Electrophilic Substitution in Indoles. Part 19.[1] Facile Syntheses of the 2a,5a-Diazacyclopenta[*j,k*]fluorene, Indolo[2,3-*a*]quinolizinone and Aspidosperma Alkaloid Ring Systems from *N*-Acyltryptamines

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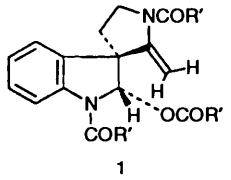
Reaction of tryptamine with diketene gave *N*-[2-(1*H*-indol-3-yl)ethyl]-3-oxobutyramide (80%) which with phosphoryl chloride in dichloromethane gave (9b*S**,9c*S**)-1,2,9b,9c-tetrahydro-5-methyl-2a,5a-diazacyclopenta[*j,k*]fluoren-3-one **13** (73%). Hydrogenation gave the 4,5-dihydro and perhydro derivatives. Michael addition of ethyl acetoacetate to benzyl acrylate gave 5-benzyl 1-ethyl 2-acetylpentanedioate (57%) which was hydrogenolysed to 4-ethoxycarbonyl-5-oxohexanoic acid (100%), the mixed anhydride of which condensed with tryptamine to give 4-ethoxycarbonyl-*N*-[2-(1*H*-indol-3-yl)ethyl]-5-oxohexanamide **19** (78%). The latter, with trifluoracetic acid anhydride gave (±)-*cis* and *trans* 1-(ethoxycarbonyl)-2,3,6,7-tetrahydro-12b-methyl-12*H*-indolo[2,3-*a*]quinolizin-4(1H)-one (**21** and **22**) (95%). *N*-[2-(1-Methylindol-3-yl)-ethyl]piperidin-2-one **31** was synthesised in three stages. The anion of **31** with diketene gave (a) *N*-[2-(1-methylindol-3-yl)ethyl]-3-(1,3-dioxobutyl)piperidin-2-one, **29** and (b) in a three-stage process, *N*-[2-(1-methylindol-3-yl)ethyl]-3-(1-oxo-2-methoxycarbonylethyl)piperidin-2-one **30**. Treatment of the dione **29** with excess of trifluoroacetic acid anhydride gave (2*S**,3*R**,12*R**)-3-acetyl-5-deethyl-5,19-didehydro-1-methyl-4-oxoaspidospermidine, **34**. Reduction of **34** with sodium cyanoborohydride gave the 20,21-dihydro derivative **35** and two (±)-diastereoisomeric alcohols **36** and **37**. Cyclisation of the ester **30** with trifluoracetic acid anhydride gave (2*S**,3*S**,12*R**)-5-deethyl-5,19-didehydro-3-methoxycarbonyl-1-methyl-4-oxoaspidospermidine **39**.

In an earlier paper[1] we showed that cyclisation of N_b-acetyltryptamines afforded spirocyclic indolines of type **1** in almost quantitative yields. The aim of this work was to develop a synthetic route to derivatives of Aspidosperma indole alkaloids with skeletons of type **2**. Our intention was to use the nucleophilic activity[1] at the indole 3-position of suitably elaborated acyl tryptamines for closure of the 12,19-ring junction, and to complete the pentacyclic system by forming the 2,3-bond *via* attack of a nucleophilic centre at C-2.



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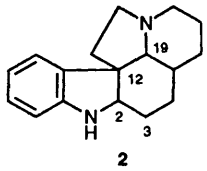

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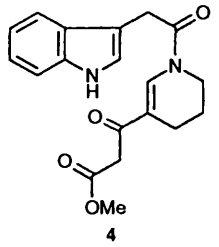

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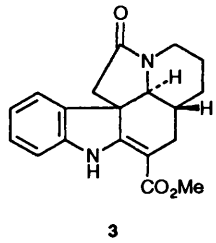

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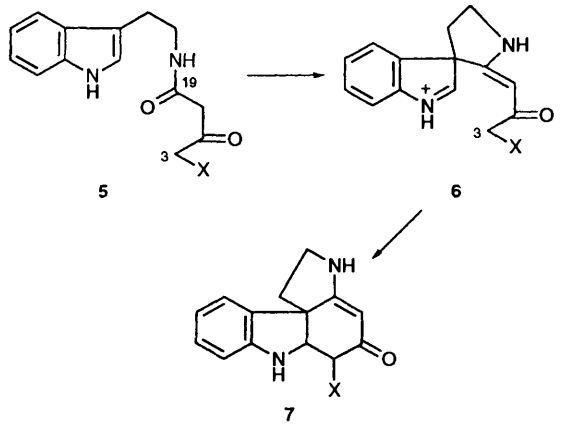
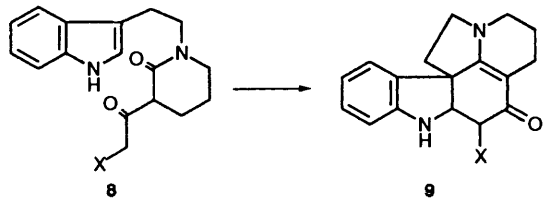
Since the pioneering synthesis of strychnine by Woodward *et al.*,[2] this type of approach has been exploited by several groups. For example by Van Tamelen *et al.*,[3] Buchi *et al.*, in their synthesis of vindorosine,[4] Pandit *et al.*[5] in their synthesis of the aspidosperma skeleton and Wenkert *et al.*[6] who described a synthesis of deethylvincadifformine **3** in which the key step was the boron trifluoride-catalysed cyclisation of the acyl enamine **4**. Introduction of an ethyl group into the starting pyridine derivative led to the synthesis of the natural compounds.[7]

In the present work, we began with attempts to cyclise relatively simple amides such as **5** with potential nucleophilic character at the C-3 position. Acylation,[8] like other electrophilic reactions,[9] proceeds at the indole 3-position, hence we expected that amides such as **5** under Bischler–Napieralski conditions would lead initially to the spirocyclic indolenium intermediate **6** (Scheme 1). Whilst normally, rearrangement of **6** to a dihydro-β-carboline would occur, in our case we hoped that the potentially nucleophilic centre at C-3 would attack the indoleninium function to give the pyrrolo[2,3-*d*]carbazole system **7**. For a successful functional group (X), more elaborate amides could be envisaged such as **8** which, on cyclisation,

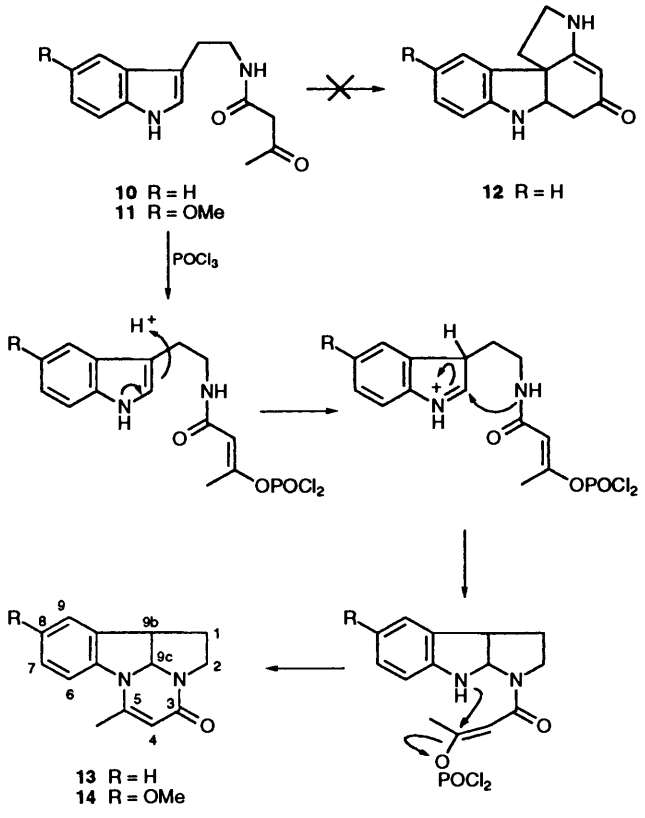


Scheme 1



might afford the pentacyclic skeleton **9**. Our proposed route differed from previous ones in that the starting amides were structurally simpler and in a different oxidation state from the various enamine derivatives referred to above. Preliminary accounts of some of this work have been reported.[10,11]

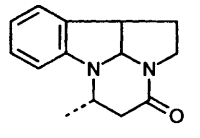
We first decided to use the keto amide **10** which might cyclise to the tetracyclic indoline **11** (Scheme 2). Reaction of

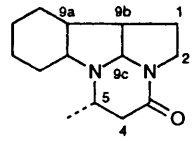


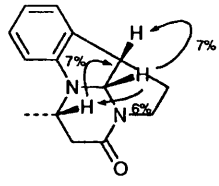
Scheme 2

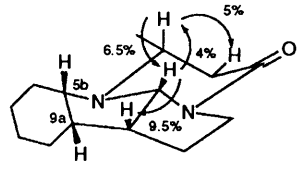
tryptamine with diketene gave an 80% yield of the required amide **10**. Attempted cyclisations with trifluoroacetic acid anhydride or boron trifluoride diethyrate were unsuccessful, but phosphoryl chloride in dichloromethane at 20 °C for 24 h, gave the indoline **13** (73%)* after chromatography, as an oil, M^+ 226.1106 (100%, $C_{14}H_{14}N_2O$).

