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Rearrangement and Photolysis of Aziridines in the Aspidosperma Series

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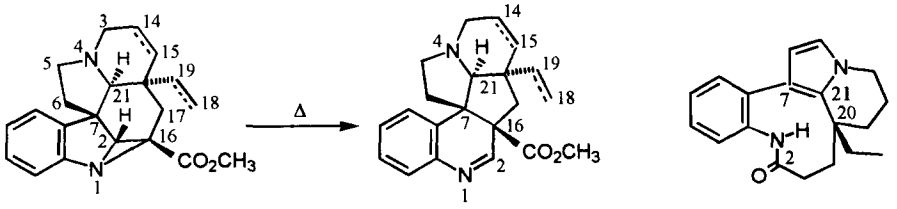
Abstract : Rearrangement of aziridine **1** by $MgBr_2$ gave 2-H-dihydro-17-dehydrovincadifformine **6**. Photolysis transformed aziridines **1** and **11** into the new compounds 1,2-seco-1,21-cyclovincadifformine **10** and 1,2-seco-1,21-cyclotabersonine **12**.

We have previously reported the flow thermolysis of aziridines **1** and **2** yielding dihydroquinolines **3** and **4** (Scheme 1), useful intermediates in the synthesis of the *Melodinus* alkaloids [1,2] (Scheme 1). In order to explore some other aspects of their reactivity, we submitted these aziridines to chemical and photochemical reactions in the order to cleave the 2,7 bond[3] with formation of "*rhazinilam* " type compounds. (-)-Rhazinilam **5** [4] has been shown to interact with tubuline, and inhibits *in vitro* the growth of KB, L1210 and P388 cells.[5,6]



1
2 : Δ-14, Δ-18
11 : Δ-14
14 : $N_4 \rightarrow O$

3
4 : Δ-14, Δ-18
(*Melodinus* type)

(-)-**5** : (-)-rhazinilam

Scheme 1

Compound **1**, in refluxing toluene, in the presence of the Lewis acid $MgBr_2$[7] (Scheme 2) yielded 2-H-dihydro-17-dehydrovincadifformine **6**, $M^{+\bullet}$ 338, whose structure was established from NMR data : H-17 at 6.98 ppm and C-17 at 148.7 ppm. HMQC and HMBC[8] experiments confirmed the connections of carbon atoms C-2 and C-7 (Table).

The stucture of compound **6** was confirmed by an alternative partial synthesis : 16-acetoxy-1,2-dehydrovincadifformine **7**[9] was transformed into azadiene **8**[10] (55%) by flow thermolysis (525-535°C, toluene). Reduction of **8** with $NaBH_3CN$ yielded a compound identical to **6** (Rf, UV, ^1H and ^{13}C NMR).[11]

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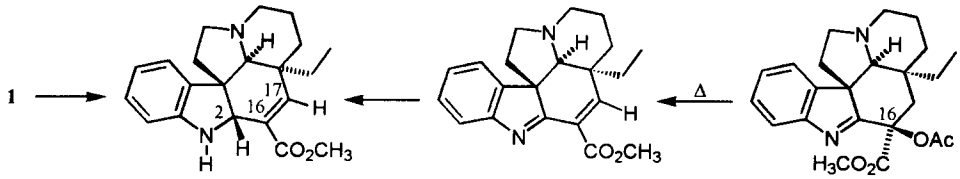


6 8 7

Scheme 2

	Compound **6**	Compound **10**
Protons	Carbons	Carbons
H-2	7, 16, 6, 8, 17, 21	7, 16, 6, 8, 17, 21, C=O
H-17	16, 20, 2, 15, 19, 21	16, 20, 2, 19, 21, C=O

Table : Main HMBC correlations

Photolysis of compound **1** (254 nm, CH_3CN, Rayonet®, T≈30°C) gave a mixture from which were separated the starting material **1** (39%), vincadifformine **9** (22%), dihydroquinoline **3**[1] (≈2%), and a new compound **10** (27%).[12] Vincadifformine **9** and dihydroquinoline **3** have already been obtained by flow thermolysis of compound **1**[1] (Scheme 3).

