Rearrangement of *Aspidosperma* Alkaloids with a Modified Tryptamine Chain. Revised Structure of the Polonovski−Potier Reaction Product of 5-Cyano-16-chloro-1-dehydrovincadifformine

Guy Lewin,*[,†,‡] Corinne Schaeffer,[§] Georges Morgant,[▽] and Dung Nguyen-Huy[▽]

Laboratoire de Pharmacognosie, Faculté de Pharmacie, bld. Becquerel, 14032 Caen Cedex, France, Laboratoire de Pharmacognosie and Laboratoire de Chimie Physique Minérale et Bioinorganique, Faculté de Pharmacie, av. J. B. Clément, 92296 Châtenay-Malabry Cedex, France, and Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France

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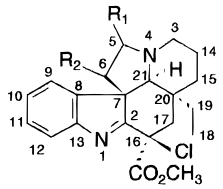
Introduction

In the monoterpenoid indole alkaloids class, the *Aspidosperma* structural group holds a pivotal position in the biosynthesis of various types of indole alkaloids which accounts for the continuing interest in this skeleton.[1,2] In a previous publication,[3] we reported on a new method of functionalization of the tryptamine chain from 16-chloro-1-dehydrovincadifformine (**1**)[4] and thus described the synthesis of epimers on C-5, **2** and **3**.[5] The very reactive 16-chloroindolenine **1** and its 14,15-dehydro analog have already elicited study of several rearrangements requiring the presence of the tertiary amine function on N-4.[6] The epimers **2** and **3** differ from **1** by the α-aminonitrile function on C-5 (e.g., a less reactive lone pair on N-4) and the presence of a leaving group on C-6. Therefore, we considered the feasibility of access to rhazinilam[7] or *Melodinus*[8] alkaloid analogs through the addition of ROH (R = H, Me, Ac) on the indolenine and then a bromine-assisted cleavage of the 2−7 bond. Treatment of the mixture **2**−**3** (4:1) at reflux under various conditions [methanol, 0.5 N methanolic HCl, H_2O−tetrahydrofuran (1:1) or H_2O−pyridine (1:1)] always resulted in recovery of starting epimers, while acetic acid or H_2O−acetic acid (1:1) led to very complex unidentifiable mixtures. Replacement of acetic acid by trifluoroacetic acid also did not provide the 2−7 bond cleavage but allowed an amazing rearrangement of the skeleton that we report in this article.



R_1 = H	R_2 = H	**1**
R_1 = CN(α)	R_2 = Br(α)	**2**
R_1 = CN(β)	R_2 = Br(α)	**3**
R_1 = CN(α)	R_2 = H	**6**

Results and Discussion

On heating, the mixture **2**−**3** in trifluoroacetic acid (3 h, reflux) provided the bright yellow compound **4** in 30% yield. Compound **4** showed in the EI mass spectrum a dihalogenated molecular ion at *m*/*z* 448−450−452 (448.0553, calcd for $C_{21}H_{22}{}^{79}Br^{35}ClN_2O_2$ 448.0553) consistent with loss of elements of HCN compared with the starting epimers. The observed UV spectrum was indicative of a strongly conjugated chromophore, while the IR spectrum revealed absence of OH and NH groups and displayed characteristic absorptions of a saturated ester and of an imine bond at 1740 and 1610 cm^{-1}. Initially, 1D and 2D homo- and heteronuclear NMR experiments led us to assign the structure **5** to this rearranged compound. Furthermore, this hypothesis was supported by the known behavior of 16-chloroindolenine **1** under the same conditions:[9] While **1** undergoes two successive bond migrations (7−21 to 2−21 and then 2−16 to 1−16) and thus evolves to the ultimate eburnane skeleton, the strongly stabilized structure of **5** could stop the reaction after the first bond migration and allow isolation of this intermediate skeleton. However, some further NMR data, especially significant ROE observed between an aromatic proton on one hand (δ 7.33, *J* = 7.8 Hz) and one H-17 (δ 3.27, *J* = 15.6 Hz) and one H-19 (δ 1.9, *J* = 15.0, 7.4 Hz) on the other hand, were not in agreement with structure **5** according to the inspection of molecular models. Therefore, we decided to settle this question through X-ray crystallographic analysis of this rearranged compound which allowed the unambiguous assignment of structure **4** (Figure 1).[10] The X-ray diffraction study was performed with suitable crystals obtained by slow crystallization from ethyl acetate [crystal data, triclinic, space group *P*1, *Z* = 4, *a* = 9.590(3) Å, *b* = 11.584(1) Å, *c* = 18.893(3) Å, α = 79.62(1)°, β = 80.54(2)°, γ = 74.00(1)°; structure refinement, *R* = 0.0471 for 2856 reflections].

