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Chemoselective Reactions of Vinylogous Amides, and the Synthesis of Two *Peripentadenia* Alkaloids

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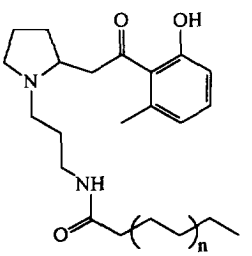
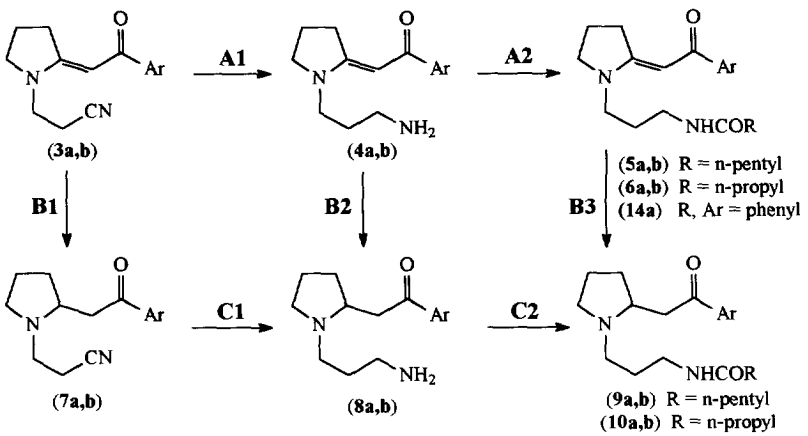
Abstract: Some chemoselective transformations of the vinylogous amide (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (**3a**) and compounds derived from it have been investigated. Methodology developed during the course of these model studies has been applied to the synthesis of the alkaloids peripentadenine (**1**) and dinorperipentadenine (**2**).

Enaminones and related compounds possessing the structural unit N—C=C—Z (Z = COR, CO_2R, CN, *etc*) are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.[1] This dual reactivity lends itself to the construction of the characteristic heterocyclic arrays found in many classes of alkaloids. Illustrations may be found in our recent syntheses of elaeocarpine,[2] lamprolobine,[3] mesembrine[4] and the mitosene skeleton,[5] amongst others; and in the publications of other authors.[6] However, two complementary problems are frequently encountered with this synthetic approach: preservation of the enaminone system during the manipulation of other functional groups elsewhere in the molecule, and selective reaction of the enaminone while leaving other functionality untouched. The challenge of finding suites of chemoselective transformations for accomplishing either objective at will forms part of our continuing research programme.

In this paper we report a variety of chemoselective reactions on compounds containing the vinylogous amide unit N—C=C—COAr. The impetus for this research came from our interest[7] in the synthesis of peripentadenine (**1**)[8] and dinorperipentadenine (**2**),[9] optically inactive pyrrolidine alkaloids isolated by Bick and co-workers from the elaeocarpaceous tree *Peripentadenia mearsii* (C. T. White) L. S. Smith, which is native to the rain forests of north Queensland. Ample precedents from our previously published work suggested a central role for a vinylogous amide intermediate of the form **3** (Scheme 1). Reductions of the nitrile group of **3** and the carbon-carbon double bond of the vinylogous amide, and N-acylation of the terminal amine resulting from nitrile reduction, are necessary stages in the proposed synthesis. Both the chemoselectivity and the timing of these steps need to be addressed, since competition between extant and newly created functional groups in both the reduction and acylation processes can be envisaged. Possible variations in the order of chemical events are depicted in the synthetic "loops" of Scheme 1.



(**1**) n = 1 Peripentadenine
(**2**) n = 0 Dinorperipentadenine

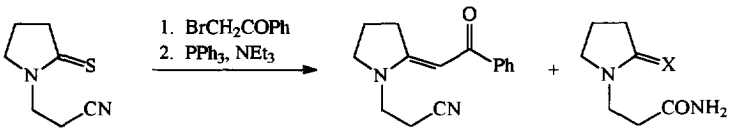


Scheme 1
Series a: Ar = Ph. Series b: Ar = 2-MeO-6-Me-C_6H_3

The intrinsically interesting chemoselective reductions labelled as A1, B1, B2 and B3 (Scheme 1) form the focus of the present study. In the latter three cases, the carbon-carbon double bond of the vinylogous amide has to be reduced without affecting the carbonyl group. Furthermore, the nitrile group in B1 and the amide carbonyl group in B3 also have to survive the chosen reaction conditions. Reduction of vinylogous amides has usually been accomplished with hydride reagents, by catalytic hydrogenation, and under dissolving metal conditions.[1] Examples in which 3-aminoketones are formed exclusively are quite often encountered in the literature, but so are examples in which amino-alcohols, enamino-alcohols, enamines, or fragmentation products are produced instead. Our own evaluation of the literature leads us to believe that the geometry of the enaminone system influences the outcome. Our impression is that conversion of the *trans*-s-*cis* enaminones **3** - **6** depicted in Scheme 1 into 3-aminoketones **7** - **10** would be most reliably accomplished with lithium aluminium hydride under carefully controlled conditions.[10,11] However, alternative reductants cannot be ignored. In the discussion that follows, model studies are described in which the best conditions for the various interconnected transformations of Scheme 1 are probed with a view to devising an optimal synthetic route to peripentadenine and dinorperipentadenine.

Model Studies

The model studies undertaken to explore the synthetic variations summarised in Scheme 1 made use of the simple benzoylmethylene compound **3a**. The alkylidene side chain was introduced by reaction between phenacyl bromide and thiolactam **11** (made in 97% yield by hydroxide-catalysed conjugate addition of pyrrolidine-2-thione to acrylonitrile[7]), followed by Eschenmoser sulfide contraction.[12] The yield of **3a** was in the range 59% - 71%. Thiolactam **11** was generally recovered (9% - 17%), and by-products isolated (< 10%) included the amides **12** and **13**, probably formed by hydrolysis of **11** and **3a** respectively during the aqueous work-up procedure employed. The *trans*-s-*cis* geometry shown in **3a** was strongly suggested by the downfield chemical shift of the hydrogen atom on C-3 of the heterocyclic ring (δ 3.41), implying anisotropic through-space deshielding by the carbonyl group.[10]



(11) (3a) (12) X = S (13) X = CHCOPh

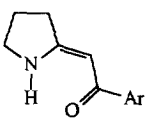
With the model substrate **3a** in hand, the synthetic "loops" of Scheme 1 were tackled. Chemoselective reduction of the nitrile group while preserving the vinylogous amide unit (transformation A1) was successfully achieved with sodium hydroxide and nickel-aluminium alloy[13] in ethanol; amine **4a** was formed in consistently high yields (94% - 97%). However, other reagents commonly used for nitrile reduction either gave mixtures of products in which the vinylogous amide unit was simultaneously (*e.g.* borane - dimethyl sulfide complex[14]) or exclusively (*e.g.* lithium aluminium hydride, *vide infra*) affected. Hydrogenation of the nitrile group in the presence of various catalysts was also unsatisfactory. A standard method, hydrogenation over rhodium on charcoal in ammoniacal ethanol,[15] led to recovery of starting material under mild conditions, and to uncharacterisable mixtures at high pressure; while at 3 atm and 35 °C, hydrogenation followed by immediate acylation of the crude isolate with hexanoyl chloride (transformation A2) yielded starting material **3a** (25%) and the desired amide **5a** (18%).

The last-mentioned reaction also highlights a potential problem with transformation A2: competing acylation of the nucleophilic vinylogous amide unit may well diminish the yield of amides **5** and **6**. Although in this specific instance alternative acylation products were not isolated, we found that treatment of the *N*-methyl analogue of **3a**[10] with hexanoyl chloride indeed gave mixtures of products in which acylation at the vinylic position was indicated by the absence of the vinylic hydrogen signal at *ca* δ 5.7. Hexanoylation of amine **4a** prepared by the nickel-aluminium/base route always gave indifferent yields of **5a**, the best (49%) being obtained in the presence of pyridine. The butanoyl and benzoyl analogues **6a** (46%) and **14** (59%) were similarly prepared with butyric anhydride and benzoyl chloride respectively.

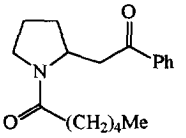
In investigating transformation B1 (reduction of the C=C unit of the enaminone), we chose as the first line of attack, and in accordance with the precedents mentioned above, the use of lithium aluminium hydride. The conversion of **3a** into **7a** was achieved in 84% yield provided that fresh reagent was used in tetrahydrofuran at 0 °C, and that the reaction time was limited to *ca* 30 minutes. At least part of the problem was due to the hydride acting competitively as a base, inducing deprotonation adjacent to the nitrile group, and thereby causing the loss of acrylonitrile by a retro-Michael reaction. Amongst identifiable by-products formed under less well controlled conditions were the hydrogen-bonded *N*-unsubstituted vinylogous amide **15a**, and (in one case in which the unseparated product mixture was treated with hexanoyl chloride), the *N*-hexanoylpyrrolidine **16**. The experimental vagaries of this reaction were avoided with the milder reducing agent sodium cyanoborohydride, another precedented reductant for vinylogous amides.[16] In methanol at pH 4, this reagent reduced **3a** to **7a** in 81% yield.

Non-hydride reducing agents failed to bring about the transformation of **3a** into **7a**. For example, catalytic hydrogenation over platinum dioxide gave complex mixtures, a result that accords with the documented ease with which over-reduction of vinylogous amides to amino-alcohols or even to products of hydrogenolysis

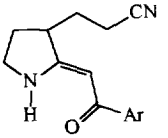
sometimes occurs under these conditions.[16,17] Significantly, base-initiated removal of acrylonitrile from **3a** became the major pathway when enaminone reduction was attempted with lithium metal in liquid ammonia;[18] the hydrogen-bonded (*Z*)-vinylogous amide **15a** was isolated in 82% yield. Base-induced elimination of acrylonitrile from **3a** was demonstrated convincingly by the rapid formation of **15a** in 93% yield with potassium *t*-butoxide (2 eq) in THF at room temperature. (At lower temperatures, mixtures of **15a** and the rearranged product **17** were isolated.) The observation suggests that the 2-cyanoethyl group may be a useful protecting group for vinylogous amides in which an NH unit might be troublesome if left undisguised.[19]



(**15a**) Ar = Ph
(**15b**) Ar = 2-MeO-6-Me-C_6H_3



(**16**)



(**17**)

The use of hydride reagents for reducing the enaminone unit of **4a** (transformation B2) was unsuccessful because intractable mixtures were obtained. With lithium aluminium hydride, for example, complexation between aluminium and the free amino group seemed to complicate the work-up. Nevertheless, the crude product mixtures displayed ^{13}C NMR signals corresponding to the desired product **8a** (*e.g.* the carbonyl resonance shifted from δ 186.9 to *ca* 199; and the vinylic signals at δ 166.8 and 85.7 disappeared). The reduction of **5a** to **9a** (transformation B3) was more encouraging, though the best yield of the desired keto-amide was 68%. This result is significant because the product is the simple benzoyl analogue of the alkaloid peripentadenine (**1**).

