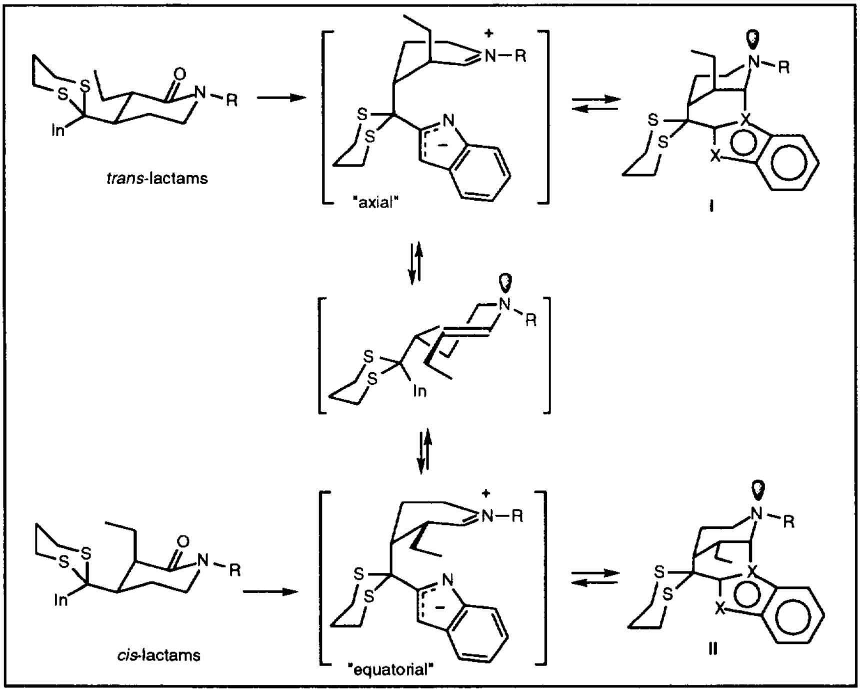
a. ^{1}H NMR Coupling constants are given in brackets (Hz).

b. Assignments were confirmed by COSY experiments.

NMR spectra is typical of these polycyclic structures. The axial orientation of the ethyl substituent was determined by the chemical shift of C-4 in the ^{13}C NMR spectra, which appears ~4 ppm more shielded than in the basic skeleton.[2]

The most characteristic ^{13}C and ^{1}H spectroscopic features of compounds **20** and **23** were the angular C-21 and 21-H chemical shifts, the presence of the indole NH, and the absence of the indole 3-H protons (Tables 5 and 6). Again, both compounds presented the C-20 ethyl substituent in an axial disposition, as deduced from the γ-gauche effect observed on C-14.

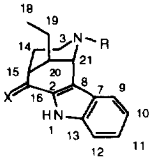
The fact that in the cyclized products the ethyl group adopts the same orientation independently of the relative configuration of the starting lactam can be explained by the iminium salt-enamine equilibrium in the basic reaction conditions, which allows the kinetic cyclization of the less hindered intermediate to give compounds type **I** (Scheme 4).



Scheme 4

The isomerization of compounds **19** and **22** to the corresponding hexahydro-1,5-methano-2-azocino[4,3-*b*]indoles **20** and **23** was accomplished as usual, by refluxing in 50% aqueous AcOH. Since in previous work we had observed only the formation of dasycarpidone precursors (type **II** compounds),[2] and because the isomerization of 20-epiderivatives lacking the keto group on C-16 occurs in such conditions,[5d] we had assumed that these would be the thermodynamically more stable products. Surprisingly, no traces of the dasycarpidone precursors were detected, even after long reaction times.