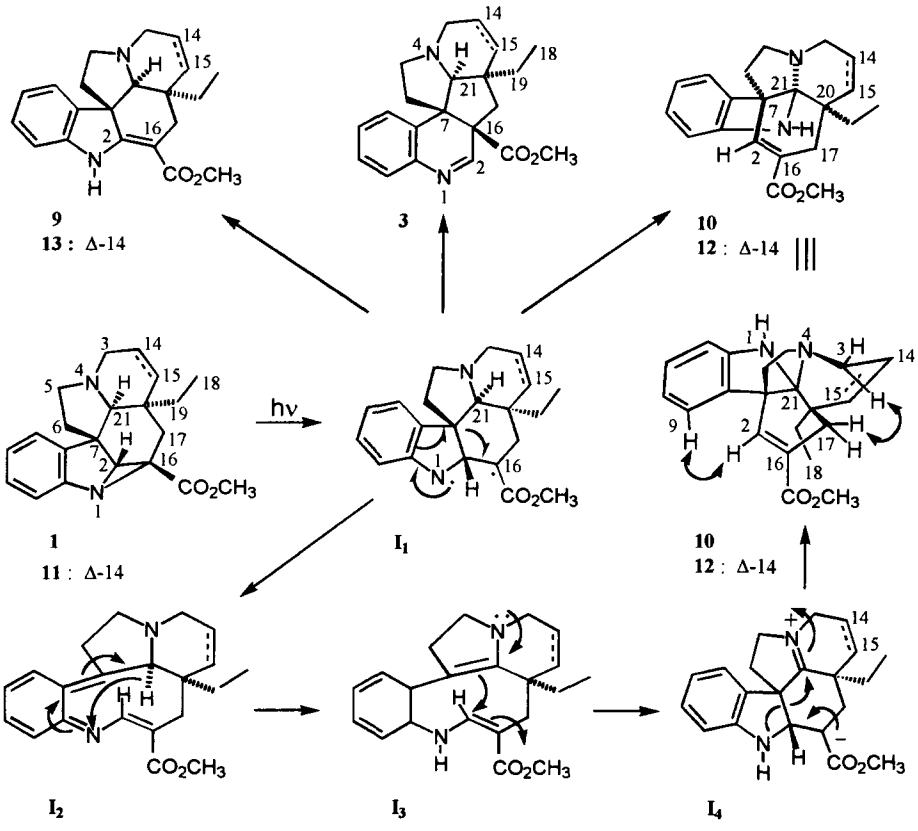
The new compound **10**, $M^{+\cdot}$ 338, shows a UV spectrum compatible with an indoline chromophore and a conjugated ester function located on C-2 and C-16 (H-2 : 7.33 ppm, C-2 : 141.1 ppm). The signals of H-21 and tertiary C-21 had disappeared while a new quaternary carbon C-21 of an aminal function was observed at 90.9 ppm in the ^{13}C NMR spectrum. Connections of carbon atoms C-2 and C-17 were established by HMQC, HMBC (see Table) and ^1H-^1H experiments.

The photochemically generated intermediate $\mathbf{I_1}$ reacts via [1,2] hydrogen migration to yield vincadifformine **9** or via a 7,2 to a 7,16 bond migration to yield compound **3**. Formation of compound **10** (Scheme 3) proceeds as follows: $\mathbf{I_1}$ rearranges to $\mathbf{I_2}$, a [1,5] hydrogen shift transformes $\mathbf{I_2}$ into a reactive "dihydrorhazinilam" type compound $\mathbf{I_3}$, which give the new compound **10** through the intermediate $\mathbf{I_4}$.

