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Reductive Methylations of 2,7-Dihydro Derivatives of Some Oxygenated Indole Alkaloids like Reserpine

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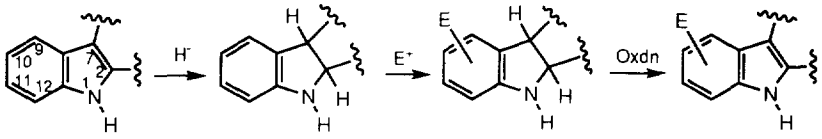
Abstract : The indole alkaloids tetraphylline (**1a**), 3-*epi*reserpine (**2a**) and reserpine (**3a**) were transformed into the corresponding 2,7-dihydro compounds (**c**) by $NaBH_3CN$ in acidic medium. These latter compounds could be further mono-methylated at the 1-position (compounds **e**) or di-methylated at the 1- and 10- positions (compounds **g**) by $H_2CO/NaBH_3CN$ depending on the conditions. The configurations were established on the basis of a detailed NMR study.

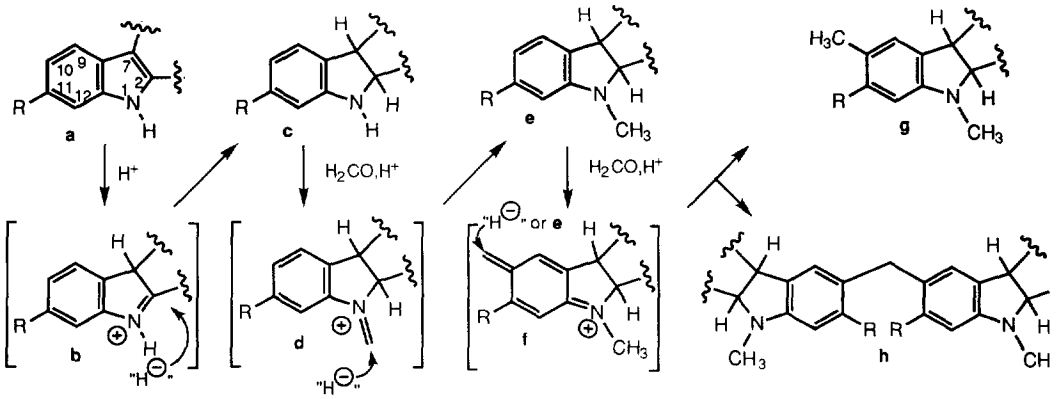
Since the Kornfeld-Woodward total synthesis of lysergic acid,[1] it has been well known that hydrogenation of the 2,7-double bond of indole[2] allows reaction of electrophiles onto C(9) or C(10), in place of the enamine reactivity at C(7). (Scheme 1). When combined with further reoxidation to the 2,7-double bond, this approach is of large synthetic value (reference 3 and references cited).



Scheme 1

Previous work from one of us had made use of the preparation of indolines through reduction of various indole alkaloids with sodium cyanoborohydride in acetic acid,[4] for the preparation of 10-hydroxy- and *N*-methyl derivatives. In the latter case a one-pot procedure in the presence of formaldehyde allowed direct obtention of *N*-methylindolines along with species **a**-**e** (R=H, scheme 2).

However when the reaction was applied to the 11-methoxy substitued alkaloid tetraphylline (**1a**),[5] a 1,10-dimethyl indoline **g** resulted. This was generated by reduction of the methylequinone iminium species **f**, whose formation was due to hydroxymethylation by formaldehyde of the electron-rich C(10). Some time later, Bobowski[6] reported on a closely related reaction using a mixture of formaldehyde and formic acid (R=OCH_3, scheme 2).

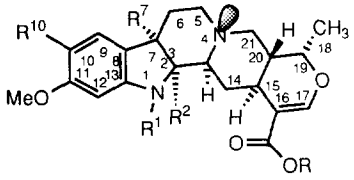


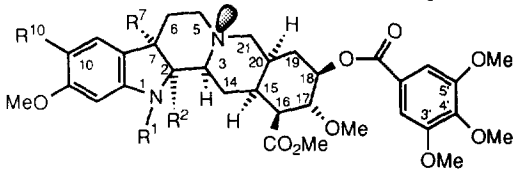
Scheme 2 (indole- based numbering) .**1**, **2**, **3**: R= OCH_3

Methylation *para* to the indolic nitrogen seems of interest with regard to the possibility of preventing *in vivo* metabolisation along biooxidative processes to the 10-hydroxy derivatives.[7]

This paper deals with the syntheses of mono- and dimethyl indolines derived from tetraphylline **1a**, 3-*epi*reserpine **2a** (according to Cook[8]), and reserpine **3a** itself, which was chosen for its biological properties on the cardiovascular system.[9] It should be noticed that **1a** and **2a** have the same configuration at C(3), and are *trans*-quinolizidines, unlike reserpine **3a**.

Preparations of 2,7-dihydro derivatives (**1-3c**), *N*-methyl (**1-3e**) and dimethyl derivatives (**1-3g**) will be discussed, and their stereochemistry will be established on the basis of NMR data and ^2H incorporation.





1a: R^2,R^7= bond, R^1 = R^{10}= H, R= Me : tetraphylline

1c: R^2=R^7= R^1= R^{10}= H, R= Me
1e: R^2=R^7= R^{10}= H, R^1= R= Me
1g: R^2=R^7= H, R^1 = R= R^{10}=Me
4g: R^2=R^7= H, R^1 = R^{10}=Me, R= $CH_2CH_2NMe_2$

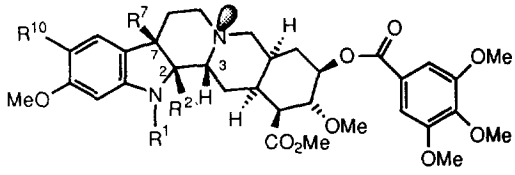
2a: R^2,R^7= bond, R^1 = R^{10}= H : *epi*reserpine

2c: R^2=R^7= R^1= R^{10}= H
2e: R^2=R^7= R^{10}= H, R^1= Me
2g: R^2=R^7= H, R^1= R^{10}=Me
2h: R^2=R^7= H, R^1 = Me, R^{10}= CH_2-(3-*epi*reserpin-10-yl)

Chemistry :

Compounds **1c** and **2c** were obtained from indoles **1a** and **2a** in 72% and 87% yield respectively (6 equivalents of $NaBH_3CN$ in TFA, at room temperature). With reserpine **3a** the reaction was much more sluggish, and the yield did not exceed 55% (TFA, 0°C, 19% **3a** recovered).