In the ^{1}H NMR spectrum a doublet at δ 5.5 (J 8 Hz) could be assigned to the 9c-H which correlated well with other tetrahydropyrroloindoles.[12,13] The four aromatic protons appeared at higher field than δ 7.27 in keeping with the change from indole to indoline; the remaining signals were assigned from decoupling experiments. The ^{13}C NMR spectrum was assigned by comparison with the literature,[7] in particular C-9b and C-9c gave two doublet signals at δ 45.1 and 79.0. This cyclisation may involve activation of the acetyl group (Scheme 2) in which prior attack of phosphoryl chloride on the ketone with release of HCl is a controlling feature. The indoline **13** was unstable, reverting to starting material when stored for a few days. Hydrogenation at atmospheric pressure gave the stable amine **15** and the perhydro derivative **16**.









In the ^{1}H NMR spectrum of **15** the methyl group (3 H, d, J 7 Hz) at δ 1.6 was shown to be *trans* to the 9b/9c-H atoms by NOE difference spectra (see **13a**). For the fully hydrogenated derivative **16** the NMR assignments and coupling constants for most of the protons were deduced from a 2D COSY 45 experiment. NOE difference spectra gave the enhancements shown in **16a**. The stereostructure of the 5b–9a ring junction was not determined, but presumably hydrogen was delivered catalytically to the same face of the molecule as for the saturation of the C-4–C-5 double bond of **13**, and therefore the *cis–cis* structure **16a** would be expected.

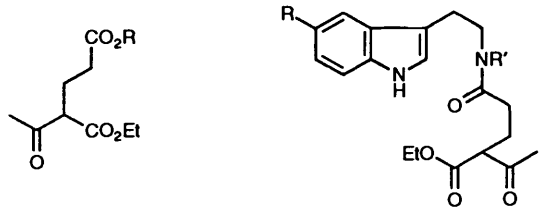
The 5-methoxy analogue **11** of the starting amide was also synthesised from 5-methoxytryptamine and when treated with phosphoryl chloride under similar conditions to those used for **10**, **11** gave the 8-methoxyindoline **14** (68%). The diazacyclopenta[*j*,*k*]fluorene ring system of **13** and **14** has been reported previously only as a product of cyclisation of *N*-substituted indoles.[14] The approach *via* the amides **10** and **11** described above is a novel although unexpected route.

We then moved to a more elaborate amide precursor. Michael addition of ethyl acetoacetate to benzyl acrylate gave the benzyl ester **17** (57%) which was hydrogenolysed to the corresponding acid **18** (100%) over palladised charcoal. Condensation of the acid with tryptamine using dicyclohexylcarbodiimide in tetrahydrofuran afforded only a small amount of product, but treatment of the acid **18** with 1 equiv. each of ethyl chloroformate and triethylamine at −5 °C gave the mixed anhydride which, without isolation, was condensed with tryptamine to give the amide **19** as a brown, viscous oil (78%) after chromatography. Similarly the methoxy substituted analogue **20** was obtained in 32% yield.

Treatment of the amide **19** with 1 equiv. of trifluoracetic acid anhydride in benzene gave, as the main product, the indolo[2,3-*a*]quinolizinone **21**. In acetonitrile as solvent, the *cis*-**21** and *trans*-**22** isomers were isolated after chromatography in the ratio of 5:1 respectively, whereas with phosphoryl chloride (1 equiv.) as the cyclisation reagent the *cis* isomer **21** was obtained in a 99:1 excess and in >95% yield. In the ^{1}H NMR spectrum of **21**, the indole-2-H was absent and there was a series of multiplets in the region δ 2–3, assigned by decoupling experiments to the 2, 3, 6 and 7 protons. In particular the 6α-H proton at δ 5.07, in the deshielding region of the amide carbonyl, showed the expected lowfield shift observed in model compounds.[15] The signal, a double double doublet, J 13, 4, 2 Hz, is acceptable for the part structure/conformation **21a**.

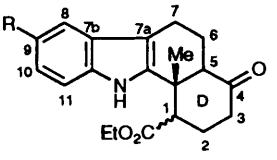
For the *trans* isomer **22**, the CH_2CH_3 signals of the ester were considerably shielded compared with the *cis* isomer **21** as

* One enantiomer only is shown in structural formulae of racemates.

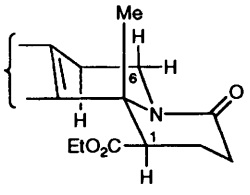


17 R = CH_2Ph
18 R = H

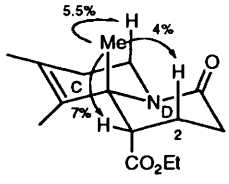
19 R = H, R' = H
20 R = OMe, R' = H



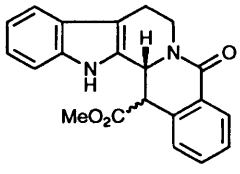
21 1-β CO_2Et, R = H
22 1-α CO_2Et, R = H
23 1-β CO_2Et, R = OMe



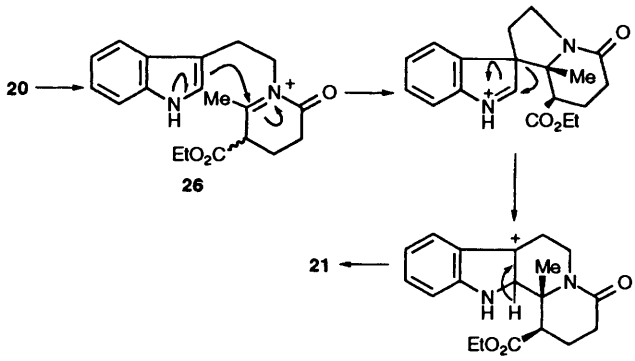
21a



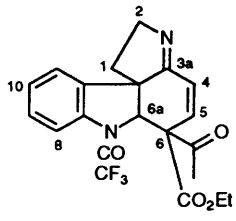
22a



24 α-CO_2Me
25 β-CO_2Me



Scheme 3



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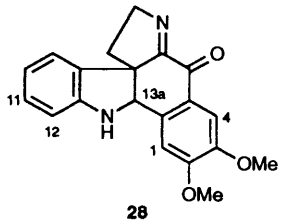

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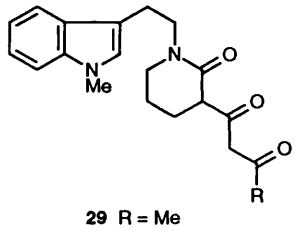


29 R = Me
30 R = OMe

was the indole-NH signal. These effects can be explained by models which show that, only in the *trans* isomer **22**, with an axial ethoxycarbonyl group, the CH_2CH_3 protons are shielded by the indole ring system for a significant part of the rotation about the axial bond. A similar effect has been reported[16] for the isomers **24** and **25**. The signals in rings C and D of the *trans* isomer **22** were assigned by decoupling experiments and the part-structure/conformation **22a** was supported by the NOE enhancements shown.

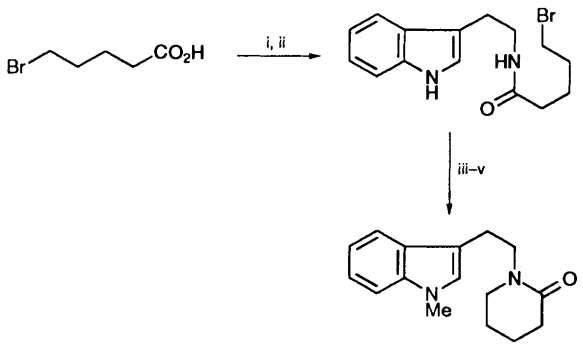
In the reaction of the amide **19** with only 1 equiv. of trifluoroacetic acid anhydride, activation by the anhydride is presumably selective at the keto group, which results in attack at this point by the amide nitrogen (Scheme 3). In the resultant iminium species **26** nucleophilic attack by the indolyl-3-position would be expected to occur predominantly on the opposite side to the bulky ethoxycarbonyl group leading mainly to the *cis* isomer **21** observed.

The 5-methoxy derivative **20** of the amide, when treated with 1 equiv. of phosphoryl chloride in acetonitrile, gave the *cis* 9-methoxyindolo[2,3-*a*]quinolizinone **23** in 63% yield. The indolo[2,3-*a*]quinolizinone system with a 12b methyl group was first reported by Winterfeld[17] in 1964.

