Notes

Methyleneindolines, Indolenines, and Indoleniniums. 20.[1] The First Biomimetic Synthesis of Scandine and Meloscine

Georgette Hugel and Jean Lévy*

Université de Reims, UA/CNRS n°492 Centre d'Etude des Substances Naturelles à Activité Biologique, Faculté de Pharmacie, F51096 Reims Cedex, France

Received February 5, 1985

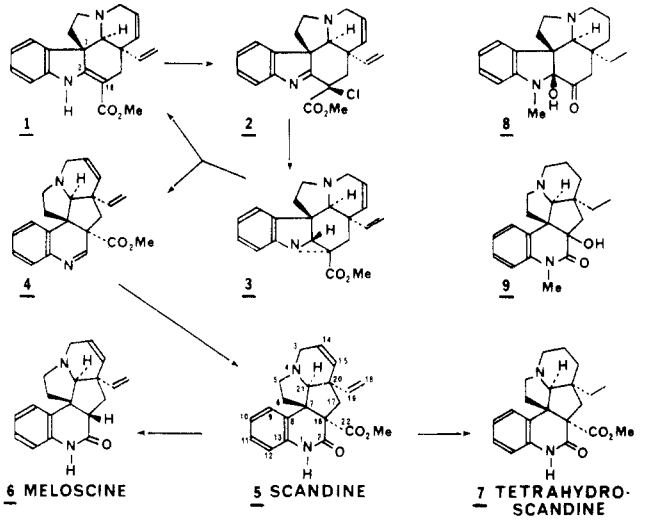
The tetrahydroquinolone *Melodinus* alkaloid scandine (**5**)[2] (Chart I) is believed to result from an oxidative rearrangement of Δ^{18}-tabersonine (**1**).[11] Although this highly probable biogenetic filiation was suggested several years ago,[2,3] no successful in vitro correlation had been performed until recently. Some months ago, we described the first example of such a transformation, i.e., the partial synthesis of tetrahydroscandine (**7**) from vincadifformine (**1**; 3,14,18,19-tetrahydro)[4] through the thermal rearrangement of a derived aziridine (viz., **3**, tetrahydro). Very shortly after, Palmisano and Danieli et al. published a partial synthesis of *N*(1)-methyltetrahydromeloscine through the rearrangement of the vincadifformine derived α-ketal **8** to 16-hydroxytetrahydromeloscine (**9**).[5]

These two different and independent routes compare in favor of the latter regarding the yield of the rearrangement step. To its advantage the shorter aziridine route is probably closer to the biosynthesis in that it allows retention of the significant methoxycarbonyl group and generation of the N(1)-unsubstituted *Melodinus* skeleton. These potentialities are now further illustrated by the successful synthesis of the natural compounds themselves, namely, scandine (**5**) and meloscine (**6**), by an extension of our previous work.

Δ^{18}-Tabersonine (**1**) was prepared from vindolinine after Langlois and Potier[6] and further oxidized[7] to the unstable 16-chloroindolenine **2**, which was reduced without purification ($NaBH_3CN$, AcOH) to the amorphous aziridine **3** (53% from **1**). A salient feature in the ^1H NMR spectrum was the AB system of the 17-methylene protons, which appeared as two doublets at 0.65 (strong anisotropic effect) and 2.67 ppm respectively (J = 12 Hz). The ^{13}C NMR spectrum compared with our previous findings[4] and was fully consistent with structure **3**.

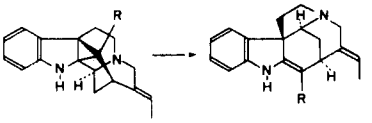
Flow thermolysis[8] of **3** was conducted in MeOH–PhMe (2:1) with a ca. 500 °C heated glass fitted column. It allowed recovery of **3** (12–44%), regeneration of **1** (18–25%), and isolation of imine **4** (7–11%). The imine proton H(2) was detected as a sharp singlet at 7.52 ppm.

