Synthesis and utilisation of 6-aminotetrahydrobenzo[7]annulenes

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7,8-Dichloro-1,2,3,4,5,6-hexahydrobenzo[*f*]quinolin-3-one 10 (R = H) is obtained by reaction of 5,6-dichloro-3,4-dihydronaphthalen-2(1*H*)-one pyrrolidine enamine 9 with acrylamide and is *N*-alkylated to 7,8-dichloro-1,2,3,4,5,6-hexahydro-4-propylbenzo[*f*]quinolin-3-one 10 (R = Pr^n). 6,7,8,9-Tetrahydro-2-methoxy-5*H*-benzo[7]annulen-6-one 5 (R = H) is converted to *N*,*N*-dipropyl(6,7,8,9-tetrahydro-2-methoxy-5*H*-benzo[7]annulen-6-yl)amine 8 and *via* the pyrrolidine enamine is reacted with acrylamide to give 2,3,4,5,6,7-hexahydro-9-methoxy-1*H*-benzo[3,4]cyclohepta[1,2-*b*]pyridin-3-one 11 (R = H) and 2,3,4,4a,5,6-hexahydro-8-methoxy-1*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-2-one 12 (R = H). Each of these is *N*-alkylated to give 11 (R = Pr^n) and 12 (R = Pr^n) which are reduced individually to 2,3,4,4a,5,6,7,11b-octahydro-9-methoxy-4-propyl-1*H*-benzo[3,4]cyclohepta[1,2-*b*]pyridine 14 (X = Y = H) and 2,3,4,4a,5,6,11,11a-octahydro-8-methoxy-1-propyl-1*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine 15 (X = Y = H) respectively. The hydroxyimino derivative 19 (R = H) of 6,7,8,9-tetrahydro-1,2-dimethoxy-5*H*-benzo[7]annulen-5-one 18 is methylated to give 19 (R = Me) which with ethyl lithiopropiolate yields ethyl 3-(6,7,8,9-tetrahydro-5-hydroxy-1,2-dimethoxy-6-methoxyimino-5*H*-benzo[7]annulen-5-yl)propiolate 20 which is catalytically reduced to 21. 6,7,8,9-Tetrahydro-1,2-dimethoxy-6-propionamido-5*H*-benzo[7]annulen-5-one 22 prepared from 19 (R = H) is reacted with sodium borohydride to give both *cis*- and *trans*-6,7,8,9-tetrahydro-5-hydroxy-1,2-dimethoxy-6-propionamido-5*H*-benzo[7]annulen-5-ol 24 and 23 which are separately reduced by BH_3–THF to *cis*- and *trans*-6,7,8,9-tetrahydro-5-hydroxy-1,2-dimethoxy-6-propylamino-5*H*-benzo[7]annulen-5-ol 26 and 25. The latter is reacted with chloroacetyl chloride and thence in two steps gives *trans*-2,3,4,4a,5,6,7,11b-octahydro-8,9-dimethoxy-4-propylbenzo[6,7]cyclohept[1,2-*b*][1,4]oxazine 29.

The concept of conformational restriction in β-phenylethylamine structures has provided a stimulus for the synthesis of novel organic molecules of pharmacological interest.[1–3] Arising from some of our previous work,[4,5] our attention has been directed towards 6-aminobenzosuberane (6-amino-tetrahydrobenzo[7]annulene) structures **1** which could be elaborated into conformationally restricted fused or bridged molecules. This paper describes two general approaches to the required structures and applications arising therefrom.

Results and discussion

The so-called Wittig–Prévost protocol has proved very useful in converting α-tetralones **2** into benzosuber-6-ones **3**.[4–7] This novel approach provides means for functionalisation of the 6-position not very easily available previously.[8,9] We have exploited this to obtain benzo[3,4]cyclohepta[1,2-*b*]pyrrole derivatives[5,7] **4** (R^1 = H, Me; R^2 = Me, Pr^n; R^3 = H, OMe).

Conversion of 2-methoxybenzosuber-6-one **5** (R = H) into enamines **6** and **7** was straightforward. Reduction of **6** gave **8**, isolated as a difumarate. Analogous amino tetralin structures have been reported.[10]

Cannon *et al.*[11] have demonstrated that acrylamide is an effective reagent for annelating pyridine rings onto β-tetralones *via* their enamines. In the present case, however, enamine **7** failed to react with acrylamide in toluene, DMF or dioxane. Since 5,6-dichloro β-tetralone pyrrolidine enamine **9** was freely available,[12] it was utilised to investigate the acrylamide reaction. This research revealed that a 58% yield of the benzo[*f*]quinolin-3-one analogue **10** (R = H) could be obtained only when the enamine and acrylamide were heated *neat* at 100 °C in the presence of toluene-*p*-sulfonic acid. Alkylation to give **10** (R = Pr^n) was effected in 74% yield with potassium *tert*-butoxide and 1-bromopropane in refluxing *tert*-butyl alcohol.[13]

Accordingly enamine **7** was subjected to similar treatment with acrylamide giving rise to three chromatographically separable products. The first was the ketone **5** (R = H) (29%) whilst the second (21%) appeared to be the expected lactam **11** (R = H) judged by the usual spectroscopic and analytical criteria (see Experimental section). The third component (15%)

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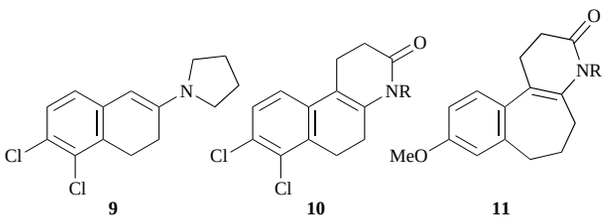
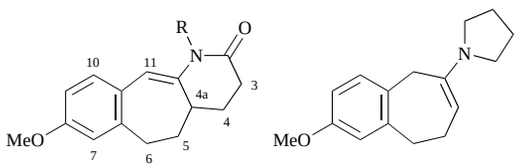


