Methyleneindolines, Indolenines, and Indoleniniums. 18.[1] A Biomimetic Entry in the *Melodinus* Alkaloids

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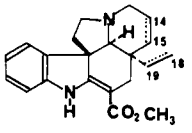
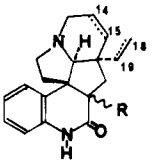
The chloroindolenine **4a** derived from vincadifformine (**1a**) was reduced to aziridine **5a**. Flow thermolysis of **5a** at 400 °C yielded imine **6a**, which was further oxidized to tetrahydroscandine (**2a**). Tetrahydromeloscine (**3a**) was prepared from **2a** following literature procedures.

The pivotal position of vincadifformine (**1a**) and of its dehydro derivatives **1b** and **1c** in the biosynthesis of various structural types of indole alkaloids has prompted study of several biomimetic in vitro rearrangements.[2-4] With efficient total syntheses of vincadifformine (**1a**)[5-7] and tabersonine (**1b**)[8,9] in hand, these rearrangements led to formal, but also practical, total syntheses.

This approach has now been extended to yet another group of alkaloids, i.e., the tetrahydroquinolone alkaloids isolated from various *Melodinus* species. Scandine (**2c**)





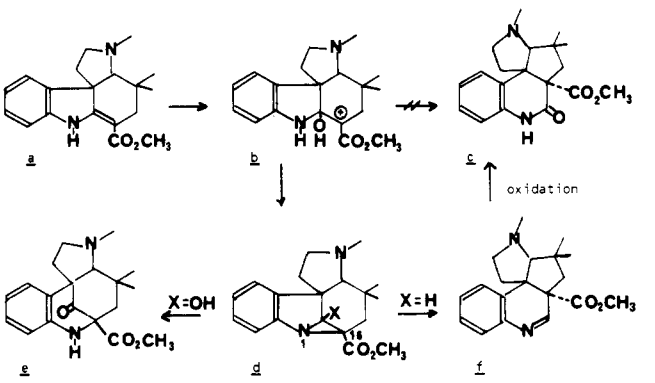
	14,15	18,19
1a	H_2	H_2
1b	Δ	H_2
1c	Δ	Δ

	14,15	18,19	R
2a	H_2	H_2	α-CO_2Me
2c	Δ	Δ	α-CO_2Me
3a	H_2	H_2	βH
3c	Δ	Δ	βH

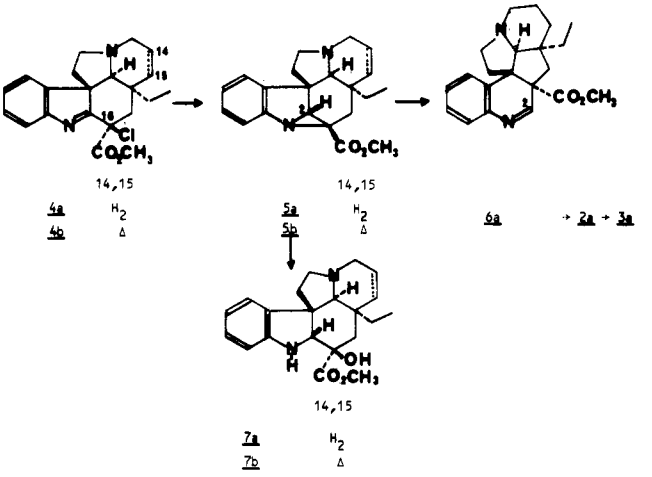
and its congener meloscine (**3c**)[10,11] formally derived from 18,19-dehydrotabersonine (**1c**) (a hitherto unnatural derivative[12] of vindolinine) through oxidation and pinacol rearrangement (Scheme I). While oxidation of the enamine system in a to equivalents of b could be performed with various reagents[3,4,13] species b was shown to rearrange easily to the isomeric quinolone e[14,15] but not to c. An intermediate hydroxyaziridine such as d (X = OH) may favor this route.[24]

In continuation of our studies concerned with the flow thermolysis of indole derivatives,[16] we reasoned that an aziridine such as d (X = H) might possess the necessary structural requirements to suffer a thermal rearrangement to f, a reduced precursor of c. Homolytic cleavage of the 1,16 bond in d (X = H), a thermodynamically favored process, would actually provide a situation allowing the ring size adjustment of d to imine f. The following transformations show that this expectation was fulfilled.