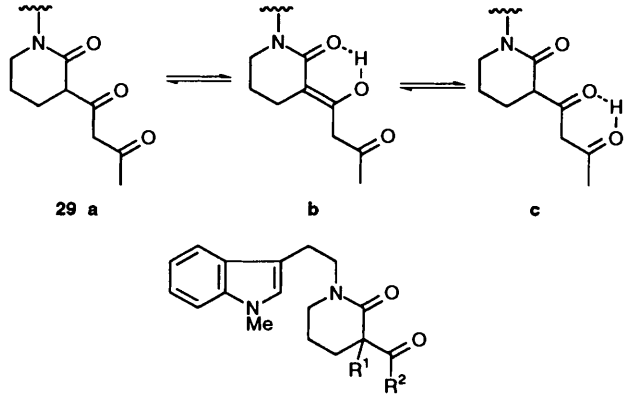
Following these results with the amides **19** and **20** we next used 10 equiv. of trifluoroacetic acid anhydride as the cyclisation reagent for **19** in dry benzene at 20 °C. After 72 h, a complex mixture was obtained. Chromatography gave an impure, unstable, yellow crystalline product tentatively identified as the pyrrolo[2,3-*d*]carbazole **27** (50%), which showed M^+ at *m/z* 420 (100%) in its FD mass spectrum. The ^1H NMR spectrum indicated that this product was mainly one component and the absence of the indole-2H signal and the 1 ppm shift to lower field of the acetyl signal, compared with the amide **19**, were in keeping with the structure proposed. The four multiplets at δ 2.5, 2.84, 4.86 and 5.44 were shown to be coupled by double resonance experiments and were assigned by comparison with the imino-ketone **28**.[18] The signals for the 12-H (δ 8.25, d) and 13a-H (δ 6.44 and 6.32, 2 × s) both appear at lower field than normally expected due to deshielding by the *N*-trifluoroacetyl group and the latter proton appears as two signals, probably due to hindered rotation about the amide bond. The remaining aromatic signals and the 1-H and 4-H signals were unexceptional and assigned by spin-decoupling experiments.

Unfortunately, although the cyclisation reaction was repeated a number of times the proposed imine **27** could not be isolated although it was identified in some of the mixtures of products. Although we did not obtain it as a completely pure product, its transient formation suggested that we should persist with this approach. We therefore moved to the synthesis and cyclisation of the lactams **29** and **30**; in these cases both cyclisation (as for **13**) on the indole nitrogen and condensation between amide nitrogen and ketone (as for **21**) would be precluded. Spirocyclic ring formation and anionic attack as outlined in Scheme 1 should be more successful than for the amides **19** and **20**.

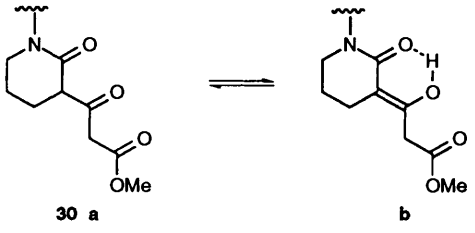
The lactam **31** was synthesised as shown in Scheme 4 from 5-bromopentanoic acid[19] in 71% yield. Treatment of this lactam **31** with lithium diisopropylamide (2 equiv.) and diketene (1 equiv.) gave the dione **29** as an oily mixture of the predominantly two enol and one keto forms **29a**, **b**, **c** (35%). The two enol protons were evident from signals at δ 15.20 and



Scheme 4 *Reagents:* i, oxalyl chloride; ii, tryptamine; iii, KH; iv, NaH; v, MeI



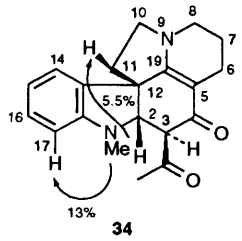
32 R^1 = H, R^2 = OCH_2Ph
33 R^2 = OCH_2Ph, R^1 = $COCH_2CO_2Me$



15.36. The lithium enolate of the lactam **31** on treatment with benzyl chloroformate gave the benzyl ester **32** (73%), the anion of which was acylated with methoxycarbonylacetyl chloride to give the diester **33** in 48% yield. Conventional hydrogenolysis of **33** proved unsuccessful but the use of ammonium formate with 10% palladised charcoal[20] gave the keto ester **30** (64%) directly as a mixture of keto and enol forms **30a** and **b**.

Treatment of the dione **29** with 10 equiv. of trifluoroacetic acid anhydride for 24 h, gave the pentacyclic amide **34** as the only isolated product (60%). The amide, M^+ 322, showed ν_{max} 1710 and 1645 cm^{-1}, and λ_{max} 253 and 308 nm, characteristic of a vinylogous amide chromophore. In the ^1H NMR spectrum the 2-H signal was a doublet, J 8 Hz at δ 4.44, shown by double resonance to be coupled to the doublet at J 3.40 (3-H) in keeping with a *trans* diaxial configuration. The NOE enhancements shown, the ^{13}C NMR spectrum and elemental analysis confirmed the structure of **34**.

Hydrogenation of the tetrasubstituted double bond of **34** predictably, proved impossible with platinum oxide catalyst with or without ammonium formate. Reduction with sodium cyanoborohydride[21] however, gave three products. The least polar on chromatography was the diketone **35**, M^+ 324, which in the ^1H NMR spectrum solution existed entirely in the enol



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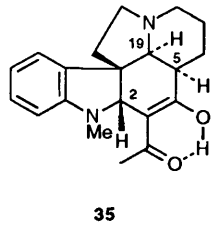

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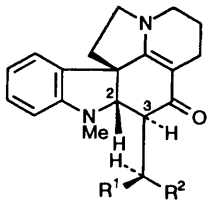
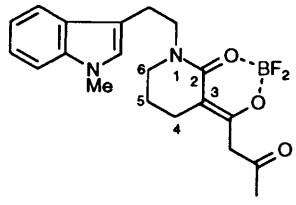
form shown. The enol-H and 2-H signals were singlets at δ 16.27 and 3.88 respectively. A doublet at δ 2.22 (J 3 Hz) was assigned to the 19-H proton. Closely analogous *cis* C_5–C_{19} junction compounds show doublets with J 3[22] and 4 Hz[7] for the 19-H whereas the *trans* ring junction has $J_{5,19} \approx 12$ Hz. The UV spectrum also [λ_{max} 256 (ε16 200) and 284 (11 770)] supported the enone chromophore.

The remaining two products were the diastereoisomeric alcohols **36** and **37** which still showed the vinylogous amide



36 R^1 = OH, R^2 = Me
37 R^1 = Me, R^2 = OH



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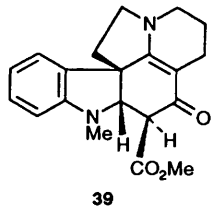

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chromophone (λ_{max} 308 nm). Both isomers showed a multiplet at δ 4.10 in their ^1H NMR spectra. In the more polar isomer this was shown by double resonance to be coupled to the 3-H (signal at δ 2.30, dd, J 6.5, 3 Hz) and to the methyl protons (δ 1.38) and in the less polar isomer to corresponding signals at δ 2.45 and 1.20 respectively. The 2-H signal in each isomer was a doublet, J 6.5 Hz at δ 3.86 and 3.45 respectively. These alcohols were not investigated further.

Attempts were made to cyclise the dione **29** with phosphoryl chloride and boron trifluoride—diethyl ether. With the former, no reaction took place even with 10 equiv. of reagent after 20 h. With the latter, only the boron complex **38** was isolated (38%). The EI mass spectrum gave M^+ (9%) at 388.1754 ($C_{20}H_{23}BF_2N_2O_3$). The ^1H NMR spectrum showed the indole-2-H proton as a singlet, δ 6.96 and 2 and 3 proton singlets at δ 3.43 and 2.28 for the terminal part of the butanedione group, and this, with the normal C=O bond at 1720 cm^{-1} in the IR indicated the position of the boron shown.

Finally, the β-keto ester **30** was treated with 10 equiv. of trifluoroacetic acid anhydride for 24 h, to give the pentacyclic ester **39** as a colourless crystalline solid (51%). The spectral properties of the ester were very similar to those of the 16-acetyl analogue **34**; the 2-H and 3-H signals were the expected doublets (J 8 Hz) at δ 4.32 and 3.24 respectively.

These results demonstrate that cyclisation of relatively simple tryptamides under different conditions can give rise to a variety of polycyclic heterocycles in good yields.

Experimental

IR spectra were recorded on a Unicam SP200 grating spectrophotometer, UV spectra were measured in absolute ethanol on a Unicam SP800 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM 360 (360 MHz) spectrometer in $CDCl_3$ unless stated otherwise. ^{13}C NMR spectra were recorded on a Bruker WM 360 spectrometer at 90.56 MHz; *J* values are given in Hz. Mass spectra were electron impact (EI), field desorption (FD) or chemical ionisation (CI, using either ammonia or isobutane as the reagent) and were measured on a Varian CH 5D double focussing instrument.

Flash chromatography was carried out as described by Still *et al.*[23] using silica gel S (Merck) 230–400 mesh. Light petroleum refers to a fraction of boiling range 40–60 °C. Dimethylformamide and diisopropylamine were distilled from calcium hydride under nitrogen before use.