9 **10** **11**

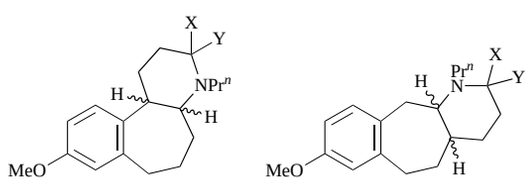


12 **13**

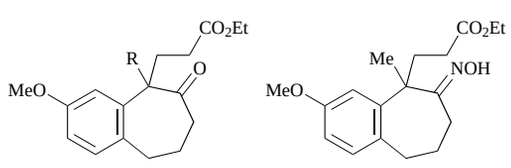
was also crystalline and isomeric ($C_{15}H_{17}NO_2$) with the second product. The plausible formulation **12** (R = H) for this third material was supported by spectroscopy, particularly by the appearance of a vinylic proton doublet (δ 5.8, J = 1.7 Hz) in the ^{1}H NMR spectrum and by the presence of 15 non-equivalent carbon atoms in the ^{13}C NMR spectrum. Furthermore the ^{13}C^1 j mod spectrum revealed four methylene groups and two methine groups, δ 33.9 and 109.8, the latter being considered to be due to the vinyl centre. Additionally, four magnetically non-equivalent protons on C_4,C_5 (δ 2.1, 2.0, 1.8, 1.6) attest to the presence of a neighbouring methine centre (δ 33.9, C_{4a}). Finally, correlated spectroscopy (COSY) and ^{13}C–^{1}H direct correlation spectroscopy (HCCOB1) confirmed structure **12** (R = H).

Since enamines (**6** and **7**) were used without purification, in the case of **7** it has to be said that the ketone **5** (R = H) was incompletely converted and that the enamine **7** was accompanied by a significant amount of the isomer **13**. This was certainly not expected since β-tetralone enamine, for example, is methylated exclusively at the benzylic carbon atom,[14] implying that β-tetralone enamine is homogenous. We presume that the greater flexibility of the seven-membered ring allows a conformational preference for **13** to counteract the conjugational advantage in **7**: fortuitously it leads to syntheses of two differently fused novel pyridobenzosuberanes.

N-Alkylation of compounds **11** (R = H) and **12** (R = H) as described for **10** (R = Pr^n) gave **11** (R = Pr^n) and **12** (R = Pr^n) respectively in excellent yields. Reduction of the double bond in each case ($NaCNBH_3$–CH_3CN–CH_3CO_2H) gave lactams **14**



14 **15**

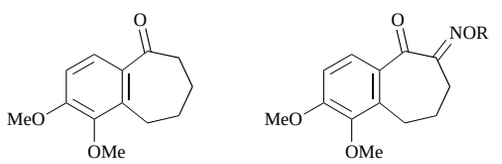


16 **17**

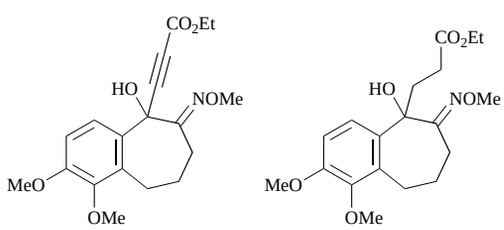
(X + Y = O) and **15** (X + Y = O) which were not isolated but were immediately reduced to **14** (X = Y = H) and **15** (X = Y = H); in the first case with $LiA1H_4$, in the second example (**15**) diborane proved to be better. It was not possible to separate the *cis*- and *trans*-isomers by flash chromatography in either **14** (X = Y = H) or **15** (X = Y = H).

The indifferent yield of **11** (R = H) obtained above stimulated interest in finding an alternative route to this ring system. Ketone **5** (R = H) which had been alkylated with ethyl bromoacetate,[7] could not be alkylated with ethyl 3-bromopropanoate (LDA–THF) although ketone **3** (R = Me, X = 7-OMe, Y = H)[5] was successfully converted to **16** (R = Me) by the same procedure. The oxime **17** (82% yield) might be considered a candidate for reductive cyclisation but this was not further investigated since a pendant methyl group was not desirable in the present work. Previously we have found that enamine **7** could be alkylated with ethyl iodoacetate,[7] however, all attempts to induce this enamine to react with three carbon electrophiles were unsuccessful so that the keto ester **5** (R = $CH_2CH_2CO_2R$) was unavailable. Although these failures are not understood, it is perhaps significant that previous workers[15] have noted a reluctance of a trimethoxy analogue of **5** (R = H) to undergo alkylation.

The classical method[16–21] for C-6 amination of benzosuberanes involves α-oximation of benzosuber-5-ones followed by reduction. In pursuance of an alternative synthesis for pyridobenzosuberanes (*e.g.* **14**), the oximation of the freely available[22] dimethoxybenzosuber-5-one **18** was briefly examined. This