Scheme I



Scheme II



In analogy with the reduction of α-chloro imines with $LiAlH_4$,[17,18] 16-chloro-1-dehydrovincadifformine (**4a**)[13] (Scheme II) was smoothy reduced ($NaBH_3CN$/AcOH, 70% ex **1a**) to the hexacyclic aziridine **5a**. The 16-hydroxy-indoline **7a** was isolated as a byproduct. Chloroindolenine **4b** similarly gave aziridine **5b** along with some **7b**. The structures of **5a,b** fitted with all spectral data. Attributes of the carbons in the ^{13}C NMR spectra (Figure

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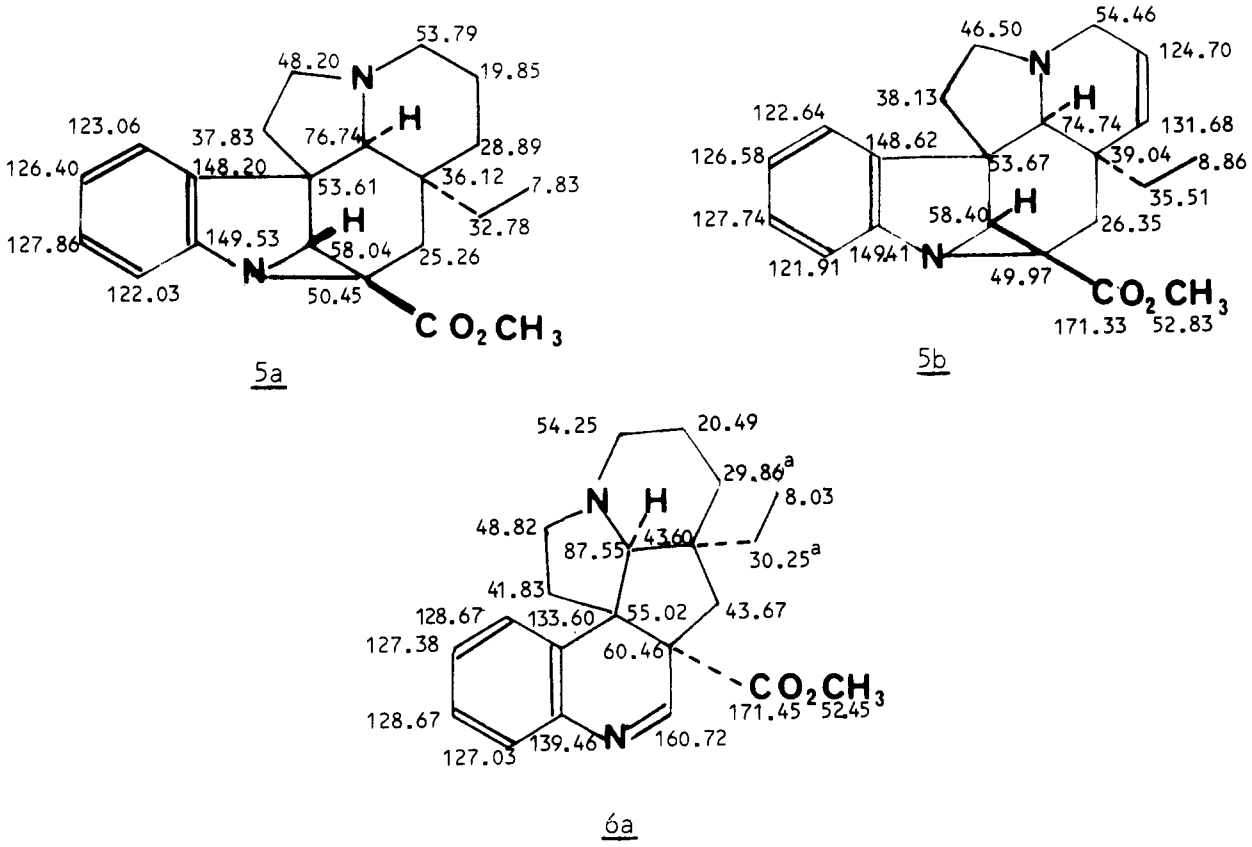

Figure 1. ^{13}C NMR spectral data of **5a**, **5b**, and **6a**. The superscript a implies the values may be interchanged.