N-Methyl derivatives **1e** and **3e** were conveniently prepared from **1c** and **3c** and formaldehyde ($NaBH_3CN$, 10 equivalents, 25°C)



3a: R^2,R^7= bond, R^1= R^{10}= H : reserpine

3c: R^2=R^7= R^1= R^{10}= H
3e: R^2=R^7= R^{10}= H, R^1= Me
3g: R^2=R^7= H, R^1= R^{10}=Me
5g: R^2= H, R^7=^{2}H, R^1 = R^{10}= Me

in acetic acid. Under the same conditions in trifluoracetic acid the reaction invariably led to the dimethyl derivatives **g**, whose formation could not be avoided (even in acetic acid at -10°C) in the case of 2,7-dihydro-3-*epi*reserpine **2c**. *N*-methyl derivative **2e** (37%) was accompanied by **2g** (10%) and "pseudodimer" **2h** (25%) resulting from a nucleophilic coupling[10] of **2e** with intermediate **2f** (scheme 2).

Dimethyl derivatives **g** could be obtained from the monomethyl analogues **e** ($NaBH_3CN$, H_2CO in TFA). However a "one-pot" procedure, starting from indole **a** was much more efficient : a solution of the indole in TFA was treated with $NaBH_3CN$ at 25°C; then the mixture was cooled to -5°C and an excess of H_2CO was added, to give **1g**, **2g** and **3g** in 65, 71 and 45 % yield respectively.

The structures of all these new indolines were supported by spectral data, namely : typical UV spectra, high resolution mass-spectra, ^1H and ^{13}C NMR, which were nearly exhaustively attributed *via* COSY, HMBC, HMQC experiments, [11] which were justified by the paucity of reliable data in the field of 2,7-dihydroindole derivatives (Tables I and II)

Stereochemical study :

This is divided into two parts. The first concerns C(3)-αH compounds *i.e.* derivatives of tetraphylline **1a** and *epi*reserpine **2a**, and the second deals with the derivatives of reserpine **3a** (C(3)-βH).

In each case, we initially demonstrated that pre-existing stereogenic centres of the starting indole were not altered. Then we established the stereochemical nature of the C/D junction and finally the relative configuration of the new centres 2 and 7, compared to C(3).

The first part of our work was mainly founded on an NMR comparison between our compounds and **4g**, a hemi-synthetic derivative of tetraphylline, whose X-ray-diffraction spectrum is available.[12] It clearly appeared that indole **1a** and indolines **1c**, **1e** and **1g** show very similar values for the chemical shifts of C(15), C(18), C(19), C(20) and their bound hydrogens. For these compounds, the value of ^3J-H(15), H(20) ~10Hz pointed out the *trans* relationship of cycles D and E. On the contrary, H(3) in dihydro derivatives **1c**, **1e** and **1f** was more strongly shielded (~1ppm) than the parent indole **1a** (to our knowledge this fact is not apparent in the literature). Otherwise, IR Bohlmann's bands[13] (~2750 cm^{-1}) and C(3) at δ : 63-64 ppm were indicative[14] of a *trans*-quinolizidine C/D ring junction for all the derivatives of tetraphylline. ^1H and ^{13}C NMR spectra of dihydro derivatives were very similar to one another. Namely : C(2)-H appeared as a doublet of doublets (6.5 Hz and 3 Hz) for **1c** and as a broad doublet (6.5 Hz) for **1e** and **1g** in agreement with Gribble's finding[14] for an all-*cis* arrangement of H(2), H(3) and H(7). However NH (**1c**) and N-CH_3 derivatives (**1e** and **1g**) slightly differed in the chemical shifts of C(2) and C(14) (downfielded by 8 ppm and 2 ppm for methylated compounds respectively), and of H(2) (shielded by 0.5 ppm) and β-H(14) (deshielded by 0.3 ppm in the *N*-methyl series). This accounts for the orientation of the *N*-Me group on the less crowded (convex) α-face of the molecule. Consequently the *N* lone pair is β–oriented and influences C(2)-H and C(14)-βH.

Dihydro derivatives **2c**, **2e** and **2g** of 3-*epi*reserpine have the same configuration at C(3) as the corresponding derivatives of tetraphylline. The chemical shifts of C(2), C(3), C(7), C(14) and those of the attached hydrogen(s) were very similar in both series. This obviously reflects a common stereochemistry (all α-H) for C(2), C(3) and C(7) in compounds **2c**, **2e** and **2g**.

