Total Synthesis of Heptacyclic *Aspidosperma* Alkaloids. Part 3.[1] Synthesis of an Advanced Intermediate in the Synthesis of Alalakine

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The preparation of a hexacyclic aminoester, which lacks only the lactone ring of alalakine, is described.

In earlier communications[1,2] we have described a synthetic approach to the obscurinervidine group of alkaloids. Having completed the synthesis of obscurinervidine **1** itself we initiated experiments directed towards the synthesis of alalakine **2**, a related alkaloid of *Aspidosperma album* R. Bent.,[3] and we now record the preparation of an advanced intermediate **3**, by an adaptation of Kuehne's biomimetic synthesis.[4]

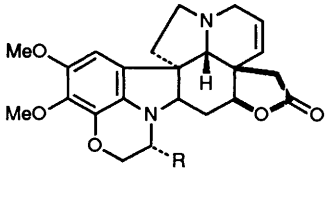
Reaction of 1-bromobutan-2-one[5] with the potassium salt of 2,3-dimethoxy-6-nitrophenol[6] gave 1-(2,3-dimethoxy-6-nitrophenoxy)butan-2-one **4**, which on hydrogenation and cyclization gave the benzoxazine **5**. Nitrosation of **5** followed by reduction, preferably by means of lithium aluminium hydride, then gave the amine **6**, which was converted into the pyrrolobenzoxazine derivative **7a** by condensation with methyl pyruvate, followed by thermal Fischer indolization. Subsequent stages to the key intermediate, the tetrahydro-β-carboline derivative **8**, were unexceptional. Hydrolysis of **7a**, followed by decarboxylation, gave the parent pyrrolobenzoxazine **9**, which afforded the gramine derivative **10** when reacted with formaldehyde and dimethylamine. Reaction of the methiodide of **10** with potassium cyanide gave the nitrile **11**, from which the tryptamine analogue **12** was obtained by reduction.

As is often observed in reactions of quaternary gramine derivatives with cyanide ion, the nitrile **11** was accompanied by a low yield of the isomeric nitrile **13**. Closure of the tetrahydro-β-carboline ring, to give **8**, was achieved when the tryptamine derivative **12** was treated with methyl pyruvate.

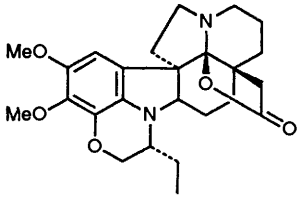
The construction of a vincadifformine-type ring system from **8** requires a 5-halogenopentanal derivative, and in order to make provision for the ultimate incorporation of the lactone function present in alalakine **2**, an acetic ester residue needs to be attached to the carbon atom adjacent to the aldehyde group. Accordingly, the tetrahydro-β-carboline **8** was condensed with the chloroformyl ester **14**[7] which, after fragmentation of the intermediate quaternary ammonium ion, and Kuehne biomimetic cyclization, gave the desired hexacyclic diester **15**, as a mixture of racemic diastereoisomers. This ester showed typical anilinoacrylate UV absorption at λ_{max}/nm 230, 302 and 344, and IR absorption at ν/cm^{-1} 1720 and 1670. The ^{13}C NMR spectrum (Table 1) exhibits signals closely similar, as far as the hydroaromatic part of the molecule is concerned, with those observed for vincadifformine **16**,[8] and the simpler diesters **17** and **18**.[7] The mass spectrum of the epimers **15** is relatively simple for a complex molecule, and in the higher mass region it is dominated by the retro Diels–Alder fragmentation of ring C, followed by fission of the 5,6 bond, which gives rise to ions at *m/z* 344(**19**) and 182(**20**).

The development of this particular route to alalakine was not pursued beyond the next stage, which involved the preferential removal of the methyl ester function by means of sodium cyanide in hexamethylphosphoramide.[7] As with the diester **17** the initial product added the elements of hydrogen cyanide, with formation of the cyano ester **3** which, like its precursor **15**, was obtained as a mixture of epimers at C-22. Prominent ions in the mass spectrum of **3** (*M*, 495), analogous to those observed in the mass spectrum of the cyano ester from **17**, arise from loss of hydrogen cyanide from the molecular ion (ion at *m/z* 468), and from retro Diels–Alder fission of ring C, followed by rupture of the 5,6 bond (ions at *m/z* 467, 285 and 182).

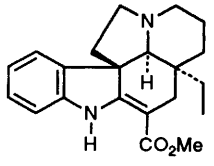
The advanced intermediate **3** has obvious potential for conversion into alalakine. Unfortunately, work on this synthetic route has perforce been temporarily suspended, but will be resumed as soon as circumstances permit.