1) were deduced from comparisons with the spectra of **1a,b**. Closure of the aziridine ring induces a deshielding of C(6) (ca. 7 ppm), a shielding of C(21) (ca. 4 ppm), and a deshielding of the aromatic carbon atoms 8, 10, and 12 (ortho and para to N).

Salient features in the 402-MHz ^1H NMR spectrum of **5b** were two singlets of one proton each at 2.85 and 3.17 ppm (H(21) and H(2)), and an intense aromatic ring effect on the chemical shifts of H(17α) ($\delta_{17\alpha H}$ 0.44, d, J = 15 Hz; $\delta_{17\beta H}$ 2.40, d, J = 15 Hz).

Molecular models show that the orientation of substituents on the aziridine ring in **5a,b**, as depicted on Scheme II, is the sole possible steric arrangement. It implies reduction of imines **4a,b** from the β-face (a situation generally encoutered in the vincadifformine series[19]), followed by inversion at C(16) during the ring closure. The structure and configuration of **5a** were ascertained by obtention of the known alcohol **4a**[4] through acid-catalyzed (TFA) ring opening.

Aziridine **5a** was dissolved in methanol–toluene (1:1) and flow thermolyzed[20] at 400 °C under a slight vacum. Thin-layer chromatography allowed recovery of the starting material (**5a**) (17%), along with isolation of vincadifformine (**1a**) (30%) and imine **6a** (15%). Presence of the C=N double bond in **6a** was established by the UV (210, 255nm), IR (1636 cm^{-1}), ^1H NMR (7.57 ppm, H(2)), and ^{13}C NMR (see Figure 1) (160.7 ppm, C(2)) spectra, which further established the diastereoisomeric purity of the compound. The m/e 138 base peak on the mass spectrum was strongly indicative[10,11] of the meloscine ring system.

While 1,2 hydrogen migration has been reported[18] during the thermolysis of aziridines, the present example apparently constitutes the first case of C–C bond migration in such systems.

Attempts at hydration–deformylation or saponification–decarboxylation of imine **6a** were unsuccessful. Therefore, completion of the correlations necessitated oxidation of **6a** to tetrahydroscandine **2a**. This oxidation was first performed in 25% yield by $KMnO_4$ treatment of an acetone solution of **6a**, acidified with $HClO_4$ in order to prevent N(4)-oxidation. A slightly better yield (45%) was gained through peracid (MCPBA) oxidation of **6a**, with Fe^{2+}-catalyzed rearrangement of the intermediate oxazirane, and subsequent reduction (SO_2) of the N(4)-oxide.

The ^{13}C NMR spectrum of the resulting lactam **2c** fitted with the data published in this series[21] and proved to be identical with that of an authentic sample[22] of tetrahydroscandine. The known α-configuration of the CO_2Me group in scandine implies inversion at C(16) during the thermal rearrangement of **5a** to **6a**.

Finally, synthetic tetrahydroscandine (**2a**) was saponified and decarboxylated[10] to **3a**, which proved to be identical with an authentic sample[23] of tetrahydromeloscine.

Intermediacy of aziridines such as **5a,c** in biogenesis is highly hypothetical and, moreover, an enzyme-catalyzed pathway cannot be inferred from the high energy demanding above rearrangement. Nevertheless, this first synthesis of the *Melodinus* alkaloid skeleton points out the high range of stereoselectivity of flow thermolysis rearrangements.

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(22) We thank Drs. M. Plat and H. Mehri for a generous gift of tetrahydroscandine.