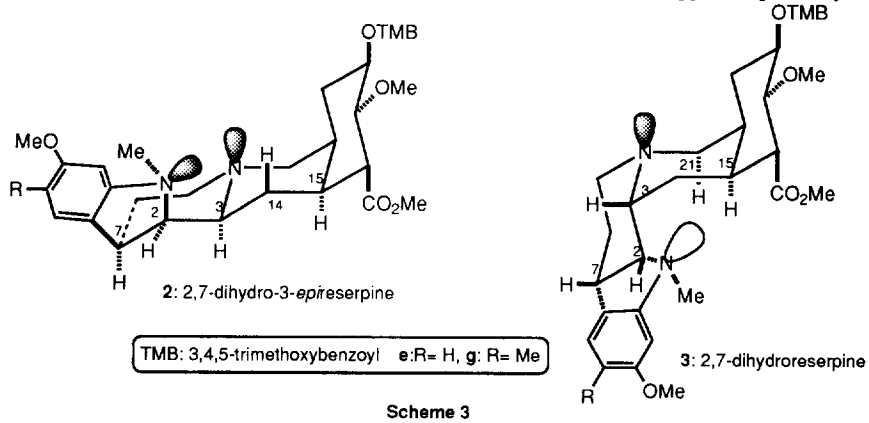
More tedious was the elucidation of the stereochemistry of the dihydro derivatives of reserpine *i.e.* : **3c**, **3e** and **3g**, due to lack of X-ray and NMR data.[15] First of all, it could be assumed that hydrogenation of the 2,7-bond did not affect the configuration of C(15), C(16), C(17), C(18) or C(20), as carbon and proton chemical shifts of **3c**, **3e**, and **3g** did not markedly differ from those of reserpine. The C/D ring junction was

still *cis*, as evidenced by the lack of Bohlmann's bands in the IR spectra, and the deshielding of H(3) which appears in the region of 3.1 ppm (2-2.4 ppm for the *trans*-quinolizidine dihydro derivatives).

The lack of resolution of ^1H NMR signals in the spectra of **3c**, **3e** and **3g**, attributed to conformational equilibria,[16] did not facilitate the determination of C(2), C(3) and C(7) stereochemistry. Fortunately, the spectra of **3g**, measured at 55°C in $CDCl_3$ (sealed tube) gave interesting information on the stereochemical relationships of hydrogens at the 2, 3 and 7 positions, which appeared respectively as a doublet of doublets (3 Hz and 8Hz), a broad doublet (~7 Hz) and a quadruplet (~ 8 Hz). In order to find the contribution of H(7) to this three- proton system, $^2H(7)$ compound **5g** was prepared (H_2CO - $NaBH_3CN$ in $CF_3CO_2{}^2H$). Its mass spectrum showed peaks at M+1 and M+2 with reference to the ^1H parent compound **3g**, which was indicative of ^2H incorporation in (at least) two positions. The ^1H NMR spectrum unambigously showed that the signal corresponding to H(7) had disappeared, while the intensity of H(12) was lowered, as a consequence of the electrophilic substitution by ^2H at this position. The H(2)-H(3) spin system was considerably simplified : H(2) appears as a doublet (2.5 Hz) and H(3) as a broadened doublet (~6.5 Hz). Thus $^3J_{2,3}$ was close to 2.5 Hz and $^3J_{2,7}$ to 8 Hz for compound **3g**, indicating an all-*cis*-β arrangement of H(2), H(3) and H(7). This conclusion was extended to compounds **3c** and **3e** which showed the same pattern for their H(2) signals (dd, J_1~6.5 Hz, J_2~2.5 Hz).

Just as in the tetraphylline and *epi*reserpine series, N(H) derivative **3c** was easily distinguishable from N(Me) ones (**3e** and **3g**) : the N(1) lone pair was turned towards the concavity of the molecule for **3e** and **3g**, so that H(2) escaped its influence (0.6 ppm upfield), and C(2) was correlatively deshielded (~7 ppm) relatively to **3c**.

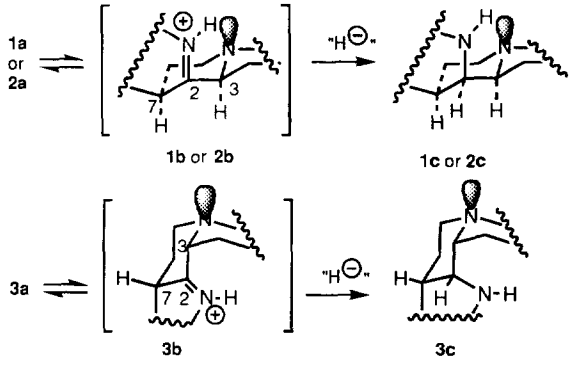
It is now interesting to compare the NMR data obtained for N(Me) derivatives of reserpine belonging to both the 3αH (*epi*) and 3βH series (Scheme 3). The N(1) lone pair of the *epi* derivatives **2e** and **2g** were significantly far from any atoms of the D ring; it weakly affected H(14)-β, which was deshielded (~0.25 ppm) compared to **2c**, whereas C(14) was shielded (~2 ppm). On the contrary, due to the more pronounced concavity of **3e** and **3g** derivatives, the N(1) lone pair in these compounds was able to come close to H(15)-α and H(21)-α which were deshielded (0.6 ppm and 1.1 ppm respectively relative to **2e** and **2g**), whereas the corresponding carbons were shielded (6.5 ppm and 7.5 ppm, respectively).



Scheme 3

Thus, the reductive methylation of N(1) and C(10) appeared to be nearly stereoselective. It did not affect the stereochemistry of any preexisting stereogenic centres, including C(3), whose epimerisation in acidic medium has been frequently asserted (reference17 and references cited).

Furthermore, the stereochemical course of the reduction of the 2,7 double bond paralleled that described by Gribble[14] for simpler indoloquinolizidine derivatives : as protonation of the 3-position of indole **a** is a reversible process, the most stable iminium **b** (with phenyl substituent at C(7) equatorial on C cycle) undergoes equatorial attack of hydride at C(2), resulting in a *cis* B/C ring junction (Scheme 4).



Scheme 4

In summary it has been demonstrated that the reagent $NaBH_3CN$, H_2CO, TFA is able to methylate both N(1) and C(10) positions and to hydrogenate stereospecifically the 2,7-double bond of some alkaloids of the yohimbine family, oxygenated at 11-position, without affecting the rest of the molecule.

Table I. ^{13}C NMR Spectral data ($CDCl_3$), δ ppm.