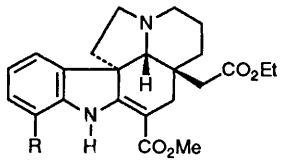
Obscurinervidine **1** R = Me
Obscurinervine R = Et



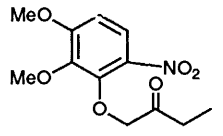
Alalakine **2**



(–)-Vincadifformine **16**



17 R = H
18 R = OMe



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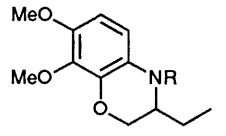
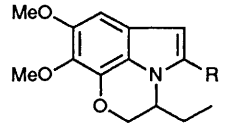
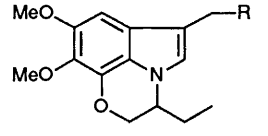


5 R = H
6 R = NH_2



7a R = CO_2Me
7b R = CO_2H
9 R = H



10 R = NMe_2
11 R = CN
12 R = CH_2NH_2

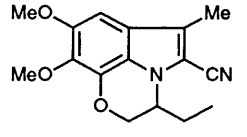


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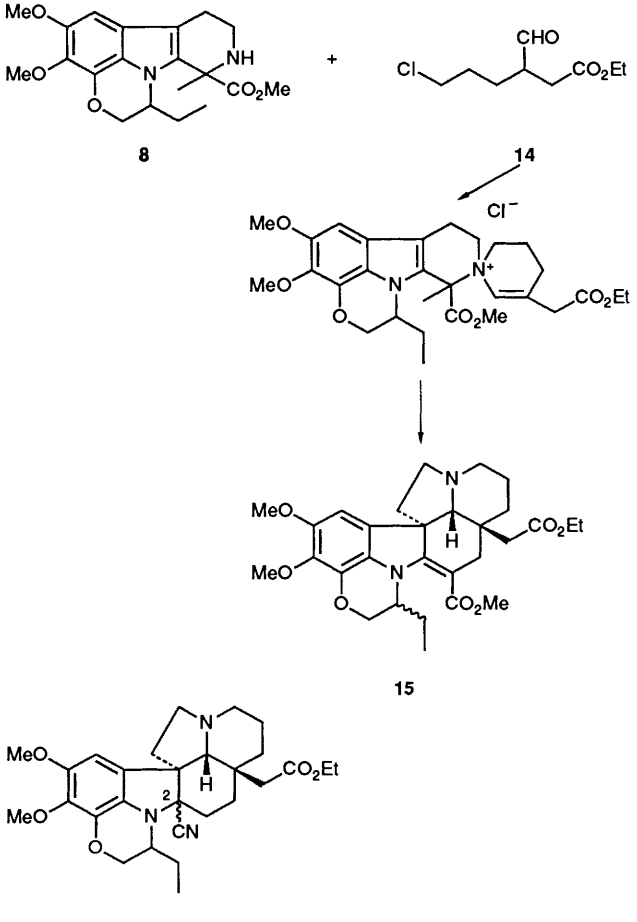
Table 1 ^{13}C NMR spectroscopic data for vincadifformine **16**, and the diesters **15**, **17** and **18**[a]

Carbon No.	δ_C Vincadifformine **16**[8]	**15**	**17**	**18**
2	167.4	162.76, 161.98	166.8	166.8
3	50.4	51.62, 51.01	50.9	50.8
5	51.6	50.29, 49.78	51.6	51.6
6	45.1	46.85, 46.54	45.4	45.3
7	55.4	58.93, 57.84	55.4	56.1
8	137.7	125.65, 124.75	137.2	132.1
9	121.0	99.60, 98.67	121.0	110.2
10	120.5	131.01, 129.87	120.6	113.6
11	127.3	148.19, 147.52	127.6	121.2
12	109.2	136.93, 136.13	109.4	144.3
13	143.7	135.82, 134.97	143.3	128.1
14	21.9	24.87, 22.07	22.1	22.1
15	32.3	33.31, 33.15	33.5	33.5
16	92.4	93.85, 93.01	93.1	93.4
17	25.6	29.92, 29.59	26.8	26.9
18	7.0	171.53, 171.26	171.5	171.3
19	29.3	37.53, 37.26	41.5	41.4
20	38.1	41.24, 41.24	38.5	38.5
21	72.4	73.25, 71.31	71.4	71.5
22	—	61.22, 61.09	—	—
23	—	67.93, 66.30	—	—
24	—	21.75, 16.63	—	—
25	—	10.15, 9.52	—	—
10-OMe }	—	{ 57.39, 57.16	—	—
11-OMe }	—	{ 56.02, 53.68	—	—
CO_2Me	168.9	167.49, 166.48	169.1	168.7
$CO_2\mathit{Me}$	50.8	50.95, 50.83	50.9	50.8
CO_2CH_2Me	—	59.85, 59.81	59.9	59.8
$CO_2CH_2\mathit{Me}$	—	14.06, 13.98	14.08	14.08
12-OMe	—	— —	—	55.42

