SYNTHESIS OF ISOVINCADINE AND 16-EPIISOVINCADINE, ANALOGS OF VINCADINE AND 16-EPIVINCADINE WITH A NEW REARRANGED SKELETON, FROM A VINCADIFFORMINE DERIVATIVE

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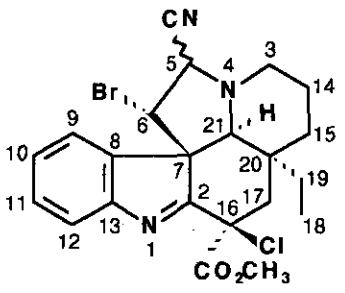
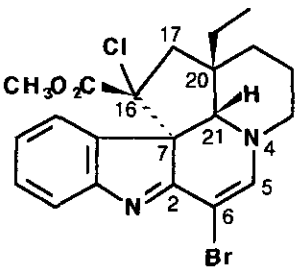
Abstract- Treatment of the rearranged indole alkaloid (**3**) under reductive conditions [a) hydrogenolysis; b) $NaBH_3CN$ in AcOH] provided 16-epiisovincadine (**6**) and isovincadine (**7**), two new rearranged analogs of the alkaloids 16-epivincadine (**9**) and vincadine (**10**).

In a previous publication,[1] we reported a new rearrangement of *Aspidosperma* alkaloids with a modified tryptamine chain. Heating of 6-bromo-16-chloro-1-dehydro-5-cyanovincadifformine (as epimers on C-5[2]) (**1** and **2**)[3] in trifluoroacetic acid provided the rearranged compound (**3**) (30%), whose structure was established by X-ray diffraction. Conversion of **1** and **2** into **3** is thought to proceed through two successive Wagner-Meerwein type 1,2 shifts on C-2 then C-7 with replacement of 2-16 and 7-6 bonds in **1** and **2** by 2-6 and 7-16 bonds in **3**. Despite this deep-seated skeletal reorganization, **3** still displays some similarity with the aspidospermane skeleton. This analogy prompted us to undertake the study of reduction compounds of **3** compared with known behavior of aspidospermane alkaloids as (-)-vincadifformine (**4**) under reductive conditions.[4-6]



1 and 2



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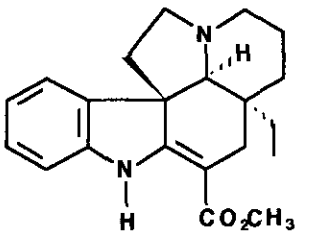
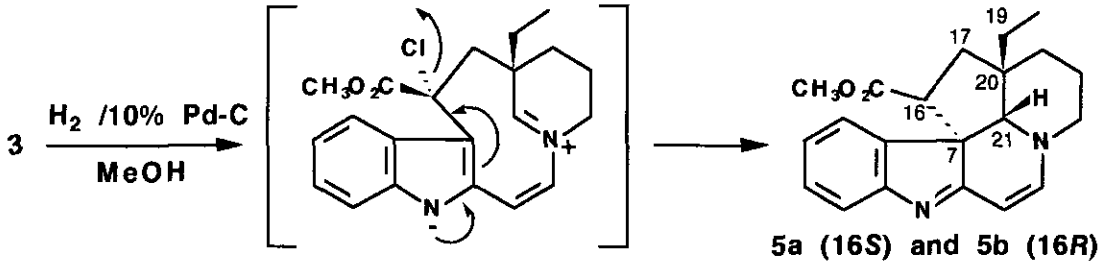