	Indoles		Tetraphylline derivatives			3-*Epi*reserpine derivatives			Reserpine derivatives		
Carbon	**1a**	**2a**	**1c**	**1e**	**1g**	**2c**	**2e**	**≠2g**	**3c**	**3e**	**≠3g**
2	133.2	133.1	63.8	71.8	71.9	63.9	72.1	71.6	63.2	70.4	70.
3	60.0	59.8	62.5	64.5	64.4	62.9	65.0	64.4	55.0	56.0	55.
5	53.2	53.0	54.1	55.0	54.7	54.2	54.6	54.0	52.6	52.3	51.
6	21.8	21.7	29.7	30.6	30.5	29.4	30.6	29.8	24.2	24.9	25.
7	107.6	108.0	39.3	40.3	40.3	39.4	40.3	39.9	40.3	40.3	40.
8	121.8	121.7	127.0	127.3	125.8	127.1	127.3	125.5*	126.4	126.8	125.2
9	118.5	118.5	123.1	122.2	124.0	123.3	122.5	124.1	123.7	122.9	124.
10	108.8	108.7	103.6	103.2	116.5	103.9	106.8	117.2	104.4	104.1	117.
11	156.0	156.0	159.6	159.9	157.4	159.6	159.9	157.3	159.8	160.0	157.
12	95.0	95.1	97.6	98.2	95.3	97.7	98.7	95.5	97.3	98.1	95.
13	136.7	136.8	150.9	155.8	153.4	150.8	155.6	152.9	151.3	155.9	153.
14	32.9	27.7	33.1	35.3	35.2	26.9	29.3	28.7	25.7	25.7	24.
15	30.6	37.2	30.5	31.5	31.4	37.4	38.2	37.7	31.7	31.7	31.
16	106.7	51.8	106.7	106.9	106.8	51.9	52.2	51.8	51.5	51.7	51.
17	154.6	78.0	154.4	154.5	154.4	77.9	78.1	77.8	77.9	77.7	77.
18	14.9	77.7	14.7	14.7	14.6	77.6	77.6	77.4	77.2	77.6	77.
19	73.7	30.4	73.4	73.5	73.3	30.3	30.4	29.8	30.0	30.1	29.
20	40.9	34.8	40.3	40.3	40.1	34.5	34.3	33.9	33.7	33.7	33.
21	56.8	59.6	57.3	58.4	58.3	60.6	61.7	60.9	52.7	53.7	53.
$H_3CO_2\underline{C}$-16	167.4	172.5	167.2	167.3	167.1	172.4	172.4	172.3	172.7	172.4	172.
$H_3\underline{C}O_2C$-16	50.9	52.0	50.7	50.9	50.7	51.7	51.7	51.5	51.9	51.5	51.
$H_3\underline{C}O$-17	-	60.8	-	-	-	60.7	60.7	60.5	60.6	60.8	60.
$H_3\underline{C}O$-11	55.7	55.7	55.1	55.3	55.5	55.2	55.4	55.3	55.3	55.3	55.
$H_3\underline{C}$-N1	-	-	-	41.0	41.5	-	42.0	42.2	-	40.5	40.
$H_3\underline{C}$-10	-	-	-	-	15.6	-	-	15.2	-	-	15.
1'	-	125.2	-	-	-	125.2	125.4	125.0*	125.2	125.3	125.0
2',6'	-	106.7	-	-	-	106.7	106.8	106.6	106.8	106.7	106.
3',5'	-	152.9	-	-	-	152.8	152.9	152.6	152.8	152.8	152.
4'	-	142.2	-	-	-	142.1	142.2	142.2	142.2	142.1	141.
$H_3\underline{C}O$-3'	-	56.2	-	-	-	56.2	56.3	55.9	56.2	56.2	55.
$H_3\underline{C}O$-5'	-	56.2	-	-	-	56.2	56.3	55.9	56.2	56.2	55.
$H_3\underline{C}O$-4'	-	60.8	-	-	-	60.7	60.9	60.4	60.9	60.8	60.
$O\underline{C}O$-1'	-	165.3	-	-	-	165.3	165.5	165.4	165.4	165.4	165.

* : These assignments could be interchanged. ≠ : $CDCl_3$+CD_3OD 10%

Table II ^{1}H NMR of dihydro derivatives ($CDCl_3$); δ ppm, multiplicity (*J* Hz)