N-[2-(1H-*Indol*-3-*yl*)*ethyl*]-3-*oxobutyramide* **10**.—Tryptamine (1 g, 6.25 mmol) in tetrahydrofuran (THF) (30 cm^3) was stirred at 0 °C under nitrogen. Diketene (0.53 g, 6.25 mmol) was added over 15 min. The reaction mixture was warmed to 20 °C and stirred for 2 h, quenched with saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 × 30 cm^3). The dichloromethane extracts were dried (Na_2SO_4) and then the solvent was removed to give a red–brown oil which crystallised from chloroform–diethyl ether to give the *amide* **10** as colourless needles (1.23 g, 80%); m.p. 77–78 °C; δ_H 2.22 (3 H, s, CH_3CO), 3.0 (2 H, t, *J* 7, Ind-CH_2), 3.34 (2 H, s, $COCH_2CO$), 3.63 (2 H, q, *J* 7, Ind-CH_2CH_2), 6.93 (1 H, br s, NHCO), 7.06 (1 H, s, Ind-2-H), 7.12 (1 H, t, *J* 8, Ind-5-H), 7.21 (1 H, t, *J* 8, Ind-6-H), 7.37 (1 H, d, *J* 8, Ind-7-H), 7.62 (1 H, d, *J* 8, Ind-4-H) and 8.15 (1 H, br s, Ind-NH); $\nu_{max}(CHCl_3)$/cm^{-1} 1712 and 1665; λ_{max}/nm 223.5 (ε/dm^3 mol^{-1} cm^{-1} 21 350) 274.5 (3690) 282 (3870) and 291 (3290); *m*/*z* (EI) 244 (58%) 143 (98) and 130 (100); (FD) 244 (100) (Found: M$^+$ 244.1211. $C_{14}H_{16}N_2O_2$ requires *M*, 244.1211).

(9bS*,9cS*)-1,2,9b,9c-*Tetrahydro*-5-*methyl*-2a,5a-*diazacyclopenta*[j,k]*fluoren*-3-*one* **13**.—The amide **10** (0.5 g, 2.05 mmol) in dichloromethane (20 cm^3) was stirred at 20 °C under an atmosphere of nitrogen. Phosphoryl chloride (0.314 g, 1.1 equiv.) was added over 5 min and the solution was stirred for 24 h, at 20 °C. The dark green solution was then washed with dilute aqueous ammonia and the aqueous layer extracted with dichloromethane (2 × 20 cm^3). The combined organic layers were dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a red–brown oil which was purified by flash chromatography. Elution with 2% methanol in ethyl acetate gave the *indoline* **13** as a red oil (0.34 g, 73%); δ_H 1.9 (1 H, m, 1-H), 2.35 (3 H, s, CH_3), 2.45 (1 H, m, 1-H), 3.4 (1 H, m, 2-H), 3.8 (1 H, m, 2-H), 4.0 (1 H, m, 9b-H), 5.25 (1 H, s, 4-H), 5.5 (1 H, d, *J* 8, 9c-H), 6.92 (1 H, t, *J* 8, 8-H), 6.98 (1 H, d, *J* 8, 9-H), 7.16 (1 H, t, *J* 8, 7-H) and 7.23 (1 H, d, *J* 8, 6-H); δ_C 20.7, 31.1, 44.0, 45.1, 79.0, 103.7, 111.6, 121.8, 125.3, 128.6, 134.2, 143.7, 149.4 and 163.1; $\nu_{max}(CHCl_3)$/cm^{-1} 1630 and 1605; λ_{max}/nm 230 (ε/dm^3 mol^{-1} cm^{-1} 6120) and 326.5 (6240); *m*/*z* (EI) 226 (M$^+$, 100%), 225 (67), 198 (13), 184 (10), 170 (20), 144 (10) and 130 (15); (FD) 226 (100) (Found: M$^+$ 226.1106. $C_{14}H_{14}N_2O$ requires *M*, 226.1106).

Hydrogenation of the Indoline **13**.—The indoline **13** (98 mg, 0.44 mmol) in ethanol (3 cm^3) was hydrogenated at atmospheric pressure using platinum oxide catalyst. When the uptake of hydrogen ceased (30 min) the catalyst was removed by filtration and then the solvent was removed under reduced pressure to give a brown solid which was purified by flash chromatography. Elution with 1% methanol in chloroform gave the (±)-*indoline* **15** as a colourless solid (59 mg, 59%); m.p. 142 °C (methanol); δ_H 1.6 (3 H, d, *J* 7, CH_3), 2.15 (1 H, dd, *J* 17, 5, 4-H), 3.3 (1 H, m, 2-H), 3.75 (1 H, m, 9b-H), 3.85 (1 H, m, 2-H), 4.0 (1 H, m, 5-H), 5.15 (1 H, d, *J* 6.4, 9c-H), 6.84 (2 H, m, ArH) and 7.1 (2 H, m, ArH); δ_C 20.0, 28.2, 36.7, 43.1, 45.2, 50.2, 81.6, 111.7, 120.1, 125.0, 128.0, 133.6 and 167.6; $\nu_{max}(CHCl_3)$/cm^{-1} 1635; λ_{max}/nm 244 (ε/dm^3 mol^{-1} cm^{-1} 8770) and 292 (2820); *m*/*z* (EI) 228 (M$^+$, 70%) 213 (100) 170 (60) and 130 (20) (Found: M$^+$ 228.1258. $C_{14}H_{16}N_2O$ requires *M*, 228.1263).

Further elution gave the (±)-*perhydro compound* **16** as colourless crystals (15 mg, 15%); m.p. 102–104 °C; δ_H 1.2–1.9 (9 H, m, 6-, 7-, 8- and 9-H_2 and 1α-H), 1.35 (3 H, d, *J* 7, CH_3), 2.1 (2 H, m, 1β-H, 4α-H), 2.4 (2 H, m, 9a-H and 4β-H), 2.9 (2 H, m, 9b-H and 2α-H), 3.2 (1 H, m, 6a-H), 3.55 (1 H, m, 5β-H), 4.33 (1 H, ddd, *J* 14, 10, 2, 2β-H) and 4.70 (1 H, d, *J* 7, 9c-H); $\nu_{max}(CHCl_3)$/cm^{-1} 1625; *m*/*z* (EI) 234 (M$^+$, 25%) 219 (30) and 191 (100) (Found: M$^+$ 234.1730. $C_{14}H_{22}N_2O$ requires *M*, 234.1732).

N-[2-(5-*Methoxy*-1H-*indol*-3-*yl*)*ethyl*]-3-*oxobutyramide* **11**.—To a solution of 5-methoxytryptamine (0.49 g, 2.6 mmol) in tetrahydrofuran (15 cm^3) under an atmosphere of nitrogen at −5 °C was added diketene (0.22 cm^3, 2.9 mmol) dropwise, over 10 min. The solution was allowed to warm to 20 °C and stirred for 24 h, by which time TLC analysis showed the reaction to be complete. The solvent was removed under reduced pressure to give a brown oil (0.87 g) which on flash chromatography and elution with chloroform–methanol (98 : 2) gave the *amide* **11** as a brown oil (0.71 g, 99%); δ_H 2.22 (3 H, s, CH_3CO), 2.96 (2 H, t, *J* 7, Ind-CH_2), 3.36 (2 H, s, $COCH_2CO$), 3.61 (2 H, m, Ind-CH_2CH_2), 3.88 (3 H, s, OMe) 6.85 (1 H, dd, *J* 8, 3, Ind-6-H), 6.95 (1 H, br s, NHCO) 7.05 (2 H, d, *J* 3, Ind-4-H and Ind-2-H), 7.25 (1 H, d, *J* 8, Ind-7-H) and 8.1 (1 H, br s, Ind-NH); ν_{max}(liq. film)/cm^{-1} 3340, 1715 and 1650; λ_{max}/nm 226 (ε/dm^3 mol^{-1} cm^{-1} 36 990), 278 (8320) and 297.5 (6680); *m*/*z* (EI) 274 (M$^+$, 2%), 173 (50) and 160 (100); (FD) 274 (100) (Found: M$^+$ 274.1321. $C_{15}H_{18}N_2O_3$ requires *M*, 274.1317).

(9bS*,9cS*)-1,2,9b,9c-*Tetrahydro*-8-*methoxy*-5-*methyl*-2a,5a-*diazacyclopenta*[j,k]*fluoren*-3-*one* **14**.—To a solution of the amide **11** (0.2 g, 0.73 mmol) in dichloromethane (15 cm^3) at 20 °C under an atmosphere of nitrogen, was added phosphoryl chloride (74 mm^3, 0.8 mmol). After being stirred for 6 h, TLC showed the reaction to be complete. The solution was washed with dilute aqueous ammonia, the aqueous layer extracted with dichloromethane (2 × 20 cm^3) and the combined organic layers dried (Na_2SO_4). The solvent was removed under reduced pressure to give a pale yellow oil (0.16 g) which on flash chromatography and elution with 4% methanol in ethyl acetate gave the *indoline* **14** (0.13 g, 68%) as a colourless solid which recrystallised from diethyl ether–chloroform; m.p. 122 °C; δ_H(400 MHz) 1.86 (1 H, m, 1-H), 2.31 (3 H, s, 5-CH_3), 2.44 (1 H, m, 1-H), 3.40 (1 H, m, 2-H), 3.78 (3 H, s, OCH_3), 3.8 (1 H, m, 2-H), 3.98 (1 H, q, *J* 8, 9b-H), 5.19 (1 H, s, 4-H), 5.48 (1 H, d, *J* 8, 9c-H), 6.7 (1 H, dd, *J* 8, 3, 7-H), 6.8 (1 H, d, *J* 3, 9-H) and 6.9 (1 H, d, *J* 8, 6-H); ν_{max}(KBr)/cm^{-1} 1640 and 1610; λ_{max}/nm 241 (ε/dm^3 mol^{-1} cm^{-1} 11 560) and 337 (14 010); *m*/*z* (EI) 256 (M$^+$, 100%) and 241 (35) (Found: C, 70.0; H, 6.2; N 10.7. $C_{15}H_{16}N_2O_2$ requires C, 70.3; H, 6.29; N, 10.9%).