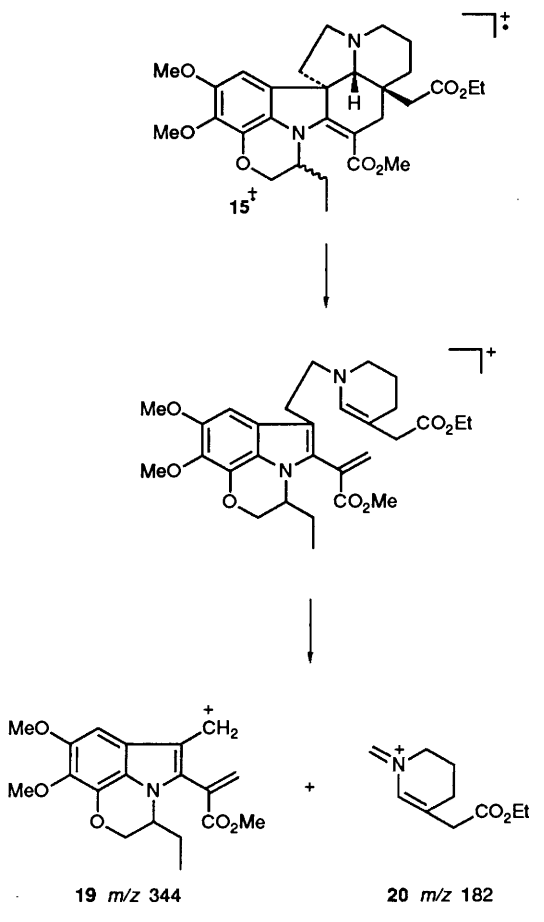
[a] Chemical shifts are quoted in ppm downfield from tetramethylsilane.



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 F.T. (^1H 90 MHz and ^{13}C), GE QE 300 (^1H 300 MHz and ^{13}C), or a Bruker 400 MHz spectrometer (^1H 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.

1-(2,3-*Dimethoxy*-6-*nitrophenoxy*)*butan*-2-*one* **4**.—To a stirred suspension of the potassium salt of 2,3-dimethoxy-6-nitrophenol (2.0 g, 8.4 mmol) in dry butan-2-one (20 cm^3), 1-bromobutan-2-one (3 g, 19.8 mmol) was added dropwise with stirring. The mixture was heated at reflux for 20 h in an atmosphere of nitrogen, then allowed to cool, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by chromatography on Kieselgel G (60 g), using ether–light petroleum (b.p. 60–80 °C) (4:1) as eluent. 1-(2,3-*Dimethoxy*-6-*nitrophenoxy*)*butan*-2-*one* (16 g, 71%) was obtained as a pale green oil (Found: C, 53.5; H, 5.5; N, 5.15. $C_{12}H_{15}NO_6$ requires C, 53.50; H, 5.55; N, 5.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1726 and 1590; $\delta_H(CDCl_3$; 90 MHz) 7.7 (1 H, d, *J* 9.5, 5-H), 6.75 (1 H, d, *J* 9.5, H-4), 4.7 (2 H, s, CH_2), 3.96 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.65 (2 H, q, *J* 7.2, CH_2) and 1.1 (3 H, t, *J* 7.2, CH_3); *m*/*z* (%) 296 (M^+, 17.9), 196 (8.9), 183 (22.7), 166 (30.9), 139 (7.3), 109 (9.8), 96 (11.7), 80 (14.9), 69 (13), 57 (100) and 43 (11.7).



3-*Ethyl*-7,8-*dimethoxy*-3,4-*dihydro*-2H-1,4-*benzoxazine* **5**.—A solution of 1-(2,3-dimethoxy-6-nitrophenoxy)butan-2-one (2.57 g, 9.5 mmol) in absolute ethanol (40 cm^3) was hydrogenated at a pressure of 30 atmospheres and at 70–80 °C for 2 h, using 5% palladium-on-carbon (0.24 g) as catalyst. The resulting mixture was allowed to cool and then filtered through a short pad of Celite. Removal of the solvent under reduced pressure gave a brown oil which was purified by chromatography on Kieselgel G (80 g) using ether–light petroleum (b.p. 40–60 °C) (30:50) as eluent, which gave 3-*ethyl*-7,8-*dimethoxy*-3,4-*dihydro*-2H-1,4-*benzoxazine* **5** as a clear oil (Found: C, 64.6; H, 7.6; N, 6.3. $C_{12}H_{17}NO_3$ requires C, 64.90; H, 7.85; N, 6.5%); δ_H($CDCl_3$; 400 MHz) 6.37 (1 H, d, *J* 8.5), 6.3 (1 H, d, *J* 8.5), 4.3 (2 H, dd, *J* 2.8, 10.5, CH_2), 3.86 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.24 (1 H, br s, NH), 3.25 (1 H, m, 3-H), 1.5 (2 H, m, CH_2) and 1.02 (3 H, t, *J* 7.5, CH_3); λ_{max}(EtOH)/nm 215, 245 and 300; *m*/*z* (%) 223 (M^+, 100), 208 (61.7), 194 (52.3), 180 (51), 162 (19.1), 151 (74), 134 (98), 108 (6.6), 97 (7.1), 80 (13.6), 68 (11.6) and 53 (12.6).