Proton		Tetraphylline derivatives			3-*Epi*reserpine derivatives			Reserpine derivatives		
		1c	**1e**	**1g**	**2c**	**2e**	**≠ 2g**	**≠ 3c**	**3e**	**≠ 3g**
H-2		3.65 dd (6.4-2.7)	3.18 dd (6.6-2.5)	3.12 dd (6.7-2.8)	3.58 dd (6.4-2.8)	3.07 bd (6.6)	3.06 m	3.59 dd (6.7-2.6)	3.01 dd (7.7-2.6)	2.98 dd (8.2-2.7)
H-3		2.25 m	2.41 bd (11.9)	2.43 bd (11.9)	1.99 m	2.15 m	2.32 m	3.14 bd (~6.0)	3.15 bd (6.7)	3.16 bd (~6.8)
H-5	α	2.79 dt (11.3-3.1)	2.12 m	2.12 m	1.90 m	1.92 td (12.4-2.0)	2.01 m	2.83	2.85 m *	2.79 m
	β	2.09 bt (10.9)	2.87 m	2.86 m	2.68 bd (11.2)	2.72 dt (12.4-3.0)	2.80 m		2.75 m *	
H-6	α	1.74 m	1.79 m	1.67 q (11.4)	1.70 m	1.72 m	1.78 bd (12.3)	1.55 m *	1.56 m **	1.55 m *
	β	1.57 dq (12.1-3.9)	1.51 m	1.48 dq (11.4-4.0)	1.54 dq (12.2-3.0)	1.46 dq (12.4-3.0)	1.45 bq (12.3)	1.62 m *	1.67 m **	1.68 m *
H-7		2.89 m	2.98 m	2.95 m	2.85 dt (11.6-6.4)	2.95 m	2.97 m	3.05 dt (10.6-6.7)	3.25 dd (14.4-6.6)	3.26 bq (~8.2)
H-9		6.95 d (8.6)	6.95 d (8.0)	6.81 s	6.97 d (8.0)	6.95 d (7.8)	6.82 s	6.98 d (7.9)	6.94 d (8.0)	6.81 s
H-10		6.25 m	6.28 dd (8.0-2.2)	-	6.28 dd (8.0-2.2)	6.31 dd (7.8-2.2)	-	6.31 dd (7.9-2.2)	6.32 dd (8-15)	-
H-12		6.26 s	6.23 d (2.0)	6.22 s	6.34 d (2.2)	6.28 bs	6.30 s	6.33 m	6.21 t (1.6)	6.25 s
H-14	α	2.71 dt (12.5-2.6)	2.86 m	2.86 m	1.31 bdd (12.0-3.1)	1.50 m	1.53 bd (~10.5)	1.51 m **	1.67 m ***	1.96 m **
	β	1.34 q (12.0)	1.68 q (12.0)	1.67 q (11.4)	1.88 q (12.0)	2.15 m	2.19 m	2.22 m **	2.17 m ***	2.20 m **
H-15		2.25 m	2.14 bt (10.5)	2.12 m	2.23 m	2.15 m	2.17 m	2.80 m	2.78 m	2.79 m
H-16		-	-	-	2.77 dd (11.3-4.7)	2.76 m	2.82 m	2.83 m	2.82 m	2.83 m
H-17		7.51 s	7.50 s	7.51 s	3.91 dd (10.9-9.5)	3.86 dd (11.0-9.5)	3.91 m	3.90 m	3.87 m	3.92 m
H-18		1.14 d (6.6) 3H	1.15 d (6.5) 3H	1.13 d (6.6) 3H	5.08 ddd (12.2-9.4-5.0)	5.08 ddd (12.4-9.5-5.0)	5.07 ddd (11.8-9.6-4.8)	5.07 ddd (10.6-9.3-4.8)	5.07 m	5.05 m
H-19	α	-	-	-	1.96 m	1.95 m	1.96 dt (12.5-3.8)	1.95 m	1.98 m	1.96 m
	β	4.36 dq (6.6-2.6)	4.37 dq (6.6-3.1)	4.35 dq (6.6-3.2)	2.33 q (12.2)	2.35 q (12.2)	2.35 m	2.17 q (12.4)	2.30 m	2.20 m
H-20		2.09 bt (10.9)	2.12 m	2.12 m	2.03 m	2.00 bd (12.0)	2.06 bd (12.0)	2.22 m	2.18 m	2.20 m
H-21	α	1.90 t (10.9)	1.89 t (10.7)	1.93 t (11.0)	2.25 bd (11.3)	2.26 dd (11.8-3.1)	2.40 bd (12.0)	3.71 dd (12.0-4.0)	3.40 dd (9.5-1.7)	3.42 dd (10.6-2.4)
	β	2.87 m	2.92 m	2.92 bd (11.0)	2.77 dd (11.3-4.7)	2.78 bd (~12.0)	2.85 bd (12.0)	2.31 bd (~11.7)	2.17 m	2.23 m
H_3C-N1		-	2.88 s	2.87 s	-	2.96 s	2.96 s	-	2.72 s	2.73 s
H_3C-10		-	-	2.12 s	-	-	2.12 s	-	-	2.12 s
H_3CO-11		3.70 s	3.78 s	3.79 s	3.75 s	3.77 s	3.82 s	3.76 s	3.75 s	3.83 s
H_3CO_2C-16		3.69 s	3.73 s	3.71 s	3.75 s	3.75 s	3.78 s	3.82 s	3.79 s	3.76 s
H_3CO-17		-	-	-	3.51 s	3.49 s	3.52 s	3.53 s	3.52 s	3.54 s
H-2'; H-6'		-	-	-	7.33 s	7.33 s	7.34 s	7.34 s	7.33 s	7.36 s
H_3CO-3'		-	-	-	3.94 s	3.94 s	3.94 s	3.93 s	3.92 s	3.93 s
H_3CO-5'		-	-	-	3.94 s	3.94 s	3.94 s	3.93 s	3.92 s	3.93 s
H_3CO-4'		-	-	-	3.92 s	3.92 s	3.92 s	3.93 s	3.92 s	3.91 s

* : these assignments could be interchanged. ≠ : $CDCl_3$ + CD_3OD 10%.

EXPERIMENTAL

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra (ν, cm^{-1}) were recorded on a BOMEM FTIR apparatus with COSMIC interferometer; UV spectra were recorded on a Varian 634 spectrophotometer; ^1H- and ^{13}C-NMR spectra were measured on a Bruker AC 300 apparatus at 300 MHz and 75 MHz, respectively. Electron impact mass spectra (E = 70 eV) were obtained on a JEOL JMS D-300 spectrometer; Kieselgel 60 PGF_{254} (Merck N° 7749) was used for thin layer chromatography and Kieselgel 60 (Merck N° 9385) for flash chromatography.
Extraction protocol: the reaction mixture was diluted in water (10 ml per ml of acetic or trifluoroacetic acid); the solution was made alkaline with 4% aqueous ammonia and extracted three fold with CH_2Cl_2. Organic extracts were combined, washed with pure water, dried ($MgSO_4$) and concentrated. The residue was purified by TLC (< 400 mg) or centrifugal chromatography (> 400 mg).