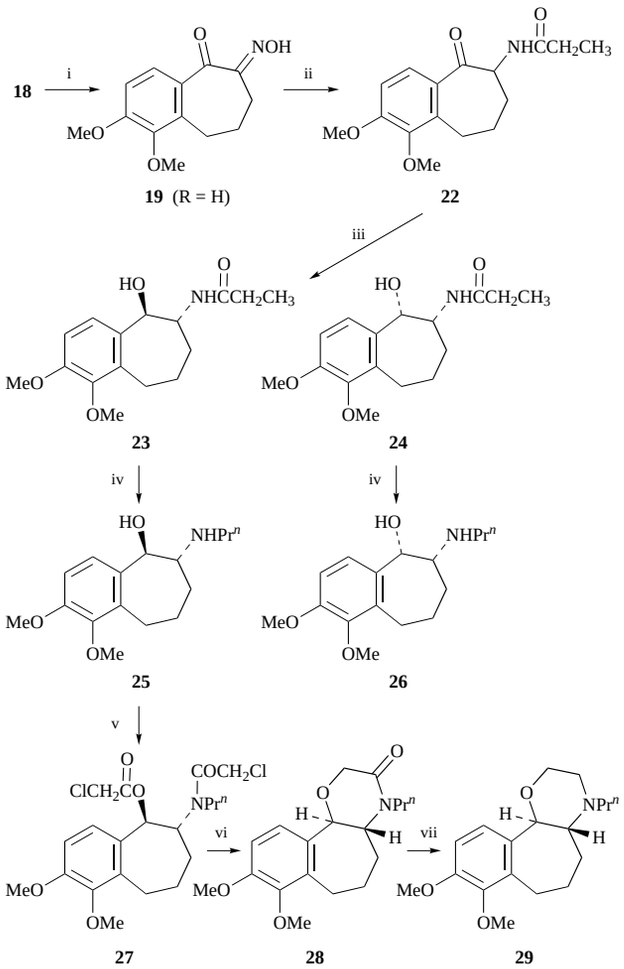
18 **19**



20 **21**

oximino ketone[20] **19** (R = H) (obtained in 96% yield: see Experimental section) was methylated to **19** (R = Me, 74%). Introduction of a three carbon nucleophile (*e.g.* $^-CH_2CH_2CO_2R$) to ketones is not easy,[23] but the lithio derivatives of ethyl propiolate ($LiC{\equiv}CCO_2Et$) has found some favour.[24–26] In the present case, the latter reagent reacted (84%) with **19** (R = Me) to give **20**. Catalytic hydrogenation of the latter gave **21** (90%) which contains the elements required for pyridobenzosuberane synthesis but was not further explored due to lack of resources. The oximino ketone **19** (R = H) has, however, proved to be a useful precursor for an 1,4-oxazinobenzosuberane.

Our synthesis of the novel octahydrobenzo[6,7]cyclohept-[1,2-*b*][1,4]oxazine ring system is outlined in Scheme 1. Catalytic hydrogenation of **19** (R = H) in the presence of propanoic anhydride gave the propionamido ketone **22** in moderate (66%) yield. The latter was reduced by sodium borohydride to give a mixture of diastereoisomers (93%) which were separated chromatographically to afford the *trans*- and *cis*-isomers **23** and **24** in a 3:1 ratio respectively. These diastereoisomers were separately converted by diborane in THF to the *n*-propylamino alcohols **25** (65%) and **26** (58%). Thereafter the *trans*-amino alcohol **25** reacted with chloroacetyl chloride and sodium hydroxide to furnish the *O*,*N*-bis(chloroacetyl) derivative **27** (54%) which readily underwent cyclisation to the tricyclic oxazinone **28** upon treatment with alcoholic potassium hydroxide. Lack of sufficient quantities of the *cis*-amino alcohol **26** frustrated a similar approach being made towards the *cis*-fused isomer. Finally, reduction of the carbonyl group in the lactam **28** was achieved using $LiAiH_4$ in refluxing THF to produce the *trans*-fused oxazine **29** (72%).



Scheme 1 *Reagents and conditions*: i, Isoamyl nitrite, HCl (g), Et_2O; ii, H_2, Pd–C, $(CH_3CH_2CO)_2O$; iii, $NaBH_4$, EtOH; iv, BH_3–THF; v, $ClCH_2COCl$, NaOH, $Cl(CH_2)_2Cl$, H_2O; vi, KOH, EtOH, room temp.; vii, $LiAlH_4$

Experimental

For general remarks see ref. 27.

N,*N*-Dipropyl(6,7,8,9-tetrahydro-2-methoxy-5*H*-benzo[7]annulen-6-yl)amine 8

A mixture of ketone **5** (R = H) (0.5 g, 2.75 mmol), di-*n*-propylamine (1.06 g, 10 mmol) and toluene-*p*-sulfonic acid (0.1 g) in dry benzene (30 cm^3) was refluxed for 12 h in a Dean and Stark apparatus. The mixture was cooled to room temperature whereupon ethanol (50 cm^3) and palladium on charcoal catalyst (0.1 g, 10%) were added. The mixture was hydrogenated overnight at an initial hydrogen pressure of 45 psi. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give a brown oil. Flash chromatography (70% ethyl acetate–hexane) gave a golden oil (0.136 g, 18%). The fumarate was recrystallised three times from ethanol to give a buff solid, mp 151–153 °C [Found: C, 61.7; H, 7.4; N, 2.5%; M^+ (free-base), 275.2249. $C_{18}H_{29}NO{\cdot}C_8H_8O_8$ requires: C, 61.5; H, 7.3; N, 2.75%; *M* (free-base), 275.2228]; ν_{max}(liquid film, free-base)/cm^{-1} 1610 (C=C); δ_H 9.8–8.9 (4H, br, exch., 4 × CO_2H), 7.1 (1H, d, aryl), 6.9–6.8 (2H, m, aryl), 6.5 (4H, s, 4 × vinyl), 3.85 (3H, s, OCH_3), 3.1–2.8 (5H, m, 2 × CH_2 + CHN), 2.75 (2H, m, CH_2), 2.6 (2H, m, CH_2), 2.15–1.9 (4H, m, 2 × CH_2), 1.75–1.6 (4H, m, 2 × CH_2) and 1.0 (6H, t, 2 × CH_3).

