Reactions of 19-Ethoxycarbonyl-19-demethylvincadifformine: Synthesis of 19-Ethoxycarbonyl-19-demethylapovincamine†

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(±)-19-Ethoxycarbonyl-19-demethylapovincamine has been prepared by the oxidative rearrangement of (±)-19-ethoxycarbonyl-19-demethylvincadifformine. An attempt to prepare strempeliopine by the reductive rearrangement of 19-ethoxycarbonyl-19-demethyl-1,2-dehydroaspidospermidine, obtained from the same starting material, was unsuccessful.

(±)-19-Ethoxycarbonyl-19-demethylvincadifformine **1**, which we prepared earlier[1] *en route* to (±)-12-demethoxycylindrocarine **2** and related alkaloids, is a versatile intermediate which we hoped to transform into a number of other alkaloids by taking advantage of the several rearrangement reactions reported on the parent alkaloid, vincadifformine.[2]

In our first experiments we envisaged the possibility of converting **1** by an oxidative rearrangement into (±)-19-ethoxycarbonyl-19-demethylvincamine **3**. However, the 16-hydroxyindolenine derivative **4**, prepared by reaction of **1** with *m*-chloroperbenzoic acid, followed by reduction of the N_b-oxide function by means of hydrogen and palladium, did not rearrange smoothly in acid solution to give the corresponding vincamine derivative as has been reported[3] for the analogous derivative of vincadifformine; instead, inseparable mixtures, which may have contained some of the desired product **3**, or intractable gums, were obtained. Similarly, ozonization of **1** in methanol and sulfuric acid at 60 °C, as described by Danieli *et al.*,[4] resulted in the formation of a very polar, unidentified product.

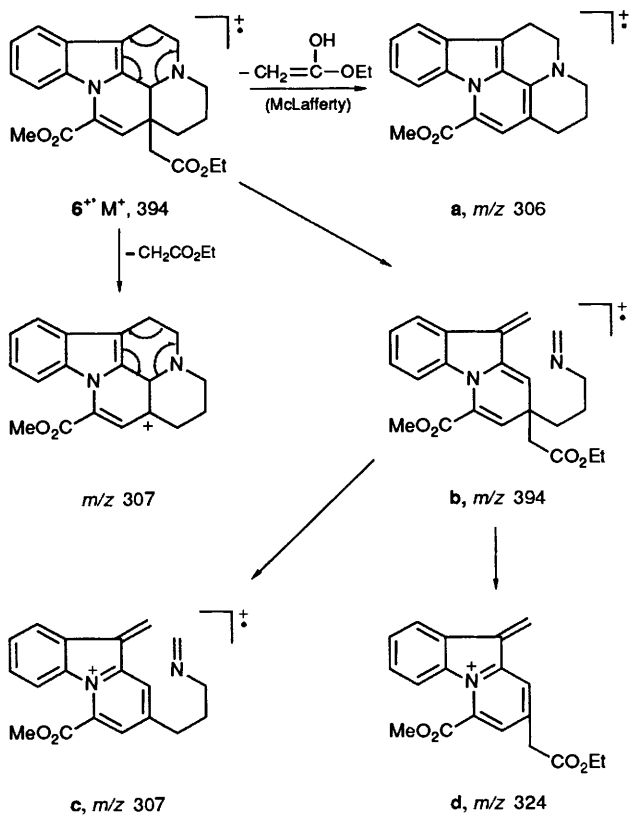
In contrast, the 16-hydroxyindolenine derivative **5**, prepared[5] by the reaction of **1** with *N*-chlorosuccinimide, rearranged smoothly when heated in trifluoroacetic acid, to give (±)-19-ethoxycarbonyl-19-demethylapovincamine **6** in 56% unoptimised yield.

The apovincamine derivative **6** was identified from its spectroscopic properties, and in particular its mass and ^{13}C NMR spectra. Its mass spectrum is dominated by McLafferty loss of the elements of ethyl acetate from the molecular ion, which gives rise to the base peak at *m/z* 306, owing to the ion **a** (Scheme 1). The second important fragmentation is the familiar retro-Diels–Alder fission of ring C; the resulting ion **b** then loses either the acetic ester residue to give the second most intense peak at *m/z* 307, owing to the ion **c**, or it loses the remnants of ring D to give the ion at *m/z* 324, owing to **d**. The facility of both these primary fragmentations is a direct consequence of the *cis* stereochemistry at the C/D and D/E ring junctions. The further fragmentation follows that observed with apovincamine (methyl apovincaminate, **7a**).[6]

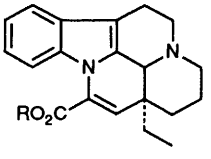
The ^{13}C NMR spectrum of 19-ethoxycarbonyl-19-demethylapovincamine also confirms the structure **6**. The spectrum is very closely similar to that of ethyl (+)-apovincaminate **7b** (see Experimental section),‡ apart from the signals owing to C-18 and C-19.