Isomerisation of reserpine ***3a*** *: 3-epireserpine* ***2a***. This was performed according to Cook's procedure.[8] Starting from reserpine (300 mg, 0.49 mmol), it gave a mixture of four products which were separated (CH_2Cl_2: MeOH 98:2) (increasing polarity): methyl 3,4,5-trimethoxybenzoate (5 mg, 4%), 3-*epi*reserpine **2a** (183 mg, 61%), reserpine (66 mg, 22%), 3-*epi*reserpin-18-ol (16 mg, 8%). 3-*epi*reserpin-18-ol : UV : 298, 271, 228; IR (film) : 3375 (broad), 3070-2860, 2840, 2085, 2755, 1725, 1630; SM : 415 ([M^++H], 25), 414 ($M^{\bullet+}$, 100), 413 (95), 399 (10), 383, 254 (12), 240, 214 (10), 200 (15), 199 (12); ^1H NMR ($CDCl_3$) : 7.83 (s, 1H, H^1), 7.32 (d, 1H, *J*=8.5, H^9), 6.83 (d, 1H, *J*=2.1, H^{12}), 6.74 (dd, 1H, *J*=8.5-2.1, H^{10}), 3.83 (s, 3H, C^{11}-OCH_3), 3.79 (s, 3H, C^{16}-CO_2CH_3), 3.59 (m, 1H, H^{18}), 3.41 (dd, 1H, *J*=11.0-9.2, H^{17}), 3.10 (bd, 1H, *J*=10.5, H^3), 2.94 (m, 1H, H^5), 2.91 (m, 1H, H^6), 2.80 (dd, 1H, *J*=11.6-1.6, H^{21}), 2.80 (m, 1H, H^6), 2.61 (m, 1H, H^{16}), 2.55 (dd, 1H, *J*=11.6-3.2, H^{21}), 2.22 (m, 1H, H^{15}), 2.18 (q, 1H, *J*=12.7, H^{19}), 1.89 (bd, 1H, *J*=12.7, H^{20}), 1.74 (m, 3H, $1H^{19}$, $2H^{14}$);^{13}C NMR: 173.0 (C^{16}-$\underline{C}O_2CH3$), 156.0 (C^{11}), 136.8 (C^{13}), 133.0 (C^2), 121.7 (C^8), 116.6 (C^9), 108.7 (C^{10}), 108.1 (C^7), 95.1 (C^{12}), 81.4 (C^{17}), 75.1 (C^{18}), 61.1 (C^{17}-$O\underline{C}H_3$), 60.0 (C^3), 59.6 (C^{21}), 55.7 (C^{11}-$O\underline{C}H_3$), 53.1 (C^5), 51.8 (C^{16}-CO_2-$\underline{C}H_3$), 51.7 (C^{16}), 37.8 (C^{15}), 35.2 (C^{20}), 33.0 (C^{19}), 27.7 (C^{14}), 21.6 (C^6).

Preparation of 2,7-dihydro derivatives ***1c, 2c*** *and* ***3c*** *from indoles* ***1a 2a*** *and* ***3a***. A 5% (w/v) solution of indole in TFA was treated with an excess of $NaBH_3CN$ in 3 portions within 15 min, at room temperature. The solution was stirred 5 min, extracted, and the residue was purified by chromatography (eluent CH_2Cl_2: MeOH 97:3).

Starting indole (quantities mmol)	2,7-dihydro indole (yield)	$NaBH_3CN$ eq	Reaction time (t min)	Other product (%)
1a (0.25)	**1c** (72%)	5	15	none
2a (0.15)	**2c** (87%)	12	30	none
3a (0.17)	**3c** (55%)	20	60	**3a** (17%)

1c: Mp: 196-198°C (dec., MeOH). $[\alpha]_D^{25}$: +90.0 (MeOH, c=0.68). UV: 296, 239, 210. IR (film): 3180, 2950, 2940, 2850, 2750, 1700, 1620. MS: 384 ($M^{\bullet+}$, 25), 353 (5), 237 (30), 224 (100), 209 (30), 174 (10), 160 (5). Anal. calc. for $C_{22}H_{28}O_4N_2$: C 68.72, H 7.34, N 7.29; found C 68.60, H 7.45, N 7.25. **2c**: Mp: 154-157°C (acetone). $[\alpha]_D^{25}$: -84.6 ($CHCl_3$, c=0.58). UV: 292, 258, 211. IR (film): 3360, 2940, 2840, 2760, 1740, 1710, 1610, 1590. HREIMS: $M^{\bullet+}$ calc. for $C_{33}H_{42}N_2O_9$: 610.2890, found 610.2923; 611([M+H]$^+$,

5), 610 ($M^{\bullet+}$, 20), 463 (5), 451 (30), 450 (100), 252 (50), 224 (15), 212 (75), 195 (70). **3c**: Mp: 206-208°C (dec., methanol/ether). $[\alpha]_D^{25}$: -74.6 ($CHCl_3$, c=0.61). UV: 293, 261, 212. IR (film): 3510, 3340, 2940, 2840, 1730, 1700, 1615, 1590. HREIMS: $M^{\bullet+}$ calc. for $C_{33}H_{42}N_2O_9$: 610.2888, found 610.2823; 611 ($[M+H]^+$, 3), 610 ($M^{\bullet+}$, 10), 463 (7), 451 (15), 450 (50), 384 (15), 252 (45), 224 (100), 212 (25), 209 (30), 195 (60).

Preparation of 1-methyl-2,7-dihydroindole derivatives ***1e, 2e, 3e, and pseudodimer 2h*** *from 2,7-dihydroindoles* ***1c, 2c and 3c.*** To a 0.2 M solution of 2,7-dihydroindole in AcOH was first added 40% (w/v) aqueous formaldehyde solution (4 molar eq), then $NaBH_3CN$ (2 molar eq), in three portions within 15 min. It was further stirred for 1 h at the same temperature, extracted, and the residue was purified by chromatography (CH_2Cl_2: MeOH 98:2, saturated with ammonia), except for **1e** which was crystallized from MeOH.