Experimental Section

Melting points were taken on a Reichert Microscop and are uncorrected. Specific rotations were measured on an electronic polarimeter Perkin-Elmer Model 241. IR spectra were measured on a Beckmann Acculab 4 and a Pye Unicam SP3-200 spectrophotometer. UV spectra were measured on a Varian 634 spectrophotometer. ^1H NMR spectra were measured on a Perkin Elmer R12B spectrometer (60 MHz) or on IEF 400, a prototype built at the University of Paris XI (402 MHz), in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were recorded on a JEOL D300 spectrometer. Separations were done on TLC and with a Chromatotron (R) apparatus with Kieselgel 60 PF_{254}Merck, eluant CH_2Cl_2/MeOH.

Aziridine 5a. To a solution of the crude chloroindolenine **4a** prepared[13] from 1 g of (-)-vincadifformine **1a** in acetic acid (15 mL) was added $NaBH_3CN$ (1 g) in portions for 1 h at room temperature. The mixture was slowly poured into saturated K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was washed, dried over $MgSO_4$, and evaporated. Separation on centrifuge chromatography with CH_2Cl_2–MeOH (99:1 v/v) yielded alcohol **7a**[4] (64 mg, 6%), and with CH_2Cl_2–MeOH (95:5 v/v) aziridine 8 (690 mg, 70%), which was crystallized from ether–hexane: colorless crystals; mp 117–121 °C; $[\alpha]_D$ -85° (*c* 0.9, MeOH); UV (MeOH) 215 (4.19), 235 sh (3.84), 275 (3.05), 284 (2.93) nm (log ϵ); IR (film 1735 cm^{-1}; ^1H NMR δ 0.42 (d, 1 H, *J* = 15 Hz, $C_{17}H$), 0.58 (t, 3 H, J = 6.7 Hz, CH_2CH_3), 3.42 (s, 1 H, C_2H), 3.77 (s, 3 H, CO_2CH_3); MS low resolution, *m/e* 338($M^{+\cdot}$), 309, 137, 124 (100%); MS high resolution, exact mass *m/e* 338.1976, calcd for $C_{21}H_{26}N_2O_2$ 338.1992.

Aziridine 5b. Under similar conditions, tabersonine **1b** (1.320 g) afforded aziridine **5b** (902 mg) and alcohol **7b**[4] (69 mg). Aziridine **5b**: amorphous; $[\alpha]_D$ -2° (*c* 1.2, MeOH); UV (MeOH) 224, 235, 277, 284 nm (analogous to that of **5a**); IR (film) 1730 cm^{-1}; ^1H NMR (402 MHz) δ 0.44 (:, 1 H, *J* = 15 Hz, $C_{17}H$), 0.75 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 2.40 (d, 1 H, *J* = 15 Hz, $C_{17}H$), 2.85 (s, 1 H, $C_{21}H$), 3.17 (s, 1 H, C_2H), 3.77 (s, 3 H, CO_2CH_3), ~5.5 (m, 2 H, $C_{14}H$–$C_{15}H$); MS, *m/e* 336 ($M^{+\cdot}$), 277, 228, 214, 135 (100%), 122, 121, 107.

Alcohol 7a. Trifluoroacetic acid (0.5 mL) was mixed to the solution of aziridine **5a** (40 mg) in ether–CH_2Cl_2 (1:1, v/v) (4mL) and the mixture was left at room temperature for 12 h. Isolation of the basic material and separation on TLC afforded a compound (35 mg) which proved to be identical ($[\alpha]_D$, R_f, MS, UV, IR, ^1H NMR) with alcohol **7a**.[4]

Flow Thermolysis of Aziridine 5a: Vincadifformine 1a and Imine 6a. The solution of aziridine **5a** (200 mg) in MeOH–toluene (1:1, v/v) (60 mL), was passed dropwise through a heated (400 °C) glass column under a slight vacuum, while the eluant was trapped in a liquid nitrogen cooled vessel. Evaporation of the solvent and separation on TLC afforded vincadifformine **1a** (62 mg (30%)) and imine **6a** (3 mg (15%)) along with recovered aziridine **5a** (35 mg (17%)). Imine **6a** was crystallized from ether–hexane: mp 115–118 °C; $[\alpha]_D$ +171° (*c* 0.9, MeOH); UV (MeOH) 210 (4.29)8 255 (3.60) nm (log ϵ); IR (film) 1636, 1735 cm^{-1}; ^1H NMR δ 0.66 (t, 3 H, *J* = 6.8 Hz, CH_2CH_3), 2.53 (s, 1 H, $C_{21}H$), 3.67 (t, 3 H, CO_2CH_3), 7.57 (s, 1 H, C_2H); MS low resolution, *m/e* 338 ($M^{+\cdot}$) 309, 280, 279, 251, 138 (100%), 124; MS exact *m/e* 338.1964, calcd for $C_{21}H_{26}N_2O_2$ 338.1994.