The intramolecular Michael reaction of intermediate $\mathbf{I_3}$ requires the coplanarity of the 2,16 double bond (conjuguated ester) and the 2,7 double bond (enamine) in the cyclononane conformer. This geometrial constraint imposes the configuration of the asymmetric centers in **10**. The ROESY experiments further revealed the proximity of H-3 and H-17 due to boat conformations of ring C and D. However, the signals of H-5 and H-17 were superimposed in the spectrum so that this deduction had to be confirmed (Scheme 3).

Thus photolysis of **11** (prepared from **13** [2]) under identical conditions yields compound **12** (10%)[13], $M^{+\cdot}$ 336, along with some tabersonine **13** which could not be completely separated from **12**. Nevertheless, the ^1H NMR spectrum exhibits well separated signals for H-3, H-5, and H-17. The ROESY experiment unambiguously confirmed the spatial proximity of H-3 and H-17, and that of H-2 and H-9. Configurations of both **12** and **10** are then 7*R*, 21*S*.

Hydrogen abstraction of H-21 in $\mathbf{I_1}$ by N-1 followed by single electron transfer or intersystem crossing of the triplet diradical would lead directly to $\mathbf{I_4}$. Such a process is not likely since the orientation of N-1, H-21, and C-21 is not adequate for such a reaction step.[14]



Scheme 3

In order to prevent a cyclisation of type **I3** ➡ **I4** and to preserve the "*rhazinilam* " type skeleton, we have studied the photoreactivity of the N-oxide **14** (Scheme 1).[15] Only tar and small amounts of unstable compounds were obtained from these reactions. The stabilization of intermediate **I3** would probably require introduction of an oxygen atom in position 3 or 5 (lactam). The skeleton of **10** and **12**, results formally from breaking of the 1,2 bond and from formation of the 1,21 bond. Such a rearrangement has not been encountered yet in the "*Aspidosperma* " series. However, recently in the "*Schizozygane* " group a compound possessing a 1,21 bond has been reported[16].