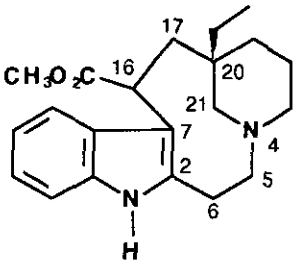
4

The reduction of **3** was performed in a two-steps sequence. The first hydrogenolysis step (H_2, 10% Pd-C in MeOH) quantitatively provided compound **(5)**. The structure of **5** was supported by spectroscopic data. Compared with that of **3**, the UV spectrum of **5** was similar while the EI mass spectrum showed a molecular ion at *m/z* 336 consistent with loss of both halogens. Compound **(5)** was homogeneous in TLC (silica gel, dichloromethane-methanol 95:5), but its ^{1}H NMR spectrum (Table 1) displayed a splitting of some signals in a 65:35 ratio, especially at δ 5.52 and 5.44 ppm (2 d, J = 7.5 Hz, H-6) and δ 6.68 and 6.70 ppm (2 d, J = 7.5 Hz, H-5), which proved **5** to be a mixture of two isomers **(5a)** (major compound) and **(5b)** (minor compound). Significant ROE observed in both isomers between H-21 and both H-19 of the ethyl chain clearly indicated a *cis* junction of cyclopentane and piperidine rings, and consequently the same stereochemistry on C-21 and on the interdependent C-7 as in **3**. Moreover, retention of configuration on C-7 and C-21 was entirely supported by inspection of molecular models. The shielding of the methoxycarbonyl signal in the major compound could be explained by aromatic anisotropy and was in favour of a 16*S* configuration (CO_2CH_3 "exo") in **5a** and 16*R* (CO_2CH_3 "endo") in **5b**. The C-16 epimerization was fully confirmed in the next step by isolation, in almost the same 16*S* / 16*R* ratio, of compounds for which configuration on C-16 was established. This epimerization can be related to the course of hydrogenolysis through a tetracyclic indole-iminium intermediate compound having a 16-benzylic chlorine (Scheme 1).

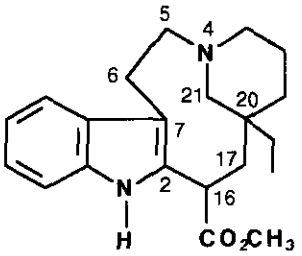


Scheme 1

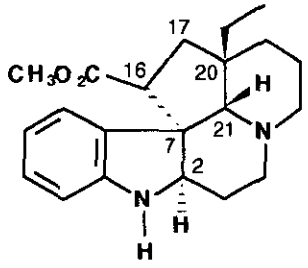
The second step sodium cyanoborohydride reduction yielded mainly the indole (**6**) as major compound (37%) and two minor derivatives (**7**) (9%) and (**8**) (9%). The structure of **6**, that we called 16-epiisovincadine, revealed most of spectral data in common with 16-epivincadine (**9**).[7,8] The EI mass spectra of **6** and **9** were superimposable with a molecular ion at *m/z* 340, a base peak at *m/z* 215 and exactly the same fragmentation pattern. ^{1}H and ^{13}C NMR spectra of **9**[8,9] and **6** (Table 1) also displayed a great similarity, particularly with a characteristic H-16 signal respectively at 5.54 and 5.60 ppm in **6** and **9**, strongly deshielded compared to vincadine (**10**) (3.80 ppm[8]), but slightly differed in some chemical shifts [especially significant is the shielding of N1-H (7.82 ppm in **6**, 8.60 ppm in **9**) owing to lack of chelation with the ester group as in **9**]. Lastly, by analogy with **9**,[8] the important downfield shift of the H-16 signal at δ 5.54 ppm is related to the close proximity of this proton to the lone pair of electrons on N-4 and clearly indicates a 16*S* stereochemistry. As **6**, the minor compound (**7**) exhibited the same indole chromophore and a same molecular ion at *m/z* 340. Compared to **6**, its EI mass spectrum differed in relative abundance of main fragmentation peaks and its ^{1}H NMR spectrum in some chemical shifts, particularly the H-16 signal shielded at δ 3.70 ppm (Table 1). The compared spectral behavior of **6** and **7** is quite similar to that of the epimeric pair vincadine (**10**) and 16-epivincadine (**9**)[7-10], leading to the assignment of **7** to be the isovincadine (16*R*) structure.



6 (16*S*,20*S*)
7 (16*R*,20*S*)



(+)-epivincadine 9 (16*S*,20*S*)
(+)-vincadine 10 (16*R*,20*S*)



8 (16*R*)

The other minor product (**8**) also showed in the EI mass spectrum a molecular ion at *m/z* 340 but displayed in the UV spectrum a typical dihydroindole chromophore in agreement with the structure (**8**). ^{1}H NMR experiments allowed for all proton assignments (Table 1) and confirmed the structure of **8**. The stereochemistry of C-21 (and interdependent C-7) and of C-2 were established through a ROESY spectrum. Significant ROE's between H-21 and H-19 confirmed the *cis* junction of cyclopentane and piperidine rings as in **3** and **5**. ROE's observed between H-9 and H-21, H-9 and both H-19, H-9 and H-16 supported a 2-7 *cis* junction. The same 16*R* stereochemistry as in **5b** was inferred from the similar chemical shift of the

methoxycarbonyl signal (3.56 ppm in **8**, 3.52 ppm in **5b**) and from the already mentioned significant ROE observed between H-9 and H-16. Lastly, in the absence of clear arguments, conformation around N-4 could not be fixed with assurance (δ H-21 at 2.43 ppm would rather support a *trans* relationship of H-21 with the N-4 lone pair of electrons,[11] but the "endo" methoxycarbonyl group orientation can interfere, as demonstrated by the deshielding of the H-21 signal in **5b** compared with **5a**). Reduction of **5** to **6**, **7** and **8** results from two possible pathways with or without cleavage of the 7-21 bond: a 16*S* stereochemistry in **5a** appears to induce reduction only via the cleavage of the 7-21 bond [compound **(6)**] while in the 16*R* configuration of **5b**, reduction proceeds through both pathways [compounds **(7)** and **(8)**].