† Laboratoire de Pharmacognosie, bld. Becquerel.
‡ Laboratoire de Pharmacognosie, av. J. B. Clément.
§ Institut de Recherches Servier.
▽ Laboratoire de Chimie Physique Minérale et Bioinorganique.

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(10) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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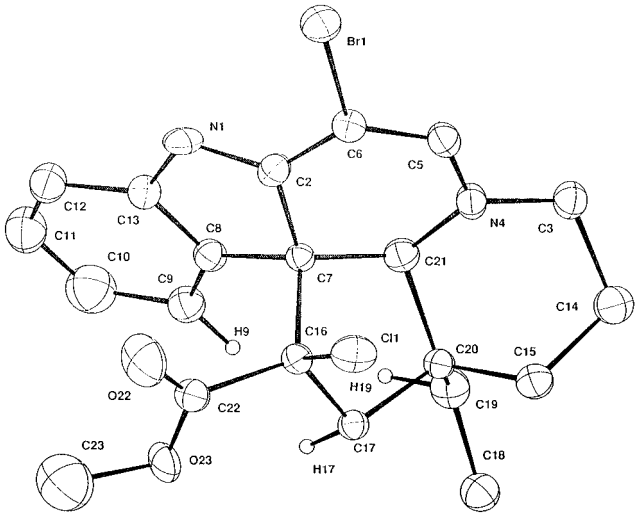

Figure 1. X-ray structure of **4** showing 50% probability displacement ellipsoids. Hydrogen atoms (except H-9, one H-17, and one H-19) are omitted for clarity.

The established structure **4** was fully in agreement with NMR data. Decrease of steric interaction between the ethyl chain and H-9 accounts certainly for the skew-boat conformation of the piperidine ring, while aromatic anisotropy explains the shielding of the methoxy signal. Lastly, X-ray-calculated distances fit with the strong observed ROE between H-9 and the pseudoaxial H-17 (d = 2.32 Å) and H-9 and one H-19 (d = 2.10 Å) (Figure 1). This structure **4** displays an important modification of the aspidospermane skeleton compared with the starting epimers since it reveals a replacement of the 2−16 and 7−6 bonds in **2** and **3** by the 2−6 and 7−16 bonds in **4**. Conversion of **2** and **3** into **4** is thought to proceed through two successive Wagner−Meerwein type 1,2-shifts on C-2 and on then C-7 (Scheme 1). The 6−7 → 6−2 1,2-shift is favored, on the one hand by the orthogonal orientation of the C6−C7 bond related to the B ring and on the other hand by assistance of the bromoiminium chain (under the same conditions, the α-aminonitrile **6** is mainly recovered and does not provide any identified rearranged compound). In other respects, in accordance with Wagner−Meerwein rearrangement theory, the 16−2 → 16−7 1,2-shift evolves with retention of configuration at C-16 since the 16-epimer of **4** is not isolated at the end of the reaction. Lastly, trifluoroacetic acid is thought to play an important role for two reasons: As a strong acid, it easily generates the 4−5 iminium which is probably the first intermediate compound of the rearrangement; as a weak nucleophile, it promotes stabilization of carbocations C-2 and then C-7 by both successive 1,2-shifts rather than solvolysis.

Isolation and identification of the rearranged compound **4** prompted us to reexamine the structure of the previously described compound **7**.[11] This compound, which arises from the α-aminonitrile **6** by a Polonovski−Potier reaction, displayed spectral data (fragmentation pattern in mass spectrometry, UV, ^{1}H and ^{13}C NMR spectra) in agreement with the most likely proposal **7** but also very similar to **4**. Therefore, additional ROE experiments were undertaken on **7**, and they revealed, as in the case of **4**, exactly the same significant Overhauser effects between an aromatic proton at δ 7.36 and one