Chart I



Selective oxidation of the imine group in **4** proved to be difficult, and several attempts failed. The difficulty was circumvented by using 2 equiv of Jones' reagent at −10 °C for 30 min, which allowed a 35% transformation to compound **5** the spectral data (IR, MS, UV, ^1H NMR) and the TLC behavior of which were identical with those of authentic scandine. The measured rotation was somewhat low, due to difficulty in crystallization (+205–210°, *c* 0.2, EtOH; lit.[2] +254°), and it was then decided to correlate **5** with two other *Melodinus* alkaloids. Catalytic hydrogenation yielded tetrahydroscandine (**7**): mp 209–211 °C; $[\alpha]_D$ +92.4° (MeOH, *c* 0.1); spectral data (IR, UV, MS, ^1H NMR) and TLC identical with reference material. Decarbomethoxylation[2] gave meloscine (**6**): mp 177–183 °C (lit.[2] mp 181–185 °C); $[\alpha]_D$ +130° (EtOH, *c* 0.04) (lit.[2] $[\alpha]_D$ +133.8°); spectral data (IR, MS, ^1H NMR) and TLC identical with reference material.

Of interest is the fact that no imine corresponding to 16-episcandine was found in the flow thermolysis products, which indicates that the rearrangement occurs with complete inversion at C(16). The reaction is then best accounted for by two simultaneous 1,2 shifts (7,2-bond → 7,16-bond and 16,1-bond → 2,1-bond). Such a rearrangement is reminiscent of the evolution of cyclopropane intermediates **8a,b** to norfluorocurarine **9a** and akuammicine **9b**, respectively.[9,10]



(1) Previous paper in this series: Vercauteren, J.; Massiot, G.; Lévy, J. *J. Org. Chem.* **1984**, *49*, 3230.
(2) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886.
(3) Daudon, M.; Mehri, M. H.; Plat, M. M.; Hagaman, E.; Wenkert, E. *J. Org. Chem.* **1976**, *41*, 3275.
(4) Hugel, G.; Lévy, J. *J. Org. Chem.* **1984**, *49*, 3275.
(5) Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S.; Demartin, F.; Masciocchi, N. *J. Org. Chem.* **1984**, *49*, 4139.
(6) Andriamialisoa, R. Z.; Diatta, L.; Rasonaivo, P.; Langlois, P.; Potier, P. *Tetrahedron* **1975**, *31*, 2347.
(7) Pierron, C.; Garnier, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1971**, 1007.
(8) Manisse, N.; Chuche, J. *Bull. Soc. Chim. Fr.* **1972**, 2422.
(9) Olivier, L.; Lévy, J.; Le Men, J.; Janot, M.-M.; Budzikiewicz, H.; Djerassi, C. *Bull. Soc. Chim. Fr.* **1965**, 868.
(10) Pousset, J. L.; Poisson, J.; Olivier, L.; Le Men, J.; Janot, M.-M. *C. R. Hebd. Seances Acad. Sci.* **1965**, *261*, 5538.

0022-3263/86/1951-1594$01.50/0

Regeneration of Δ^{18}-tabersonine from **3** also necessitates cleavage of the 1,16-bond, along with a shift of H(2), either to N(1) or to C(16).

This synthesis of scandine from the readily available Δ^{18}-tabersonine is though to mimic in a very short process one more biotransformations of the highly versatile *Aspidosperma* precursors.

Experimental Section

Melting points were taken on a Reichert Microscop and are uncorrected. ^{1}H NMR spectra were measured on a Perkin-Elmer R12B spectrometer (60 MHz) or on IEF 400, a prototype built at the University of Orsay (402 MHz), in $CDCl_3$ using Me_4Si as internal standard. Separations were done on TLC and with a Chromatotron (R) apparatus with Kieselgel 60 PF_{254} (Merck) and eluant CH_2Cl_2/MeOH.

16-Chloroindolenine 2. *t*-BuOCl (6% w/v solution in CH_2Cl_2, 6.4 mL) was added over a period of 1 h to a solution of Δ^{18}-tabersonine (**1**)[6] (720 mg) and triethylamine (0.32 mL) in methylene chloride (35 mL) under cooling at 0 °C. Evaporation of the solvent and crystallization from acetone gave **2** (564 mg, 71%): mp 150–158 °C dec; MS, *m/z* 368 ($M^{+\cdot}$), 370; UV λ_{max} 222, 275 nm; IR ν_{CO} 1735 cm^{-1}.