Table 5. ^{1}H NMR Data of hexahydro-1,5-methano-2-azocino[4,3-*b*]indoles.[a,b]



H-atom	20	23 ref. 2	9	10[c] epidasycarpidone	25	11 epiuleine
21-Heq	4.07 br s	3.97 d (3)	4.27 d (2)	4.18 br s	3.99 br s	4.03 d (2)
3-Heq	2.32 br d (10)	2.38 dt (10,3)	2.45 dd (12,4)	2.48 br dd (12,5)	2.40 br s	2.44 dd (10,4)
3-Hax	1.92-2.20 m	1.90-2.20 m	2.08 tt (12,3)	1.94-2.04 m	1.80-2.10 m	2.05 td (11,5)
14-Heq	1.92-2.20 m	1.90-2.20 m	1.63 br d (12)	1.67 br d (12)	1.80-2.10 m	1.40 br d (12)
14-Hax	1.92-2.20 m	1.90-2.20 m	2.25 ddd (12,8,5)	2.16-2.32 m	2.15-2.25 m	2.18-2.30 m
15-Heq	2.50 br s	2.50 br s	2.65 br s	2.65 m	1.80-2.10 m	2.63 br s
12-H	7.50 d (7)	7.33 d (7)	7.50 d (7)	7.53 br d (8)	7.35 br d (7)	7.34 br d (7)
11-H	7.15 t (7)	7.17 t (7)	7.27-7.45 m	7.37 td (8,1)	7.15 br t (7)	7.18 br t (7)
10-H	7.05 d (7)	7.09 t (7)	7.19 t (7)	7.17 td (8,1)	7.05 br t (7)	7.10 br t (7)
9-H	7.55 d (7)	7.85 d (7)	7.64 d (7)	7.71 br d (8)	7.55 br d (7)	7.56 br d (7)
20-Heq	2.32 m	2.32 br t (7)	2.18 t (7)	2.16-2.32 m	2.15-2.25 m	1.87 br t (7)
$C\mathit{H}_ACH_3$	1.76-1.82 m	1.60-1.75 m	1.75-1.89 m	1.61-1.80 m	1.60-1.80 m	1.62-1.78 m
$C\mathit{H}_BCH_3$	1.92-2.20 m	1.90-2.20 m	1.88-1.97 m	1.98-2.10 m	1.80-2.10 m	1.92-2.08 m
$CH_2C\mathit{H}_3$	1.05 t (7)	1.04 t (7)	1.02 t (7)	1.02 t (7)	1.01 t (7)	1.01 t (7)
SCHeq	2.74 dt (12, 3)	2.75 dt (15,3)	–	–	–	–
SCHax	3.00 td (12, 2)	2.99 ddd (15,13,2)	–	–	–	–
SCHax'	3.18 td (12, 2)	3.16 ddd (15,13,3)				
$SCCH_2$	1.92-2.20 m	1.90-2.20 m	–	–	–	–
NCH_3	–	2.26 s	–	2.26 s	2.26 s	2.26 s
NCH_2Ph	3.22 d (14) 3.84 d (14)	–	3.24 d (14) 3.77 d (14)	–	–	–
1-H	8.58 s	8.55 br s	9.50 br s	10.1 br s	9.10 br s	8.30 br s
$C\mathit{H}_3COH$	–	–	–	–	1.60 s	–
CCH_2	–	–	–	–	–	4.95 s 5.19 s

a. Coupling constants are given in brackets.
b. All assignments have been confirmed by COSY (H,H) and (H,C) experiments.
c. For comparison, see reference 5e.

20-Epidasycarpidone **10**[5e] and its *N*-benzyl analogue **9** were obtained cleanly by treatment of dithianes **23** and **20** with $(CF_3CO_2)_2IPh$ in CH_3CN-H_2O (Scheme 5).[11] The transformation was made evident from the IR absorption at 1642 cm^{-1}, and the ^{13}C NMR peak at δ 195.4, characteristic of the conjugated carbonyl (C-16). Comparison of the ^{13}C NMR data with those described for dasycarpidone[4d] (Table 6) showed a very similar chemical shift of the C-21 methine carbon (δ 54.7). However, the C-14 methylene carbon and the C-20 methine carbon appear to be more shielded in compound **10** (Δδ 6 ppm for C-4, and Δδ 3.4 ppm for C-20) than in dasycarpidone, demonstrating the axial orientation of ethyl group.

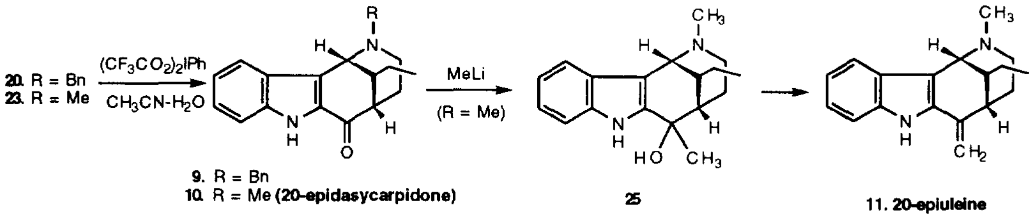
Table 6. ^{13}C NMR Data of hexahydro-1,5-methano-2-azocino[4,3-*b*]indoles.