Hydrolysis and decarboxylation of the vincadifformine derivative **1** has already been shown[1] to give the rather unstable indolenine derivative **8**, which adds the elements of hydrogen cyanide to give the more stable, easily isolated nitrile ester **9**. Regeneration of the indolenine **8** by means of silver tetrafluoroborate, followed by a reductive rearrangement, should give the amino ester **10**, which is conveniently set up for cyclization to strempeliopine **11**, the alkaloid of *Strempeliopsis strempelioides* K. Schum.[7] This alkaloid has already been synthesised by Trojánek and Hájiček by a procedure which involved the reductive rearrangement of the indolenine related to **8**, but with an allyl group in place of the acetic ester residue, followed by appropriate manipulation of the allyl group in the rearranged species. This reductive rearrangement, which involved the use of zinc and copper sulfate in acetic acid, proved to

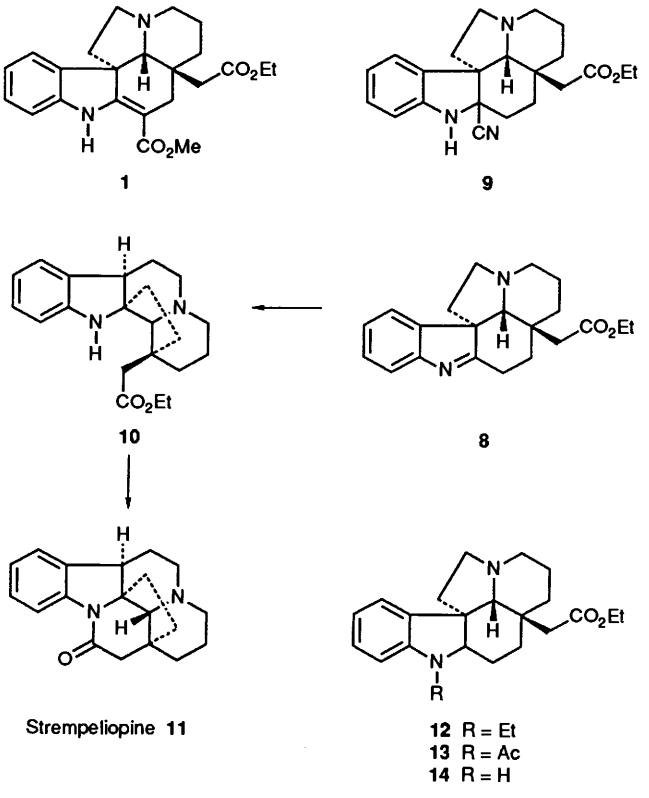
† Throughout this paper the biogenetic numbering system is adopted.
‡ The ^{13}C NMR spectrum of ethyl apovincaminate appears not to have been recorded in the literature. We therefore wish to thank Dr. Cs. Szántay very warmly for the generous gift of a sample of ethyl apovincaminate, on which the quoted ^{13}C NMR data were determined.



Scheme 1



7a R = Me
7b R = Et



be a very capricious reaction, in which the quality and particle size of the zinc used were of crucial importance. Unfortunately, we have been unable to obtain information concerning the exact source of the zinc used by the Czech workers.

In our hands the analogous reduction of the indolenine **8**, using the zinc samples available in our laboratory, gave a multiplicity of products, of which three were identified. However, none of these was the result of the desired rearrangement to the strempeliopine ring system. The three products identified were 19-ethoxycarbonyl-N_a-ethyl-19-demethylaspidospermidine **12**, which presumably arises by reduction of the second product, N_a-acetyl-19-ethoxycarbonyl-19-demethylaspidospermidine **13**, and 19-ethoxycarbonyl-19-demethylaspidospermidine **14**.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on either a Perkin-Elmer 1420 or 1310 spectrophotometer. UV absorption spectra were obtained on a Unicam PU 8800 spectrometer. NMR spectra were recorded on either a JEOL FX90Q FT (^{1}H 90 MHz and ^{13}C), GE QE 300 (^{1}H 300 MHz and ^{13}C) or a Bruker 400 MHz spectrometer (^{1}H 400 MHz and ^{13}C). Solutions in deuteriochloroform, with tetramethylsilane as internal standard, were used, unless otherwise stated. *J* values are given in Hz. Mass spectra were recorded on a Kratos MS 25 instrument; accurate mass measurements were carried out on an AEI/Kratos MS 902/50 spectrometer.