3-*Ethyl*-7,8-*dimethoxy*-N-*nitroso*-3,4-*dihydro*-2H-1,4-*benzoxazine*.—To a solution of 3-ethyl-7,8-dimethoxy-3,4-dihydro-2*H*-1,4-benzoxazine **5** (26.31 g, 0.117 mol) in concentrated hydrochloric acid (27.4 cm^3) and crushed ice (40 g), sodium nitrite (8.63 g, 0.125 mol) in water (41 cm^3) was added dropwise at such a rate that the temperature of the solution remained below 5 °C. After the addition was complete the reaction mixture was stirred for one hour and then extracted with benzene (4 × 150 cm^3). The combined organic fractions were washed with water (100 cm^3), dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (200 g) using benzene as eluent, which gave 3-*ethyl*-7,8-*dimethoxy*-N-*nitroso*-3,4-*dihydro*-2H-1,4-*benzoxazine* (25.3 g, 87%) as a yellow oil (Found: C, 57.15; H, 6.35; N, 11.1%; M^+, 252.110 61. $C_{12}H_{16}N_2O_4$ requires C, 57.0; H, 6.55; N, 11.0%; *M*, 252.110 999); δ_H($CDCl_3$; 400 MHz) 7.3 (1 H, d, *J* 9.1, 5-H), 6.65 (1 H, d, *J* 9.1, 6-H), 5.1 (1 H, m, 3-H), 4.5 (1 H, dd, *J* 1.5, 12, 2-H), 3.93 (1 H, dd, *J* 2.8, 12, 2-H), 3.95 (3 H, s, OMe), 3.87 (3 H, s, OMe), 1.55 (2 H, m, CH_2) and 0.9 (3 H, t, *J* 7.5, CH_3); δ_C146.02 (C-8), 138.3 (C-8a), 138.13 (C-4a), 128.45 (C-7), 109.5 (C-6), 105.2 (C-5), 69.58 (C-2), 60.87 (OMe), 56.66 (OMe), 50.9 (C-3), 25.04 (CH_2) and 9.87 (CH_3); *m*/*z* (%) (M^+ not observed), 223 (100), 209 (7.9), 194 (53.7), 151 (11.5), 140 (27.2), 94 (10.8), 80 (24.7), 69 (46.5) and 53 (24.7).

3-*Ethyl*-7,8-*dimethoxy*-3,4-*dihydro*-2H-1,4-*benzoxazine*-N-*amine* **6**.—To a solution of 3-ethyl-7,8-dimethoxy-N-nitroso-3,4-dihydro-2*H*-1,4-benzoxazine (20.9 g, 83 mmol) in dry ether (450 cm^3) and dry tetrahydrofuran (76 cm^3), cooled to 0 °C, a solution of lithium aluminium hydride (9.44 g, 0.24 mol) in dry ether (400 cm^3) was added dropwise, with stirring, at such a rate that the temperature remained below 10 °C. After the addition was complete the solution was stirred at 5–10 °C for a further 2 h after which 30% sodium hydroxide solution (96 cm^3) was added dropwise. The aqueous phase was extracted with ether (3 × 100 cm^3), the combined ethereal extracts were washed with water (200 cm^3), and then dried ($MgSO_4$). Concentration of the solution under reduced pressure gave a brown oil which was purified by chromatography on Kieselgel G (200 g) using benzene–ether as eluent. This gave 3-*ethyl*-7,8-*dimethoxy*-3,4-*dihydro*-2H-1,4-*benzoxazine*-N-*amine* **6** (18.4 g, 93%) as a colourless oil (Found: C, 60.5; H, 7.55; N, 11.75. $C_{12}H_{18}N_2O_3$ requires C, 60.2; H, 7.7; N, 11.5%); ν_{max}($CHCl_3$)/cm^{-1} 3435 and 1607; δ_H($CDCl_3$; 400 MHz) 6.75 (1 H, d, *J* 9), 6.4 (1 H, d, *J* 9), 4.3 (1 H, dd, *J* 2.5, 11.5, 2-H), 4.2 (1 H, dd, *J* 6, 11.5, 2-H), 3.85 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.5 (2 H, br s, NH_2), 3.3 (1 H, m, 3-H), 1.85 (2 H, m, CH_2) and 0.96 (3 H, t, *J* 7, CH_3); *m*/*z* (%) 238 (M^+, 100), 223 (88), 209 (65.4), 194 (39.5), 165 (28), 136 (27), 80 (30.7), 69 (38.1) and 53 (19.3).