C-atom	20	23 ref. 2	9	10[a]	dasycarpidone ref. 4d	25	11 20-epiuleine[b]
C-21	52.5	53.9	52.9	54.7	56.2	55.2	55.1 (55.3)
C-3	43.7	45.9	44.1	46.1	46.0	46.9	46.3 (46.2)
C-14	24.6	24.6	24.2	23.9	30.1	24.9	28.1 (27.8)
C-15	37.8	37.1	45.7	45.0	46.3	43.0	38.0 (37.7)
C-16	53.4	53.3	195.4	195.4	193.5	72.0	141.6 (141.1)
C-2	135.7	135.7	133.8	133.3	132.9	136.6	136.2 (136.4)
C-13	135.9	135.8	139.5	138.1	138.1	141.9	136.5 (136.6)
C-12	111.1	111.1	112.6	112.8	112.7	111.6	110.9 (111.0)
C-11	119.7	119.6	124.9	126.7	126.9	120.0	122.9 (122.6)
C-10	122.3	122.3	122.1	122.0	121.1	122.1	120.0 (119.8)
C-9	119.7	119.6	120.8	120.8	119.9	119.9	119.4 (119.0)
C-8	127.3	127.4	127.7	127.0	127.8	128.0	128.2 (127.9)
C-7	122.4	122.4	124.9	124.4	122.0	120.0	111.0 (110.0)
C-20	41.3	40.9	46.5	46.2	49.6	44.2	44.5 (44.2)
NCH_3	–	44.8	–	44.6	44.0	45.3	44.5 (44.4)
NCH_2Ph	60.5	–	60.2	–	–	–	–
$\mathit{C}H_2CH_3$	24.5	24.6	23.3	23.3	24.8	24.9	23.4 (23.3)
$CH_2\mathit{C}H_3$	12.2	12.2	11.8	11.7	11.8	12.7	12.1 (12.0)
SCH_2 SCH_2'	26.7 29.2	26.7 29.2	–	–	–	–	–
$SC\mathit{C}H_2$	24.0	23.9	–	–	–	–	–
CCH_3	–	–	–	–	–	32.0 and 37.1	–
CCH_2	–	–	–	–	–	–	105.4 (106.1)

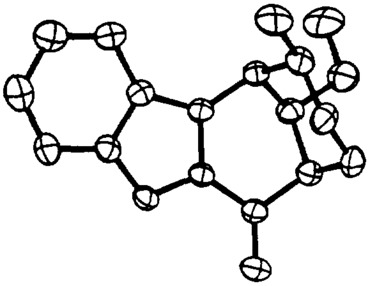
a. For comparison, see reference 5e

b. The described values[13] are given in brackets.

Finally, we carried out the transformation of 20-epidasycarpidone (**10**) to 20-epiuleine (**11**), following the classical method described by Dolby and Bière,[12] by treatment of 20-epidasycarpidone with MeLi and alumina dehydration of the resulting alcohol **25**. 20-Epiuleine was obtained, and was characterized by comparison of its spectral data with those described in the literature.[13]



Scheme 5



Scheme 6. ORTEP plot of 20-epidasycarpidone (**10**)[14]

ACKNOWLEDGEMENTS

Support for this research has been provided by the CIRIT (Generalitat de Catalunya) through grant QFN92-4303. We also thank the CIRIT for a fellowship given to one of us (P.F.).