7,8-Dichloro-1,2,3,4,5,6-hexahydrobenzo[*f*]quinolin-3-one 10 (R = H)[12]

A mixture of 5,6-dichloro-3,4-dihydronaphthalen-2(1*H*)-one pyrrolidine enamine **9** (5 g, 19 mmol), acrylamide (2.7 g, 38 mmol) and toluene-*p*-sulfonic acid (0.1 g) was stirred vigorously at 100 °C for 3 h. The molten mixture was allowed to cool to room temperature and water (40 cm^3) was added. The brown solid that precipitated was collected and triturated with hot ethanol to give the title compound as a pale brown powder (2.95 g, 58%), mp >230 °C (Found: C, 57.9; H, 4.2; N, 5.3; Cl, 25.6%; M^+, 271.0162, 269.0190, 267.0212. $C_{13}H_{11}NOCl_2$ requires: C, 58.2; H, 4.1; N, 5.3; Cl, 26.5%; *M*, 271.0159, 269.0188, 267.0218); ν_{max}(Nujol)/cm^{-1} 3240 (N–H), 1680 (C=O) and 1610 (C=C); δ_H 9.55 (1H, s, exch., N*H*), 7.4 (1H, d, aryl), 7.1 (1H, d, aryl), 2.9 (2H, t, CH_2), 2.6–2.4 (4H, m, 2 × CH_2) and 2.3 (2H, t, CH_2).

7,8-Dichloro-1,2,3,4,5,6-hexahydro-4-propylbenzo[*f*]quinolin-3-one 10 (R = Pr^n)

To a solution of potassium *tert*-butoxide (1.47 g, 12 mmol) in *tert*-butyl alcohol (50 cm^3) at room temperature under nitrogen, was added the lactam **10** (R = H) (2.41 g, 9 mmol) in portions. The resulting mixture was heated at reflux for 2 h, and then allowed to cool to 40 °C whereupon 1-bromopropane (1.35 g, 11 mmol) was added dropwise. The mixture was stirred at 60 °C overnight and then allowed to cool to room temperature. Water (100 cm^3) was added and the mixture was extracted with ether (4 × 50 cm^3). The combined organic extracts were washed with water (2 × 50 cm^3), then dried and the solvent was removed *in vacuo* to give a brown solid. Flash chromatography (2% ethanol–chloroform) gave the title compound as a white powder (2.07 g, 74%), mp 150–151 °C (Found: C, 61.8; H, 5.6; N, 4.4; Cl, 23.0%; M^+, 313.0623, 311.0664, 309.0697. $C_{16}H_{17}NOCl_2$ requires: C, 61.9; H, 5.5; N, 4.5; Cl, 22.9%; *M*, 313.0628, 311.0658, 309.0687); ν_{max}(Nujol)/cm^{-1} 1685 (C=O) and 1610 (C=C); δ_H 7.3 (1H, d, aryl), 7.0 (1H, d, aryl), 3.65–3.6 (2H, t, CH_2), 3.1–3.05 (2H, t, CH_2), 2.7–2.5 (6H, m, 2 × CH_2 + CH_2), 1.6–1.5 (2H, m, CH_2) and 0.9 (3H, t, CH_3).

Reaction of 6,7,8,9-tetrahydro-2-methoxy-5*H*-benzo[7]annulen-6-one 5 (R = H) with pyrrolidine and acrylamide

To a stirred solution of ketone **5** (R = H) (1.5 g, 7.8 mmol) and toluene-*p*-sulfonic acid (0.1 g) in dry benzene (40 cm^3) was added pyrrolidine (1.11 g, 15.6 mmol) and the resulting mixture was heated at reflux in a Dean and Stark apparatus for 2 h. The solvent was then removed under reduced pressure to give the enamine as a brown oil which was not purified further. Acrylamide (1.11 g, 15.6 mmol) was added in one portion to the oil and the resulting dark mixture was stirred vigorously at 100 °C for 3 h and then allowed to cool to room temperature. Water (30 cm^3) was added and the mixture was extracted with dichloromethane (5 × 100 cm^3). The combined organic extracts were dried and the solvent was removed *in vacuo* to give a brown gum. Flash chromatography (80% ethyl acetate–hexane) permitted the separation of three components. The first compound eluted from the column was unreacted starting material **5** (R = H) (0.435 g, 29% recovery) identified by TLC and ^1H NMR comparison with an authentic sample of the ketone. The second component obtained from the column was 2,3,4,5,6,7-*hexahydro*-9-*methoxy*-1H-*benzo*[3,4]*cycloheptal*[1,2-b]*pyridin*-3-*one* **11** (R = H) as a white powder. Recrystallisation from ethanol gave white crystals (0.4 g, 21%), mp 202–203 °C (Found: C, 73.9; H, 7.0; N, 5.6%; M^+, 243.1261. $C_{15}H_{17}NO_2$ requires: C, 74.1; H, 7.0; N, 5.75%; *M*, 243.1259); ν_{max}(Nujol)/cm^{-1} 3310 (N–H) and 1690 (C=O, lactam) δ_H 8.1 (1H, s, exch., NH), 7.1 (1H, d, aryl), 6.7 (2H, m, aryl), 3.8 (3H, s, OCH_3), 2.8–2.5 (6H, m, 2 × CH_2 + CH_2), 2.2 (2H, m, CH_2) and 2.05 (2H, t, CH_2). This was followed from the column by 2,3,4,4a,5,6-*hexahydro*-8-*methoxy*-1H-*benzo*[5,6]*cyclohepta*[1,2-b]*pyridin*-2-*one* **12** (R = H) as an off-white solid. Recrystallisation from ethanol gave colourless crystals (0.28 g, 15%), mp 177–179 °C (Found: C, 74.1; H, 7.0; N, 5.6%; M^+, 243.1267. $C_{15}H_{17}NO_2$ requires: C, 74.1; H, 7.0; N, 5.75%; *M*, 243.1259) ν_{max}(Nujol)/cm^{-1} 3305 (N–H) and 1685 (C=O), lactam); δ_H 8.5 (1H, s, exch., NH), 7.0 (1H, d, aryl), 6.7 (2H, m, aryl), 5.9 (1H, d, *J* 1.7, vinyl), 3.8 (3H,