Table 1. NMR Chemical Shift Values of Compounds (5a, 5b, 6, 7 and 8) in $CDCl_3$ [a]

	5a	**5b**	**6**	**7**	**8**	**6**	**9**[b]
Atom N°	δ_H	δ_H	δ_H	δ_H	δ_H	δ_C	δ_C
2					4.01	134.1	133.7
3	3.42 / 3.12	3.42 / 2.95	2.65 / 2.46	2.42 / 2.33	2.75 / 1.96	53.7	53.8
5	6.68	6.70	2.95 / 2.46	2.63 / 2.40	2.87 / 2.16	53.8	54.0
6	5.52	5.44	3.22 / 2.51	3.25 / 2.65	1.72 / 1.41	30.6	26.2
7						112.8	111.5
8						127.2	127.6
9	7.43	7.46	7.04	7.40	7.22	119.3	117.9
10	7.04	7.06	7.27	7.10	6.74	119.9	118.7
11	7.31	7.30	7.09	7.02	7.05	120.8	121.4
12	7.43	7.46	7.64	7.27	6.59	110.4	110.6
13						135.2	135.7
14	1.93 / 1.65	1.85 / 1.65	1.84 / 1.53	1.37 / 1.15	1.76 / 1.48	23.9	23.6
15	2.05 / 1.42	2.01 / 1.25	1.61 / 1.06	1.55 / 1.29	1.78 / 1.48	36.6	37.3
16	3.27	3.12	5.54	3.70	2.77	39.4	40.9
17	2.57 / 1.70	2.36 / 1.85	2.37 / 2.11	2.48 / 2.05	2.39 / 1.61	39.0	42.8
18	1.10	1.12	0.55	0.92	0.93	7.4	7.3
19	1.91 / 1.88	1.90	0.94	1.29 / 1.18	1.71 / 1.51	35.4	35.6
20						35.2	35.6
21	3.31	3.59	2.16 / 1.81	3.18 / 1.60	2.43	60.7	60.8
$CO_2\underline{C}H_3$	3.17	3.52	3.55	3.68	3.56	53.7	51.9
$\underline{C}O_2CH_3$						176.2	175.6
NH			7.82	7.69	2.45		

[a]500 MHz for ^1H and 125.8 MHz for ^{13}C; [b]From reference 9

The new synthesized compounds **(6)** and **(7)** are analogs of (+)-16-epivincadine **(9)** and (+)-vincadine

(10), two alkaloids also readily available from (-)-vincadiformine **(4)**.[6-12] Since some alkaloids with a C7 → C2 transposed tryptamine chain have already been described [*eg* melonine [13]], the possible future isolation from a plant of **6** and **7** can be conceivable.

EXPERIMENTAL

UV spectra were acquired on a Unicam SP 1800, IR spectra on a Perkin-Elmer 457 spectrophotometer and optical rotations on a Schmidt-Haensch polarimeter. MS was obtained at an ionizing voltage of 70 ev. NMR experiments were performed at 500.13 MHz and 125.77 MHz for ^{1}H and ^{13}C respectively. The homonuclear ^{1}H-^{1}H and heteronuclear ^{1}H-^{13}C chemical shift correlated 2D diagrams were obtained using the standard COSY 90 and HMQC, HMBC pulse sequences respectively. Two dimensional rotating frame Overhauser spectroscopy (ROESY) spectra were recorded in the phase sensitive mode TPPI. *J* values are given in Hz. TLC data were obtained with Merck 60 F 254 silica gel precoated on aluminium sheets. Compounds were visualized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid.