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 on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, SDS). TLC was performed on SiO_2 (silica gel 60 F254, Macherey-Nagel) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Draggendorff or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

***N*-Benzyl-3-ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidin-2-ones (15 and 16).** To a solution of tetrahydropyridine **12** (0.5 g, 2.21 mmol) in CH_2Cl_2 (10 ml) cooled at -20°C, MCPBA (458 mg, 2.65 mmol) was slowly added. After stirring for 1 h at -20°C, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract, dried and evaporated, was purified by flash column chromatography to yield ***N*-benzyl-3-ethyl-3-piperidein-2-one** (**7**, 244 mg, 51%): IR (NaCl) 1670 (CO), 1630 (C=C) cm^{-1}; ^{1}H NMR 1.07 (t, J = 8 Hz, 3H, CH_3), 2.22-2.30 (m, 2H, 5-H), 2.34 (q, J = 8 Hz, 2H, CH_2CH_3), 3.28 (t, J = 7 Hz, 2H, 6-H), 4.64 (s, 2H, CH_2Ph), 6.24 (br s, 1H, 4-H), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR 12.8 (CH_3), 23.5 and 23.7 (C-5 and CH_2CH_3), 44.7 (C-6), 49.9 (CH_2Ph), 127.1, (Ph-*p*), 27.8 and 128.4 (Ph-*o* and Ph-*m*), 131.7 (C-4), 137.0 and 137.7 (C-3 and Ph-*ipso*), 165.4 (C-2).

To a solution of 2-(2-indolyl)-1,3-dithiane **6** (294 mg, 1.25 mmol) in dry THF (10 ml), cooled at -78°C and under argon atmosphere, *n*-BuLi (1.6 M, 1.80 ml, 2.88 mmol) was added dropwise. After 20 min a solution of lactam **7** (244 mg, 1.13 mmol) in dry THF (10 ml) was slowly added, and the mixture was maintained at -78°C for 1.5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 ml), the layers were separated, and the aqueous phase was extracted with AcOEt. The organic extracts, dried and evaporated furnished a foam, which, after flash chromatography (EtAcO-hexane gradient), yielded a mixture of *trans*-piperidone **15** and *cis*-piperidone **16**. Compound **15** (Lower Rf, 164 mg, 30%): IR (NaCl) 3350 (NH), 1629 (CO) cm^{-1}; MS *m/z* (%) 450(M$^+$, 4), 345 (2), 253 (4), 234 (100),160 (14), 120 (5), 91 (32). Anal. Cald for $C_{26}H_{30}N_2OS_2$: C, 69.30; H, 6.71; N 6.22. Found: C, 69.09; H, 6.37; N, 5.84. Compound **16** (Higher Rf, 242 mg, 43%): IR (NaCl) 3350 (NH), 1630 (CO) cm^{-1}; MS *m/z* (%) 450 (M$^+$, 18), 359 (2), 343 (7), 253 (36), 234 (100), 160 (21), 120 (16), 91 (49). Anal. Cald for $C_{26}H_{30}N_2OS_2$: C, 69.30; H, 6.71; N, 6.22. Found: C, 69.51; H, 6.77; N, 5.99.

3-Ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]-1-methylpiperidin-2-ones (17 and 18). Operating as above, from tetrahydropyridine **13** (0.5 g, 3.3 mmol), CH_2Cl_2 (15 ml), and MCPBA (863 mg, 4.9 mmol) an oil was obtained, which after flash column chromatography (CH_2Cl_2-CH_3OH, 99:1) gave **3-ethyl-*N*-methyl-3-piperidein-2-one (8**, 240 mg, 52%): IR (NaCl) 1667 (CO), 1622 (C=C) cm^{-1}; ^{1}H NMR 0.95 (t, *J* = 8 Hz, 3H, CH_3), 2.10-2.30 (m, 4H, CH_2CH_3 and 5-H), 2.90 (s, 3H, NCH_3), 3.28 (t, *J* = 7 Hz, 2H, 6-H), 6.15 (br s, 1H, C=CH); ^{13}C NMR 13.3 (CH_3), 23.9 and 24.0 (CH_2CH_3 and C-5), 35.1 (NCH_3), 48.1 (C-6), 130.5 (C-4), 137.4 (C-3), 166.4 (CO).