Methyl 3-*Ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine*-5-*carboxylate* **7a**.—3-Ethyl-7,8-dimethoxy-3,4-dihydro-2*H*-1,4-benzoxazine-*N*-amine **6** (10.35 g, 0.043 mol) was dissolved in ethanol (185 cm^3) and methyl pyruvate (4.74 g, 0.046 mol) was added. The mixture was stirred for one hour and then concentrated under reduced pressure. The residue was then slowly heated to 130 °C under reduced pressure (15 mmHg) for one hour. The crude product was purified by chromatography on Kieselgel G (180 g) using benzene–ether as eluent. This gave the *title compound* **7a** (7.5 g, 56%) as a clear, pale brown oil (Found: M^+, 305.1262. $C_{16}H_{19}NO_5$ requires *M*, 305.1263); ν_{max}($CHCl_3$)/cm^{-1} 1700 and 1592; δ_H($CDCl_3$; 90 MHz) 7.1 (1 H, s, 7-H), 6.64 (1 H, s, 6-H), 5.05 (1 H, m, 3-H), 4.3 (2 H, m, OCH_2), 3.94 (3 H, s, CO_2CH_3), 3.9 (3 H, s, OMe), 3.85 (3 H, s, OMe), 1.4 (2 H, m, CH_2) and 0.94 (3 H, t, *J* 7.2, CH_3); *m*/*z* (%) 305 (M^+, 100), 276 (14), 223 (34.7), 194 (19.6), 160 (3.4), 133 (11.7) and 77 (16.2).

3-*Ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine*-5-*carboxylic Acid* **7b**.—A mixture of pyrrolobenzoxazine **7a** (7.5 g, 24 mmol) and 2 mol dm^{-3} sodium hydroxide solution (71.5 cm^3) was boiled under reflux for 2.5 h. The solution was cooled to 0 °C and concentrated hydrochloric acid was added until the mixture was acid to litmus. The precipitate was collected at the pump, dried, and recrystallized from benzene–ether, which gave 3-ethyl-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine*-5-*carboxylic acid* **7b** (6.73 g, 94%) as colourless prisms, m.p. 165–167 °C (Found: C, 62.0; H, 5.95; N, 4.55%; M^+, 291.110 02. $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.85; N, 4.80%; *M*, 291.110 66); ν_{max}($CHCl_3$)/cm^{-1} 1690; δ_H($CDCl_3$; 90 MHz) 9.0 (1 H, br s, OH), 7.27 (1 H, s, 7-H), 6.68

(1 H, s, 6-H), 5.1 (1 H, m, 3-H), 4.65 (1 H, dd, *J* 1.2, 12, OCH_2), 4.25 (1 H, dd, *J* 2.4, 12, OCH_2), 3.96 (3 H, s, OMe), 3.85 (3 H, s, OMe), 1.8–1.55 (2 H, m, CH_2) and 1.0 (3 H, t, *J* 7.2, CH_3); *m/z* (%) 291 (M^+, 100), 276 (58.1), 262 (16.5), 204 (21.8), 160 (17), 104 (10.3), 77 (21.9), 55 (52.6) and 44 (25.2).

3-*Ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine* **9**.—Carboxylic acid **7b** (1 g, 3.4 mmol) and its copper salt (74 mg) were added to freshly distilled quinoline (31 cm^3). The resulting mixture was heated at reflux for 5 h, then cooled to room temperature. The mixture was diluted with ether (30 cm^3) and washed with dilute hydrochloric acid (2 mol dm^{-3}; 4 × 30 cm^3), water (30 cm^3), dilute sodium carbonate solution (2 × 30 cm^3), and water (30 cm^3). The ethereal layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by chromatography on Kieselgel G (40 g) using benzene–ether as eluent, which gave 3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine* **9** (0.79 g, 94%) as a clear, colourless oil (Found: C, 67.7; H, 7.1; N, 5.6%; M^+ 247.120 81. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.65%; *M*, 247.120 835); δ_H($CDCl_3$; 90 MHz) 7.1 (1 H, d, *J* 2.57), 6.7 (1 H, s, 7-H), 6.3 (1 H, d, *J* 2.57), 4.4–4.1 (3 H, m, OCH_2CH), 3.95 (3 H, s, OMe), 3.85 (3 H, s, OMe), 1.7 (2 H, m, CH_2CH_3) and 1.0 (3 H, t, *J* 7.2, CH_3); *m/z* (%) 247 (M^+, 79.4), 232 (100), 218 (7.4), 160 (10.4), 133 (16.8), 104 (10.2), 77 (44.8) and 55 (21.1).

6-*Dimethylaminomethyl*-3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine* **10**.—A mixture of 40% aqueous dimethylamine solution (0.85 g, 5.05 mmol) and glacial acetic acid (0.85 g) was cooled in ice; when the temperature had fallen to 5 °C, pyrrolobenzoxazine **9** (1.2 g, 4.8 mmol) and 40% aqueous formaldehyde (26 mg, 80 mmol) were added. The mixture was stirred at room temperature overnight after which it was made alkaline to litmus by the addition of dilute potassium hydroxide solution. The aqueous phase was extracted with chloroform (2 × 50 cm^3) and the combined extracts were dried ($MgSO_4$), concentrated under reduced pressure, and the residue chromatographed on Kieselgel G (40 g) using benzene–ether as eluent, which gave the *title compound* **10** (1.4 g, 94%) as a yellow oil (Found: C, 67.3; H, 7.75; N, 8.55. $C_{17}H_{24}N_2O_3$ requires C, 67.10; H, 7.8; N, 9.0%); δ_H($CDCl_3$; 90 MHz) 7.05 (1 H, s, 7-H), 6.7 (1 H, s, 5-H), 4.5–4.05 (3 H, m, OCH_2CH), 3.9 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.55 (2 H, s, CH_2N), 2.3 (6 H, s, NMe_2), 1.85 (2 H, m, CH_2CH_3) and 1.0 (3 H, t, *J* 7.2, CH_3); *m/z* (%) 304 (M^+, 25.5), 260 (100), 232 (5), 161 (5.5), 69 (10.9) and 44 (1).