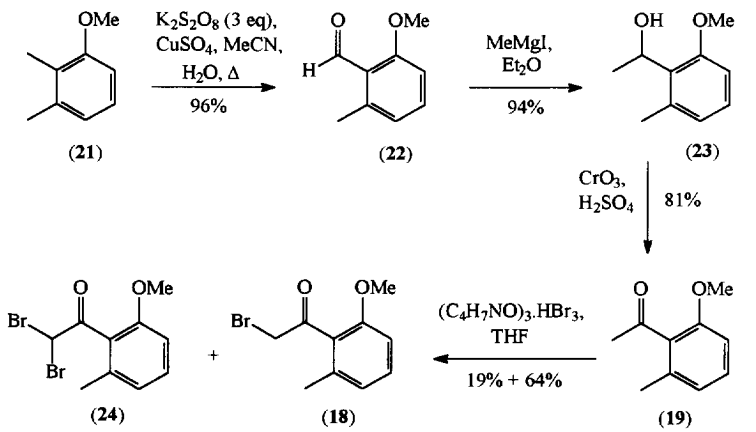
The remaining transformations (C1 and C2) of Scheme 1 were not of especial concern, since Bick *et al.* have previously shown that **7b** can be efficiently reduced to **8b** by catalytic hydrogenation over platinum dioxide,[8] after which acylation of the amino group is straightforward. Of greater interest to us was whether our successful reduction of nitrile groups with nickel-aluminium alloy and base could be used for converting the model system **7a** into **8a**. In the event, no matter how the conditions were varied, competitive reduction of the carbonyl group always occurred, and we isolated an inseparable mixture of **8a** and two corresponding diastereoisomeric benzylic alcohols in a ratio of approximately 1:1:1.

In summary, we have shown that it is possible to achieve high-yielding chemoselective reductions of a vinylogous amide in the presence of a nitrile (transformation B1), and *vice versa* (transformation A1). Furthermore, both **4** and **7** would be appropriate intermediates in a synthetic strategy having peripentadenine-like products **9** or **10** as the goal. The sequence A1 → A2 → B3 has the advantage in terms of yields, and it also demonstrates the surprising robustness of the vinylogous amide unit under conditions potentially deleterious to its survival. On the other hand, if one resorts to the method of Bick *et al.*[8] for accomplishing the conversion of nitriles **7** into **8**, then the sequence B1 → C1 → C2 is by no means inferior. There are thus viable alternative strategies available for preparing products of general formula **9** and **10**, and in the final analysis, all are worthy of consideration when undertaking the synthesis of the target alkaloids, as will be illustrated below.

Synthesis of peripentadenine and dinorperipentadenine[7]

Although these two alkaloids have never been formally synthesised, Bick *et al.* prepared the *O*-methyl alkaloids **9b** and **10b** from pyrrole or Δ^1-pyrrolinium precursors for the purposes of structural confirmation.[8,9] Compounds **7b** and **8b** were key intermediates in Bick's approach. The synthetic investigations described below thus converge in part with the earlier route to the *O*-methyl alkaloids.

The substituted phenacyl bromide **18** was prepared from the corresponding ketone **19**, made in turn in three steps from 2,3-dimethylanisole (**21**) by reported procedures[20,21] (Scheme 2), with the following modifications. Firstly, the unusual oxidation of 2,3-dimethylanisole (**21**) with potassium persulphate[21] gave an excellent yield (96%) of the light-sensitive, rather unstable aldehyde **22**, which was used without further purification because of its tendency to decompose during distillation. Secondly, the reported oxidation of the benzylic alcohol **23** to ketone **19** with activated manganese dioxide[20] gave variable results in our hands; but with Jones reagent, yields of **19** were reliably high (*ca* 81%). Selective bromination of ketone **19** with pyrrolidone hydrotribromide[22] gave the required phenacyl bromide **18** (64%) along with a small quantity of the dibrominated compound **24** (19%). This by-product could not be avoided; if reaction was terminated early, the yield of **18** suffered. Salt formation between **18** and thiolactam **11** was best achieved by mixing the neat reagents followed by dispersal in acetone once reaction was under way. Sulfide contraction was performed in acetonitrile solution in the presence of triphenylphosphine and triethylamine, and gave the pivotal vinylogous amide **3b** in 88% yield after purification by column chromatography. Conversion of this compound into the *O*-methyl alkaloids **9b** and **10b** by variants of the synthetic "loops" shown Scheme 1 was then undertaken.



Scheme 2

The sequence A1 → A2 → B3 proceeded smoothly. Chemoselective reduction of the nitrile group of **3b** with nickel-aluminium alloy in basic ethanol gave the unstable amine **4b** (94%), which was immediately acylated with hexanoyl or butanoyl chloride in pyridine to give amides **5b** and **6b** in yields of 43% and 65% respectively. As in the model sequence, this unsatisfactory acylation step could not be improved. Finally, chemoselective reduction of the carbon-carbon double bond of the vinylogous amide unit in **5b** and **6b** with lithium aluminium hydride afforded *O*-methylperipentadenine (**9b**) and *O*-methyldinorperipentadenine (**10b**) in yields of 75% and 55% respectively.

In contrast with the model sequence, the diversionary loop A1 → B2 also proved successful. The free amino group of vinylogous amide **4b** provided no interference when reduction was performed with sodium cyanoborohydride at pH 4, and product **8b** was isolated in 89% yield. The last alternative of interest for our purposes, selective reduction of **3b** to the nitrile-bearing aminoketone **7b** (transformation B1), was accomplished, as in the model sequence, with lithium aluminium hydride (79%). Some loss of the cyanoethyl side chain was observed, and the N-H vinylogous amide **15b** was isolated as a by-product (4%). Bick and co-workers previously reported the conversion of **7b** into **8b** by catalytic hydrogenation over platinum dioxide (*ca* 71% yield).[8] They also acylated **8b** with hexanoyl or butanoyl chloride under Schotten-Baumann conditions to form the *O*-methyl alkaloids **9b** and **10b**. Thus our alternative syntheses of **7b** and **8b** complete formal syntheses of the *O*-methylperipentadenine (**9b**) and *O*-methyldinorperipentadenine (**10b**).

Demethylation of the *O*-methyl alkaloids was simply accomplished by treatment with boron tribromide in dichloromethane. Peripentadenine (**1**) and dinorperipentadenine (**2**) were obtained in yields of 92% and 59% respectively. Spectroscopic data (^{1}H and ^{13}C NMR and IR spectra) compared favourably with those obtained on the authentic alkaloids.[23] In particular, ^{13}C NMR chemical shifts agreed to within ± 1 δ units for almost all signals; the largest discrepancy (-3.7 ppm), for the ketone carbonyl group, can probably be ascribed to concentration-dependent intramolecular hydrogen bonding effects involving the free phenolic group. In addition, since we used exhaustive two-dimensional NMR experiments to assign signals, we have been able to clarify several unassigned or incorrectly assigned ^{1}H NMR signals reported in the earlier work.

Experimental Section

Routine measurements were performed on Kofler micro hot-stage (m.p.), and on Pye-Unicam SP3-300 or Jasco FT/IR-5000 (IR), Cary 2300 (UV), VG 7070E (MS) and Bruker AC-200 (NMR) spectrometers. Unless otherwise stated, IR spectra were recorded on liquid films, and NMR spectra in $CDCl_3$ solution. ^{1}H spectra were measured at 200.13 MHz, and ^{13}C spectra at 50.32 MHz. DEPT and CH-correlated spectra and decoupling techniques were used routinely for the assignment of NMR signals. Thin-layer chromatography was on pre-coated silica gel plates (Merck DC-Plastikfolien Kieselgel 60 F_{254}, or Whatman Silica Gel 60A F_{254} glass plates). Merck Kieselgel 60 (particle size 0.063 - 0.200 mm) or Macherey Nagel Kieselgel 60 (particle size 0.063 - 0.200 mm) was used as the absorbent for conventional preparative column chromatography, Merck Kieselgel 60 (particle size 0.040 - 0.063 mm) was used for preparative flash chromatography, and ICN Silica Gel Woelm (particle size 0.032 - 0.063 mm) was used for preparative medium pressure column chromatography. All solvents were distilled before use.

*1-(2-Cyanoethyl)pyrrolidine-2-thione (**11**)*

Pyrrolidine-2-thione (305 mg, 3.01 mmol) was stirred in undried THF (10 ml) with a catalytic amount of sodium hydroxide (*ca* 10 mg) and acrylonitrile (0.24 ml, 0.19 g, 3.6 mmol). After 17 h, the solvent was evaporated *in vacuo*, and the residual yellow liquid was partitioned between dichloromethane (10 ml) and water (10 ml). The aqueous phase was extracted with dichloromethane (2 x 10 ml), and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product (461 mg) was distilled (bulb-to-bulb, 125°C/0.6 mm Hg) to give *1-(2-cyanoethyl)pyrrolidine-2-thione (**11**)* as a yellow liquid (450 mg, 97%), R_F (benzene-ethyl acetate 2:1) 0.39; λ_{max} (EtOH) 269 nm (ϵ_{max} 15000); ν_{max} (film) 2240 (w, CN), 1510 (s, N-C=S), 1125 (m, C=S) cm^{-1}; δ_H 4.00 (2H, t, *J* 6.4 Hz, chain NCH_2), 3.94 (2H, t, *J* 7.3 Hz, ring NCH_2),

3.06 (2H, t, *J* 7.9 Hz, CH_2CS), 2.88 (2H, t, *J* 6.4 Hz, CH_2CN), 2.17 (2H, quintet, *J ca* 7.6 Hz, ring 4-H); δ_C 202.5 (C=S), 117.6 (CN), 55.8 (ring NCH_2), 44.4 (CH_2CS), 43.4 (chain NCH_2), 19.6 ($CH_2CH_2CH_2$), 14.3 (CH_2CN); *m/z* 156 (5%, $M^+ + 2$), 155 (11, $M^+ + 1$), 154 (100, M^+), 153 (10), 126 (19), 121 (15), 114 (76), 101 (22), 100 (38), 93 (10) (Found: M^+, 154.0557. $C_7H_{10}N_2S$ requires 154.0564).

(E)-*2-Benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (3a)*

Phenacyl bromide (1.303 g, 6.55 mmol) was added to a solution of 1-(2-cyanoethyl)pyrrolidine-2-thione (**11**) (1.008 g, 6.54 mmol) in acetone (5 ml). The mixture was left at 3°C for 15 h. The solvent was evaporated *in vacuo* and the product, a salt, was dissolved with heating in acetonitrile (20 ml). Triphenylphosphine (1.72 g, 6.54 mmol) was added with stirring, followed by the dropwise addition over 5 min of triethylamine (1.00 ml, 0.73 g, 7.2 mmol) in acetonitrile (2 ml). After 30 min, the mixture was filtered through Celite and evaporated *in vacuo* to give an oily solid, which was triturated with ethyl acetate (30 ml) and again filtered through Celite. The organic phase was extracted with HCl (2M, 3 x 20 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange solid (949 mg), which was separated by column chromatography with hexane/acetone mixtures as eluant to give unconverted thiolactam **11** as a yellow oil (80 mg, 8%), R_F (hexane-acetone 1:1) 0.73. The combined aqueous extracts were made basic with aqueous ammonia solution (25%) and extracted with dichloromethane (3 x 20 ml). The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Column chromatography of the yellow solid (1.304 g) with hexane/acetone and hexane/ethyl acetate mixtures as eluant gave additional thiolactam **11** (13 mg, 1%) and *(E)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (3a)* (1.117 g, 71%), purified by recrystallisation as cream-coloured plates, m.p. 124.5 - 125.5°C (from benzene/hexane); R_F (hexane-acetone 1:1) 0.32; ν_{max} 3065 (w, =C-H), 2995 (m), 2875 (w), 2255 (w, CN), 1624 (s), 1593 (s), 1578 (vs), 1534 (vs), 1482 (s), 1299 (s), 1206 (s) cm^{-1}; δ_H 7.86 (2H, m, Ar *o*-H), 7.45 -7.35 (3H, m, Ar *m*- and *p*-H), 5.70 (1H, s, =CH), 3.65 (2H, t, *J* 6.7 Hz, chain NCH_2), 3.57 (2H, t, *J* 7.2 Hz, ring NCH_2), 3.41 (2H, dt, *J* 7.8 and 1.0 Hz, ring 3-H), 2.68 (2H, t, *J* 6.7 Hz, CH_2CN), 2.05 (2H, quintet, *J ca* 7.5 Hz, ring 4-H); δ_C 187.6 (C=O), 166.1 (NC=CH), 141.2 (Ar C-1), 130.3 (Ar C-4), 127.8 (Ar C-3, C-5), 126.9 (Ar C-2, C-6), 117.5 (CN), 86.7 (NC=CH), 52.7 (ring NCH_2), 41.9 (chain NCH_2), 33.3 (ring C-3), 20.7 (ring C-4), 14.6 (CH_2CN) (Found: C, 74.77; H, 6.62; N, 11.59. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71; N, 11.66%).