Operating as above, from dithiane **6** (683 mg, 4.51 mmol), THF (20 ml), *n*-BuLi (1.6 M, 4 ml, 9.92 mmol) and piperideinone **8** (400 mg, 4.1 mmol), a mixture of **3-ethyl-1-methyl-4-piperidein-2-ones** *trans*-**17** and *cis*-**18** was obtained, which was flash chromatographed (hexane-AcOEt, 3:7). **17** (Lower Rf, 252 mg, 27%): IR ($CHCl_3$) 3350 (NH), 1626 (CO) cm^{-1}; MS *m/z* (%) 374 (M$^+$, 6), 234 (100), 160 (14), 140 (9). **18** (Intermediate Rf, 252 mg, 27%): IR ($CHCl_3$) 3400 (NH), 1631 (CO) cm^{-1}; MS *m/z* (%) 374 (M$^+$, 14), 253 (10), 234 (100), 160 (18), 140 (6). Anal. Cald for $C_{20}H_{26}N_2OS_2$: C, 64.13; H, 7.00; N, 7.48. Found: C, 64.24; H, 6.89; N, 7.52.

***N*-Benzyl-6,6-(propylenedisulfanyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-2,11b-diazocino[4,3-*a*]indole (19), and *N*-benzyl-6,6-(propylenedisulfanyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indole (20).** To a solution of *cis*-piperidone **16** (53 mg, 0.12 mmol) in THF (5 ml) cooled at -78°C, an excess of 65% dispersion of Red-Al® was added, the reaction mixture was allowed to reach room temperature, and its evolution was tlc monitorized after 1 h. The procedure was repeated until the reaction was complete (3 h). The reaction was quenched with H_2O, the phases separated, and the aqueous layer was extracted with AcOEt. The organic extracts, dried and evaporated yielded an oil which was flash chromatographed (hexane-AcOEt, 7:3) to isolate compounds **19** and **20**. Compound **19** (Higher Rf, 37 mg, 70%): MS *m/z* (%) 434 (M$^+$, 1), 300 (1), 200 (93), 149 (4), 91 (100). Anal. Cald for $C_{26}H_{30}N_2OS_2$: C, 71.85; H, 6.96; N 6.44; S, 14.75. Found: C, 71.89; H, 7.17; N, 6.26; S, 14.97. Compound **20** (Lower Rf, 12 mg, 23%): MS *m/z* (%) 434 (M$^+$, 18), 405 (12), 359 (27), 328 (71), 301 (21), 237 (23), 180 (26), 91 (100). Anal. Cald for $C_{26}H_{30}N_2S_2$: C, 71.85; H, 6.96; N 6.44. Found: C, 71.87; H, 7.20; N, 6.63.

***N*-Benzyl-3-ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidine (*trans*-21).** To a solution of *trans*-piperidone **15** (66 mg, 0.14 mmol) in THF (10 ml) cooled at -78°C, $LiAlH_4$ (5 mg, 0.13 mmol) was added. The cold bath was removed, and after 15 min, the formation of a single product with higher Rf than the starting piperidone was oberved by tlc. The mixture was poured on H_2O, the layers were separated and the aqueous phase was extracted with AcOEt. The combined organic solutions, dried and evaporated, gave an oil which was flash chromatographed (hexane-AcOEt, 7:3) to yield piperidine *trans*-**21** (56 mg, 64%): ^{1}H RMN 0.82 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.30-1.40 (m, 1H, $5H_a$), 1.42-1.54 (m, 1H, CH_ACH_3), 1.67 (m, 1H, CH_BCH_3), 1.69-1.79 (m, 1H, 3-H_a), 1.80-2.00 (m, 6H), 2.00-2.18 (m, 1H), 2.50-2.59 (m, 2H, SCH_e), 2.62 (br t, *J* = 13 Hz, 2H, SCH_a), 2.84-2.96 (m, 1H), 3.28 (d, *J* = 14 Hz, 1H, CH_APh), 3.45 (d, *J* = 14 Hz, 1H, CH_BPh), 6.74 (s, 1H, In-3H), 7.09 (t, *J* = 7 Hz, 1H, In-5H), 7.16 (t, *J* = 7 Hz, 1H, In-6H), 7.25 (s, 5H, Ph-H), 7.32 (d, *J* = 7 Hz, 1H, In-7H), 7.57 (d, *J* = 7 Hz, 1H, In-4H), 8.56 (br s, 1H, In-NH); ^{13}C RMN 11.4 (CH_2CH_3), 25.0 (CH_2CH_3), 25.8 (SCH_2CH_2), 27.3 (C-5), 28.2 and 29.1 (SCH_2), 39.6 (C-3), 50.6 (C-4), 53.2 (C-6), 57.7 (C-2), 59.2 (SCS), 63.0 (NCH_2Ph), 105.5 (In-C2), 110.9 (In-C7), 119.8 (In-C4), 120.5 (In-