6-*Dimethylaminomethyl*-3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine Methiodide*.—Pyrrolobenzoxazine **10** (2.5 g, 8.2 mmol) was added to iodomethane (21 cm^3, 0.34 mol) with rapid stirring. The resulting solution was stirred overnight at room temperature, during which period most of the product crystallized. Crystallization was completed by cooling in ice, and the solid was collected, washed twice with ice-cold ether, and dried. The *methiodide* was obtained as colourless prisms (3.5 g, 96%), m.p. 210 °C (decomp.) (Found: C, 48.3; H, 6.05; N, 6.0. $C_{18}H_{27}IN_2O_3$ requires C, 48.40; H, 6.05; N, 6.25%); δ_H($CHCl_3$; 400 MHz) 7.6 (1 H, s), 6.9 (1 H, s), 4.69 (2 H, s, CH_2N), 4.45–4.35 (3 H, m, OCH_2CH), 3.9 (3 H, s, OMe), 3.8 (3 H, s, OMe), 3.15 (9 H, s, $\overset{+}{N}Me_3$), 1.9 (2 H, m, CH_2) and 1.1 (3 H, t, *J* 7, CH_3); *m/z* (%) (M^+, not observed), 261 (5.4), 232 (5.7), 128 (38.4) and 58 (100).

6-*Cyanomethyl*-3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*-[1,2,3-de]-2H-1,4-*benzoxazine* **11**.—To a solution of potassium cyanide (0.18 g, 2.7 mmol) in water (5 cm^3), 6-dimethylaminomethyl-3-ethyl-8,9-dimethoxy-3,4-dihydropyrrolo[1,2,3-*de*]-2*H*-1,4-benzoxazine methiodide (0.2 g, 0.9 mmol) was added. The mixture was boiled under reflux for 2.5 h, during which period an oil separated from the solution, This oil was extracted with chloroform (3 × 30 cm^3), and the combined extracts were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by chromatography on Kieselgel G (80 g) using benzene–ether as eluent, which gave two main fractions. 3-*Ethyl*-8,9-*dimethoxy*-6-*methyl*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine*-5-*carbonitrile* **13** (0.18 g, 14%) was obtained as an oil (Found: C, 67.0; H, 6.6; N, 9.5. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); ν_{max}($CHCl_3$)/cm^{-1} 2215 and 1620; δ_H($CDCl_3$; 90 MHz) 6.6 (1 H, s, 7-H), 4.6–4.2 (3 H, m, CH_2CH), 3.9 (3 H, s, OMe), 3.8 (3 H, s, OMe), 2.4 (3 H, s, 6-Me), 1.87 (2 H, m, CH_2) and 1.0 (3 H, t, *J* 7.2, CH_3); *m/z* (%) 286 (M^+, 100), 271 (62.6), 256 (11.9), 212 (7.5), 171 (1.7), 143 (1), 105 (1.5) and 77 (0.6).

The second fraction contained 6-*cyanomethyl*-3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo* [1,2,3-de]-2H-1,4-*benzoxazine* **11** (0.85 g, 70%), which was obtained as a clear oil (Found: C, 67.05; H, 6.2; N, 9.6%; M^+, 286.130 91. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%; *M*, 286.131 734); ν_{max}($CHCl_3$)/cm^{-1} 2230 and 1600; δ_H($CDCl_3$; 90 MHz) 7.1 (1 H, s, 5-H), 4.4–4.1 (3 H, m, CH_2CH), 3.95 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.7 (2 H, s, CH_2CN), 1.8 (2 H, m, CH_2) and 1.0 (3 H, t, *J* 7, CH_3); *m/z* (%) 286 (M^+, 97.6), 271 (100), 216 (14.2), 166 (13), 143 (1.1), 105 (53.2), 83 (19.6) and 69 (30.7).