s, OCH_3), 2.8–2.7 (2H, m, CH_2), 2.65–2.6 (1H, m, CH), 2.55–2.4 (2H, m, CH_2), 2.2–2.1 (1H, m, CH_2), 2.0–1.9 (1H, m, CH_2), 1.85–1.8 (1H, m, CH_2) and 1.7–1.6 (1H, m, CH_2); δ_C 171.1 (C=O), 158.0 (ArOCH_3, *ipso*), 141.2, 137.6, 132.0 (aryl), 127.4 (CH=*C*), 115.1, 111.3 (aryl), 109.8 (*C*H=C), 55.4 (ArO*C*H$_3$), 38.9 (*C*H–C=), 34.7 (Ar*C*H$_2$CH$_2$), 33.0 (ArCH$_2$*C*H$_2$), 31.0 (CO*C*H$_2$CH$_2$) and 27.0 (COCH$_2$*C*H$_2$).

2,3,4,5,6,7-Hexahydro-9-methoxy-4-propyl-1*H*-benzo[3,4]-cyclohepta[1,2-*b*]pyridin-3-one 11 (R = Pr^n)

To a stirred solution of potassium *tert*-butoxide (0.75 g, 6.69 mmol) in *tert*-butyl alcohol (30 cm^3) at room temperature under nitrogen, was added lactam **11** (R = H) (1.2 g, 5 mmol) in four equal portions. The resulting suspension was heated at 90 °C for 2 h and then cooled to room temperature, whereupon 1-bromopropane (0.98 g, 8 mmol) was added dropwise. The reaction mixture was then heated at 65 °C for 4 h and again cooled to room temperature. Water (100 ml) was added and the mixture was extracted with ether (4 × 75 cm^3). The combined extracts were washed with brine, then dried and evaporated to leave an oil. Flash chromatography (30% ethyl acetate–hexane) gave the title compound as an off-white solid (1.27 g, 89%), mp 142–144 °C (Found: C, 75.7; H, 7.95; N, 4.9%, M$^+$, 285.1738. $C_{18}H_{23}NO_2$ requires: C, 75.8; H, 8.05; N, 4.9%; *M*, 285.1729); ν_{max}(Nujol)/cm^{-1} 1690 (C=O, lactam); δ_H 7.1 (1H, d, aryl), 6.8–6.7 (2H, m, aryl), 3.8 (3H, s, OCH_3), 3.6 (2H, t, CH_2), 2.6–2.4 (6H, m, 2 × CH_2 + CH_2), 2.2–2.1 (4H, m, 2 × CH_2), 1.7–1.5 (2H, m, CH_2) and 1.0–0.9 (2H, t, CH_3).

***cis*- and *trans*-2,3,4,4a,5,6,7,11b-Octahydro-9-methoxy-4-propyl-1*H*-benzo[3,4]cyclohepta[1,2-*b*]pyridine 14 (X = Y = H)‡**

To a stirred suspension of compound **11** (R = Pr^n) (0.25 g, 0.88 mmol) in acetonitrile (20 cm^3) at room temperature under nitrogen was added sodium cyanoborohydride (0.13 g, 2 mmol) in portions. Glacial acetic acid was added to maintain the reaction mixture at pH 6 and stirring was continued at room temperature overnight. The reaction was quenched with concentrated hydrochloric acid (5 cm^3) and the solvent was removed *in vacuo*. The residue was taken up in aqueous sodium hydroxide (25 cm^3, 10%) and extracted with dichloromethane (5 × 50 cm^3). The combined organic extracts were washed with brine, then dried and the solvent was removed *in vacuo* to give a viscous oil (0.22 g, 87%) which was used immediately without further purification. This oil was dissolved in THF (10 cm^3) and added dropwise to a suspension of lithium aluminium hydride (0.047 g, 1.23 mmol) in dry THF (10 cm^3) at room temperature under nitrogen. The resulting mixture was refluxed for 1 h and then stirred at room temperature for a further 2 h. Ethanol (1 cm^3) was added carefully, followed by saturated aqueous sodium sulfate (4 cm^3). The inorganic salts were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether (20 cm^3) and was washed with brine. The organic layer was dried and the solvent was removed to give an oil which was purified by column chromatography (alumina, 20% ethyl acetate–hexane) to give the title compound as a viscous clear oil (0.172 g, 82%) (Found: C, 78.9; H, 9.7; N, 4.9%; M$^+$, 273.2093. $C_{18}H_{27}NO$ requires: C, 79.1; H, 9.9; N, 5.1%; *M*, 273.2093); ν_{max}(liquid film)/cm^{-1} 1610 (C=C); δ_H 7.1 (1H, 2 × d, aryl), 6.7–6.6 (2H, m, aryl), 3.8 [3H, 2 × s, OCH_3, *cis*:*trans* (1:4)], 3.1–3.05 (2H, m, CH_2), 2.8–2.75 (1H, m, CHN), 2.7–2.6 (2H, m, CH_2), 2.5–2.4 (2H, m, CH_2), 2.1–2.0 (2H, m, CH_2), 1.9–1.7 (5H, m, 2 × CH_2 + CH), 1.6–1.2 (4H, m, 2 × CH_2) and 0.9–0.8 (3H, 2 × t, CH_3). The ratio of *cis*:*trans*-isomers was estimated as 1:4 respectively.