Oxidation of Imine 6a: Tetrahydroscandine 2a. (a) Powdered $KMnO_4$ (20 mg) was admixed to the solution of imine **6a** (42 mg) and $HClO_4$ (24 mg) in 4 mL of acetone and the reaction mixture was stirred for 4 h at room temperature; a further 20 mg of $KMnO_4$ was added, and the reaction mixture was left 3 more h at room temperature and then overnight +4 °C. Acetone was evaporated and the residue was dissolved in CH_2Cl_2 and washed with an aqueous solution of $NaSO_3H$ and then $NaHCO_3$. Separation on TLC gave **6a** (8 mg) and tetrahydromeloscandine **2a** (12 mg (25%)).

(b) *m*-Chloroperbenzoic acid (25 mg) was added to a solution of imine **6a** (18 mg) in 3 mL of CH_2Cl_2, and the mixture was stirred at room temperature during 30 h. After addition of a catalytic amount of ferrous sulfate, the reaction was left 18 more h. The reaction mixture was reduced with SO_2 (aqueous $NaHSO_3$ + HCl), then K_2SO_3 was added until pH 8–9, the solution was extracted with CH_2Cl_2, and TLC separation gave tetrahydroscandine **2a**: 9 mg (45%); crystallized in methanol; mp 210, 213 °C; $[\alpha]_D$ +95° (*c* 0.1, MeOH); UV (MeOH) 213 (4.40), 254 (3.94), 281 (3.41), 290 (3.29), nm (log ϵ); IR (film) 1580, 1665, 1740 cm^{-1}; ^1H NMR δ 0.63 (t, 3 H, *J* = 6.8 Hz, CH_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 8.71 (s, 1 H, NH); ^{13}C NMR δ 7.32 (C_{18}), 19.38 (C_{14}), 30.14 (C_{19} or C_{15}), 30.79 (C_{15} or C_{19}), 41.05 (C_6), 43.05 (C_{20}), 43.34 (C_{17}), 48.35 (C_3)8 52.53 (OCH_3), 53.80 (C_5), 58.83 (C_7), 64.55 (C_{16}), 86.84 (C_{21})8 115.43 (C_{12}), 123.77 (C_{10}), 127.33 (C_9), 128.38 (C_{11}), 139.43 (C_8), 133.90 (C_{13}), 169.90 (-CO), 171.09 (C_2); MS, *m/e* 354 ($M^{+\cdot}$), 325, 209, 295, 138 (100%), 124; MS exact *m/e* 354.1948, calcd for $C_{21}H_{26}N_2O_3$ 354.1943. Compound **2a** was identical (mp; $[\alpha]_D$; R_f, IR, MS, UV) with an authentic sample.

Tetrahydromeloscine 3a. Saponification and decarboxylation of tetrahydroscandine **2a** (18 mg) afforded[10] tetrahydromeloscine **3a** (10 mg), which was identical (mp, $[\alpha]_D$, R_f, IR, MS, ^1H NMR) with an authentic sample.

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Registry No. **1a**, 3247-10-7; **1b**, 4429-63-4; **2a**, 91201-55-7; **3a**, 24306-56-7; **4a**, 32789-67-6; **5a**, 91208-71-8; **5b**, 91201-53-5; **6a**, 91201-54-6; **7a**, 60933-81-5.

(23) An authentic sample of tetrahydromeloscine was kindly provided to us several years ago by Dr. K. Bernauer.

(24) See the review: Saxton, J. E. *Nat. Prod. Rep.* **1984**, *1*, 21 and especially page 40.