On occasion, two further by-products could be isolated (<10% combined yield) and identified: *3-(1-(2-thioxo)pyrrolidinyl)propanamide (12)*, as colourless spars, m.p. 121 - 121.5°C (from ethyl acetate), R_F (hexane-acetone 1:1) 0.16; ν_{max} 3340 (s, H-bonded N-H), 3160 (s, H-bonded N-H), 2980 (m), 2940 (m), 2880 (m), 2780 (w), 1677 (vs), 1619 (m), 1518 (vs), 1435 (s), 1410 (vs), 1326 (s), 1301 (s), 1116 (s) cm^{-1}; δ_H 6.63 and 5.77 (2 x 1H, 2 x br s, NH_2), 3.97 (2H, t, *J* 6.7 Hz, chain NCH_2), 3.76 (2H, t, *J* 7.3 Hz, ring NCH_2), 2.99 (2H, t, *J* 7.9 Hz, CH_2CS), 2.58 (2H, t, *J* 6.7 Hz, CH_2CONH_2), 2.02 (2H, quintet, *J ca* 7.6 Hz, ring 4-H); δ_C 201.25 (C=S), 172.9 (C=O), 55.8 (ring NCH_2), 44.8 (CH_2CS), 44.1 (ring NCH_2), 32.0 (CH_2CONH_2), 19.7 (ring C-4) (Found: C, 48.74; H, 7.26; N, 16.16. $C_7H_{12}N_2OS$ requires C, 48.81; H, 7.02; N, 16.26%); and *(E)-3-(1-(2-benzoyl-methylene)pyrrolidinyl)propanamide (13)*, as light yellow plates, m.p. 177 - 178°C (from aqueous ethanol); R_F (hexane-acetone 1:1) 0.10; ν_{max} 3535 (w), 3415 (w), 3011 (m), 1689 (s), 1579 (s), 1540 (vs), 1484 (s) cm^{-1}; δ_H 7.84 (2H, m, Ar *o*-H), 7.45 - 7.3 (3H, m, Ar *m*- and *p*-H), 6.36 and 5.65 (2 x 1H, 2 x br s, $CONH_2$), 5.69 (1H, s, =CH), 3.65 (2H, t, *J* 6.7 Hz, chain NCH_2), 3.47 (2H, t, *J* 7.3 Hz, ring NCH_2), 3.34 (2H, t, *J* 7.9 Hz, ring 3-H), 2.48 (2H, t, *J* 6.7 Hz, CH_2CONH_2), 1.96 (2H, quintet, *J ca* 7.6 Hz, ring 4-H); δ_C 187.8 (PhC=O), 172.8 ($CONH_2$), 166.9 (NC=CH), 141.8 (Ar C-1),

130.5 (Ar C-4), 128.1 (Ar C-3, C-5), 127.2 (Ar C-2, C-6), 86.6 (NC=$\underline{C}$H), 53.5 (ring N$\underline{C}H_2$), 42.4 (chain N$\underline{C}H_2$), 33.9 (ring C-3), 31.9 ($\underline{C}H_2CONH_2$), 21.0 (ring C-4) (Found: C, 69.54; H, 7.06; N, 10.76. $C_{15}H_{18}N_2O_2$ requires C, 69.75; H, 7.02; N, 10.84%).

Reduction of (E)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (3a)

(a) With a nickel-aluminium alloy.- To a stirred solution of (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)-pyrrolidine (**3a**) (228 mg, 0.95 mmol) in 96% ethanol (5 ml) was added nickel-aluminium alloy (340 mg) and sodium hydroxide solution (3M, 5 ml) at room temperature. Evolution of hydrogen was observed. After 50 min, the mixture was filtered through Celite, and the filtrate was evaporated *in vacuo*. The crude product was dissolved in water (10 ml), made basic with aqueous ammonia solution (25%), and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give *(E)-1-(3-aminopropyl)-2-benzoylmethylenepyrrolidine (4a)* as an unstable yellow oil (224 mg, 97%), used in subsequent reactions without further purification; R_F (ethanol-ammonia 400:1) 0.13; ν_{max} 3400 (br, w, N-H), 3110 (w), 3080 (w), 3010 (w), 2980 (m), 2880 (m), 1600 (s), 1578 (s), 1531 (vs), 1482 (s) cm^{-1}; δ_H 7.86 (2H, m, Ar *o*-H), 7.4 - 7.3 (3H, m, Ar *m*- and *p*-H), 5.76 (1H, s, =C$\underline{H}$), 3.45 - 3.3 (6H, m, ring and chain N$\underline{C}H_2$, ring 3-H), 2.70 (2H, t, *J* 6.9 Hz, C$\underline{H}_2NH_2$), 2.0 - 1.5, underlying 1.96 and 1.72 (6H; v br s, N$\underline{H}_2$; quintet, *J ca* 7.5 Hz, ring 4-H; and quintet, *J ca* 7.1 Hz, C$\underline{H}_2CH_2NH_2$); δ_C 186.9 (C=O), 166.8 (N$\underline{C}$=CH), 141.7 (Ar C-1), 129.7 (Ar C-4), 127.6 (Ar C-3, C-5), 126.7 (Ar C-2, C-6), 85.7 (NC=$\underline{C}$H), 52.3 (ring N$\underline{C}H_2$), 43.7 (chain N$\underline{C}H_2$), 39.1 ($\underline{C}H_2NH_2$), 33.6 (ring C-3), 29.6 ($\underline{C}H_2CH_2NH_2$), 20.4 (ring C-4).

(b) With fresh lithium aluminium hydride.- Fresh $LiA\ell H_4$ (54 mg, 1.4 mmol) was added under nitrogen to a stirred solution of (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (**3a**) (299 mg, 1.24 mmol) in THF (20 ml) at 0°C. Water (several drops) was added after 40 min to quench unreacted hydride. The mixture was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (283 mg), which was purified by column chromatography using hexane/ethyl acetate mixtures as eluant to give *2-benzoylmethyl-1-(2-cyanoethyl)-pyrrolidine (7a)* as a yellow oil (253 mg, 84%), R_F (ethyl acetate) 0.52; ν_{max} 2973 (s), 2259 (w, CN), 1686 (vs), 1452 (s), 1373 (s) cm^{-1}; δ_H 7.95 (2H, m, Ar *o*-H), 7.6 - 7.4 (3H, m, Ar *m*- and *p*-H), 3.29, 3.2 - 3.0 and 3.02 (5H; dd, *J* 15.4, 3.4 Hz, C$\underline{H}_a$H$_b$COPh; m, ring NC$\underline{H}_a$H$_b$, NC$\underline{H}$CH$_2$ and chain NC$\underline{H}_a$H$_b$; and dd, *J* 15.4, 7.7 Hz, CH$_a\underline{H}_b$COPh), 2.61 and *ca* 2.53 (3H; ddd, *J* 12.4, 7.0, 5.4 Hz, chain NCH$_a\underline{H}_b$; and m, C$\underline{H}_2$CN), 2.30 (1H, dd [q?], *J* 17.0, 8.5 Hz, ring NCH$_a\underline{H}_b$), 2.2 - 2.0 (1H, m, ring 3-H$_a$), 1.9 - 1.75 (2H, m, ring 4-H), 1.6 - 1.45 (1H, m, ring 3-H$_b$); δ_C 199.2 (C=O), 137.0 (Ar C-1), 133.2 (Ar C-4), 128.7 (Ar C-3, C-5), 128.1 (Ar C-2, C-6), 118.9 (CN), 60.2 (N$\underline{C}$H), 53.3 (ring NCH$_2$), 49.8 (chain N$\underline{C}H_2$), 43.9 ($\underline{C}H_2$COPh), 31.3 (ring C-3), 22.7 (ring C-4), 17.5 ($\underline{C}H_2$CN); *m/z* 243 (1%, M^+ + 1), 242 (5, M^+), 202 (14), 124 (8), 123 (100, M^+ - PhCOCH$_2$), 122 (10), 105 (32, PhCO$^+$), 83 (11), 82 (16), 77 (23, Ph$^+$) (Found: M^+, 242.1416. $C_{15}H_{18}N_2O$ requires 242.1419).

(c) With sodium cyanoborohydride.- Sodium cyanoborohydride (28 mg, 0.45 mmol) was added with stirring to a solution of (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (**3a**) (98 mg, 0.41 mmol) in methanol (1.0 ml). Bromocresol green (0.5% in ethanol, 1 drop) was added, followed by hydrochloric acid (12M) at intervals such that the pH of the solution remained at *ca* 4. Sodium hydroxide solution (2 M, 10 ml) was added after 1 h, and the mixture was extracted with dichloromethane (3 x 10 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (101 mg), which was separated by flash chromatography using hexane-acetone (2:1) as eluant, to give *2-benzoylmethyl-1-(2-cyanoethyl)pyrrolidine (7a)* as a clear oil (80 mg, 81%); characterisation as above.

(d) With lithium aluminium hydride, followed by acylation.- Somewhat aged $LiA\ell H_4$ (34 mg, 0.90 mmol) was