19-*Ethoxycarbonyl*-19-*demethylapovincamine* **6**.—A solution of 19-ethoxycarbonyl-19-demethylvincadifformine **1** (0.2 g, 0.5 mmol)[1] and *N*-chlorosuccinimide (66 mg, 0.5 mmol) in dry trifluoroacetic acid (20 cm^3) was stirred at room temp. for 4 h in a nitrogen atmosphere, then heated at reflux for 3 h. The solution was concentrated under reduced pressure, the residue was taken up in ethyl acetate, washed with 2 mol dm^{-3} sodium hydroxide and dried ($MgSO_4$). The crude product was chromatographed on Kieselgel G (35 g), using ethyl acetate as eluent, which gave 19-*ethoxycarbonyl*-19-*demethylapovincamine* (105 mg, 55%) as a colourless gum (Found: C, 69.75; H, 6.8; N, 6.85%; M^+, 394.1905. $C_{23}H_{26}N_2O_4$ requires C, 70.05; H, 6.60; N, 7.1%; *M*, 394.1893); $\nu_{max}(CHCl_3)$/cm^{-1} 1720 and 1638; λ_{max}(EtOH)/nm 202, 226, 272 and 313; λ_{min}/nm 215, 244 and 294; $\delta_H(CDCl_3$; 400 MHz) 7.47–7.1 (4 H, m, Ar-H), 6.47 (1 H, s, 17-H), 4.28 (1 H, br s, 21-H), 4.18 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 3.94 (3 H, s, OMe), 2.17 (2 H, s, 19-H), 3.3–1.2 (10 H, m) and 1.28 (3 H, t, *J* 7, $CO_2CH_2CH_3$); δ_C 171.37 (CO_2Et), 163.65 (CO_2Me), 134.13 (C-13), 130.34 (C-2), 128.96 (C-8), 127.61 (C-16), 126.86 (C-17), 122.07 (C-11), 120.33 (C-10), 118.26 (C-9), 112.52 (C-12), 108.98 (C-7), 60.45 (CH_2CH_3), 56.32 (C-21), 52.47 (OMe), 51.40 (C-5), 44.71 (C-3), 39.53 (C-19), 36.81 (C-20), 29.31 (C-15), 20.42 (C-14), 16.35 (C-6) and 14.24 ($CO_2CH_2CH_3$); *m/z* (%) 394 (M^+, 3.8), 324 (1.6), 321 (1.2), 307 (24.7), 306 (47.3) and 248 (0.7).

Ethyl apovincaminate **7b**.—δ_C 163.34 (CO_2Et), 133.89 (C-13), 130.93 (C-2), 128.93 (C-8), 128.32 (C-16), 127.84 (C-17), 121.62 (C-11), 120.03 (C-10), 118.05 (C-9), 112.42 (C-12), 108.51 (C-7), 61.64 ($CO_2CH_2CH_3$), 55.58 (C-21), 51.37 (C-5), 44.81 (C-3), 37.57 (C-20), 28.60 (C-19), 27.20 (C-15), 20.28 (C-14), 16.28 (C-6), 14.12 ($CO_2CH_2CH_3$) and 8.68 (C-18).

19-*Ethoxycarbonyl*-19-*demethyl*-1,2-*dehydroaspidospermidine* **8**.—(*a*) A stirred mixture of 19-ethoxycarbonyl-19-demethylvincadifformine **1** (1.8 g, 4.5 mmol) and sodium cyanide (4.5 g, 92 mmol) in dry hexamethylphosphoramide

(HMPA) (225 cm^3) was heated at 75 °C for 4.5 d in an atmosphere of nitrogen. The mixture was cooled, diluted with water (400 cm^3) and extracted with diethyl ether (5 × 250 cm^3). The combined extracts were washed with water (5 × 400 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (100 g), with chloroform as eluent, to give 2-cyano-19-ethoxycarbonyl-19-demethylaspidospermidine **9** (0.78 g, 47%), which was crystallised from aqueous methanol and obtained as colourless prisms, m.p. 113–114 °C (lit.,[1] m.p. 115.5 °C) (Found: M^+, 365.19768. $C_{22}H_{27}N_3O_2$ requires *M*, 365.21031); ν_{max}(Nujol)/cm^{-1} 3340, 2220, 1720, 1604 and 1590; λ_{max}(EtOH)/nm 204, 239 and 290; δ_H($CDCl_3$; 90 MHz) 7.0 (2 H, m, Ar-H), 6.8 (2 H, m, Ar-H), 4.0 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 3.4–1.3 (18 H, m) and 1.2 (3 H, t, *J* 7, $CO_2CH_2CH_3$); *m/z* (%) 365 (M^+, 4.9), 338 (20.6), 320 (3.1), 277 (13.9), 250 (18.2), 210 (4.5), 182 (100), 154 (16.2) and 109 (9.1).