(±)-5-*Benzyl* 1-*Ethyl* 2-*Acetylpentanedioate* **17**.—A solution of potassium *tert*-butoxide (0.012 mol) in THF (50 cm^3) was added over 30 min to a solution of ethyl acetoacetate (6.5 g, 0.05 mol) and benzyl acrylate[24] (from acrylyl chloride[25]) in THF (100 cm^3) and heated at reflux for 3 h. Vigorous reaction

occurred on warming. The mixture was neutralised with acetic acid (15 cm^3) and the tetrahydrofuran saturated with water (200 cm^3). The aqueous solution was extracted with chloroform (3 × 30 cm^3) and the combined extracts washed with water and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give a light brown oil which was distilled under reduced pressure yielding the *benzyl ester* **17** (8.3 g, 57%) as a clear oil; b.p. 158–162 °C/0.1 mmHg; δ_H 1.25 (3 H, t, *J* 7, CH_3CH_2), 2.15 (2 H, q, *J* 7, $CHCH_2CH_2$), 2.2 (3 H, s, CH_3C), 2.4 (2 H, t, *J* 7, $CH_2CH_2C{=}O$), 3.55 (1 H, t, *J* 7, COCHCO), 4.2 (2 H, q, *J* 7, CH_3CH_2O), 5.1 (2 H, s, OCH_2Ph) and 7.35 (5 H, s, ArH); ν_{max}(liq. film)/cm^{-1} 1727 and 1709; *m/z* (FD) 292 (M^+, 100%) (Found: C, 65.8; H, 7.0. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%).

(±)-4-*Ethoxycarbonyl*-5-*oxohexanoic Acid* **18**.—The above benzyl ester **17** (10 g, 0.034 mol) in absolute alcohol (60 cm^3) was hydrogenated for 90 min at atmospheric pressure using 5% palladium on charcoal (0.6 g). The reaction mixture was filtered and solvent removal from the filtrate under reduced pressure gave the *acid* **18** as a clear oil; δ_H 1.3 (3 H, t, *J* 7, CH_3CH_2), 2.18 (2 H, q, *J* 7, $CHCH_2$), 2.28 (3 H, s, CH_3CO), 2.44 (2 H, t, *J* 7, CH_2CH_2CO), 3.58 (1 H, t, *J* 7, OCHCO), 4.2 (2 H, q, *J* 7, CH_3CH_2O) and 12.84 (1 H, s, OH) (Found: C, 53.3; H, 6.9. $C_{19}H_{14}O_5$ requires C, 53.5; H, 7.0%).

(±)-4-*Ethoxycarbonyl*-N-[2-(1H-*indol*-3-*yl*)*ethyl*]-5-*oxohexanamide* **19**.—To a solution of the above acid **18** (5 g, 0.025 mol) in THF (75 cm^3) cooled to 0 °C, was added triethylamine (2.53 g, 0.025 mol) in THF (30 cm^3) followed by ethyl chloroformate (2.71 g, 0.025 mol) in THF (30 cm^3). The solution was stirred at 0 °C for 30 min and then tryptamine (4 g, 0.025 mol) in THF (30 cm^3) was added over 10 min, and the mixture warmed to 20 °C and stirred for a further 16 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 × 50 cm^3). The organic extracts were combined, dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a brown oil which was purified by flash chromatography.

Elution with ethyl acetate gave the *amide* **19** (6.7 g, 78%) as a light brown oil; δ_H 1.24 (3 H, t, *J* 7, CH_3CH_2), 2.13 (4 H, m, $CHCH_2CH_2CO$), 2.19 (3 H, s, CH_3CO), 2.99 (2 H, t, *J* 7, Ind-CH_2), 3.55 (1 H, t, *J* 7, COCHCO), 3.59 (2 H, q, *J* 7, Ind CH_2CH_2), 4.16 (2 H, q, *J* 7, CH_3CH_2O), 5.5 (1 H, br s, NHCO), 7.05 (1 H, s, Ind-2-H), 7.12 (1 H, t, *J* 8, Ind-5-H), 7.18 (1 H, t, *J* 8, Ind-6-H), 7.32 (1 H, d, *J* 8, Ind-7-H), 7.60 (1 H, d, *J* 8, Ind-4-H) and 8.15 (1 H, br s, Ind-NH); ν_{max}(liq. film)/cm^{-1} 3375, 1730, 1705 and 1645; λ_{max}/nm 228 (ε/dm^3 mol^{-1} cm^{-1} 22 350) 275 (7050) 282 (7400) and 291 (6370); *m/z* (EI) 344 (M^+, 3%) 143 (88) and 130 (80) (Found: M^+ 344.1725. $C_{19}H_{24}N_2O_4$ requires *M*, 344.1735).

(±)-4-*Ethoxycarbonyl*-N-[2-(5-*methoxy*-1H-*indol*-3-*yl*)-*ethyl*]-5-*oxohexanamide* **20**.—To a solution of 4-ethoxycarbonyl-5-oxohexanoic acid (0.25 g, 1.24 mmol) in THF (20 cm^3) at 0 °C under an atmosphere of nitrogen was added triethylamine (0.14 g, 1.36 mmol) in THF (5 cm^3) followed by ethyl chloroformate (0.15 g, 1.36 mmol) in THF (5 cm^3) and the solution was stirred for 15 min at 0 °C. 5-Methoxytryptamine (0.24 g, 1.24 mmol) in THF (5 cm^3) was added over 5 min and the solution was warmed to 20 °C and stirred for 24 h at which time filtration and solvent removal gave a brown oil (0.65 g). Chromatography and elution of this with ethyl acetate gave the amide **20** as a brown oil (0.15 g, 32%); δ_H 1.12 (3 H, t, *J* 7, $CH_3CH_2CO_2$), 2.15 (4 H, m, CH_2CH_2CONH), 2.25 (3 H, s, CH_3CO), 2.95 (2 H, t, *J* 7, Ind-CH_2), 3.63 (3 H, m, Ind-CH_2CH_2, COCHCO), 3.88 (3 H, s, OCH_3), 4.17 (2 H, m, $CH_3CH_2CO_2$), 5.62 (1 H, br s, NHCO), 6.87 (1 H, dd, *J* 8, 2, Ind-6-H), 7.02 (2 H, m, Ind-2-H and 4-H), 7.26 (1 H, d, *J* 8, Ind-7-H) and 8.07 (1 H, br s, Ind-NH); ν_{max}(liq. film)/cm^{-1} 1730, 1710 and 1650; λ_{max}/nm 224 (ε/dm^3 mol^{-1} cm^{-1} 24 100) 277 (6835) 292 (5400) and 310 (3810); *m/z* (EI) 374 (M^+, 1%), 173 (25), 160 (30) and 43 (100) (Found: C, 64.1; H, 6.9; N, 7.35. $C_{20}H_{26}N_2O_5$ requires C, 64.15; H, 7.00; N, 7.48%).

(1R*,12bR*)- *and* (1S*,12bR*)-1-*Ethoxycarbonyl*-2,3,6,7-*tetrahydro*-12b-*methyl*-12H-*indolo*[2,3-a]*quinolizin*-4-(1H)-*one* **21** and **22**.—The amide **19** (0.2 g, 0.58 mmol) in dry acetonitrile (20 cm^3) was stirred at 20 °C under an atmosphere of nitrogen. Trifluoracetic acid anhydride (0.12 g, 0.58 mmol) was added over 5 min and the mixture stirred for 48 h. The solvent was removed under reduced pressure to give a dark yellow oil which was purified by flash chromatography. Elution with chloroform gave the cis-*indolo*[2,3-a]*quinolizinone* **21** (0.15 g, 79%) as colourless crystals (ethyl acetate); m.p. 237–238 °C; δ_H 1.34 (3 H, t, *J* 7, CH_3CH_2O), 1.8 (3 H, s, 12b-Me), 2.2 (2 H, m, 2-H_2), 2.51 (1 H, m, 3α-H), 2.67 (1 H, dt, *J* 18, 4, 3β-H), 2.71 (1 H, ddd, *J* 16, 4, 2, 7β-H), 2.83 (1 H, ddd, *J* 16, 10, 5, 7α-H), 3.01 (2 H, m, 1-H and 6β-H), 4.3 (2 H, q, *J* 7, CH_3CH_2O), 5.07 (1 H, ddd, *J* 13, 4, 2, 6α-H), 7.1 (1 H, t, *J* 8, Ind-5-H), 7.19 (1 H, t, *J* 8, Ind-6-H), 7.31 (1 H, d, *J* 8, Ind-7-H), 7.52 (1 H, d, *J* 8, Ind-4-H) and 9.2 (1 H, br s, Ind-N-H); δ_C 14.0, 20.3, 21.1, 22.4, 30.2, 38.3, 49.9, 59.7, 62.1, 109.1, 111.3, 118.5, 119.8, 122.6, 125.9, 136 (2 signals), 171.4 and 174; ν_{max}($CHCl_3$)/cm^{-1} 3430, 1720 and 1633; λ_{max}/nm 223 (ε/dm^3 mol^{-1} cm^{-1} 37 600) 273 (8200) 280 (8140) and 290.5 (6300); *m/z* (EI) 326 (M^+, 60%), 311 (100) and 183 (45) (Found: M^+ 326.1636. $C_{19}H_{22}N_2O_3$ requires *M*, 326.1636).