added with stirring to a solution of (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (**3a**) (101 mg, 0.42 mmol) in THF (10 ml). The mixture was heated under reflux for 20 h, allowed to cool and evaporated *in vacuo*. Ether (10 ml) was added, followed by a few drops of water. The mixture was dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil (80 mg), which was dissolved in chloroform (10 ml). Sodium hydrogen carbonate (159 mg, 1.89 mmol) and hexanoyl chloride (0.10 ml, 98 mg, 0.73 mmol) were added with stirring. After 18 h, the mixture was washed with water (10 ml) and with saturated sodium hydrogen carbonate solution (10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (141 mg), which was purified by flash chromatography with ethyl acetate/hexane (1:2) and ethyl acetate as eluants to give *(Z)-2-benzoylmethylenepyrrolidine (15a)* (19 mg, 24%) as colourless plates, mp 115.5 - 117.5°C (from benzene-hexane); R_F (hexane-ether 1:1) 0.52; ν_{max} 3280 (w, br, N-H), 3060 (w), 3000 (m), 2960 (m, sh), 2940 (m, sh), 2880 (w), 1680 (m), 1609 (vs), 1576 (vs), 1519 (vs), 1292 (s), 1263 (s) cm^{-1}; δ_H 10.28 (1H, br s, NH), 7.88 (2H, m, Ar *o*-H), 7.40 (3H, m, Ar *m*- and *p*-H), 5.81 (1H, s, =CH), 3.66 (2H, t, *J* 7.04 Hz, NCH_2), 2.74 (2H, t, *J* 7.82 Hz, ring 3-H), 2.05 (2H, quintet, *J ca* 7.5 Hz, ring 4-H); δ_C 188.0 (C=O), 169.2 (NC=CH), 140.3 (Ar C-1), 130.4 (Ar C-4), 128.1 (Ar C-3, C-5), 126.9 (Ar C-2, C-6), 86.5 (NC=CH), 47.7 (NCH_2), 32.8 (ring C-3), 21.3 (ring C-4) (Found: C, 76.70; H, 6.95; N, 7.49. $C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%); and a small quantity of *1-hexanoyl-2-benzoylmethylpyrrolidine (16)* as yellow crystals (16 mg, 13%), R_F (hexane-ether 1:1) 0.43; δ_H 8.12 (2H, m, Ar *o*-H), 7.55 - 7.45 (3H, m, Ar *m*- and *p*-H), 4.6 - 4.5 (1H, m, NCH), 3.89 (1H, dd, *J* 14.5, 3.0 Hz, CH_aH_bCOPh), 3.55 - 3.4 and 3.48 (2H; m, ring NCH_aH_b; and dd, *J* 7.0 and 4.4 Hz, ring NCH_aH_b), 2.69 (1H, dd, *J* 14.5 and 10.4 Hz, CH_aH_bCOPh), 2.28 (2H, m, *J ca* 7.7 Hz, $NCOCH_2$), 2.05 - 1.8 (3H, m, ring 3-H_a and ring H-4), 1.8 - 1.6 (3H, m, ring 3-H_b and $NCOCH_2CH_2$), 1.4 - 1.25 (4H, m, $CH_2CH_2CH_3$), 0.91 (3H, br t, *J ca* 6.6 Hz, CH_3); δ_C 199.1 (PhC=O), 172.1 (amide C=O), 136.6 (Ar C-1), 133.2 (Ar C-4), 128.6 (Ar C-3, C-5), 128.5 (Ar C-2, C-6), 54.6 (NCH), 47.1 (NCH_2), 42.4 (CH_2COPh), 35.1 ($NHCOCH_2$), 31.7 (hexanoyl C-4), 29.4 (ring C-3), 24.5 (hexanoyl C-3), 23.9 (ring C-4), 22.5 (hexanoyl C-5), 14.1 (CH_3).

Alternative routes to (Z)-2-benzoylmethylenepyrrolidine (15a)

(a) To a stirred solution of (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine (**3a**) (87 mg, 0.36 mmol) in THF (25 ml) under nitrogen was added potassium *t*-butoxide (93 mg, 0.83 mmol). After 25 min, the solvent was evaporated *in vacuo* to give a brown solid, which was partitioned between saturated sodium chloride solution (10 ml) and dichloromethane (3 x 10 ml). The extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange solid, which was purified by flash chromatography using hexane-acetone mixtures as eluant to give (*E*)-2-benzoylmethylenepyrrolidine (**15a**) as colourless crystals (63 mg, 93%); characterisation as described above.

(b) When the reaction was repeated at -70°C for 40 min, (*E*)-2-benzoylmethylenepyrrolidine (**15a**) (38%) and *(Z)-2-benzoylmethylene-3-(2-cyanoethyl)pyrrolidine (17)* (31%) were isolated. The latter was recrystallised to give colourless spars, mp 103 - 104°C (from ethyl acetate/hexane), R_F (hexane-acetone 2:1) 0.31; ν_{max} 3289 (vw, br, N-H), 3017 (m), 2965 (m), 2257 (vw, C≡N), 1616 (vs), 1583 (s), 1529 (s), 1264 (s) cm^{-1}; δ_H 10.25 (1H, br s, 1-H), 7.87 (2H, m, Ar *o*-H), 7.5 - 7.35 (3H, m, Ar *m*- and *p*-H), 5.75 (1H, s, =CH), 3.75 - 3.5 (2H, m, NCH_2), 3.1 - 2.95 (1H, m, ring 3-H), 2.6 - 2.4 (2H, m, CH_2CN), 2.4 - 2.2 (1H, m, ring 4-H_a), 2.2 - 2.05 (1H, m, $CH_aH_bCH_2CN$), 1.9 - 1.75 (1H, m, $CH_aH_bCH_2CN$), 1.75 - 1.6 (1H, m, ring 4-H_b); δ_C 188.8 (C=O), 169.3 (NC=CH), 140.0 (Ar C-1), 130.8 (Ar C-4), 128.2 (Ar C-3, C-5), 127.0 (Ar C-2, C-6), 118.9 (CN), 86.0 (NC=CH), 46.1 (NCH_2), 43.3 (ring C-3), 28.3 (CH_2CH_2CN), 27.6 (ring C-4), 15.2 (CH_2CN) (Found: C, 74.65; H, 6.71; N, 11.52. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71; N, 11.66%).

Acylation of (E)-1-(3-aminopropyl)-2-benzoylmethylenepyrrolidine (4a)

(a) With hexanoyl chloride.- (*E*)-1-(3-Aminopropyl)-2-benzoylmethylenepyrrolidine (**4a**) (133 mg, 0.54 mmol) was dissolved in pyridine (0.5 ml, 0.5 g, 6 mmol). Hexanoyl chloride (0.12 ml, 0.12 g, 0.87 mmol) was added with stirring, and the temperature was decreased to 0°C. After 1.5 h, ether (10 ml) was added and the mixture was washed with water (10 ml) and saturated sodium chloride solution (3 x 10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (139 mg). The aqueous phases were combined, back-extracted with dichloromethane (3 x 10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a further quantity of yellow oil (31 mg). The oils were combined and purified by column chromatography with hexane/ethyl acetate mixtures as eluant to give *(E)-2-benzoylmethylene-1-(3-hexanoylaminopropyl)pyrrolidine (5a)* as an orange-yellow oil (91 mg, 49%), R_F (ethyl acetate) 0.12; ν_{max} 3670 (w), 3450 (m, free N-H), 3310 (br, w, H-bonded N-H), 3070 (w), 3000 (s), 2960 (s), 2940 (s), 2870 (m), 1664 (s, N-C=O), 1621 (s), 1602 (s), 1591 (vs), 1535 (vs), 1486 (vs), 1472 (s), 1306 (s), 1216 (s) cm^{-1}; δ_H 7.83 (2H, m, Ar *o*-H), 7.45 - 7.35 (3H, m, Ar *m*- and *p*-H), 6.34 (1H, br t, *J ca* 7 Hz, NH), 5.68 (1H, s, =CH), 3.42, 3.37, 3.33 and 3.26 (8H; t, *J* 7.3 Hz, ring NCH_2; t, *J ca* 7 Hz, ring 3-H; t, *J* 7.4 Hz, chain NCH_2; and q, *J* 6.6 Hz, CH_2NHCO), 2.15 (2H, t, *J* 7.6 Hz, $NHCOCH_2$), 1.97 (2H, quintet, *J ca* 7.4 Hz, ring 4-H), 1.82 (2H, quintet, *J ca* 7.2 Hz, CH_2CH_2NHCO), 1.60 (2H, quintet, *J* 7.4 Hz, hexanoyl 3-H), 1.3 - 1.2 (4H, m, hexanoyl 4-H, 5-H), 0.86 (3H, t, *J* 6.6 Hz, CH_3); δ_C 187.5 (PhC=O), 173.4 (NHC=O), 167.0 (NC=CH), 141.8 (Ar C-1), 130.1 (Ar C-4), 127.8 (Ar C-3, C-5), 126.8 (Ar C-2, C-6), 86.1 (NC=CH), 52.5 (ring NCH_2), 44.0 (chain NCH_2), 36.8 (CH_2NHCO), 36.4 ($NHCOCH_2$), 33.7 (ring C-4), 31.2 (hexanoyl C-4), 26.4 (CH_2CH_2NHCO), 25.2 (hexanoyl C-3), 22.1 (hexanoyl C-5), 20.6 (ring C-4), 13.6 (CH_2CH_3); *m/z* 343 (5%, $M^+ + 1$), 342 (24, M^+), 237 (10, M^+ - PhCO), 215 (15), 214 (98, $M^+ - C_5H_{11}CONHCH_2$), 201 (37), 173 (42), 172 (15), 122 (15), 102 (75, $PhCO^+$), 96 (100), 77 (39, Ph^+) (Found: M^+, 342.2306. $C_{21}H_{30}N_2O_2$ requires 342.2307).

(b) With butyric anhydride.- Butyric anhydride (containing *ca* 25% butyric acid; 110 mg, *ca* 0.68 mmol) was added to a stirred solution of (*E*)-1-(3-aminopropyl)-2-benzoylmethylenepyrrolidine (**4a**) (165 mg, 0.68 mmol) in dry pyridine (0.5 ml) at 0°C. The mixture was allowed to warm to room temperature over 17.5 h, after which more butyric anhydride (55 μl, 53 μg, 0.34 mmol) was added, followed 2 h later by more pyridine (0.5 ml). After an additional 3 h, ether (10 ml) was added and the mixture was washed with saturated sodium chloride solution (3 x 10 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (198 mg), which was purified by flash chromatography with hexane/acetone mixtures as eluant to give *(E)-2-benzoylmethylene-1-(3-butanoylaminopropyl)pyrrolidine (6a)* as a yellow oil (97 mg, 46%), R_F (acetone) 0.62; ν_{max} 3455 (w), 3317 (br, w), 3069 (w), 3005 (s), 2977 (s), 2879 (m), 1668 (vs), 1623 (s), 1602 (s), 1579 (vs), 1532 (vs), 1482 (vs), 1467 (s), 1300 (s), 1233 (s) cm^{-1}; δ_H 7.81 (2H, m, Ar *o*-H), 7.4 - 7.3 (3H, m, Ar *m*- and *p*-H), 6.82 (1H, br t, *J ca* 5.4 Hz, NH), 5.67 (1H, s, =CH), 3.40, 3.35, 3.31 and 3.24 (8H; t, *J* 7.39 Hz, ring NCH_2; t, *J* 8.0 Hz, ring 3-H; t, *J* 7.7 Hz, chain NCH_2; and q, *J* 6.5 Hz, CH_2NHCO; on decoupling at δ 1.79, the latter signal → d, *J* 5.9 Hz), 2.13 (2H, t, *J* 7.5 Hz, $NHCOCH_2$), 1.95 (2H, quintet, *J ca* 7.5 Hz, ring 4-H), 1.79 (2H, quintet, *J ca* 7.2 Hz, CH_2CH_2NHCO), 1.62 (2H, 6 lines, *J ca* 7.4 Hz, CH_2CH_3), 0.89 (3H, t, *J* 7.3 Hz, CH_3); δ_C 187.5 (PhC=O), 173.4 (NHC=O), 167.1 (NC=CH), 141.9 (Ar C-1), 130.1 (Ar C-4), 127.8 (Ar C-3, C-5), 126.9 (Ar C-2, C-6), 86.1 (NC=CH), 52.6 (ring NCH_2), 44.0 (chain NCH_2), 38.3 (CH_2NHCO), 36.7 ($NHCOCH_2$), 33.8 (ring C-3), 26.4 (CH_2CH_2NHCO), 20.6 (ring C-4), 19.0 (CH_2CH_3), 13.6 (CH_2CH_3); *m/z* 314 (9, M^+), 214 (100, $M^+ - C_3H_7CONHCH_2$), 201 (52), 195 (15, M^+ - $PhCOCH_2$), 172 (30), 128 (22, $C_3H_7CONHC_3H_6^+$), 122 (28), 110 (13), 105 (100, $PhCO^+$), 98 (13), 97 (17), 96 (100), 91 (14, $C_7H_7^+$), 77 (52, Ph^+) (Found: M^+, 314.1992. $C_{19}H_{26}N_2O_2$ requires 314.1994).