Hydrogenolysis of Methyl (1*R*,2a*S*,13b*R*,13c*S*)-8-Bromo-1-chloro-2a-ethyl-(2a,3,4,5,13b,13c-hexahydro-2a,13b-ethanoindolo[3,2-*a*]quinolizine)-1-carboxylate (3): A solution of **3** (202 mg, 0.45 mmol) in MeOH (30 mL) was hydrogenated under 1 atm pressure of hydrogen with 10% Pd-C (200 mg) at room temperature for 2 h. The catalyst was separated and the filtrate was concentrated to dryness. A fifth of this residue (38 mg) in MeOH (3 mL) was mixed with 5% aqueous $NaHCO_3$ and the solution was extracted with CH_2Cl_2. After standard work-up, the residue was purified by TLC on silica gel (CH_2Cl_2-MeOH 95:5) to yield **5** (20 mg, 66%).

Methyl (1*R*,*S*,2a*S*,13b*S*,13c*S*)-2a-Ethyl-(2a,3,4,5,13b,13c-hexahydro-2a,13b-ethanoindolo[3,2-*a*]quinolizine)-1-carboxylate (5a) and **(5b)**: amorphous pale yellow solid; TLC (silica gel, CH_2Cl_2-MeOH 95:5) R_f 0.30 ; UV (EtOH) λ_{max} nm (log ε) 226 (4.07), 243 (4.05), 292 (3.35), 303 (3.46), 313 (3.46), 388 (4.13); IR (CH_2Cl_2) 1735 cm^{-1}; EIMS *m/z* (% rel int) 336 (100, $M^{+\cdot}$), 277 (26), 168 (32); Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.05; H, 7.16; N, 8.26.

Reduction of 5a and 5b with Sodium Cyanoborohydride:

The remaining part of the hydrogenolysis crude residue (154 mg) was dissolved in AcOH (15 mL). After addition of $NaBH_3CN$ (95 mg, 1.5 mmol), the mixture was kept at room temperature for 20 h. The solution was diluted with iced water, treated with 2N aqueous NaOH until pH 9 was reached, and extracted with CH_2Cl_2. After standard treatment of the organic layer, the dry residue was purified by TLC on silica gel (CH_2Cl_2-MeOH 97:3) to provide the pure compounds **6** (45 mg), **7** (11 mg) and **8** (11 mg) in 37%, 9% and 9% respective yields from **3**.

Methyl (1*S*,3*S*)-2*H*-3,7-Methanoazacycloundecino[4,5-*b*]indole-3-ethyl-1,2,4,5,6,8,9,10-octahydro-1-carboxylate (6): mp 143-145°C (MeOH); TLC (silica gel, CH_2Cl_2-MeOH 97:3) R_f 0.80 (CAS, greenish grey); $[\alpha]_D$ = +24° (c = 1.1, CH_2Cl_2); UV (EtOH) λ_{max} nm 228, 285, 292; IR (CH_2Cl_2) 3380, 1720 cm^{-1}; EIMS *m/z* (% rel int) 340 (18, $M^{+\cdot}$), 215 (100), 126 (75), 124 (25); HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.2151, found 340.2150; Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.15; H, 8.35; N, 8.18.

Methyl (1*R*,3*S*)-2*H*-3,7-Methanoazacycloundecino[4,5-*b*]indole-3-ethyl-1,2,4,5,6,8,9,10-octahydro-1-carboxylate (7): mp 177-178°C (MeOH); TLC (silica gel, CH_2Cl_2-MeOH 97:3) R_f 0.27 (CAS, grey); $[\alpha]_D$ = +15° (c = 0.5, $CHCl_3$); UV (EtOH) λ_{max} nm 229, 285, 292; IR (CH_2Cl_2) 3380, 1720 cm^{-1}; EIMS *m/z* (% rel int) 340 (28, $M^{+\cdot}$), 215 (48), 210 (39), 126 (61), 124 (100); HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.2151, found 340.2155.

Methyl (1*R*,2a*S*,8a*R*,13b*R*,13c*S*)-2a-Ethyl-(2a,3,4,5,7,8,8a,9,13b,13c-decahydro-2a,13b-ethanoindolo[3,2-*a*]quinolizine)-1-carboxylate (8): amorphous solid; TLC (silica gel, CH_2Cl_2-MeOH 97:3) R_f 0.23 (CAS, orange); $[\alpha]_D$ = -48° (c = 0.5, $CHCl_3$); UV (EtOH) λ_{max} nm (log e) 249 (3.81), 301 (3.46); IR (CH_2Cl_2) 3340, 1720 cm^{-1}; EIMS *m/z* (% rel int) 340 (100, $M^{+\cdot}$), 254 (25), 253 (30), 239 (31), 139 (68), 138 (67), 124 (56); HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.2151, found 340.2153.

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