Further elution gave the trans-*indolo*[2,3-a]*quinolizinone* **22** as colourless crystals (ethyl acetate) (30 mg, 16%); m.p. 242–243 °C; δ_H 0.72 (3 H, t, *J* 7, CH_3CH_2O), 1.76 (3 H, s, 12b-Me), 2.12 and 2.34 (2 H, m, 2-H_2), 2.58 (1 H, ddd, *J* 16, 7, 2, 3α-H), 2.76 (3 H, m, 3β-H and 7-CH_2), 3.0 (1 H, ddd, *J* 12, 9, 5, 6β-H), 3.22 (1 H, t, *J* 4, 1, β-H), 3.77 (2 H, q, *J* 7, CH_3CH_2O), 5.16 (1 H, dt, *J* 12, 4, 6α-H), 7.12 (1 H, t, *J* 8, Ind-5-H), 7.18 (1 H, t, *J* 8, Ind-6-H), 7.32 (1 H, d, *J* 8, Ind-7-H), 7.48 (1 H, d, *J* 8, Ind-4-H) and 8.2 (1 H, br s, Ind-NH); δ_C 13.5, 19.2, 20.8, 22.1, 28.1, 37.2, 48, 58.4, 60.7, 110.0, 111.0, 118.4, 119.6, 122.0, 126.3, 135.0, 137.0, 169.7 and 171.4; ν_{max}($CHCl_3$)/cm^{-1} 3450, 1725 and 1625; λ_{max}/nm 224.5 (ε/dm^3 mol^{-1} cm^{-1} 35 000) 275 (6800), 282 (6800) and 291 (5700); *m/z* (EI) 326 (M^+, 30%) 311 (100) and 183 (30); (FD) 326 (100) (Found: M^+ 326.1633. $C_{19}H_{22}N_2O_3$ requires *M*, 326.1636).

Reaction of the Amide **19** *with Phosphoryl Chloride*.—The amide **19** (0.125 g, 0.29 mmol) was stirred in dry acetonitrile (10 cm^3) at 20 °C under an atmosphere of nitrogen. Phosphoryl chloride (31 mm^3, 0.29 mmol) was added and the mixture was stirred for 30 h. The reaction was quenched with dilute aqueous ammonia and the mixture extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a pale yellow solid. Crystallisation from ethyl acetate gave the *cis*-indoloquinolizinone **21** (94 mg, 99%). Analysis of the crude material by ^1H NMR spectroscopy showed a trace amount of the *trans*-isomer **22**.

(1R*,12bR*)-1-*Ethoxycarbonyl*-2,3,6,7-*tetrahydro*-9-*methoxy*-12b-*methyl*-12H-*indolo*[2,3-a]*quinolizin*-4(1H)-*one* **23**.—Phosphoryl chloride (31 mm^3, 0.27 mmol) was added over 5 min, to a solution of the 5-methoxyamide **20** (0.1 g, 0.27 mmol) in dry acetonitrile (10 cm^3) under an atmosphere of nitrogen at 20 °C. After being stirred for 20 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 cm^3) and the mixture extracted with dichloromethane (3 × 10 cm^3).

The extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a green oil (78 mg) which was purified by flash chromatography. Elution with 99% dichloromethane in methanol gave the *title compound* **23** as a clear oil (63%) which crystallised from diethyl ether; m.p. 161 °C; δ_H 1.32 (3 H, t, $CH_3CH_2CO_2$), 1.78 (3 H, s, 12b-Me), 2.19 (2 H, m, 2-H_2), 2.51 (1 H, m, 3α-H), 2.67 (1 H, dt, *J* 18, 4, 3β-H), 2.70 (1 H, ddd, *J* 16, 4, 2, 7β-H), 2.80 (1 H, ddd, *J* 16, 10, 5, 7α-H), 3.0 (2 H, m, 1α-H and 6β-H), 3.84 (3 H, s, OMe), 4.29 (2 H, q, $CH_3CH_2CO_2$), 5.07 (1 H, ddd, *J* 12, 5, 2, 6α-H) 6.84 (1 H, dd, *J* 8, 2, Ind-6-H), 6.93 (1 H, d, *J* 2, Ind-4-H), 7.22 (1 H, d, *J* 8, Ind-7-H) and 9.06 (1 H, br s, Ind-NH); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 and 1625; λ_{max}/nm 226 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 33 590), 276 (9415), 296 (6110) and 309 (4070); *m/z* (EI) 356 (M^+, 40%) 341 (100) and 213 (45) (Found: C, 67.6; H, 6.8; N, 8.1. $C_{20}H_{24}N_2O_4$ requires C, 67.4; H, 6.8; N, 7.9%).

Cyclisation of the Amide **19** *with Excess of Trifluoracetic Acid Anhydride*.—To a solution of the amide **19** (45 mg, 0.133 mmol) in dry benzene (10 cm^3) at 20 °C under an atmosphere of nitrogen was added trifluoracetic acid anhydride (TFAA) (0.2 cm^3, 1.33 mmol) over 5 min. An orange–brown solution formed immediately and the solution was stirred at 20 °C for 72 h. Removal of solvent under reduced pressure gave a red–brown oil (70 mg) which was purified by flash chromatography. Elution with ethyl acetate–methanol (1:1) gave the (±)-*pyrrolo*[2,3-d]*carbazole* **27** as a yellow solid (28 mg, 50%); δ_H 1.42 (3 H, t, *J* 7, $CH_3CH_2CO_2$), 2.5 and 2.84 (2 H, m, 1-H_2), 3.1 (3 H, s, CH_3CO), 4.46 (2 H, m, $CH_3CH_2CO_2$), 4.86 and 5.44 (2 H, m, 2-H_2), 6.32 and 6.44 (0.3 H and 0.7 H, 2 × s, 6a-H), 7.02 (1 H, d, *J* 8, 11-H), 7.23 (1 H, t, *J* 8, 10-H), 7.48 (1 H, t, *J* 8, 9-H), 7.68 (1 H, d, *J* 7.5, 4-H), 8.25 (1 H, d, *J* 8, 8-H) and 8.87 (1 H, d, *J* 7.5, 5-H); *m/z* (FD) 420 (M^+, 100%) 392 (85) and 324 (50). Further data on this product was not obtained due to its instability.

(±)-N-[2-(1-*Methylindol*-3-*yl*)*ethyl*]-3-(1,3-*dioxobutyl*)-*piperidin*-2-*one* **29**.—To a stirred solution of diisopropylamine (0.55 cm^3, 3.9 mmol) in THF (4 cm^3) under an atmosphere of nitrogen at 0–4 °C was added a solution of butyllithium in hexane (0.822 mol dm^{-3}; 4.74 cm^3, 3.9 mmol). After 15 min, at 0–4 °C the solution was cooled to −78 °C. *N*-[2-(1-Methylindol-3-yl)ethyl]piperidin-2-one[26] (0.5 g, 1.95 mmol) in THF (5 cm^3) was added dropwise and the mixture stirred at −78 °C for 30 min. Then diketene (153 mm^3, 1.9 mmol) in THF (4 cm^3) was added over 5 min and stirred for a further 2 h at −78 °C. The mixture was then warmed to 0 °C and the reaction quenched with 10% hydrochloric acid to pH 2. The mixture was extracted with dichloromethane (3 × 30 cm^3) and the combined extracts were washed with water and dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a brown oil (0.8 g). Flash chromatography, eluting with 2% methanol in dichloromethane gave the *dione* **29** as a clear oil, shown to be a mixture of predominantly two enol forms (0.23 g, 35%); δ_H 1.70 (2 H, m, 5-H_2), 1.90 and 2.15 (1 H, 2 × m, 4-H enol **c**), 2.08 (1.5 H, s, CH_3CO, enol **c**), 2.28 (1.5 H, s, CH_3CO, enol **b**), 2.32 (1 H, t, 4-H enol **b**), 3.06 (2 H, t, *J* 7, Ind-CH_2), 3.20 (2 H, t, *J* 4, 6-H_2), 3.34 (0.5 H, t, *J* 7, 3-H enol **c**), 3.36 (1 H, s, $COCH_2COCH_3$, enol **b**) 3.68 (2 H, t, *J* 7, Ind-CH_2CH_2), 3.75 (3 H, s, NCH_3), 5.72 (0.5 H, s, COCH=COH enol **c**), 6.93 (1 H, 2 × s, Ind-2-H), 7.12 (1 H, t, *J* 8, Ind-5-H), 7.24 (1 H, t, *J* 8, Ind-6-H), 7.31 (1 H, d, *J* 8, Ind-7-H), 7.66 (1 H, m, Ind-4-H), 15.20 (0.5 H, s, enol-OH **b**) and 15.36 (0.5 H, br s, enol-OH **c**); ν_{max}(film)/cm^{-1} 1720, 1635 and 1600; λ_{max}/nm 226 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 35 520) and 275 (13 640); *m/z* (EI) 340 (M^+, 80%), 298 (10), 256 (25), 157 (100) and 144 (60) (Found: C, 70.7; H, 7.4; N, 8.0. $C_{20}H_{24}N_2O_3$ requires C, 70.56; H, 7.11; N, 8.23%).