C5), 121.8 (In-C6), 126.8 (Ph-*p*), 128.0 (Ph-*o*), 128.6 (In-C3a), 129.0 (Ph-*m*), 135.8 (In-C7a), 138.3 (In-C2), 138.6 (Ph-*ipso*); MS *m/z* (%) 436 (M^+, 10), 407 (1), 361 (55), 330 (10), 273 (5), 234 (16), 200 (54), 174 (29), 91 (100). Anal. Calcd for $C_{26}H_{32}N_2S_2$: C, 71.51; H, 7.39; N, 6.42. Found: C, 71.48; H, 7.40; N, 6.32.

12-Ethyl-1-methyl-6,6-(propylenedisulfanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-2,11b-diazocino[4,3-*a*]indole (22), 12-ethyl-1-methyl-6,6-(propylenedisulfanyl)-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indole (23), and 3-ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]-1-methylpiperidines (24). Method a. Operating as for the preparation of compounds **19** and **20**, from piperidin-2-one *cis*-**18** (50 mg, 0.13 mmol), Red-Al® (excess), and THF (5 ml), a mixture of compounds **22-24** was obtained, which was flash chromatographed (hexane-AcOEt, 3:7). Methanodiazocinoindole **22** (Higher Rf, 20 mg, 42%): MS *m/z* (%) 358 (M^+, 4), 252 (1), 224 (2), 180 (2), 167 (2), 125 (10), 124 (100). Anal. Cald for $C_{20}H_{26}N_2S_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 66.99; H, 7.45; N, 7.93. Methanoazocinoindole **23** (Lower Rf, 4 mg, 8%): IR ($CHCl_3$) 3400 (NH) cm^{-1}; MS *m/z* (%) 358 (M^+, 3), 342 91), 288 (29), 230 (70), 221 (15), 205 (60), 171 (55), 161 (27), 149 (60), 124 (55), 107 (72), 84 (54), 57 (100). Anal. Cald for $C_{20}H_{26}N_2S_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 67.18; H, 7.45; N, 8.02. **Method b.** To a solution of lactam *trans*-**17** (130 mg, 0.35 mmol) in THF (10 ml), DIBAH (0.1 M in THF, 1.4 ml, 0.14 mmol was added. After 2 h at room temperature, the mixture was poured on H_2O and extracted with AcOEt. The organic extracts, dried and evaporated yielded an oil which was flash chromatographed (CH_2Cl_2-MeOH, 93:7) to isolate compounds **22** (higher Rf, 60 mg, 62%), **23** (lower Rf, 22 mg, 23%) and ***trans*-24** (intermediate Rf, 20 mg, 10%).Piperidine ***trans*-24**: ^1H NMR 0.78 (t, J = 7 Hz, 3H, $CH_2C\mathit{H}_3$), 1.35 (br d, J = 11 Hz, 1H), 1.64 (br d, J = 11 Hz, 1H), 1.55-1.65 (m, 1H, $C\mathit{H}_ACH_3$), 1.80-1.90 (m, 2H, $SCH_2C\mathit{H}_2$), 2.02 (td, J = 11 and 4 Hz, 1H), 2.14 (s, 3H, NCH_3), 2.62 (br d, J = 11 Hz, 2H), 2.90 (t, J = Hz, 2H), 2.78 (d, J = Hz, 1H, 2-H_e), 6.77 (d, J = 7 Hz, 1H, In-3H), 7.11 (t, J = 7 Hz, 1H, In-5H), 7.18 (t, J = 7 Hz, 1H, In-6H), 7.35 (d, J = 7 Hz, 1H, In-7H), 7.60 (d, J = 7 Hz, 1H, In-4H), 8.57 (br s, 1H, In-NH); ^{13}C RMN 12.3 ($\mathit{C}H_3CH_2$), 19.6 ($CH_3\mathit{C}H_2$), 24.0 (C-5), 24.9 ($SCH_2\mathit{C}H_2$), 27.8 and 28.8 (SCH_2), 38.9 (C-3), 46.5 (NCH_3), 53.8 (C-4)), 57.1 (C-6), 58.6 (SCS), 59.0 (C-2), 105.0 (In-C3), 110.8 (In-C7), 119.7 (In-C4), 120.5 (In-C5), 121.8 (In-C7), 128.7 (In-C3a), 135.9 (In-C7a), 138.6 (In-C2); MS *m/z* (%) 360 (M^+, 42), 285 (58), 234 (63), 197 (51), 160 (25), 98 (100). Anal. Cald for $C_{20}H_{28}N_2S_2$: C, 66.62; H, 7.83; N, 7.77. Found: C, 66.57; H, 7.98; N, 7.68.