(c) With benzoyl chloride.- Benzoyl chloride (38 μl, 46 mg, 0.33 mmol) was added with stirring to a solution of (*E*)-1-(3-aminopropyl)-2-benzoylmethylenepyrrolidine (**4a**) (73 mg, 0.30 mmol) in pyridine (0.5 ml, 0.5 g, 6 mmol) at 0°C. Ether (10 ml) was added after 110 min, and the mixture was washed with water (10 ml) and saturated sodium chloride solution (2 x 10 ml). The aqueous phases were back-extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil (92 mg), which was purified by column chromatography using hexane/ethyl acetate mixtures as eluant to give *(E)-1-(3-benzoylaminopropyl)-2-benzoylmethylenepyrrolidine (14a)* as an orange oil (62 mg, 59%), R_F (ethyl acetate) 0.14; ν_{max} 3443 (w), 3340 (br, w), 3065 (w), 3005 (m), 1660 (s), 1579 (s), 1538 (vs), 1484 (s) cm^{-1}; δ_H 7.85 - 7.7 (4H, m, Ar *o*-H), 7.45 - 7.25 (6H, m, Ar *m*- and *p*-H), 6.72 (1H, br s [t?], NH), 5.74 (1H, s, =CH), 3.55 - 3.35 (8H, m, ring 3-H, 2 x NCH_2, CH_2NHCO), 2.1 - 1.8 (4H, m, ring and chain $CH_2CH_2CH_2$); δ_C 187.8 (=CHCOPh), 167.7, 167.6 (NC=CH, NHCOPh), 141.9, 134.1 (Ar C-1), 131.6, 130.4 (Ar C-4), 128.6, 128.1 (Ar C-3, C-5), 127.2, 126.9 (Ar C-2, C-6), 86.3 (NC=CH), 52.7 (ring NCH_2), 44.1 (chain NCH_2), 37.6 ($CH_2NHCOPh$), 34.1 (ring C-3), 26.5 ($CH_2CH_2NHCOPh$), 20.9 (ring C-4); *m/z* 349 (3%, M^+ + 1), 348 (13, M^+), 229 (12, M^+ - $PhCOCH_2$), 214 (44), 201 (29), 173 (21), 120 (11, $PhCONH^+$), 106 (14), 105 (100, $PhCO^+$), 97 (19), 96 (56), 95 (14) (Found: M^+, 348.1833. $C_{22}H_{29}N_2O_3$ requires 348.1838).

2-Benzoylmethyl-1-(3-hexanoylaminopropyl)pyrrolidine (9a)

$LiAlH_4$ (10 mg, 0.26 mmol) was added to a stirred solution of (*E*)-2-benzoylmethylene-1-(3-hexanoylaminopropyl)pyrrolidine (**5a**) (88 mg, 0.26 mmol) in dry THF (10 ml) at 0°C. After 75 min, more $LiAlH_4$ (9 mg, 0.24 mmol) was added and after a further 105 min, water (*ca* 1 ml) was added to quench the reaction. The mixture was dried ($MgSO_4$), filtered through Celite and evaporated *in vacuo* to give a yellow oil (76 mg), which was purified by column chromatography with 3%, 5% and 7% solutions of methanol in ammonia-saturated chloroform as eluant to give some starting material **9a** (< 1 mg), R_F (ethanol-ammonia 400:1) 0.89; a mixture of starting material and product (12 mg); and *2-benzoylmethyl-1-(3-hexanoylaminopropyl)pyrrolidine (9a)* as a yellow oil (61 mg, 68%), R_F (ethanol-ammonia 400:1) 0.54; ν_{max} 3343 (m, free N-H), 3071 (w, H-bonded N-H), 2963 (vs), 2937 (vs), 2879 (s), 2813 (m), 1677 (vs), 1602 (m), 1581 (m), 1523 (s), 1451 (s), 1213 (s) cm^{-1}; δ_H 7.95 (2H, m, Ar *o*-H), 7.6 - 7.4 (3H, m, Ar *m*- and *p*-H), 6.97 (1H, br s, NH), 3.48 (1H, dt, *J* 13.4, 6.3 Hz, CH_aH_bNHCO), 3.30 (1H, br d, *J ca* 11.2 Hz, CH_aH_bCOPh), 3.25 - 3.1 (2H, m, ring NCH_aH_b and CH_aH_bNHCO), 3.05 - 2.9 (2H, m, NCH and CH_aH_bCOPh), 2.84 (1H, dt, *J* 12.0, 7.8 Hz, chain NCH_aH_b), 2.35 (1H, dt, *J* 12.0, 5.0 Hz, chain NCH_aH_b), 2.25 - 2.0 and 2.15 (4H; m, ring NCH_aH_b and ring 3-H_a; and t, *J* 7.7 Hz, $NHCOCH_2$), 1.85 - 1.4 (7H, m, ring 4-H, hexanoyl 3-H, ring 3-H_b and CH_2CH_2NHCO), 1.35 - 1.25 (4H, 2 x m, hexanoyl 4-H, 5-H), 0.88 (3H, t, *J* 6.6 Hz, CH_3); δ_C 199.3 (PhC=O), 172.9 (NHC=O), 137.1 (Ar C-1), 133.1 (Ar C-4), 128.5 (Ar C-3, C-5), 127.9 (Ar C-2, C-6), 61.1 (NCH), 53.3 (2 x NCH_2), 43.7 (CH_2COPh), 38.8 (CH_2NHCO), 36.8 ($NHCOCH_2$), 31.4 (hexanoyl C-4), 31.1 (ring C-3), 27.3 (CH_2CH_2NHCO), 25.4 (hexanoyl C-3), 22.4 (ring C-4), 22.3 (CH_2CH_3), 13.8 (CH_2CH_3); *m/z* 344 (3%, M^+), 225 (57, M^+ - $PhCOCH_2$), 224 (24), 202 (21), 156 (32, $C_5H_{11}CONHC_3H_6^+$), 153 (19), 125 (20), 120 (35, $PhCOCH_3^+$), 105 (100, $PhCO^+$), 96 (23), 84 (16), 82 (47), 77 (71, Ph^+) (Found: M^+, 344.2462. $C_{21}H_{32}N_2O_2$ requires 344.2464).

1-(2-Methoxy-6-methylphenyl)ethanone (19)

Jones reagent[24] (0.5 ml) was added dropwise over 1 h to a mechanically stirred solution of 1-(2-methoxy-6-methylphenyl)ethan-1-ol[20] (**23**) (0.213 g, 1.28 mmol) in acetone (10 ml). The mixture was diluted with water

(10 ml) and extracted with dichloromethane (3 x 10 ml). The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil (0.192 g), which was separated by flash chromatography using hexane/ether (3:1) to give *1-(2-methoxy-6-methylphenyl)ethanone (19)* as a yellow oil (0.171 g, 1.04 mmol, 81%), R_F (hexane-ether 2:1) 0.47; δ_H 7.15 (1H, br t, *J ca* 8.0 Hz, Ar 4-H), 6.72 (2H, overlapping d, *J* 6.5, 8.1 Hz, Ar 3-H, 5-H), 3.72 (3H, s, OCH_3), 2.44 (3H, s, $COCH_3$), 2.19 (3H, s, $ArCH_3$); δ_C 204.7 (C=O), 155.7 (Ar C-1), 134.7 (Ar C-3), 130.7 (Ar C-2), 129.4 (Ar C-5), 122.4 (Ar C-4), 107.9 (Ar C-6), 54.9 (OCH_3), 31.5 ($COCH_3$), 18.4 ($ArCH_3$). These data agree with those reported in the literature.[20]

Bromination of 1-(2-methoxy-6-methylphenyl)ethanone (19)

To a stirred solution of 1-(2-methoxy-6-methylphenyl)ethanone (**19**) (4.97 g, 30.3 mmol) and 2-pyrrolidone (2.64 g, 31.0 mmol) in dry THF (300 ml) was added pyrrolidone hydrotribromide (16.5 g, 33.3 mmol) in dry THF (300 ml) dropwise over 12.5 h in the dark. The mixture was filtered through Celite and evaporated *in vacuo*. The crude product was dissolved in ether (200 ml) and washed with water (100 ml) and saturated sodium thiosulfate solution (100 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil (9.3 g). This was separated by medium pressure liquid chromatography with hexane/dichloromethane (2:1) as eluant and azobenzene (15 mg) as indicator to give *2,2-dibromo-1-(2-methoxy-6-methylphenyl)ethanone (24)* as a yellow solid (1.89 g, 19%), which was recrystallised as white needles, mp 83.5 - 84°C (from carbon tetrachloride/hexane); R_F (hexane-dichloromethane 2:1) 0.45; ν_{max} 3000 (w), 2970 (w), 2950 (w), 2850 (w), 1714 (s, C=O), 1597 (m), 1579 (s), 1470 (s), 1266 (vs), 1171 (s), 1134 (s), 1100 (vs), 1080 (vs) cm^{-1}; δ_H 7.32 (1H, br t, *J ca* 8.0 Hz, 4-H), 6.88 (1H, d with fine structure, *J ca* 7.6 and 0.7 Hz, 5-H), 6.79 (1H, br d, *J ca* 8.4 Hz, 3-H), 6.68 (1H, s, $CHBr_2$), 3.86 (3H, s, OCH_3), 2.36 (3H, s, $ArCH_3$); δ_C 190.2 (C=O), 157.2 (C-2), 139.9 (C-6), 132.0 (C-4), 124.0 (C-1), 123.6 (C-5), 108.3 (C-3), 55.9 (OCH_3), 45.3 ($CHBr_2$), 19.5 ($ArCH_3$) (Found: $^{79}M^+$, 319.9052. $C_{10}H_{10}Br_2O_2$ requires 319.9048); and *2-bromo-1-(2-methoxy-6-methyl-phenyl)ethanone (18)* as a lachrymatory clear liquid that became orange with time (4.74 g, 64%), R_F (hexane-dichloromethane 2:1) 0.36; ν_{max} 3080 (w), 3010 (w), 2970 (m), 2950 (m), 2850 (m), 1690 (vs, C=O), 1596 (s), 1578 (vs), 1461 (vs), 1429 (s), 1295 (s), 1267 (vs), 1096 (s), 1077 (vs) cm^{-1}; δ_H 7.26 (1H, br t, *J ca* 8.0 Hz, 4-H), 6.83 (1H, d with fine structure, *J ca* 7.7 and 0.9 Hz, 5-H), 6.77 (1H, br d, *J ca* 8.3 Hz, 3-H), 4.36 (2H, s, CH_2Br), 3.82 (3H, s, OCH_3), 2.27 (3H, s with fine structure, *J ca* 0.3 Hz, $ArCH_3$); decoupling at δ 2.27 simplifies 7.26 (dd, *J* 8.3, 7.7 Hz), 6.83 (dd, *J* 7.7, 0.9 Hz), 6.77 (dd, *J* 8.3, 1.0 Hz); δ_C 197.1 (C=O), 156.7 (C-2), 137.7 (C-6), 131.0 (C-1, C-4), 123.1 (C-5), 108.2 (C-3), 55.6 (OCH_3), 36.6 (CH_2Br), 19.2 ($ArCH_3$); *m/z* 244 (2%, $^{81}M^+$), 242 (2, $^{79}M^+$), 227 (5, $^{79}M^+ - CH_3$), 167 (12), 163 (16, $ArCOCH_2^+$), 149 (100, $ArCO^+$), 110 (12), 97 (12), 91 (11, $C_7H_7^+$) (Found: $^{79}M^+$, 241.9944. $C_{10}H_{11}BrO_2$ requires 241.9943).