The second fraction, eluted with chloroform containing 1% methanol, contained 19-ethoxycarbonyl-19-demethyl-1,2-dehydroaspidospermidine **8** (0.32 g, 21%) as an orange–yellow oil (lit.,[1] unstable); ν_{max}($CHCl_3$)/cm^{-1} 1720 and 1570; λ_{max}(EtOH)/nm 220, 225 and 259; δ_H($CDCl_3$; 90 MHz) 7.6–7.0 (4 H, m, Ar-H), 3.95 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 3.29–1.2 (17 H, m) and 1.1 (3 H, t, *J* 7, $CO_2CH_2CH_3$); *m/z* (%) 338 (M^+, 100), 294 (7.9), 268 (40.2), 250 (84.7) and 251(57).

(*b*) Silver tetrafluoroborate (31 mg, 0.15 mmol) in dry tetrahydrofuran (THF) (10 cm^3) was added, dropwise by syringe, to a solution of 2-cyano-19-ethoxycarbonyl-19-demethylaspidospermidine **9** (48 mg, 0.12 mmol) in dry THF (20 cm^3) under a nitrogen atmosphere. The resulting black suspension was stirred at room temp. for 4 h, then the reaction mixture was diluted with dilute aqueous ammonium hydroxide (7 cm^3) and extracted with dichloromethane (3 × 30 cm^3). The combined organic fractions were washed with dilute aqueous ammonium hydroxide and water, filtered through a short column of Celite, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by chromatography on Kieselgel G (15 g), using chloroform as eluent, which gave 19-ethoxycarbonyl-19-demethyl-1,2-dehydroaspidospermidine **8** (15 mg, 34%) as a pale yellow oil (Found: C, 74.55; H, 7.55; N, 8.5. $C_{21}H_{26}N_2O_2$ requires C, 74.0; H, 7.70; N, 8.30%), identical (IR, UV, NMR and mass spectra) with that obtained by procedure (*a*).

Attempted Reductive Rearrangement of 19-*Ethoxycarbonyl*-19-*demethyl*-1,2-*dehydroaspidospermidine*.—A suspension of silver tetrafluoroborate (0.75 g, 3.8 mmol) in dry THF (20 cm^3) was added dropwise to a stirred solution of the mixture of cyano compound **9** (0.78 g, 2.1 mmol) and indolenine **8** (0.32 g, 0.94 mmol) [prepared as in (*a*)] in dry THF (40 cm^3), kept in the dark and under nitrogen. After 15 min the solution became dark and stirring at room temp. was continued for 4 h, then the solvent was removed under reduced pressure. The residue was taken up in glacial acetic acid (125 cm^3). Zinc dust (12.5 g) and copper(II) sulfate pentahydrate (61 mg) were added to the solution, which was then heated to 105 °C and kept at this temperature for 6 h under nitrogen. After 3 h, more zinc (7.3 g) and copper sulfate (42 mg) were added. The mixture was then filtered while hot and the solid residue washed with hot acetic acid. The solution was concentrated under reduced pressure and the residue partitioned between diethyl ether (550 cm^3) and 7% aqueous ammonium hydroxide (340 cm^3). The combined organic extracts were washed with water (250 cm^3) and brine (200 cm^3), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on neutral alumina (20 g), using benzene–chloroform (100:1) as eluent. Four fractions were obtained. The first fraction yielded 19-*ethoxycarbonyl*-N_a-*ethyl*-19-*demethylaspidospermidine* **12** (267 mg, 16%) (Found: C, 75.0; H, 8.85; N, 7.85%; M^+, 368.24633. $C_{23}H_{32}N_2O_2$ requires C, 75.0; H, 8.7; N, 7.6%; *M*, 368.246365); ν_{max}($CHCl_3$)/cm^{-1} 1720 and 1600; λ_{max}(MeOH)/nm 226, 258 and 304; λ_{min}/nm 236 and 280; δ_H($CDCl_3$; 300 MHz) 7.5–6.4 (4 H, m, Ar-H), 4.0 (2 H, q, *J* 7.5, $CO_2CH_2CH_3$), 3.6–1.2 (20 H, m) and 1.15 (6 H, 2t, *J* 7.5, $CO_2CH_2CH_3$ and NCH_2CH_3); *m/z* (%) 368 (12.7), 340 (1.8), 339 (4.0), 323 (9.6), 295 (6.7), 294 (3.6), 281 (33.1), 280 (100), 252 (14.2), 210 (4.4), 183 (14.6), 182 (99.7), 144 (10.9) and 130 (10.4).