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7. Procedure: A solution of compound **1** (12 mg, 0,036 mmole) and $MgBr_2$ (20 mg, 0,10 mmole) in toluene (4 mL) was refluxed for 2h30, then washed with aqueous $NaHCO_3$, compound **6** (5 mg, 40%) was separated as a foam : $[\alpha]_D$ -220.7 (c 0,4, MeOH); UV 207, 240 (sh), 301 nm; ^1H NMR ($CDCl_3$, 300 MHz): 0.66 (t, 3H, 7.5, 18-H_3), 1,05 (m, 2H, H_2-19), 1,28 (m, 1H, H-15), 1.55 (m, 2H, H_2-14), 1.86 (bd, 1H, 13.5, H-15), 2.03 (m, 2H, 3-H, H-6), 2.21 (m, 1H, H-6), 2.29 (s, 1H, H-21), 2.36 (m, 1H, H-5), 3.03 (bd, 1H, 10.5, H-3), 3.14 (td, 1H, 3.0, 9.0, H-5), 3.78 (s, 3H, CO_2CH_3), 4.40 (s, 1H, H-2), 4.47 (bs, 1H, H-1), 6.48 (d, 1H, 7.5, H-9), 6.65 (td, 1H, 7.5, 1.5, H-10), 6.98 (m, 2H, H-11, H-17), 7.06 (d, 1H, 7.5, H-12); ^{13}C NMR (CDCl3, 75 MHz): 7.7 (18), 23.4 (14), 34.0 (15), 34.3 (19) 40.4 (20), 43.8 (6), 51.7 (OCH_3), 52.5 (3 + 5), 53.5 (7), 63.7 (2), 72.7 (21), 108.5 (12), 118.0 (10), 123.3 (9), 127.8 (11), 130.4 (16), 134.4 (8), 148.7 (17), 149.1 (13), 167.5 (C=O); MS: m/z 338 ($M^{+\cdot}$), 309, 208, 144, 130, 124; HRMS: obs. 338.1987, calc. for $C_{21}H_{26}N_2O_2$: 338.1994.
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11. Procedure : A solution of azadiene **8** (40 mg, 0.12 mmole) in a mixture of AcOH (3 mL) and H_2O (3 mL) was stirred with $NaBH_3CN$ (20 mg, 0.32 mmole) for 15 min. After work-up and tlc, compound **6** (14 mg, 35%) and 2,16-dihydrovincadifformine (18 mg, 45%) were separated.
12. Compound **10**: F 75-80°C, 185-190°C (CH_2CL_2 / MeOH); $[\alpha]_D$ -45.9 (c 0.3, MeOH); UV 205, 222 (sh), 247 (sh), 303 nm; IR (film) 3380, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): 0.62 (t, 3H, 7.5, H_3-18), 0.95 (m, 1H, H-19), 1.18 (m, 1H, H-19), 1.29 (td, 1H, 4.5, 13.5, H-15), 1.57 (bd, 1H, 13.5, H-14), 1.87 (m, 4H, H_2-6, H-15, H-14), 2.29 (d, 1H, 16.5, H-17), 2.51 (td, 1H, 3.0, 12.0, H-3), 2.66 (m, 2H, H-5, H-17), 2.82 (m, 2H, H-3, H-5), 3.76 (s, 3H, CO_2CH_3), 4.05 (s, 1H, 1-H D_2O exch), 6.52 (d, 1H, 6.7, H-12), 6.68 (t, 1H, 6.7, H-10), 7.00 (t, 1H, 6.7, H-11), 7.08 (d, 1H, 6.7, H-9), 7.33 (d, 1H, 2.3, H-2); ^{13}C NMR ($CDCl_3$): 7.8 (18), 21.3 (14), 25.7 (17 + 19), 29.1 (15), 41.2 (20), 42.5 (6), 45.7 (3), 49.6 (5), 51.7 (OCH_3), 55.6 (7), 90.9 (21), 107.7 (12), 118.2 (10), 121.7 (9), 124.9 (16), 127.8 (11), 133.3 (8), 141.2 (2), 150.1 (13), 168.1 (C=O); MS: m/z 338 ($M^{+\cdot}$), 309, 137; HRMS: obs.: 338.1993, calc. for $C_{21}H_{26}N_2O_2$: 338.1994.
13. Compound **12**: (containing < 10% of tabersonine); ^1H NMR ($CDCl_3$): 0.72 (t, 3H, 6.8, H_3-18), 1.14 (m, 2H, H_2-19), 1.95 (m, 2H, H_2-6), 2.31 (dd, 1H, 4.5, 15.8, H-17), 2.57 (m, 1H, H-5), 2.68 (d, 1H, 15.8, H-17), 2.89 (t, 1H, 8.0, 5-H), 3.16 (d, 1H, 15.8, H-3), 3.42 (dd, 1h, 2.3, 15.8, H-3), 3.74 (s, 3H, CO_2CH_3), 3.86 (s, 1H, H-1), 5.77 (s, 2H, H-14, H-15), 6.47 (d, 1H, 9.0, H-12), 6.69 (t, 1H, 6.8, H-10), 7.00 (t, 1H, 6.8, H-11), 7.13 (d, 1H, 9.0, H-9), 7.39 (d, 1H, 4.5, H-2); ^{13}C NMR ($CDCl_3$): 8.0 (18), 22.6 (19), 29.7 (17), 42.5 (6), 44.7 (20), 47.6 (3), 49.0 (5), 51.7 (OCH_3), 55.6 (7), 89.7 (21), 107.4 (12); 118.0 (10), 122.3 (9), 124.5 (16), 124.6 (14), 128.0 (11), 129.8 (15), 138.6 (8), 142.3 (2), 150.3 (13), 167.7 (C=O); MS: m/z 336 ($M^{+\cdot}$), 321, 307, 277, 249, 214, 168, 135.
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