2,3,4,4a,5,6-Hexahydro-8-methoxy-4-propyl-1*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-2-one 12 (R = Pr^n)

To a stirred solution of potassium *tert*-butoxide (1.25 g, 11.14 mmol) in *tert*-butyl alcohol (100 cm^3) at room temperature under nitrogen was added the lactam **12** (R = H) (2.4 g, 9.88 mmol) in portions. The resulting mixture was refluxed, for 1 h and then allowed to cool to room temperature, whereupon 1-bromopropane (1.46 g, 11.88 mmol) was added dropwise. The mixture was heated at 60 °C overnight and then again allowed to attain room temperature. Water (150 cm^3) was added and the mixture was extracted with ether (4 × 100 cm^3). The combined organic extracts were washed with brine, then dried and the solvent was removed *in vacuo* to give an orange oil. Flash chromatography (50% ethyl acetate–hexane) gave the title compound as a pale yellow oil (2.44 g, 87%) (Found: C, 75.5; H, 8.1; N, 4.6; M$^+$, 285.1729. $C_{18}H_{23}NO_2$ requires: C, 75.8; H, 8.1; N, 4.9%; *M*, 285.1729); ν_{max}(liquid film)/cm^{-1} 1685 (C=O, lactam) and 1610 (C=C); δ_H 7.1 (1H, d, aryl), 6.8 (2H, m, aryl), 6.0 (1H, s, vinyl), 3.8 (3H, s, OCH_3), 2.7–2.55 (4H, m, 2 × CH_2), 2.5–2.4 (2H, m, CH + 1 × CH_2), 2.2–2.05 (3H, m, CH_2 + 1 × CH_2), 1.95–1.9 (1H, m, 1 × CH_2), 1.7–1.5 (3H, m, CH_2 + 1 × CH_2) and 1.0–0.9 (3H, t, CH_3).

***cis*- and *trans*-2,3,4,4a,5,6,11,11a-Octahydro-8-methoxy-1-propyl-1*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-2-one 15 (X + Y = O)‡**

To a stirred solution of compound **12** (R = Pr^n) (0.46 g, 1.16 mmol) in acetonitrile (20 cm^3) at room temperature under nitrogen, was added sodium cyanoborohydride (0.28 g, 4.48 mmol) in portions. The reaction mixture was maintained at pH 6 by the addition of glacial acetic acid and stirred overnight. The mixture was then quenched by the addition of concentrated hydrochloric acid (20 cm^3) and the solvent was removed *in vacuo*. The residue was taken up in aqueous sodium hydroxide (30 cm^3, 2 M) and the aqueous phase was extracted with ether (4 × 75 cm^3). The combined organic layers were washed with brine, then dried and the solvent was removed *in vacuo* to give a yellow oil. Flash chromatography (40% ethyl acetate–hexane) gave the title compound as a clear oil (0.37 g, 80%) (Found: C, 75.0; H, 9.0; N, 4.7%; M$^+$, 287.1885. $C_{18}H_{25}NO_2$ requires: C, 75.25; H, 8.7; N, 4.9%; *M*, 287.1885); ν_{max}(liquid film)/cm^{-1} 1685 (C=O, lactam) and 1610 (C=C); δ_H 7.1 (1H, d, aryl), 6.7 (2H, d, aryl) 4.0–3.9 (1H, m, CHN), 3.8 (3H, s, OCH_3), 3.35–3.1 (2H, m, CH_2), 3.0–2.9 (1H, m, CH_2), 2.75–2.2 (7H, complex, 3 × CH_2 + CH), 2.0–1.8 (2H, m, CH_2), 1.75–1.5 (3H, m, CH_2 + 1 × CH_2) and 0.9 (3H, t, CH_3).

***cis*- and *trans*-2,3,4,4a,5,6,11,11a-Octahydro-8-methoxy-1-propyl-1*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine 15 (X = Y = H)‡**

To a stirred solution of borane–THF complex (5 cm^3, 5 mmol, 1.0 M solution in THF) at 0 °C under nitrogen, was added dropwise a solution of lactam **15** (X + Y = O) (0.3 g, 1.04 mmol) in dry THF (10 cm^3). When the addition was complete, the reaction mixture was stirred at room temperature overnight. The mixture was then cooled again to 0 °C, and excess hydride was destroyed by the careful addition of water (3 cm^3). Hydrochloric acid (5 cm^3, 5 M) was added and the mixture was heated at reflux for 2 h and then allowed to cool to room temperature. The solvent was removed *in vacuo* and water (20 cm^3) was added to the residue which was basified (pH 10) with solid sodium hydroxide. The resulting mixture was extracted with chloroform (4 × 50 cm^3) and the combined organic extracts were washed with brine, then dried and the solvent was removed *in vacuo* to give an oil. Flash chromatography (60% ethyl acetate–hexane) gave the title compound as a clear viscous oil (0.22 g, 77%) (Found: C, 78.7; H, 9.9; N, 5.0%; M$^+$, 273.2092. $C_{18}H_{27}NO$ requires: C, 79.1; H, 9.9; N, 5.1%; *M*, 273.2093); ν_{max}(Nujol)/cm^{-1} 1610 (C=C); δ_H 7.1 (1H, d, aryl), 6.7–6.6 (2H, m, aryl), 3.8 (3H, s, OCH_3), 3.2–2.6 (9H, complex, 4 × CH_2 + CHN), 2.3–1.5 (9H, complex, 4 × CH_2 + CH) and 0.9 (3H, t CH_3).

‡ The terms *cis* and *trans* refer to the steric relationship at the bridgeheads between the cycloheptane and piperidine rings.