(E)-1-(2-Cyanoethyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (3b)

2-Bromo-1-(2-methoxy-6-methylphenyl)ethanone (**18**) (240 mg, 0.99 mmol) was added with swirling to 1-(2-cyanoethyl)pyrrolidine-2-thione (**11**) (148 mg, 0.96 mmol). After 6 h, acetone (0.5 ml) was added, and the mixture was subjected to ultrasonic irradiation to break up the cream solid that had formed. After storage at -23°C for 46 h, acetonitrile (2 ml) was added, whereupon some of the salt dissolved after gentle warming. Triphenylphosphine (259 mg, 0.99 mmol) in acetonitrile (1.5 ml) was added to the slightly warmed suspension, and further dissolution took place. Triethylamine (0.15 ml, 0.11 g, 1.1 mmol) in acetonitrile (1.5 ml) was added dropwise with stirring over 5 min, leading to complete salt dissolution. After 40 min, the mixture was filtered through Celite and evaporated *in vacuo*. Ethyl acetate (10 ml) was added and the mixture was again

filtered through Celite and extracted with aqueous HCl (2M, 3 x 10 ml). The extracts were combined, made basic with 25% ammonia solution and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (258 mg), which was separated by column chromatography with hexane/acetone and hexane/ethyl acetate mixtures as eluants to give a yellow oil, *(E)-1-(2-cyanoethyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (3b)* (237 mg, 88%), R_F (hexane-acetone 1:1) 0.44; ν_{max} 3070 (w), 2970 (sh, m), 2900 (w), 2870 (w), 2840 (w), 2250 (w, CN), 1618 (s), 1578 (s), 1537 (vs), 1481 (s), 1465 (s), 1299 (s), 1258 (s), 1089 (s) cm^{-1}; δ_H 7.12 (1H, br t, *J ca* 7.9 Hz, Ar 4-H), 6.73 (2H, overlapping d, *J* 7.3, 8.1 Hz, Ar 3-H, 5-H), 5.14 (1H, s, =C<u>H</u>), 3.74 (3H, s, OC<u>H</u>$_3$), 3.49 and 3.45 (4H; t, *J* 7.3 Hz, ring NC<u>H</u>$_2$; and t, *J* 6.7 Hz, chain NC<u>H</u>$_2$), 3.16 (2H, br s, ring 3-H; at 50°C → t, *J* 7.7 Hz), 2.57 (2H, t, *J* 6.6 Hz, C<u>H</u>$_2$CH$_2$CN), 2.24 (3H, s, ArC<u>H</u>$_3$), 1.95 (2H, quintet, *J ca* 7.5 Hz, ring 4-H); δ_C 191.0 (Ar<u>C</u>=O), 164.1 (N<u>C</u>=CH), 154.9 (Ar C-2), 134.6 (Ar C-6), 133.5 (Ar C-1), 127.7 (Ar C-4), 121.9 (Ar C-5), 117.3 (CN), 107.7 (Ar C-3), 92.4 (NC=<u>C</u>H), 55.0 (O<u>C</u>H$_3$), 52.4 (ring N<u>C</u>H$_2$), 41.5 (chain N<u>C</u>H$_2$), 32.4 (ring C-3), 20.4 (ring C-4), 18.4 (Ar<u>C</u>H$_3$), 14.0 (<u>C</u>H$_2$CN); *m/z* 284 (50%, M^+), 269 (24, $M^+ - CH_3$), 253 (31, $M^+ - CH_3O$), 188 (56, $ArCOCHCN^+$), 163 (23, M^+ - Ar), 149 (100, $ArCO^+$), 148 (78), 136 (11), 135 (12), 123 (21) (Found: M^+, 284.1525. $C_{17}H_{20}N_2O_2$ requires 284.1525).

Reduction of (E)-1-(2-cyanoethyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (3b)

(a) With a nickel-aluminium alloy.- To a stirred solution of (*E*)-1-(2-cyanoethyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (**3b**) (1.579 g, 5.55 mmol) in ethanol (96%, 40 ml) maintained at room temperature was added nickel-aluminium alloy (2.4 g) and sodium hydroxide solution (3M, 40 ml). After 40 min, the mixture was filtered through Celite and evaporated *in vacuo*. The residue was poured into water (10 ml) and extracted with dichloromethane (2 x 20 ml, 10 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil, crude *(E)-1-(3-aminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (4b)* (1.502 g, 94%), R_F (ethanol-ammonia 200:1) 0.14; ν_{max} 3295 (w), 3067 (w), 2943 (s), 1633 (s), 1581 (s), 1540 (vs), 1484 (vs), 1469 (vs), 1438 (s), 1300 (s), 1260 (vs), 1213 (s), 1090 (s) cm^{-1}; δ_H 7.10 (1H, dt, *J ca* 7.7, 1.5 Hz, Ar 4-H), 6.72 (2H, overlapping d, *J* 6.8 and 7.8 Hz, Ar 5-H, 3-H), 5.20 (1H, s, =C<u>H</u>), 3.73 (3H, s, OC<u>H</u>$_3$), 3.5 - 3.0, underlying 3.38 and 3.22 (6H; br s, ring 3-H; t, *J* 7.1 Hz, ring NC<u>H</u>$_2$; and t, *J* 7.1 Hz, chain NC<u>H</u>$_2$), 2.62 (2H, t, *J*, 6.8 Hz, C<u>H</u>$_2$NH$_2$), 2.26 (3H, s, ArC<u>H</u>$_3$), 1.91 (2H, br quintet, *J ca* 6.8 Hz, ring 4-H), 1.65 (2H, quintet, *J* 6.8 Hz, C<u>H</u>$_2$CH$_2$NH$_2$), 1.36 (2H, br s, N<u>H</u>$_2$); δ_C 190.0 (Ar<u>C</u>=O), 164.7 (N<u>C</u>=CH), 154.7 (Ar C-2), 134.2 (Ar C-6), 134.0 (Ar C-1), 127.0 (Ar C-4), 121.5 (Ar C-5), 107.5 (Ar C-3), 91.1 (NC=<u>C</u>H), 54.8 (O<u>C</u>H$_3$), 51.7 (ring N<u>C</u>H$_2$), 43.1 (chain N<u>C</u>H$_2$), 38.6 (<u>C</u>H$_2$NH$_2$), 32.6 (ring C-3), 29.1 (<u>C</u>H$_2$CH$_2$NH$_2$), 19.9 (ring C-4), 18.2 (Ar<u>C</u>H$_3$); *m/z* 289 (1%, $M^+ + 1$), 288 (6, M^+), 245 (13), 202 (12), 186 (34), 150 (11), 149 (100, $ArCO^+$), 124 (13), 123 (13), 110 (18), 105 (10, $PhCO^+$), 97 (22), 96 (94), 91 (39, $C_7H_7^+$) (Found: M^+, 288.1832. $C_{17}H_{24}N_2O_2$ requires 288.1838).

(b) With lithium aluminium hydride.- Fresh $LiAlH_4$ (43 mg, 1.1 mmol) was added to a stirred solution of (*E*)-1-(2-cyanoethyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (**3b**) (325 mg, 1.14 mmol) in dry THF (10 ml) at 0°C under nitrogen. After 15 min, water was added to destroy unreacted hydride. The mixture was dried ($MgSO_4$), filtered through Celite, and evaporated *in vacuo* to give a yellow oil (300 mg), which was purified by flash chromatography using hexane/acetone (4:1) as eluant to give *1-(2-cyanoethyl)-2-(2-methoxy-6-methylbenzoylmethyl)pyrrolidine (7b)* as a clear oil (257 mg, 79%), R_F (hexane-acetone 2:1) 0.52; ν_{max} 2973 (s), 2255 (w, C≡N), 1697 (vs, C=O), 1583 (s), 1471 (vs), 1297 (s), 1266 (vs), 1099 (s) cm^{-1}; δ_H 7.22 (1H, m, *J* 8.0 Hz, Ar 4-H), 6.77 (2H, overlapping d, *J* 7.5 and 7.9 Hz, Ar 3-H, 5-H), 3.81 (3H, s, OC<u>H</u>$_3$), 3.2 -

2.95 (4H, m, ring and chain NC$\underline{H}_a\underline{H}_b$, C$\underline{H}_a\underline{H}_b$COAr and NC$\underline{H}$), 2.9 - 2.7 (1H, m, CH$_a\underline{H}_b$COAr), 2.60 and 2.55 - 2.45 (3H; dd, *J* 7.5, 5.16 Hz, chain NCH$_a\underline{H}_b$; and m, C$\underline{H}_2$CH$_2$CN), 2.3 - 2.2 and 2.22 (5H; m, ring NCH$_a$H$_b$; s, OC$\underline{H}_3$; and m, ring 3-H$_a$), 1.85 - 1.7 (2H, m, ring 4-H), 1.65 - 1.45 (1H, m, NCHCH$_a\underline{H}_b$); δ_C 206.6 (C=O), 156.0 (Ar C-2), 135.4 (Ar C-6), 130.7 (Ar C-1), 129.9 (Ar C-4), 122.9 (Ar C-5), 118.8 (CN), 108.2 (Ar C-3), 59.3 (NCH), 55.4 (OCH$_3$), 53.0 (ring NCH$_2$), 49.5 (CH$_2$COAr), 49.3 (chain NCH$_2$), 31.0 (ring C-3), 22.4 (ring C-4), 18.8 (ArCH$_3$), 17.3 (CH$_2$CH$_2$CN); *m/z* 286 (5%, M$^+$), 149 (59, ArCO$^+$), 137 (12, M$^+$ - ArCO), 135 (17), 122 (17), 123 (100, M$^+$ - ArCOCH$_2$), 121 (11, Ar$^+$), 91 (C$_7$H$_7^+$), 83 (18), 82 (15) (Found: M$^+$, 286.1704. $C_{17}H_{22}N_2O_2$ requires 286.1681.); and *(Z)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (15b)* as a colourless solid (11 mg, 4%), R_F (hexane-acetone 2:1) 0.45; ν_{max} 3295 (br, w), 3017 (s), 2889 (w), 1610 (vs), 1583 (s), 1527 (vs), 1511 (vs), 1469 (s), 1297 (s), 1264 (vs), 1090 (s) cm^{-1}; δ_H 10.18 (1H, br s, NH), 7.14 (1H, t, *J* 7.9 Hz, Ar 4-H), 6.75 (2H, overlapping d, *J* 7.5 and 8.1 Hz, Ar 3-H, 5-H), 5.25 (1H, s, =CH), 3.79 (3H, s, OCH$_3$), 3.65 (2H, t, *J* 7.0 Hz, ring NCH$_2$), 2.68 (2H, t, *J* 7.8 Hz, ring 3-H), 2.28 (3H, s, ArCH$_3$), 2.04 (2H, quintet, *J ca* 7.4 Hz, ring 4-H); δ_C 191.8 (C=O), 168.2 (NC=CH), 155.8 (Ar C-2), 135.6 (Ar C-6), 133.0 (Ar C-1), 128.2 (Ar C-4), 122.4 (Ar C-5), 108.2 (Ar C-3), 92.0 (NC=CH), 55.8 (OCH$_3$), 47.6 (ring NCH$_2$), 32.6 (ring C-3), 21.2 (ring C-4), 19.2 (ArCH$_3$); *m/z* 231 (8%, M$^+$), 149 (20, ArCO$^+$), 101 (23), 99 (20), 98 (31), 91, (27, C$_7$H$_7^+$), 83 (20), 70 (33), 44 (28), 43 (37), 41 (30), 40 (100) (Found: M$^+$, 231.1252. $C_{14}H_{17}NO_2$ requires 231.1259).