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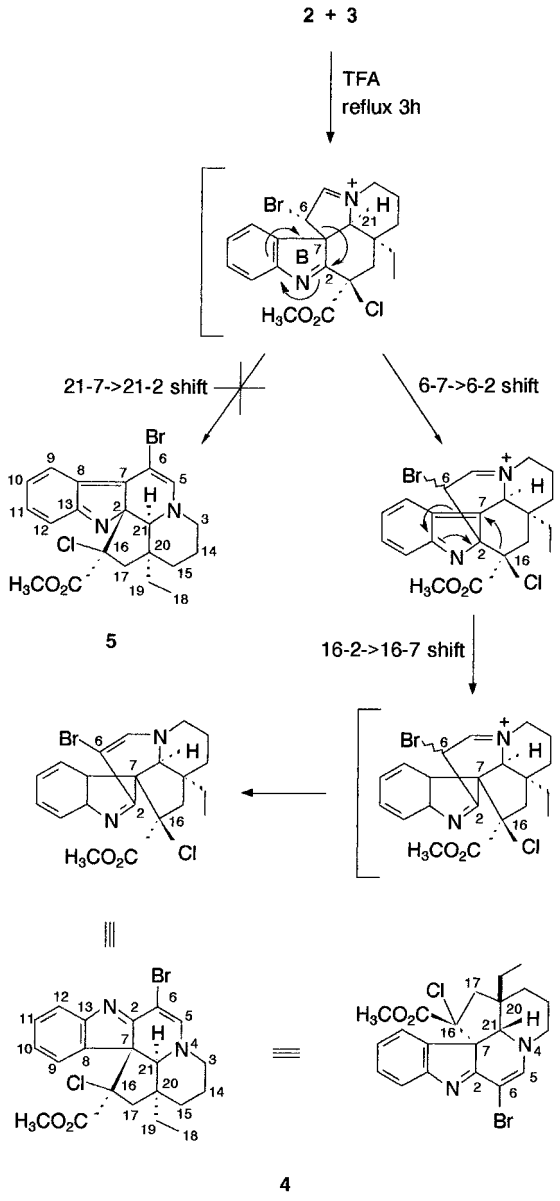
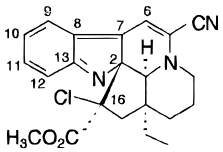
Scheme 1



H-17 (δ 3.29) and one H-19 (δ 1.86). Furthermore, no ROE was observed between H-6 and an aromatic proton. The great similarity between the spectral properties of **4** and **7** (especially the above-mentioned ROE experiments) proves the presence of the same skeleton in both compounds. Consequently, this analogy allows us to replace for the Polonovski−Potier reaction compound of **6** our first hypothesis **7** by the structure **8**. This rearrangement, **6** → **8**, is thought to proceed initially via **9**, the attempted 4−5 iminium Polonovski-Potier intermediate, which can then evolve to **8** according to the same mechanism as the mixture **2**−**3** (Scheme 1).

Conclusion

Though failing in its initial goal of access to rhazinilam or *Melodinus* alkaloids analogs, this study, which allowed identification of the rearranged compounds **4** and **8**, seems to us noteworthy for at least three reasons. (a) Such rearrangement as **2**−**3** → **4** or **6** → **8** had already been achieved by flow thermolysis at 620−630 °C starting from 1,2-dehydroaspidospermidine, through two succes-



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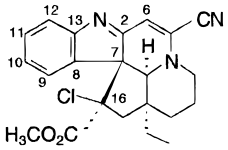

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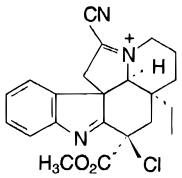

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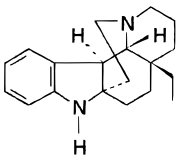

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sive [1,5] sigmatropic shifts.[12] Our results demonstrate that appropriate functionalization of the aspidospermane skeleton on the tryptamine chain and on C-16 affords under mild conditions (reflux of TFA for **4**, dichloromethane at 0 °C for **8**) the same deep-seated skeletal reorganization, according to classic carbocation rearrangements. (b) The mild conditions for this rearrangement throw light on the biogenesis of melonine **10**,[13] a natural indole alkaloid with a C-7 → C-2 transposed tryptamine chain, as the second postulated intermediate compound (Scheme 1). (c) Lastly, the **6** → **8** rearrangement is reminiscent of the synthesis of vinorelbine from 15′,20′-dehydro-20′-deoxyvinblastine[14,15] because both reactions proceed through a fragmentation of the tryptamine chain: at C6−C7 in our rearrangement and at C5−C6 in the synthesis of vinorelbine. So the **6** → **8** rearrangement provides a further example of the great potential of the Polonovski−Potier reaction in the chemistry of alkaloids.