Starting material (quantities, mmol)	1-Me-2,7-dihydro product (yield)	Reaction temperature	Other products (%)
1c (0.2)	**1e** (92%)	20°C	none
2c (0.1)	**2e** (37%)	-10°C	**2g** (10%) **2h** (25%)
3c (0.1)	**3e** (52%)	20°C	none

1e: Mp: 140-142°C (MeOH). $[\alpha]_D^{25}$: +95.0 (MeOH, c=0.17). UV: 298, 242. IR (KBr): 2950, 2850, 2840, 2750, 1700, 1620. MS HREIMS $M^{\bullet+}$ calc. for $C_{23}H_{30}O_2N_4$: 398.2205, found 398.2213: 398 ($M^{\bullet+}$, 15), 237 (16), 224 (100), 209 (20), 188 (8), 174 (7), 161 (5). **2e**: $[\alpha]_D^{25}$: -63.0 ($CHCl_3$, c=0.71). UV: 294, 263, 211. IR (film): 3050, 2870, 2845, 2820, 2775, 1735, 1715, 1620, 1590. MS HREIMS calc. for $C_{34}H_{44}N_2O_9$: 624.3047, found 624.3028; 625 ($[M+H]^+$, 10), 624 ($M^{\bullet+}$, 25), 451 (25), 450 (100), 232(10), 252 (35), 212 (20), 195 (45). **3e**: $[\alpha]_D^{25}$: -186.0 ($CHCl_3$, c=0.35). UV: 297, 262, 213. IR (film): 2935, 2840, 1735, 1710. MS HREIMS calc. for $C_{34}H_{44}N_2O_9$: 624.3047, found 624.3039; 624 ($M^{\bullet+}$, 10), 450 (100), 252 (20), 195 (20).

2h: $[\alpha]_D^{25}$: -138.0 ($CHCl_3$, c= 0.66). UV: 298, 259, 212. IR (film): 3060, 2860, 2855, 2810, 2770, 1735, 1715, 1620, 1590. MS (FAB, glycerol matrix): 1261.2 ($[M+H]^+$, 30), 637.4 (20), 450.3 (45), 252.2 (25), 195.1 (100). ^1H NMR ($CDCl_3$): 7.34 (s, 4H, $2H^{2'}+2H^{6'}$), 6.67 (s, 2H, $2H^{9}$), 6.30 (s, 2H, $2H^{12'}$), 5.08 (ddd, 2H, *J*=12.0-10.0-5.0, $2H^{18}$), 3.94 (s, 12H, $2C^{3'}$-OCH_3+$2C^{5'}$-OCH_3), 3.92 (s, 6H, $2C^{4'}$-OCH_3), 3.88 (m, 2H, $2H^{17}$), 3.79 (s, 6H, $2C^{11}$-OCH_3), 3.82-3.72 (m, 2H, C^{10}-CH_2-C^{10}), 3.76 (s, 6H, $2C^{16}$-CO_2CH_3), 3.50 (s, 6H, $2C^{17}$-OCH_3), 3.00 (bd, 2H, *J*=7, $2H^{2}$), 2.95 (s, 6H, $2N^{1}$-CH_3), 2.88 (dt, 2H, *J*=11.2-6.5, $2H^{7}$) 2.77 (m, 4H, $2\beta H^{16}+2H^{21}$), 2.68 (m, 2H, $2\beta H^{5}$), 2.36 (q, 2H, *J*=12.5, $2\beta H^{19}$), 2.23 (bd, 2H, *J*=11.5, $2\alpha H^{21}$), 2.13 (m, 6H, $2H^{3}+2\beta H^{14}+2H^{15}$), 2.00 (bd, 2H, *J*=12.5, $2H^{20}$), 1.93 (m, 2H, $2\beta H^{19}$), 1.87 (bt, 2H, *J*=11.5, $2\alpha H^{5}$), 1.65 (m, 2H, $2\alpha H^{6}$), 1.49 (bd, 2H, *J*=5.5, $2\alpha H^{14}$), 1.37 (bq, 2H, *J*=12.5, $2\beta H^{6}$). ^{13}C NMR ($CDCl_3$): 172.3 (C^{16}-$\underline{C}O_2CH_3$), 165.3 ($\underline{C}$OTMB), 157.3 (C^{11}), 153.1 (C^{13}), 152.8 ($C^{3'}+C^{5'}$), 142.0 ($C^{4'}$), 126.2 (C^{8}), 125.3 ($C^{1'}$), 123.9 (C^{9}), 121.0 (C^{10}), 106.7 ($C^{2'}+C^{6'}$), 96.0 (C^{12}), 78.0 (C^{17}), 77.5 (C^{18}), 72.0 (C^{2}), 64.9 (C^{3}), 61.6 (C^{21}), 60.8 ($C^{4'}$-O$\underline{C}H_3$), 60.6 (C^{17}-O$\underline{C}H_3$), 56.2 ([$C^{3'}+C^{5'}$])-O$\underline{C}H_3$), 55.8 (C^{11}-O$\underline{C}H_3$), 54.5 (C^{5}), 52.1 (C^{16}), 51.7 (C^{16}-$CO_2\underline{C}H_3$), 42.7 (N^{1}-$\underline{C}H_3$), 40.4 (C^{7}), 38.0 (C^{15}), 34.2 (C^{20}), 30.7 (C^{6}), 30.3 (C^{19}), 29.2 (C^{14}), 28.8 (C^{10}-$\underline{C}H_2$-C^{10}).

*Preparation of 1,10-dimethyl-2,7-dihydroindole derivatives **1g**, **2g**, **3g** from indoles **1a**, **2a** and **3a**.* A solution of 0.1 M of indole in TFA was treated portionwise with $NaBH_3CN$ (4 molar eq) at -5°C within 15 min. Then a 40% (w/v) aqueous formaldehyde solution (8 molar eq) was added, followed by $NaBH_3CN$ (3 molar eq). The reaction was continued for 15 min at -5°C, then for 30 min at room temperature. After extraction the residue was crystallized from MeOH for compounds **1g** and**3g**, and chromatographed (eluent $CHCl_3$:MeOH 95:5) for compound **2g**.