6-(2-*Aminoethyl*)-3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*-[1,2,3-de]-2H-1,4-*benzoxazine* **12**.—(*a*) To a cooled solution of benzoxazine **11** (2.3 g, 8.0 mmol) in dry tetrahydrofuran (20 cm^3) a suspension of lithium aluminium hydride (1 g, 26 mmol) in dry ether (30 cm^3) was added dropwise over a period of 25 min. The mixture was stirred overnight at ambient temperature and then diluted with water (20 cm^3) and sulfuric acid (6 mol dm^{-3}; 30 cm^3). The aqueous phase was extracted with ether (3 × 60 cm^3), after which the pH of the solution was adjusted to 10 by the addition of 2 mol dm^{-3} potassium hydroxide solution. The solution was then extracted with ethyl acetate (4 × 100 cm^3), and the organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The oily residue was chromatographed on a column of neutral alumina, and the product eluted with dichloromethane–ether (7:1). 6-(2-*Aminoethyl*)-3-*ethyl*-8,9-*dimethoxy*-3,4-*dihydropyrrolo*[1,2,3-de]-2H-1,4-*benzoxazine* **12** (1.56 g, 77%) was obtained as a yellow oil (Found: M^+, 290.162 76. $C_{16}H_{22}N_2O_3$ requires *M*, 290.163 032); ν_{max}($CHCl_3$)/cm^{-1} 3400, 1680 and 1590; δ_H($CDCl_3$; 90 MHz) 6.9 (1 H, s, 7-H), 6.65 (1 H, s, 5-H), 4.42 (3 H, m, CH_2CHN), 3.90 (6 H, s, 2 × OMe), 3.2–2.8 (4 H, m), 1.6 (2 H, br s, NH_2), 1.8 (2 H, m, CH_2) and 1.0 (3 H, t, *J* 7.1, CH_3); *m/z* (%) 290 (M^+, 30), 260 (100), 232 (3.2), 187 (3.2), 161 (12.1), 119 (34) and 55 (12.6).

(*b*) To a solution of pyrrolobenzoxazine **11** (100 mg, 0.3 mmol) and cobaltous chloride hexahydrate (142 mg, 0.6 mmol) in methanol (4 cm^3) sodium borohydride (0.11 g, 3 mmol) was added, at room temperature. The mixture was then stirred for one hour. Hydrochloric acid (3 mol dm^{-3}; 1.2 cm^3) was added and stirring continued unitl all the black precipitate had dissolved. The methanol was removed under reduced pressure, unchanged starting material was removed by extraction with ether, and the aqueous layer made alkaline with concentrated ammonia solution. The product was then extracted into chloroform (3 × 20 cm^3), the chloroform extracts were dried ($MgSO_4$), and evaporated. Chromatography of the residue on neutral alumina, as described above, gave the desired amine **12** (77 mg, 77%) as a brown oil, identical (IR, NMR and mass spectra) with the amine prepared by method (*a*).

Methyl 1-*Ethyl*-4,5-*dimethoxy*-10-*methyl*-1,2,7,8,9,10-*hexahydropyrido*[4′,5′;4,5]*pyrrolo*[1,2,3-de]-1,4-*benzoxazine*-10-*carboxylate* **8**.—A solution of 6-(2-aminoethyl)-3-ethyl-8,9-dimethoxy-3,4-dihydropyrrolo[1,2,3-*de*]-2*H*-1,4-benzoxazine (3.61 g, 12.4 mmol) and methyl pyruvate (1.83 g, 17.9 mmol) in dry methanol (100 cm^3) was refluxed under nitrogen for 22 h. The cooled solution was concentrated under reduced pressure, and the residue was partitioned between saturated aqueous sodium carbonate solution (200 cm^3) and dichloromethane (400 cm^3). The aqueous phase was extracted twice with ether (2 × 400 cm^3), washed with brine, dried ($MgSO_4$), and the solvent removed. The residue was chromatographed on a silica gel column (80 g). Elution with dichloromethane–ether (7:1) yielded the *title compound* **8** (3.9 g, 86%) as colourless prisms, m.p. 75–78 °C (Found: C, 63.85; H, 6.6; N, 6.95%; M^+, 374.183 04. $C_{20}H_{26}N_2O_5$ requires C, 64.1; H, 6.95; N, 7.4%; *M*, 374.184 159); $\nu_{max}(CHCl_3)/cm^{-1}$ 3510, 1720 and 1600; $\delta_H(CDCl_3$; 90 MHz) 6.6 (1 H, s, 8-H), 4.7–4.1 (3 H, m, OCH_2CH), 3.95 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.73 (3 H, s, CO_2Me), 3.3 (2 H, m, 6-H), 2.8 (2 H, m, 7-H), 2.2 (1 H, s, NH), 1.7 (2 H, m, CH_2Me), 1.2 (3 H, s, 4-Me) and 1.0 (3 H, s, CH_2Me); *m*/*z* (%) 374 (M^+, 9.9), 315 (100), 201 (8.5), 169 (4.8), 145 (4.5), 94 (28.8) and 69 (30.6).