(±)-3-*Benzyloxycarbonyl*-N-[2-(1-*methylindol*-3-*yl*)*ethyl*]-*piperidin*-2-*one* **32**.—To a solution of diisopropylamine (1.2 cm^3, 8.6 mmol) in THF (5 cm^3) under an atmosphere of nitrogen at 0–4 °C was added a solution of butyllithium in hexane (0.822 mol cm^{-3}; 10.5 cm^3, 8.6 mmol). The solution was stirred at 0–4 °C for 20 min and then cooled to −78 °C. The lactam **31** (2.0 g, 7.8 mmol) in THF (15 cm^3) and hexamethylphosphoramide (4 cm^3) was added dropwise, with stirring and then the solution stirred for 30 min at −78 °C. Benzyl chloroformate (1.44 cm^3, 8.6 mmol) was added rapidly to the brown solution at −78 °C and a clear solution formed after 5 min which was stirred for 2 h at −78 °C and then slowly warmed to 0 °C. The reaction was quenched with dilute hydrochloric acid and extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a clear oil which on flash chromatography and elution with dichloromethane–ethyl acetate (95:5) gave the benzyl ester **32** as a clear oil (2.23 g, 73%); δ_H 1.64 and 1.82 (2 H, m, 5-H_2), 2.02 (2 H, m, 4-H_2) 3.03 (2 H, t, *J* 7, Ind-CH_2), 3.14 (2 H, m, 6-H_2), 3.48 (1 H, t, *J* 7, 3-H), 3.62 and 3.68 (2 H, 2 × t, *J* 7, Ind-CH_2CH_2), 3.70 (3 H, s, NMe), 5.22 (2 H, s, $COCH_2Ph$), 6.68 (1 H, s, Ind-2-H), 7.10 (1 H, t, *J* 8, Ind-5-H), 7.22 (1 H, t, *J* 8, Ind-6-H), 7.30–7.50 (6 H, m, Ar and Ind-7-H) and 7.65 (1 H, d, *J* 8, Ind-4-H); ν_{max}(film)/cm^{-1} 1735 and 1640; λ_{max}/nm 226 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 36 560), 280 (5625) and 289 (6100); *m/z* (FD) 390 (100%) (Found: C, 73.7; H, 7.0; N, 7.4. $C_{24}H_{26}N_2O_3$ requires C, 73.82; H, 6.7; N, 7.18%).

(±)-3-*Benzyloxycarbonyl*-N-[2-(1-*methylindol*-3-*yl*)*ethyl*]-3-(1-*oxo*-2-*methoxycarbonylethyl*)*piperidin*-2-*one* **33**.—To a suspension of sodium hydride (28 mg, 1.16 mmol) (washed 3 times with benzene) in benzene (5 cm^3) at 20 °C under an atmosphere of nitrogen was added the benzyl ester **32** (0.3 g, 0.77 mmol) in benzene (5 cm^3) over 5 min. The solution was stirred for 30 min at 20 °C, then methoxycarbonylacetyl chloride (freshly prepared) was added dropwise and the solution was stirred at 20 °C for 1 h. TLC showed that no reaction had occurred and the solution was gently heated at reflux for 7 h. The mixture was then cooled to 0 °C, acidified with dilute hydrochloric acid and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with water and dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a brown oil. Flash chromatography and elution with ethyl acetate–dichloromethane (2:98) gave the required ester **33** as a clear oil (0.18 g, 48%); δ_H 1.7 (2 H, m, 5-H), 2.08 and 2.60 (2 H, m, 4-H_2), 3.02 (2 H, m, Ind-CH_2), 3.16 (2 H, m, 6-H), 3.64 (2-H, m, Ind-CH_2CH_2), 3.66 (3 H, s, OMe), 3.71 (3 H, s, NMe), 3.72 and 4.14 (2 H, ABq, *J* 16, $COCH_2CO_2Me$), 5.25 (2 H, ABq, *J* 13, OCH_2Ph), 6.86 (1 H, s, Ind-2-H), 7.11 (1 H, t, *J* 8, Ind-5-H), 7.22 (1 H, t, *J* 8, Ind-6-H), 7.3 (1 H, d, *J* 8, Ind-7-H), 7.36 (5 H, m, ArH) and 7.63 (1 H, d, *J* 8, Ind-4-H); ν_{max}(film)/cm^{-1} 1770–1710 and 1640; λ_{max}/nm 226 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 35 530) and 289 (5520); *m/z* (EI) 490 (M^+, 35%), 459 (5), 390 (35), 157 (98) and 144 (100) (Found: C, 68.6; H, 6.5; N, 5.4. $C_{28}H_{30}N_2O_6$ requires C, 68.6; H, 6.2; N, 5.7%).

(±)-N-[2-(1-*Methylindol*-3-*yl*)*ethyl*]-3-(2-*methoxycarbonyl*-1-*oxoethyl*)*piperidin*-2-*one* **30**.—To the diester **33** (0.25 g, 0.51 mmol), in methanol (10 cm^3) was added ammonium formate (0.13 g, 2.04 mmol) and the mixture hydrogenated for 90 min over 10% palladium on charcoal (50 mg). The catalyst was filtered off and water (50 cm^3) added to the filtrate. The mixture was then extracted with dichloromethane (3 × 30 cm^3) and the combined extracts were dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a light brown oil. Flash chromatography, elution with ethyl acetate–hexane (1:1), gave the *title ester* **30** as a clear oil (0.116 g, 64%)

in a mixture of keto and enol forms; δ_H 1.8 (2 H, m, 5-H_2), 2.18 (1 H, m, 4-H, keto form), 2.36 (1 H, t, *J* 6, 4-H, enol form), 3.04 (2 H, m, Ind-CH_2), 3.21 (2 H, t, *J* 6, 6-H), 3.31 (1 H, s, $COCH_2CO$, enol form), 3.56 (0.5 H, t, *J* 7, 3-H, keto form), 3.67 (2 H, t, *J* 7, Ind-CH_2CH_2), 3.74 (6 H, 2 × s, NCH_3, OCH_3), 3.85 (1 H, ABq, *J* 15, $COCH_2CO$ keto form), 6.89 and 6.92 (1 H, 2 × s, Ind-2-H), 7.12 (1 H, t, *J* 8, Ind-5-H), 7.23 (1 H, t, *J* 8, Ind-6-H), 7.30 (1 H, d, *J* 8, Ind-7-H), 7.62 and 7.64 (1 H, 2 × d, *J* 8, Ind-4-H) and 15.2 (0.5 H s, enol-OH); ν_{max}(liquid)/cm^{-1} 1745 and 1635; λ_{max}/nm 225 (ε/dm^3 mol^{-1} cm^{-1} 39 100) and 269 (13 920); *m/z* (EI) 356 (M^+, 40%), 325 (30), 283 (11), 157 (100) and 144 (92) (Found: M^+ 356.1741. $C_{20}H_{24}N_2O_4$ requires *M*, 356.1736).

(2S*,3R*,12R*)-3-*Acetyl*-5-*deethyl*-5,19-*didehydro*-1-*methyl*-4-*oxoaspidospermidine* **34**.—The dione **29** (50 mg, 0.15 mmol) in dichloromethane (5 cm^3) at 20 °C, under an atmosphere of nitrogen was treated dropwise with trifluoroacetic acid anhydride (TFAA) (0.215 cm^3, 1.5 mmol). After being stirred at 20 °C for 24 h TLC analysis showed no starting material and a major product. The mixture was added to dilute aqueous sodium hydrogen carbonate and then extracted with diethyl ether (3 × 20 cm^3). The combined diethyl ether extracts were dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a yellow oil. Flash chromatography, eluting with ethyl acetate gave the title *didehydroaspidospermidine* **34** as yellow crystals (28 mg, 60%); m.p. 158–166 °C (diethyl ether–hexane); δ_H 1.8–2.4 (6 H, m, 6-, 7- and 11-H_2), 2.22 (3 H, s, CH_3CO), 2.64 (3 H, s, NCH_3), 3.30 (1 H, ddd, *J* 12, 8, 4, 8-H or 10-H), 3.4 (2 H, m and d, *J* 8, 3-H and 8-H or 10-H), 3.5 (1 H, d, t, *J* 13, 4, 8-H or 10-H), 3.74 (1 H, ddd, *J* 12, 10, 6, 8-H or 10-H), 4.44 (1 H, d, *J* 8, 2-H), 6.5 (1 H, d, *J* 8, 17-H), 6.72 (1 H, t, *J* 8, 15-H), 6.88 (1 H, d, *J* 8, 14-H) and 7.18 (1 H, t, *J* 8, 16-H); δ_C 17.9, 21.5, 32.3, 32.8, 37.6, 45.0, 50.6, 52.3, 58.2, 70.8, 100.9, 107.9, 118.2, 121.1, 128.9, 132.2, 148.8, 163.2, 186.5 and 208.7; ν_{max}($CHCl_3$)/cm^{-1} 1710, 1645 and 1570; λ_{max}/nm 253 (ε/dm^3 mol^{-1} cm^{-1} 14 030) and 308 (23 580); *m/z* (EI) 322 (M^+, 100%), 307 (25), 279 (95), 157 (56) and 144 (60) (FD) 322 (M^+, 100) (Found: C, 74.1; H, 7.1; N, 8.9. $C_{20}H_{22}N_2O_2$ requires C, 74.5; H, 6.9; N, 8.7%).