Starting material (mmol)	1,10-Dimethyl derivative (yield)
1a (0.5)	**1g** (65%)
2a (0.7)	**2g** (71%)
3a (1.0)	**3g** (44.5%)

1g: Mp: 190-192°C (MeOH). $[\alpha]_D^{25}$: +81.0 ($CHCl_3$, c=0.49). UV: 305, 245, 213. IR (KBr): 2940, 2800, 2760,1700,1615. HREIMS: $M^{\bullet+}$ calc. for $C_{24}H_{32}N_2O_4$: 412.2362, found 412.2399; 413([M+H]$^+$, 15),, 412($M^{\bullet+}$, 70), 381 (15), 262 (15),237 (20), 225 (15), 224 (100), 210 (35), 202 (15),188 (10) , 160 (10), 150 (8), 149 (10), 132 (5), 122 (5). **2g**: $[\alpha]_D^{25}$: -80.7 ($CHCl_3$, c=0.59). UV: 295, 250, 210. IR (film) 3000, 2940, 2840, 2760, 1730, 1710, 1615, 1590. HREIMS: $M^{\bullet+}$ calc. for $C_{35}H_{46}N_2O_9$: 638.3202, found 638.3051; 639([M+H]$^+$, 20), 638 ($M^{\bullet+}$, 50), 607 (8), 451 (25), 450 (100), 252 (25), 212 (15), 195 (35). **3g**: Mp: 197°C (MeOH). $[\alpha]_D^{25}$: -89.0 ($CHCl_3$, c=0.32). UV: 294, 258, 212. IR (film): 3000, 2940, 2840, 1735, 1710, 1615, 1590. HREIMS: $M^{\bullet+}$ calc. for $C_{35}H_{46}N_2O_9$: 638.3203, found 638.3224; 639([M+H]$^+$, 5), 638 ($M^{\bullet+}$, 10), 462 (5), 451 (25), 450 (100), 252 (45), 212 (25), 195 (50).

*Preparation of 7-^{2}H-1,10 dimethyl-2,7-dihydroreserpine **5g** from reserpine **3a**.* A solution of reserpine (80 mg, 0.13 mmol) in 99.5% $CF_3CO_2{}^2H$ (1.2 ml) was treated portionwise with $NaBH_3CN$ (80 mg, 1.3 mmol), at 0°C, within 25 min. Then 40% (w/v) aqueous formaldehyde was added (0.6 ml : 0.8 mmol), followed by $NaBH_3CN$ (40 mg, 0.66 mmol) and the solution was stirred further 30 min at 0°C. Extraction gave a residue (89 mg) which was chromatographed (eluent CH_2Cl_2-MeOH 96:4) to furnish **5g** (35 mg, 42%). **5g**: UV: 299, 260, 214. IR (film): 2950, 2850, 1740, 1710, 1610, 1590. MS: 641 (15), 640 (17), 451 (95), 252 (50), 195 (100). ^{1}HNMR ($CDCl_3$: CD_3OD 90:10, T=328°K) : 7.35 (s, 2H, $H^{2'}$, $H^{6'}$), 6.80 (s, 1H, H^9), 6.25 (s, 0.17H, residual H^{12}), 5.03 (m, 1H, H^{18}), 3.93 (s, 6H, $C^{3'}$+$C^{5'}$-OCH_3), 3.92 (m, 1H, H^{17}), 3.90 (s, 3H, $C^{4'}$-OCH_3), 3.82 (s, 3H, C^{11}-OCH_3), 3.75 (s, 3H, C^{16}-CO_2CH_3), 3.52 (s, 3H, C^{17}-OCH_3), 3.42 (dd, 1H, *J*=4.0-11.5, H^{21}), 3.26 (bt, 1H, *J*~6.5, H^3), 3.06 (d, 1H, *J*=2.5, H^2), 2.95-2.67 (m, 4H, $2H^5$, H^{15}, H^{16}), 2.74 (s, 3H, N^1-CH_3), 2.32 (bd, 1H, H^{21}), 2.32-2.15 (m, 3H, H^{14}, H^{19}, H^{20}), 2.12 (s, 3H, C^{10}-CH_3), 1.96 (m, 1H, H^{19}), 1.83-1.65 (m, 2H, H^6, H^{14}), 1.57 (m, 1H, H^6); ^{13}C NMR ($CDCl_3$) : 172.5 (C^{16}-$\underline{C}O_2CH_3$), 165.4 (C^{18}-O$\underline{C}$O-Ar), 157.5 (C^{11}), 153.8 (C^{13}), 152.9 ($C^{3'}$, $C^{5'}$), 142.2 ($C^{4'}$), 125.8* (C^8), 125.4* ($C^{1'}$), 124.3 (C^9), 117.2 (C^{10}), 106.8 ($C^{2'}$, $C^{6'}$), 95.3 (weak, residual $\underline{C}^{12}$-H), 77.8** (C^{17}), 77.6** (C^{18}), 70.5 (C^2), 60.6 ($C^{4'}$-O$\underline{C}H_3$, C^{17}-O$\underline{C}H_3$), 56.2 ($C^{3'}$-O$\underline{C}H_3$, $C^{5'}$-O$\underline{C}H_3$), 56.1*** (C^3), 55.4*** (C^{11}-O$\underline{C}H_3$), 53.0 (C^{21}), 52.5 (C^5), 51.9 (C^{16}), 51.4 (C^{16}-$CO_2\underline{C}H_3$), 41.3 (N^1-$\underline{C}H_3$), 40.4 (weak, t, C^7), 34.0 (C^{20}), 31.9 (C^{15}), 30.2 (C^{19}), 25.8 (C^6), 25.2 (C^{14}), 15.7 (C^{18}).

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