Hexacyclic Diester **15**.—A solution of the tetrahydro-β-carboline derivative **8** (1.51 g, 4 mmol), ethyl 6-chloro-3-formylhexanoate **14**[7] (1.1 g, 4.8 mmol), and toluene-*p*-sulfonic acid (20 mg) in toluene (100 cm^3) was refluxed under nitrogen in a Dean–Stark apparatus for 100 h. Further portions of chloroaldehyde (2 × 0.5 g) were added to the mixture after 70 and 90 h. To the hot solution, diazabicycloundecene (1.5 cm^3) was then added and heating continued for a further 10 h. Removal of the solvent under reduced pressure gave a brown oil which was chromatographed on Kieselgel G (80 g) using dichloromethane–ether (7:1) as eluent, which gave the *hexacyclic diester* **15** (0.73 g, 34.5%) as a pale yellow oil. Trituration with a small amount of ether gave a microcrystalline mixture of diastereoisomers, m.p. 130–138 °C (Found: C, 65.85; H, 7.25; N, 5.05%; M^+, 526.267 869. $C_{29}H_{38}N_2O_7$ requires C, 66.10; H, 7.2; N, 5.3%; *M*, 526.266); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 and 1670; λ_{max}(MeOH)/nm 203, 210, 230, 302 and 344; λ_{min}/nm 274, 316; $\delta_H(CDCl_3$; 400 MHz) 6.44, 6.42 (1 H, 2 s, 9-H), 4.85, 4.54 (1 H, dd, *J* 2, 12), 4.3, 4.2 (1 H, dd, *J* 2, 12, 23-H), 4.0 (2 H, 2q, *J* 7, $CO_2CH_2CH_3$), 3.9, 3.89 (3 H, 2s, OMe), 3.86, 3.83 (3 H, 2s, OMe), 3.7, 3.68 (3 H, 2s, CO_2Me), 3.2–1.2 (17 H, m), 1.15, 1.12 (3 H, 2t, *J* 7, $CO_2CH_2CH_3$) and 1.0, 0.9 (3 H, 2t, *J* 7.5, CH_3); $\delta_C(CDCl_3)$ 171.53, 171.26 (C-18), 167.49, 166.48 (CO_2Me), 162.76, 161.98 (C-2), 148.19, 147.52 (C-11), 136.93, 136.13 (C-12), 135.82, 134.97 (C-13), 131.01, 129.87 (C-10), 125.65, 124.75 (C-8), 99.60, 98.67 (C-9), 93.85, 93.01 (C-16), 73.25, 71.31 (C-21), 67.93, 66.30 (C-23), 61.22, 61.09 (C-22), 59.85, 59.81 (CO_2CH_2Me), 58.93, 57.84 (C-7), 57.39, 57.16, 56.02, 53.68 (2 × OMe), 51.62, 51.01 (C-3), 50.95, 50.83 (CO_2Me), 5.29, 49.78 (C-5), 46.85, 46.54 (C-6), 37.53, 37.26 (C-19), 41.24 (C-20), 33.31, 33.15 (C-15), 29.92, 29.59 (C-17), 24.87, 22.07 (C-14), 21.75, 16.63 (C-24), 14.06, 13.98 (OCH_2CH_3), and 10.15 and 9.52 (C-25); *m*/*z* (%) 526 (M^+, 17.4, 344 (7.9), 260 (0.4), 210 (0.4) and 182 (100).

Hexacyclic Nitrile Ester **3**.—Sodium cyanide (0.2 g, 4 mmol) was added to the hexacyclic diester **15** (108 mg, 0.2 mmol) in dry hexamethylphosphoramide (10 cm^3). The mixture was heated at 82 °C for 102 h under nitrogen, and then cooled, diluted with water (20 cm^3), and extracted with ether (5 × 50 cm^3). The combined extracts were washed with water (5 × 20 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (25 g) using light petroleum (b.p. 40–60 °C)–ether (60:40) as eluent, which gave the *hexacyclic nitrile ester* **3** (58 mg, 57%) as colourless needles, m.p. 143–145 °C (Found: M^+, 495.2727. $C_{28}H_{37}N_3O_5$ requires *M*, 495.2733); $\nu_{max}(CHCl_3)/cm^{-1}$ 2240 and 1725; λ_{max}(MeOH)/nm 218, 250 and 300; λ(MeOH)/nm 278; $\delta_H(CDCl_3$; 300 MHz) 6.35, 6.30 (1 H, 2s, 9-H), 4.4, 4.3 (3 H, m, OCH_2CH), 4.1 (2 H, 2q, *J* 7.2, $CO_2CH_2CH_3$), 3.9, 3.89 (3 H, 2s, OMe), 3.82, 3.80 (3 H, 2s, OMe), 3.3–1.2 (19 H, m), 1.15, 1.2 (3 H, 2t, *J* 7.2, $CO_2CH_2CH_3$), and 0.9, 0.8 (3 H, 2t, *J* 7, 25-H); *m*/*z* (%) 495 (M^+, 3.9), 469 (6.9), 468 (21.3), 423 (1.7), 286 (9.7), 234 (1.8), 183 (11.6) and 182 (100).

Acknowledgements

We thank the Algerian Government for financial support (to A. B.).

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Paper 1/06234D
Received 11*th December* 1991
Accepted 31*st December* 1991