(2S*,5R*,12R*,19S*)-3-*Acetyl*-5-*deethyl*-1-*methyl*-4-*oxoaspidospermidine* **35**.—The dehydroaspidospermidine **34** (42 mg, 0.13 mmol) in methanol (5 cm^3) at 20 °C under nitrogen was treated with trifluoroacetic acid (0.2 cm^3) and sodium cyanoborohydride (29 mg, 0.46 mol) and the mixture stirred for 5 min at 20 °C. The reaction was then quenched with 10% aqueous sodium hydrogen carbonate, and the mixture extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a light brown oil. Flash chromatography and elution with chloroform gave the title *deethylaspidospermidine* **35** as a colourless solid (7 mg, 17%); m.p. 57–58 °C; δ_H 1.4–2.0 (5 H, m, CH_2 and CH), 2.14 (3 H, s, CH_3CO), 2.22 (1 H, d, *J* 3, 19-H), 2.36 (3 H, m, CH_2 and CH), 2.54 (3 H, s, NCH_3), 2.91 (1 H, br s, 8-H or 10-H), 3.08 (2 H, m, CH_2), 3.88 (1 H, s, 2-H), 6.48 (1 H, d, *J* 8, 17-H), 6.80 (1 H, t, *J* 8, 15-H), 7.14 (2 H, m, 14-H and 16-H) and 16.27 (1 H, s, enol); ν_{max}($CHCl_3$)/cm^{-1} 1730; λ_{max}/nm 256 (ε/dm^3 mol^{-1} cm^{-1} 16 200) and 284 (11 771); *m/z* (EI) 324 (M^+, 70%), 296 (30) and 279 (43) (Found: M^+ 324.1818. $C_{20}H_{24}N_2O_2$ requires *M*, 324.1838).

Elution with 2.5% methanol in chloroform gave the less polar alcohol, (±)-**36** or **37** (8.8 mg, 21%) as a slightly impure colourless solid; m.p. 74–77 °C; δ_H 1.20 (3 H, d, *J* 7, CH_3CHOH), 1.9–2.6 (6 H, m, 3 × CH_2), 2.48 (1 H, dd, *J* 6.5, 3, 3-H), 2.93 (3 H, s, NCH_3), 3.3–3.8 (4 H, m, 8-H_2 and 10-H_2), 3.45 (1 H, d, *J* 6.5, 2-H), 4.07 (1 H, m, CH_3CHOH), 5.66 (1 H, br s, OH), 6.48 (1 H, d, *J* 8, 17-H), 6.63 (1 H, t, *J* 8, 15-H), 6.74 (1 H, d, *J* 8, 14-H) and 7.14 (1 H, t, *J* 8, 16-H); ν_{max}($CHCl_3$)/cm^{-1} 3500–3100 (OH) 1645, 1605 and 1555; λ_{max}/nm 257 (ε/dm^3 mol^{-1} cm^{-1} 12 340) and 308 (19 640); *m/z* (EI) 324 (M^+, 91%), 280 (90) and 77 (100) (Found: M^+ 324.1825. $C_{20}H_{24}N_2O_4$ requires *M*, 324.1838).

Further elution with 2.5% methanol in chloroform gave the more polar alcohol **37** or **36** (15.7 mg, 37%) as a colourless solid; m.p. 206–207 °C; δ_H 1.37 (3 H, d, *J* 7, CH_3CHOH), 1.8–2.5 (6 H, m, methylenes), 2.30 (1 H, dd, *J* 6.5, 3, 3-H), 2.92 (3 H, s, NCH_3), 3.2–3.8 (4 H, m, 8-H and 10-H_2), 3.46 (1 H, br s, OH), 3.86 (1 H, d, *J* 6.5, 2-H), 4.12 (1 H, m, CH_3CHOH), 6.48 (1 H, d, *J* 8, 17-H), 6.64 (1 H, t, *J* 8, 15-H), 6.80 (1 H, d, *J* 8, 14-H) and 7.14 (1 H, t, *J* 8, 16-H); ν_{max}($CHCl_3$)/cm^{-1} 3600–3100, 1645, 1605 and 1555; λ_{max}/nm 260 (ε/dm^3 $mol^{-1}cm^{-1}$ 13 660) and 308 (22 453); *m/z* (EI) 324 (M^+, 13%), 280 (40), 157 (94), 144 (96) and 43 (100) (Found: M^+ 324.1820. $C_{20}H_{24}N_2O_2$ requires *M*, 324.1838).

Attempted Cyclisation of the Dione **29** *with Boron Trifluoride–Diethyl Ether*.—The above dione **29** (50 mg, 0.14 mmol) was dissolved in boron trifluoride–diethyl ether (5 cm^3, freshly distilled) at 0 °C under an atmosphere of nitrogen. After 30 min at 0 °C the mixture was warmed to 20 °C for 90 min by which time no starting material remained (TLC). The mixture was treated with an excess of dilute aqueous sodium carbonate (50 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The ether layers were combined, dried (Na_2SO_4) and then the solvent was removed under reduced pressure to give a brown oil which was purified by flash chromatography. Elution with ethyl acetate gave the *boron complex* **38** as a colourless crystalline solid (22 mg, 38%); m.p. 107–108 °C (diethyl ether–hexane); δ_H 1.68 (2 H, m, 5-H_2), 2.28 (3 H, s, CH_3CO), 2.30 (2 H, t, *J* 7, 4-H_2), 3.15 (2 H, t, *J* 7, Ind-CH_2), 3.18 (2 H, t, *J* 6, 6-H_2), 3.43 (2 H, s, $COCH_2CO$), 3.75 (3 H, s, NCH_3), 3.82 (2 H, t, *J* 7, Ind-CH_2CH_2), 6.96 (1 H, s, Ind-2-H), 7.12 (1 H, t, *J* 8, Ind-5-H), 7.24 (1 H, t, *J* 8, Ind-6-H), 7.31 (1 H, d, *J* 8, Ind-7-H) and 7.57 (1 H, d, *J* 8, Ind-4-H); ν_{max}($CHCl_3$)/cm^{-1} 1720 and 1620; λ_{max}/nm 225 (ε/dm^3 mol^{-1} cm^{-1} 27 400) and 283 (16 180); *m/z* (EI) 388 (M^+, 9%), 340 (2), 157 (67) and 144 (100) (Found: M^+ 388.1754. $C_{20}H_{23}N_2O_3BF_2$ requires *M*, 388.1759).

(2S*,3S*,12R*)-5-*Deethyl*-5,19-*didehydro*-3-*methoxycarbonyl*-1-*methyl*-4-*oxoaspidospermidine* **39**.—To a stirred solution of the keto ester **30** (62 mg, 0.175 mmol) in dichloromethane (5 cm^3) at 20 °C under an atmosphere of nitrogen was added TFAA (0.25 cm^3, 1.75 mmol). The solution was stirred for 24 h at 20 °C by which time no starting material remained. The mixture was added to an excess of saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a yellow oil. Flash chromatography and elution with ethyl acetate gave the *title didehydroaspidospermidine* **39** as a colourless solid (30 mg, 51%); m.p. 204–206 °C (diethyl ether); δ_H 1.8–2.4 (6 H, m, 3 × CH_2), 2.74 (3 H, s, NCH_3), 3.24 (1 H, d, *J* 8, 3-H), 3.28 (1 H, m, 8-H or 10-H), 3.38 (1 H, t, *J* 10, 8-H or 10-H), 3.50 (1 H, dt, *J* 13, 4, 8-H or 10-H), 3.74 (1 H, ddd, *J* 12, 10, 6, 8-H or 10-H), 3.78 (3 H, s, OCH_3), 4.32 (1 H, d, *J* 8, 2-H), 6.52 (1 H, d, *J* 8, 17-H), 6.71 (1 H, t, *J* 8, 15-H), 6.89 (1 H, d, *J* 8, 14-H) and 7.18 (1 H, t, *J* 8, 16-H); ν_{max}($CHCl_3$)/cm^{-1} 1735, 1645 and 1575; λ_{max}/nm 253 (ε/dm^3 mol^{-1} cm^{-1} 12 440) and 308 (21 530); *m/z* (EI) 338 (M^+, 11%) 279 (10), 260 (20), 229 (25), 157 (85), 151 (100) and 144 (75) (Found: M^+ 338.1648. $C_{20}H_{22}N_2O_3$ requires *M*, 338.1630).

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