Experimental Section

MS was obtained at an ionizing voltage of 70 eV. NMR experiments were performed at 500.13 and 125.77 MHz for ^{1}H and ^{13}C NMR, 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 aluminum sheets.

TFA-Catalyzed Rearrangement of 2−3 to 4. A solution of **2**−**3** (4:1) (1.187 g, 2.5 mmol) in trifluoroacetic acid (15 mL) was heated at reflux under nitrogen for 3.5 h. The mixture was diluted with iced water, neutralized with 5 N aqueous NaOH, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated. The dried residue was purified by flash chromatography on silica gel (CH_2Cl_2−MeOH, 98.5:1.5) and then crystallized from EtOAc to give pure **4** (338 mg, 30%) as bright yellow crystals.

4: mp 228−230 °C; TLC (silica gel, CH_2Cl_2−MeOH, 98:2) R_f 0.33; $[\alpha]_D = +268$ ($c = 0.92$, $CHCl_3$); UV (EtOH) λ_{max} (nm) (log ϵ) 232 (4.06), 246 (3.94), 267 sh (3.70), 290 (3.43), 310 (3.43), 320 (3.42), 418 (3.94); IR (CH_2Cl_2) 1735, 1590, 1530, 1435, 1240, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, $J = 7.4$, H-18), 1.74 (m, $J = 12.1$, 9.8, 9.4, 4.7, 1.9, H-14), 1.87 (m, $J = 15.0$, 7.4, H-19), 1.93 (m, $J = 15.0$, 7.4, H-19), 2.00 (m, $J = 12.1$, 11.3, 9.8, 5.5, 5.1, H-14), 2.02 (m, $J = 14.1$, 9.8, 1.9, H-15), 2.16 (m, $J = 14.1$, 5.5, 5.5, H-15), 2.18 (d, $J = 15.6$, H-17), 3.10 (s, 3H, CO_2CH_3), 3.20 (m, $J = 13.7$, 9.4, 4.7, H-3), 3.27 (d, $J = 15.6$, H-17), 3.45 (s, H-21), 3.53 (m, $J = 13.7$, 11.3, 5.1, H-3), 6.95 (s, H-5), 7.04 (t, $J = 7.8$, H-10), 7.33 (d, $J = 7.8$, H-9), 7.34 (t, $J = 7.8$, H-11), 7.60 (d, $J = 7.8$, H-12); ^{13}C NMR ($CDCl_3$) δ 7.7 (C-18), 17.2 (C-14), 26.2 (C-15), 28.9 (C-19), 47.7 (C-17), 48.4 (C-20), 48.8 (C-3), 52.6 (CO_2CH_3), 67.6 (C-7), 73.3 (C-21), 79.2 (C-16), 81.2 (C-6), 119.6 (C-12), 122.0 (C-10), 123.6 (C-9), 130.2 (C-11), 135.3 (C-8), 147.6 (C-5), 156.8 (C-13), 167.0 (C-2), 170.5 (CO_2CH_3); EIMS *m*/*z* (rel intensity) 452 [29, $M^{\bullet+}$ ($^{81}Br^{37}Cl$)], 450 [100, $M^{\bullet+}$ ($^{81}Br^{35}Cl$ and $^{79}Br^{37}Cl$)], 448 [76, $M^{\bullet+}$ ($^{79}Br^{35}Cl$)], 414 (26), 355 (22), 332 (12), 266 (15), 248 (21), 246 (29); HRMS calcd for $C_{21}H_{22}{}^{79}Br^{35}ClN_2O_2$ 448.0553, found 448.055. Anal. Calcd for $C_{21}H_{22}BrClN_2O_2$: C, 56.08; H, 4.93; N, 6.23; Hal, 25.65. Found: C, 56.36; H, 5.04; N, 6.09; Hal, 25.58.

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Supporting Information Available: EIMS, IR, and ^{1}H and ^{13}C NMR spectra and 2D NMR plots (HMQC, ROESY) of compound **4** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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