The second fraction was mainly impure N_a-acetyl-19-ethoxycarbonyl-19-demethylaspidospermidine contaminated with an unidentified product.

The third fraction yielded N_a-*acetyl*-19-*ethoxycarbonyl*-19-*demethylaspidospermidine* **13** (0.31 g, 18%), which was obtained as a colourless oil (Found: C, 72.15; H, 7.8; N, 7.2%; M^+, 382.2262. $C_{23}H_{30}N_2O_3$ requires C, 72.25; H, 7.85; N, 7.3%; *M*, 382.22563); ν_{max}/cm^{-1} 1720, 1640 and 1600; λ_{max}(MeOH)/nm 210, 251, 278 and 288; λ_{min}/nm 224; δ_H($CDCl_3$; 300 MHz) 8.15 (1 H, m, 12-H), 7.27–7.0 (3 H, m, Ar-H), 4.1 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 4.0 (1 H, dd, *J* 2 and 7, 2-H), 3.3–2.9 (2 H, m), 2.53 (1 H, s, 21-H), 2.26 (3 H, s, $COCH_3$), 2.4–1.2 (14 H, m) and 1.2 (3 H, t, *J* 7, $CO_2CH_2CH_3$); δ_C 171.4 (C-18), 168.38 ($COCH_3$), 140.8 (C-13), 137.35 (C-8), 127.81 (C-11), 124.33 (C-9), 122.23 (C-10), 118.36 (C-12), 69.15 (C-21), 67.56 (C-2), 60.05 ($CO_2CH_2CH_3$), 53.46 (C-7), 52.8 (C-3), 52.23 (C-5), 42.47 (C-19), 39.22 (C-6), 35.84 (C-20), 34.55 (C-15), 25.81 (C-16), 24.37 (C-17), 23.22 ($COCH_3$), 21.47 (C-14) and 14.25 ($CO_2CH_2CH_3$); *m/z* (%) 382 (M^+, 15.9), 340 (3.5), 337 (5.6), 295 (32), 294(88.1), 293 (4.5), 251 (4.2), 210 (4.8), 182 (100), 144 (6), 130 (11.5) and 43 (8.2).

The fourth fraction contained 19-*ethoxycarbonyl*-19-*demethylaspidospermidine* **14** (0.17 g, 11%), which was obtained as a colourless oil (Found: C, 74.4; H, 8.25; N, 8.1%; M^+, 340.21571. $C_{21}H_{28}N_2O_2$ requires C, 74.1; H, 8.20; N, 8.20%; *M*, 340.21506); ν_{max}($CHCl_3$)/cm^{-1} 3380, 1720, 1630 and 1604; λ_{max}(MeOH)/nm 210, 244 and 295; λ_{min}/nm 226 and 275; δ_H($CDCl_3$; 300 MHz) 7.1–6.9 (2 H, m, Ar-H), 6.7–6.6 (2 H, m, Ar-H), 4.0 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 3.5 (1 H, dd, *J* 11 and 10), 3.1 (2 H, m), 2.9–1.3 (16 H, m) and 1.2 (3 H, t, *J* 7, $CO_2CH_2CH_3$); δ_C 171.7 (C-18), 149.6 (C-13), 134.30 (C-8), 127.5 (C-11), 122.7 (C-9), 119.1 (C-10), 110.58 (C-12), 69.83 (C-21), 64.80 (C-2), 59.8 ($CO_2CH_2CH_3$), 53.52 (C-7), 53.50 (C-3), 52.5 (C-5), 42.4 (C-19), 38.0 (C-6), 36.13 (C-20), 34.9 (C-15), 28.1 (C-16), 24.3 (C-17), 21.55 (C-14) and 14.2 ($CO_2CH_2CH_3$); *m/z* (%) 340 (M^+, 14.9), 312 (7.2), 295 (21.0), 252 (52.5), 210 (5.9), 182 (100), 144 (16.9) and 130 (15.6).

Acknowledgements

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