Acylation of (E)-1-(3-aminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (4b)

(a) With hexanoyl chloride.- Pyridine (0.5 ml, 0.5 g, 6 mmol) and hexanoyl chloride (95μl, 93 mg, 0.69 mmol) were added to **4b** (180 mg, 0.63 mmol) with stirring. The solution was cooled to 0°C, and after 1 h it was diluted with ether (10 ml) and washed with water (10 ml) and saturated sodium chloride solution (2 x 10 ml). The aqueous phases were combined and back-extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (184 mg), which was purified by column chromatography with ethyl acetate/ hexane mixtures and 3%, 5% and 8% solutions of methanol in ammonia-saturated chloroform as eluants to give *(E)-1-(3-hexanoylaminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (5b)* as a yellow oil (104 mg, 43%), R_F (ethyl acetate) 0.08; ν_{max} 3383 (w, N-H), 2965 (s), 2939 (s), 2869 (m), 1722 (m), 1677 (s), 1581 (s), 1540 (vs), 1469 (s), 1266 (vs), 910 (s) cm^{-1}; δ_H 7.11 (1H, t, *J* 7.9 Hz, Ar 4-H), 6.90 (1H, br t, *J ca* 5.4 Hz, NH), 6.73 (2H, overlapping d, *J* 7.6 and 8.6 Hz, Ar 5-H, 3-H), 5.16 (1H, s, =CH), 3.74 (3H, s, OCH$_3$), 3.5 - 2.9, underlying 3.40, 3.17 and 3.09 (8H; br s, ring 3-H; t, *J* 7.24 Hz, ring NCH$_2$; t, *J* 7.0 Hz, chain NCH$_2$; and q, *J* 6.3 Hz, CH$_2$NHCO), 2.24 (3H, s, ArCH$_3$), 2.06 (2H, t, *J* 7.5 Hz, NHCOCH$_2$), 1.94 (2H, br quintet, *J ca* 7.0 Hz, ring 4-H), 1.70 (2H, quintet, *J ca* 7.0 Hz, CH$_2$CH$_2$NHCO), 1.54 (2H, quintet, *J* 7.4 Hz, hexanoyl 3-H), 1.35 - 1.15 (4H, m, hexanoyl 4-H, 5-H), 0.86 (3H, t, *J* 6.7 Hz, CH$_3$); δ_C 190.9 (ArC=O), 173.6 (NHC=O), 165.8 (NC=CH), 155.3 (Ar C-2), 135.0 (Ar C-6), 134.4 (Ar C-1), 127.9 (Ar C-4), 122.4 (Ar C-5), 108.2 (Ar C-3), 91.8 (NC=CH), 55.5 (OCH$_3$), 52.4 (ring NCH$_2$), 43.8 (chain NCH$_2$), 36.6 (CH$_2$NHCO), 36.1 (NHCOCH$_2$), 33.3 (ring C-3), 31.2 (hexanoyl C-4), 26.1 (CH$_2$CH$_2$NHCO), 25.2 (hexanoyl C-3), 22.1 (CH$_2$CH$_3$), 20.5 (ring C-4), 18.8 (ArCH$_3$), 13.7 (CH$_2$CH$_3$); *m/z* 387 (5%, M$^+$ + 1), 386 (27, M$^+$), 258 (27, M$^+$ - C$_5$H$_{11}$CONHCH$_2$), 202 (14), 186 (41), 149 (100, ArCO$^+$), 97 (18) (Found: M$^+$, 386.2568. $C_{23}H_{39}N_2O_3$ requires 386.2569).

(b) With butanoyl chloride.- To a stirred solution of **4b** (127 mg, 0.44 mmol) in pyridine (0.5 ml, 0.5 g, 6 mmol) at 0°C was added butanoyl chloride (50 μl, 51 mg, 0.48 mmol). The mixture was left to stand at -23°C for 67 h, after which further acid chloride (45 μl, 46 mg, 0.43 mmol) was added with stirring. After 1 h, the

mixture was poured into ether (10 ml) and washed with water (10 ml) and saturated sodium chloride solution (2 x 10 ml). The aqueous phases were combined and back-extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil (157 mg), which was purified by column chromatography with ethyl acetate and a 3% solution of methanol in ammonia-saturated chloroform as eluants to give *(E)-1-(3-butanoylaminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)-pyrrolidine (6b)* as a yellow oil (102 mg, 65%), R_F (ethyl acetate) 0.05; ν_{max} 3455 (w, H-bonded N-H), 3381 (w, free N-H), 3071 (w), 3009 (s), 2973 (s), 1668 (s), 1621 (s), 1581 (s), 1538 (vs), 1484 (vs), 1469 (s), 1300 (s), 1260 (s) cm^{-1}; δ_H 7.11 (1H, t, *J* 7.9 Hz, Ar 4-H), 7.04 (1H, br t, *J ca* 5.6 Hz, NH), 6.73 (2H, overlapping d, *J* 7.7 and 8.6 Hz, Ar 5-H, 3-H), 5.29 (1H, s, =CH), 3.74 (3H, s, OCH_3), 3.6 - 2.8, underlying 3.40, 3.17 and 3.08 (8H; br s, ring 3-H; t, *J* 7.2 Hz, ring NCH_2; t, *J* 7.2 Hz, chain NCH_2; and q, *J* 6.3 Hz, CH_2NHCO), 2.24 (3H, s, $ArCH_3$), 2.1 -1.9 and 2.03 (4H; m, ring 4-H; and t, *J* 7.5 Hz, $NHCOCH_2$), 1.69 (2H, quintet, *J ca* 7.1 Hz, CH_2CH_2NHCO), 1.55 (2H, 6 lines, *J ca* 7.4 Hz, CH_2CH_3), 0.85 (3H, t, *J* 7.3 Hz, CH_2CH_3); δ_C 190.9 (ArC=O), 173.4 (NHC=O), 165.7 (NC=CH), 155.2 (Ar C-2), 134.9 (Ar C-6), 134.4 (Ar C-1), 127.9 (Ar C-4), 122.3 (Ar C-5), 108.1 (Ar C-6), 91.5 (NC=CH), 55.4 (OCH_3), 52.4 (ring NCH_2), 43.8 (chain NCH_2), 37.9 (CH_2NHCO), 36.5 ($NHCOCH_2$), 33.4 (ring C-3), 26.0 (CH_2CH_2NHCO), 20.5 (ring C-4), 18.9 (CH_2CH_3), 18.8 ($ArCH_3$), 13.5 (CH_2CH_3); *m/z* 358 (13%, M^+), 258 (16, M^+ - $C_3H_7CONHCH_2$), 202 (13), 188 (10), 186 (32), 150 (11), 149 (100, $ArCO^+$), 128 (30, $C_3H_7CONHC_3H_6^+$), 122 (12), 110 (18), 97 (31), 96 (46), 91 (20, $C_7H_7^+$) (Found: M^+, 358.2256. $C_{21}H_{30}N_2O_3$ requires 358.2256).

1-(3-Aminopropyl)-2-(2-methoxy-6-methylbenzoylmethyl)pyrrolidine (8b)

Sodium cyanoborohydride (26 mg, 0.42 mmol) was added with stirring to a solution of (*E*)-1-(3-aminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (**4b**) (94 mg, 0.33 mmol) in methanol (0.8 ml). Bromocresol green (0.5% in ethanol, 1 drop) was added, followed by hydrochloric acid (12M, 1 drop) such that the pH of the solution was brought to *ca* 4. Sodium hydroxide solution (2 M, 10 ml) was added after 80 min, and the mixture was extracted with chloroform (3 x 10 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (91 mg), which was separated by column chromatography using chloroform saturated with ammonia as eluant, to give *1-(3-aminopropyl)-2-(2-methoxy-6-methylbenzoyl-methyl)pyrrolidine (8b)* as a clear oil (83 mg, 89%), R_F (ammonia-saturated chloroform) 0.21; δ_H 7.12 (1H, t, *J* 8.0 Hz, Ar 4-H), 6.68 (2H, overlapping d, *J* 8.4 and 8.6 Hz, Ar 3-H, 5-H), 3.71 (3H, s, OCH_3), 3.1 - 2.95 (2H, m, ring NCH_aH_b and CH_aH_bCOAr), 2.8 - 2.6 and 2.64 (5H; m, NCH, chain NCH_aH_b and CH_aCH_bCOAr; and t, *J* 6.8 Hz, CH_2NH_2), 2.15 - 2.0 and 2.14 (6H; s, $ArCH_3$; and m, ring and chain NCH_aH_b, ring 3-H_a), 1.75 - 1.4 (5H, m, ring and chain $CH_2CH_2CH_2$, ring 3-H_b), 1.22 (2H, br s, NH_2); δ_C 206.8 (C=O), 155.4 (Ar C-2), 135.3 (Ar C-6), 130.9 (Ar C-1), 129.7 (Ar C-4), 122.8 (Ar C-5), 108.1 (Ar C-3), 60.3 (NCH), 55.3 (OCH_3), 53.3 (ring NCH_2), 52.0 (chain NCH_2), 49.5 (CH_2COAr), 40.6 (CH_2NH_2), 32.4 (chain $CH_2CH_2CH_2$), 30.8 (ring C-3), 22.0 (ring C-4), 18.8 ($ArCH_3$); *cf.* reference 8.

O-*Methylperipentadenine (9b)*

To a stirred solution of (*E*)-1-(3-hexanoylaminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (**5b**) (124 mg, 0.32 mmol) in THF (10 ml) under nitrogen at 0°C was added $LiAlH_4$ (15 mg, 0.38 mmol). After 60 min, further $LiAlH_4$ (12 mg, 0.31 mmol) was added, and after 170 min the mixture was stored at -23°C for 19 h. Water was then added to quench unreacted hydride. The mixture was dried ($MgSO_4$), filtered through Celite and evaporated *in vacuo* to give a yellow oil (118 mg), which was purified by column

chromatography using 0.5% ammonia in isopropyl alcohol as eluant to give *1-(3-hexanoylaminopropyl)-2-(2-methoxy-6-methylbenzoylmethyl)pyrrolidine (O-methylperipentadenine, **9b**)* as a clear oil (88 mg, 71%), R_F (ethanol-ammonia 400:1) 0.69; ν_{max} 3455 (w, H-bonded N-H), 3279 (br, w, free N-H), 3071 (w), 3029 (s), 3011 (s), 2965 (vs), 1660 (vs), 1521 (s), 1471 (vs), 1266 (s), 1225 (s) cm^{-1}; δ_H 7.23 (1H, t, *J* 8.0 Hz, Ar 4-H), 7.12 (1H, br m, NH), 6.78 (2H, overlapping d, *J ca* 7.8 and 8.6 Hz, Ar 5-H, 3-H), 3.81 (3H, s, OCH_3), 3.55 - 3.3 (1H, m, CH_aH_bNHCO), 3.25 - 3.05 (3H, m, CH_aH_bNHCO, ring NCH_aH_b and CH_aH_bCOAr), 3.0 - 2.85 (2H, m, NCH and chain NCH_aH_b), 2.78 (1H, dd, *J* 16.0, 8.8 Hz, CH_aH_bCOAr), 2.37 (1H, dt, *J* 12.1, 5.0 Hz, chain NCH_aH_b), 2.22 (3H, s, $ArCH_3$), 2.2 - 2.05 (4H, m, ring NCH_aH_b, $NHCOCH_2$ and ring 3-H_a), 1.85 - 1.5 (7H, m, ring 4-H, CH_2CH_2NHCO, hexanoyl 3-H and ring 3-H_b), 1.3 - 1.2 (4H, m, hexanoyl 4-H, 5-H), 0.86 (3H, t, *J* 6.6 Hz, CH_2CH_3); δ_C 206.5 (ArC=O), 172.9 (NHC=O), 156.1 (Ar C-2), 135.4 (Ar C-6), 130.7 (Ar C-1), 130.0 (Ar C-4), 123.0 (Ar C-5), 108.3 (Ar C-3), 60.6 (NCH), 55.4 (OCH_3), 53.1 (2 x NCH_2), 49.0 (CH_2COAr), 39.0 (CH_2NHCO), 36.8 ($NHCOCH_2$), 31.4 (hexanoyl C-4), 30.9 (ring C-3), 26.9 (CH_2CH_2NHCO), 25.4 (hexanoyl C-3), 22.3 (CH_2CH_3), 22.2 (ring C-4), 18.9 ($ArCH_3$), 13.8 (CH_2CH_3); *m/z* 388 (5%, M^+), 246 (11), 239 (11, M^+ - ArCO), 232 (16, M^+ - $C_5H_{11}CONHC_3H_6$), 276 (14), 225 (89, M^+ - $ArCOCH_2$), 224 (14), 157 (11), 156 (100, $C_5H_{11}CONHC_3H_6^+$), 149 (48, $ArCO^+$), 135 (14), 99 (14), 96 (21), 91 (19, $C_7H_7^+$) (Found: M^+, 388.2725. $C_{23}H_{36}N_2O_3$ requires 388.2725).