General method for the isomerisation of methanodiazocinoindoles 19 and 22 (20 and 23). A solution of metanodiazocinoindoles **19** or **22** in 50% aqueous AcOH (0.1 M) is refluxed for 2 h. The mixture is basified with Na_2CO_3 and extracted with AcOEt. The organic extracts, dried and evaporated are flash chromatographed (hexane-AcOEt, 3:7) to yield metanoazocinoindoles **20** and **23** in 70-75% yield.

General method for the dithiane transformation into a keto group (9 and 10). To a solution of compounds **20** or **23** (1 equivalent) in CH_3CN-H_2O (9:1, 0.16 M), $(CF_3CO_2)_2IPh$ (2,5 equivalents) is added. The mixture is stirred at room temperature for 1.5 h, poured on aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts, dried and evaporated yield an oil which is flash chromatographed (CH_2Cl_2) to give ***N*-benzyl-12-ethyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indole 9** (64%) or **20-epidasycarpidone 10** (72%), respectively. Compound **9**: IR (NaCl) 3300 (NH), 1650 (CO) cm^{-1}. Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.13; H, 6.42; N, 7.27.

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14. Crystal data of compound **10**: $C_{17}H_{20}N_2O$. Fw=268.35, monoclinic, **a**=10.303(4); **b**=12.790(4); **c**=11.291(4)Å; $\alpha = 90°$, β=91.02(3)°. $\gamma = 90°$. V=1487.6(9)$Å^3$, $P2_1/c$, Dx=1.198 g cm^{-3}, Z=4, F(000)=576, (Mo Kα)=0.71069 Å, μ (Mo Ka)=0.075 mm^{-1}. A prismatic crystal (0.1x0.1x0.2 mm) was selected and mounted on an Enraf-Nonius CAD4 diffractometer. Unit cell parameters were determined from automatic centring of 25 reflections ($12 \leq \theta \leq 21°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using a $\sigma/2\theta$ scan technique. 4300 Reflections were measured in the range $2.41 \leq \theta \leq 29.99$. 2583 Reflections were assumed as observed applying the condition $I > 2\ \sigma(I)$. Three reflections were measured every two hours as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarization, but not absorption corrections were made. The structure was solved by Direct methods, using SHELXS computer program (Sheldrick, G. M. *Acta Cryst.*, **1990**, *A46*, 467-473) and refined by full-matrix least-squares method, with the SHELX93 computer program (Sheldrick, G. M., 1994, in preparation), using 4250 reflections (very negative intensities were not assumed). The minimized function was $\Sigma w\ | |Fo| - |Fc| |^2$, where $w = [\sigma^2 (I) + (0.3649\ P)^2]^{-1}$, and $P = (|Fo|^2 + 2\ |Fc|^2)/3$. f, f'And f''were taken from International Tables of X-Ray Crystallography (International Tables of X-Ray Crystallography, (1974). Ed. Kynoch press, vol IV, pp 99-100 and 149). All H atoms were computed and refined with an overall isotropic temperature factor using a riding model. The final R (on F) factor was 0.041, wR (on $|F|^2$)=0.104 and goodness of fit = 0.280 for all observed reflections. The number of refined parameters was 192. max. shift/ e.s.d =0.000, mean shift/e.s.d. = 0.008. Max. and min. peaks in the final difference synthesis was 0.160 and -0.203 e$Å^{-3}$, respectively. Tables of atomic coordinates, bond lengths and angles, and thermal parameters (supplementary material) are available on request from the Cambridge Crystallographic Data Center.

(*Received in UK* 4 *December* 1995; *revised* 31 *December* 1995; *accepted* 8 *January* 1996)