Ethyl 3-(6,7,8,9-tetrahydro-3-methoxy-5-methyl-6-oxo-5*H*-benzo[7]annulen-5-enyl)propionate 16 (R = Me)

To a suspension of sodium hydride (1.0 g, 25 mmol, 60% dispersion in mineral oil) in dry DMF (100 cm^3) at 0 °C under nitrogen, was added dropwise a solution of ketone **3** (R = Me, X = 7-OMe, Y = H) (4.08 g, 20 mmol) in dry DMF (20 cm^3). When the initial vigorous evolution of hydrogen gas had subsided, the orange suspension was allowed to reach room temperature over 1 h whereupon ethyl 3-bromopropionate (4.52 g, 25 mmol) in dry DMF (10 cm^3) was added dropwise. The resulting mixture was stirred at room temperature overnight and then diluted with water (100 cm^3). The mixture was extracted with ether (4 × 150 cm^3) and the combined ethereal extracts were washed with water, then dried and the solvent was removed *in vacuo* to give an orange oil. Flash chromatography (20% ethyl acetate–hexane) gave the title compound as a clear oil (5.76 g, 84%) (Found: C, 70.7; H, 8.15%; M^+, 304.1675. $C_{18}H_{24}O_4$ requires: C, 71.05; H, 7.9%; *M*, 304.1675); ν_{max}(liquid film)/cm^{-1} 1740 (C=O, ester), 1710 (C=O) and 1610 (C=C); δ_H 7.1 (1H, d, aryl), 6.9 (1H, d, aryl), 6.7 (1H, dd, aryl), 4.1–4.0 (2H, q, $CO_2CH_2CH_3$), 3.8 (3H, s, OCH_3), 2.7–2.6 (3H, m, CH_2 + 1 × CH_2), 2.4–2.3 (1H, m, CH_2), 2.2–2.1 (4H, m, 2 × CH_2), 2.1–1.9 (2H, m, CH_2), 1.4 (3H, s, CH_3) and 1.2 (3H, t, $CO_2CH_2CH_3$).

Ethyl 3-(6,7,8,9-tetrahydro-3-methoxy-5-methyl-6-hydroxyimino-5*H*-benzo[7]annulen-5-yl)propionate 17

A mixture of compound **16** (R = Me) (1.22 g, 4 mmol), hydroxylamine hydrochloride (0.42 g, 6 mmol) and pyridine (0.65 cm^3) in ethanol (20 cm^3) was heated at reflux overnight. The reaction mixture was allowed to cool and then poured into chloroform (100 cm^3). The organic phase was washed with hydrochloric acid (2 × 40 cm^3, 2 M) and brine, then dried and the solvent was removed *in vacuo* to give a pale yellow oil which crystallised on standing. Recrystallisation from toluene–hexane (9:1) gave the title compound as off-white crystals (1.05 g, 82%), mp 134–136 °C (Found: C, 67.8; H, 8.05; N, 4.35%; M^+, 319.1784. $C_{18}H_{25}NO_4$ requires: C, 67.7; H, 7.8; N, 4.4%; *M*, 319.1784) ν_{max}(Nujol)/cm^{-1} 3460, 3300 (OH, oxime), 1735 (C=O, ester) and 1620 (C=C); δ_H 8.2 (1H, br, exch., =NOH), 7.0 (1H, d, aryl), 6.9 (1H, d, aryl), 6.7 (1H, dd, aryl), 4.1–4.0 (2H, q, $CO_2CH_2CH_3$), 3.8 (3H, s, OCH_3), 2.7–2.5 (3H, m, CH_2 + 1 × CH_2), 2.45–2.3 (3H, m, CH_2 + 1 × CH_2), 2.2–2.1 (2H, m, CH_2), 2.0–1.9 (2H, m, CH_2), 1.5 (3H, s, CH_3) and 1.2 (3H, t, $CO_2CH_2CH_3$).

6,7,8,9-Tetrahydro-1,2-dimethoxy-6-hydroxyimino-5*H*-benzo-[7]annulen-5-one 19 (R = H)

To a stirred solution of compound **18**[22] (10 g, 45.45 mmol) in dry ether (300 cm^3) at room temperature, was added dropwise isoamyl nitrite (10.65 g, 91 mmol) in dry ether (20 cm^3) whilst dry hydrogen chloride gas was passed through the reaction mixture. After the addition was complete, the mixture was stirred for 1 h during which time a copious precipitate formed. The solid (5.21 g) was removed by filtration and the filtrate was concentrated *in vacuo* to give a red oil. Flash chromatography (50% ethyl acetate–hexane) gave an orange solid (5.65 g). The combined solids were recrystallised from toluene to give the title compound as pale brown crystals (10.86 g, 96%), mp 159–161 °C (lit.,[20] 165–166.5 °C; lit.,[21] 168–169 °C) (Found: C, 62.7; H, 6.2; N, 5.6%. Calc. for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.0; N, 5.6%); ν_{max}(Nujol)/cm^{-1} 3230 (OH), 1705 (C=O) and 1620 (C=C); δ_H 12.2 (1H, s, exch., =NOH), 7.5 (1H, d, aryl), 7.1 (1H, d, aryl), 3.9 (3H, s, OCH_3), 3.7 (3H, s, OCH_3), 2.8–2.75 (2H, t, CH_2), 2.5–2.45 (2H, t, CH_2) and 1.9–1.8 (2H, m, CH_2).