O-*Methyldinorperipentadenine (**10b**)*

The above procedure was repeated with (*E*)-1-(3-butanoylaminopropyl)-2-(2-methoxy-6-methylbenzoylmethylene)pyrrolidine (**6b**) (83 mg, 0.23 mmol), THF (15 ml) and $LiAlH_4$ (18 + 9 + 9 mg, 0.94 mmol). After workup, the crude yellow oil obtained (77 mg) was purified by column chromatography using ammonia/isopropyl alcohol mixtures as eluant to give starting material as a clear oil (13 mg, 16%) and *1-(3-butanoylaminopropyl)-2-(2-methoxy-6-methylbenzoylmethyl)pyrrolidine (O-methyldinorperipentadenine, **10b**)* as a yellow oil (46 mg, 55%), R_F (isopropyl alcohol-ammonia 200:1) 0.51; ν_{max} 3455 (w, H-bonded N-H), 3277 (br, w, H-bonded N-H), 3029 (s), 3011 (s), 2973 (s), 1714 (vs), 1660 (s), 1521 (s), 1471 (s), 1366 (s), 1266 (s), 1229 (s), 670 (s) cm^{-1}; δ_H 7.23 (1H, m, *J* 8.0 Hz, Ar 4-H), 7.10 (1H, br m, NH), 6.78 (2H, overlapping d, *J* 7.8, 8.3 Hz, Ar 3-H, 5-H), 3.80 (3H, s, OCH_3), 3.49 (1H, ddd, *J* 13.4, 12.0, 5.8 Hz, CH_aH_bNHCO), 3.25 - 3.1 (3H, m, CH_aH_bNHCO, ring NCH_aH_b and CH_aH_bCOAr), 2.95 - 2.85 (2H, m, NCH and chain NCH_aH_b), 2.79 (1H, dd, *J* 15.8, 8.8 Hz, CH_aH_bCOAr), 2.35 (1H, dt, *J* 12.2, 5.1 Hz, chain NCH_aH_b), 2.22 (3H, s, $ArCH_3$), 2.25 - 2.05 and 2.14 (4H; m, ring NCH_aH_b and ring 3-H_a; and *J* 7.4 Hz, $NHCOCH_2$), 1.85 - 1.5 and 1.62 (7H, m, ring 4-H, CH_2CH_2NHCO and ring 3-H_b; and 6 lines, *J ca* 7.3 Hz, CH_2CH_3), 0.91 (3H, t, *J* 7.3 Hz, CH_2CH_3); δ_C 206.6 (ArC=O), 172.7 ($NHC=O$), 156.1 (Ar C-2), 135.5 (Ar C-6), 130.7 (Ar C-1), 130.0 (Ar C-4), 123.0 (Ar C-5), 108.2 (Ar C-3), 60.6 (NCH), 55.4 (OCH_3), 53.1 (2 signals, NCH_2), 49.1 (CH_2COAr), 39.0 (CH_2NHCO), 38.7 ($NHCOCH_2$), 30.8 (ring C-3), 27.0 (CH_2CH_2NHCO), 22.2 (ring C-4), 19.1 (CH_2CH_3), 18.9 ($ArCH_3$), 13.7 (CH_2CH_3); *m/z* 361 (1%, M^+ + 1), 360 (4, M^+), 232 (10, M^+ - $C_3H_7CONHC_3H_6$), 198 (10), 197 (75, M^+ - $ArCOCH_2$), 196 (12), 149 (39, $ArCO^+$), 135 (14), 128 (100, $C_3H_7CONHC_3H_6^+$), 96 (16), 91 (16, $C_7H_7^+$) (Found: M^+, 360.2411. $C_{21}H_{32}N_2O_3$ requires 360.2413).

*Peripentadenine (**1**)*

To a stirred solution of *O*-methylperipentadenine (**9b**) (64 mg, 0.16 mmol) in dry dichloromethane (10 ml) at 0°C was added *via* a cannula a solution of boron tribromide (0.2 ml, 0.5 g, 2 mmol) in dry dichloromethane

(2 ml). The mixture was allowed to warm to room temperature over 4.5 h. It was again cooled to 0°C, and saturated sodium chloride solution was added dropwise with stirring over 10 min. The mixture was separated, and the aqueous phase was extracted with chloroform (2 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow foam (76 mg), which was purified by column chromatography using 0.25% ammonia in isopropyl alcohol as eluant to give *peripentadenine (1)*[8] as a yellow oil (55 mg, 92%), R_F (isopropyl alcohol-ammonia 400:1) 0.41; ν_{max} 3263 (br, m), 2995 (m), 2965 (vs), 2867 (m) 1660 (vs), 1606 (s), 1587 (s), 1534 (s), 1467 (vs), 1289 (s) cm^{-1}; δ_H (pyridine-d_5) *ca* 8.6 (1H, br s, NH), 7.22 (1H, t, *J* 7.8 Hz, Ar 4-H), 7.02 (1H, d, *J* 8.1 Hz, Ar 3-H), 6.77 (1H, d, *J* 7.5 Hz, Ar 5-H), 4.2 - 4.0 (2H, m, ring NCH_aH_b and OH?), 3.85 -3.3 and 3.55 (5H, m, CH_aH_bCOAr, ring $NCHCH_2$ and chain NCH_aH_b; and q, *J* 6.3 Hz, CH_2NHCO), 3.2 -3.0 (1H, m, H_aH_bCOAr), 3.0 - 2.8 (1H, m, chain NCH_aH_b), 2.5 - 1.9, 2.35 and 2.34 (10H, m, ring NCH_aH_b, ring 3-H, ring 4-H; t, *J* 7.5 Hz, $NHCOCH_2$; and s, $ArCH_3$), 1.9 - 1.6 and 1.73 (4H, m, chain $NCH_2CH_2CH_2NH$; and quintet, *J* 7.5 Hz, $NHCOCH_2CH_2$), 1.3 - 1.1 (4H, m, $CH_2CH_2CH_3$), 0.76 (3H, t, *J* 7.0 Hz, chain CH_3); δ_C 203.6 (ArC=O), 175.2 (NHC=O), 156.1 (Ar C-2), 137.0 (Ar C-1), 131.8 (Ar C-4), 126.5 (Ar C-6), 122.2 (Ar C-5), 114.6 (Ar C-3), 64.3 (ring NCH), 53.1 (ring NCH_2), 51.6 (chain NCH_2), 45.1 (CH_2COAr), 36.4 (CH_2NHCO), 36.3 (hexanoyl C-2), 31.3 (hexanoyl C-4), 30.2 (ring C-3), 25.5 (chain $NCH_2CH_2CH_2NH$), 25.3 (hexanoyl C-3), 22.2 (hexanoyl C-5), 21.9 (ring C-4), 20.3 ($ArCH_3$), 13.8 (chain CH_3); *m/z* 375 (1%, M^+ + 1), 374 (3, M^+), 225 (30, M^+ - $ArCOCH_2$), 224 (10), 156 (56, $C_5H_{11}CONHC_3H_6^+$), 153 (15), 150 (28), 136 (14), 135 (100, $ArCO^+$), 125 (21), 109 (12), 107 (19, Ar^+) (Found: M^+, 374.2569. $C_{22}H_{34}N_2O_3$ requires 374.2569).

Dinorperipentadenine (2)

The above procedure was repeated with *O*-methyldinorperipentadenine (**10b**) (30 mg, 83 μmol) in dichloromethane (5 ml), and boron tribromide (80 μl, 0.2 g, 0.9 mmol) in dichloromethane (2 ml). Workup yielded a yellow oil (30 mg), which was purified by flash chromatography using methanol/benzene/ethyl acetate 1/2/1 and 1/1/1 as eluant to give *dinorperipentadenine (2)*[9] as a yellow oil (17 mg, 59%), R_F (isopropyl alcohol-ammonia 400:1) 0.33; ν_{max} 3290 (br, m), 2970 (s), 2940 (sh, s), 1658 (s), 1651 (s), 1462 (s), 907 (vs) cm^{-1}; δ_H 7.37 (1H, br s, NH), 7.17 (1H, t, *J* 7.8 Hz, Ar 4-H), 6.94 (1H, d, *J* 8.0 Hz, Ar 3-H), 6.71 (1H, d, *J* 7.5 Hz, Ar 5-H), 3.95 - 3.6 (3H, m, OH? and CH_2NHCO), 3.6 - 3.15 (4H, m, ring NCH_aH_b, CH_2COAr and ring $NCHCH_2$), 3.15 - 2.9 (2H, m, chain NCH_2), *ca* 2.44 (1H, m, ring NCH_aH_b), 2.32 (3H, s, $ArCH_3$), 2.3 - 1.95 and 2.18 (8H; m, ring 3-H, ring and chain $CH_2CH_2CH_2$; and t, *J* 7.5 Hz, $NHCOCH_2$), 1.59 (2H, 6 lines, *J ca* 7.4 Hz, chain CH_2CH_3), 0.87 (3H, t, *J* 7.3 Hz, chain CH_3); δ_C 203.4 (ArC=O), 175.1 (NHC=O), 156.7 (Ar C-2), 137.4 (Ar C-1), 132.3 (Ar C-4), 125.9 (Ar C-6), 122.6 (Ar C-5), 114.9 (Ar C-3), 64.5 (ring $NCHCH_2$), 53.1 (ring NCH_2), 51.7 (chain NCH_2), 45.1 (CH_2COAr), 38.2 ($NHCOCH_2$), 36.3 (CH_2NHCO), 30.3 (ring C-3), 25.6 (chain $NCH_2CH_2CH_2NH$), 21.8 (ring C-4), 20.8 ($ArCH_3$), 19.1 (chain CH_2CH_3), 13.7 (chain CH_3); *m/z* 346 (3%, M^+), 197 (18, M^+ - $ArCOCH_2$), 150 (45), 136 (9), 135 (100, $ArCO^+$), 107 (8, Ar^+), 82 (12), 77 (13) (Found: M^+, 346.2260. $C_{20}H_{30}N_2O_3$ requires 346.2256).

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