Aziridine 3. The 16-chloroindolenine **2** prepared from 720 mg 1 was dissolved in AcOH (20 mL) and portionwise added with $NaBH_3CN$ (1 g) over a period of 1 h at room temperature. The solution was poured into a saturated aqueous solution of K_2CO_3 and extracted with CH_2Cl_2. Purification through centrifuge TLC (Chromatotron^R, silica, 99:1 CH_2Cl_2/MeOH) afforded 382 mg aziridine **3** (53% from 1), which could not be induced to crystallize: $[\alpha]_D$ +49° (*c* 1.4, MeOH); MS, found for $M^{+\cdot}$ 334.1692 (calcd for $C_{21}H_{22}N_2O_2$ 334.1676); MS, *m/z* (relative intensity) 105 (60), 119 (80), 120 (43), 133 (100), 167 (12), 201 (13), 214 (10), 228 (28), 229 (12), 275 (6), 333 (7), 334 (11); UV λ_{max} 212, 230 (sh), 270, 280 nm; IR (film) ν_{CO} 1730 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.65 (1 H, d, J = 12 Hz) and 2.67 (1 H, d, J = 12 Hz) [H-17 and H-17′], 3.8 (3 H, s, CO_2CH_3), 5–6 (5 H, m, olefinic protons), 7–7.4 (4 H, m, aromatic protons); ^{13}C NMR δ (carbon number) 26.1 (17), 37.6 (6), 41.3 (20), 45.8 (5), 49.5 (16), 53.0 (OMe), 53.4 (7), 54.5 (3), 57.4 (2), 74.6 (21), 113.7 (18), 122.0 (12), 122.6 (9), 124.7 (14), 126.9 (10), 128.1 (11), 129.8 (15), 143.9 (19), 147.9 (8), 149.1 (13), 170.9 (22).

Flow Thermolysis of Aziridine 3. Aziridine **3** (44 mg) in MeOH–PhH (2:1, 20 mL) was passed through a glass fitted column heated at 495–510 °C under a slight vacuum (water pump) while the eluant was trapped in a liquid nitrogen cooled vessel. Evaporation of the solvent and separation on TLC afforded Δ^{18}-tabersonine (**1**), 8 mg (18%), and imine **4**, 5 mg (11%), along with recovered aziridine **3**, 13 mg (29%). Imine **4**: $[\alpha]_D$ +161° (*c* 0.5 MeOH); UV λ_{max} 215, 270 nm; IR ν_{CO} 1725 cm^{-1}, ν_{CN} 1610 cm^{-1} (weak); MS, found for $M^{+\cdot}$ 334.1600 (calcd for $C_{21}H_{22}N_2O_2$ 334.1676); MS, *m/z* (relative intensity) 105 (21), 119 (28), 120 (35), 134 (100), 170 (20), 214 (29), 275 (38), 276 (16), 303 (5), 334 (75); ^{1}H NMR δ 3.61 (3 H, s, CO_2CH_3), 4.8–6 (5 H, m, olefinic protons), 7.2–7.5 (4 H, m, aromatic protons), 7.52 (1 H, s, H-2); ^{13}C NMR δ (carbon number) 40.8 (6), 45.5 (17), 47.0 (20), 48.2 (3), 52.4 (OMe), 53.9 (5), 54.6 (7), 60.3 (16), 85.1 (21), 114.8 (18), 123.4 (14), 126.3 (12*), 127.3 (10), 128.6 (9*), 128.7 (11), 131.5 (15), 133.2 (8), 140.2 (13), 142.4 (19), 159.9 (2), 170.6 (22) [*may be inverted].

Oxidation of Imine 4. Imine **4** (14 mg) in acetone (2 mL) was added with 2 equiv of Jones' reagent at −10 °C. After 30 min, the solution was placed at +4 °C for 2 more hours. The solvent was evaporated at room temperature under vacuum, and an aqueous 10% solution of $NaHSO_3$ (2 mL) was added. After basification with Na_2CO_3, the solution was extracted with CH_2Cl_2. Separation on TLC afforded imine **4**, 3.5 mg (25%), and scandine (**5**), 5 mg (35%): $[\alpha]_D$ +206–210° (*c* 0.2, MeOH) [lit.[2] $[\alpha]_D$ +254°]; the IR, UV, MS, and ^{1}H NMR spectra and the R_f were identical with those of an authentic sample.

Hydrogenation of Synthetic Scandine (5). Catalytic hydrogenation (PtO_2, 20 mg) of synthetic scandine (**5**) (2 mg) in methanol (1 mL) followed by crystallization from hexane–CH_2Cl_2 gave tetrahydroscandine **7**, which was identical with an authentic sample: mp 209–211 °C; $[\alpha]_D$ +92.4° (MeOH, *c* 0.1); IR, MS, and R_F were all identical with an authentic sample.

Meloscine (6). Saponification and decarboxylation[2] of synthetic scandine (**5**) (5 mg) afforded meloscine (**6**) (3.5 mg), which was identical [mp 177–183 °C (lit.[2] mp 181–185 °C); $[\alpha]_D$ +130° (*c* 0.04, EtOH) (lit.[2] $[\alpha]_D$ +133.8°); IR; MS; 400-MHz ^{1}H NMR) with an authentic sample.

Acknowledgment. Thanks are due to H. Bailla (Faculté des Sciences, Reims), S. K. Kan (Orsay), E. Kremp (Strasbourg), and M. Merle (ICI-Pharma, Reims) for spectral measurements and to Prof. M. Plat (Chatenay-Malabry) for a generous gift of reference samples and spectra.

Registry No. 1, 58471-12-8; **2**, 97674-39-0; **3**, 97674-40-3; **4**, 97674-41-4; **5**, 24314-59-8; **6**, 24314-51-0; **7**, 91201-55-7.

(11) **Note added in proof**: This rearrangement apparently better accounts for the configuration of scandine presented in Chart I[2] than for the revised – configuration of the COOMe later proposed.[3] Moreover, the NMR spectrum of the amine resulting from the reduction of **4** exhibited a COOMe signal at 3.61 ppm, which reflected an anisotropic effect of the benzene ring consistent with the depicted configuration.

The Total Synthesis of Optically Pure (9*R*,13*S*)- and (9*R*,13*R*)-7-Deoxy-13-dihydrodaunomycinone

Richard A. Russell*

Department of Chemistry, University College, The University of New South Wales, Campbell, A.C.T., Australia 2601

Robert W. Irvine and Ronald N. Warrener

Department of Chemistry, The Faculties, The Australian National University, Canberra, A.C.T., Australia 2601

Received May 21, 1985

13-Dihydrodaunomycin **1** has long been recognized as the major human metabolite of the antineoplastic anthracycline daunomycin **2**.[1] Whilst **1** has been prepared by microbial[2] and chemical reduction[3] of **2**, no attempt to assign the stereochemistry at C13[4] has been reported. Recently Cassinelli et al. have reported[5] that 4-demethoxydaunomycin **3** (idarubicin) can be reduced microbially to afford an idarubicinol **4** identical with that excreted by patients treated with **3**. These authors initially assigned the 13*R* stereochemistry to this product, although this was subsequently corrected by Broadhurst et al.,[6] who showed that the totally synthetic 13*S* isomer corresponded to the biologically obtained product. As both dihydroderivatives **1** and **4** are active antineoplastic agents,[2,7] routes leading

(1) (a) Bachur, N. R. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 573. (b) Takanashi, S.; Bachur, N. R. *J. Pharmacol. Exp. Ther.* **1975**, *195*, 41.

(2) (a) Aszalos, A. A.; Bachur, N. R.; Hamilton, B. K.; Langlukke, A. F.; Roller, P. P.; Sheikh, M. Y.; Sutphin, M. C.; Thomas, M. C.; Wareheim, D. A.; Wright, L. H. *J. Antibiot.* **1977**, *30*, 50. (b) Marshall, V. P.; McGovren, J. P.; Richard, F. A.; Richard, R. E.; Wiley, P. F. *J. Antibiot.* **1978**, *31*, 336.

(3) Arcamone, F. "Doxorubicin Anticancer Antibiotics"; Academic Press: New York, 1981.

(4) The numbering used here is that commonly accepted for anthracyclines. Systematic notations C9, C11, and C13, referred to above, become C8, C10, and C11, respectively.

(5) Cassinelli, G.; Green, A.; Merli, S.; Penco, S.; Rivola, G.; Vigevani, A.; Zini, P.; Arcamone, F. *Gazz. Chim. Ital.* **1984**, *114*, 185.

(6) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Tetrahedron Lett.* **1984**, 6059.

(7) Casazza, A. M.; Barbieri, B.; Fumagalli, A.; Geroni, M. C. *Proc. Am. Assoc. Cancer Res.* **1983**, *24*, 251.

0022-3263/86/1951-1595$01.50/0