6,7,8,9-Tetrahydro-1,2-dimethoxy-6-methoxyimino-5*H*-benzo-[7]annulen-5-one 19 (R = Me)

To a stirred suspension of sodium hydride (0.77 g, 19.25 mmol, 60% dispersion in mineral oil) in dry THF (60 cm^3) at 0 °C under nitrogen, was added compound **19** (R = H) (3 g, 11.95 mmol) in portions. The resulting mixture was allowed to reach room temperature and was stirred for 1 h and then cooled to 0 °C. Methyl iodide (2.7 g, 19 mmol) in THF (10 cm^3) was added dropwise and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100 cm^3) and washed with water and brine, then dried and the solvent was removed to give a green oil. Flash chromatography (30% ethyl acetate–hexane) afforded the title compound as a pale yellow solid (2.23 g, 74%), mp 126–128 °C (Found: C, 63.75; H, 6.35; N, 5.6%; M^+, 263.1153. $C_{14}H_{17}NO_4$ requires: C, 63.9; H, 6.45; N, 5.3%; *M*, 263.1158); ν_{max}(Nujol)/cm^{-1} 1705 (C=O) and 1610 (C=C); δ_H 7.8 (1H, d, aryl), 6.9 (1H, d, aryl), 4.1 (3H, s, $ArOCH_3$), 3.9 (3H, s, $ArOCH_3$), 3.8 (3H, s, $=NOCH_3$), 3.0–2.95 (2H, t, CH_2), 2.65–2.6 (2H, t, CH_2) and 2.1–2.0 (2H, m, CH_2).

Ethyl 3-(6,7,8,9-tetrahydro-5-hydroxy-1,2-dimethoxy-6-methoxyimino-5*H*-benzo[7]annulen-5-yl)propiolate 20

To a solution of ethyl propiolate (0.52 g, 5.3 mmol in dry THF (10 cm^3) at −78 °C under nitrogen, was added dropwise, *n*-butyllithium (3.3 cm^3, 5.3 mmol, 1.6 M solution in hexanes). The resulting mixture was stirred for 30 min whereupon a solution of compound **19** (R = Me) (1.2 g, 4.56 mmol) in dry THF (10 cm^3) was added dropwise. The mixture was stirred at −78 °C for 1.5 h and then acetic acid (0.5 cm^3) was added. The orange solution was slowly allowed to reach room temperature and ether (20 cm^3) was added. The organic phase was washed with saturated aqueous sodium hydrogen carbonate and brine, dried and the solvent was removed *in vacuo* to give a brown oil. Flash chromatography (30% ethyl acetate–hexane) afforded the title compound as pale yellow crystals (1.38 g, 84%), mp 121–123 °C (Found: C, 63.6; H, 6.4; N, 3.7%; M^+, 361.1527. $C_{19}H_{23}NO_6$ requires: C, 63.15; H, 6.4; N, 3.9%; *M*, 361.1525); ν_{max}(Nujol)/cm^{-1} 3450 (OH, oxime), 1730 (C=O, ester) and 1610 (C=C); δ_H 7.65 (1H, d, aryl), 6.85 (1H, d, aryl), 4.7 (1H, s, exch., OH), 4.3–4.2 (2H, q, $CO_2CH_2CH_3$), 3.9 (3H, s, $ArOCH_3$), 3.85 (3H, s, $ArOCH_3$), 3.75 (3H, s, $=NOCH_3$), 3.2–2.95 (3H, m, CH_2 + 1 × CH_2), 2.4–2.3 (1H, m, CH_2), 1.9–1.85 (1H, m, CH_2), 1.75–1.7 (1H, m, CH_2) and 1.35–1.3 (3H, t, $CO_2CH_2CH_3$); δ_C 158.0 (C=$NOCH_3$), 153.5 ($CO_2CH_2CH_3$), 153.4 ($ArOCH_3$, *ipso*), 146.6 ($ArOCH_3$, *ipso*), 133.1, 131.1, 123.4, 110.1 (aryl), 87.1 (O_2C–C≡C), 77.3 [ArC(OH)–C≡], 73.5 (O_2C–C≡C), 62.5 ($ArOCH_3$), 62.3 ($CO_2CH_2CH_3$), 61.2 ($ArOCH_3$), 55.9 (=$NOCH_3$), 24.7 (ArCH_2), 24.1 (N=CCH_2), 23.3 ($ArCH_2CH_2$) and 14.2 ($CO_2CH_2CH_3$).

Ethyl 3-(6,7,8,9-tetrahydro-5-hydroxy-1,2-dimethoxy-6-methoxyimino-5*H*-benzo[7]annulen-5-yl)propionate 21

A mixture of compound **20** (0.35 g, 0.97 mmol), acetic acid (4 cm^3) and platinum(IV) oxide catalyst (0.1 g) in ethanol (120 cm^3) was hydrogenated at an initial hydrogen pressure of 45 psi for 4 days. The catalyst was then filtered off and the filtrate was concentrated *in vacuo* to give a golden oil. Flash chromatography (20% ethyl acetate–hexane) gave the title compound as a pale yellow viscous oil (0.32 g, 90%) (Found: C, 62;75; H, 8.2; N, 3.7%; M^+, 365.4257. $C_{19}H_{27}NO_6$ requires: C, 62.5; H, 7.4;. N, 3.8%; *M*, 365.4254); ν_{max}(liquid film)/cm^{-1} 3450 (OH), 1740 (C=O, ester) and 1610 (C=C); δ_H 7.55 (1H, d, aryl), 6.8 (1H, d, aryl), 4.15–4.0 (3H, br, $CO_2CH_2CH_3$ + exch., OH), 3.85 (6H, s, 2 × $ArOCH_3$), 3.75 (3H, s, $=NOCH_3$), 3.35–3.25 (1H, m, CH_2), 3.1–3.0 (1H, m, CH_2), 2.7–2.6 (1H, m, CH_2), 2.45–2.35 (5H, m, 2 × CH_2 + CH_2), 2.05–1.95 (1H, m, CH_2), 1.6–1.5 (1H, m, CH_2) and 1.25–1.2 (3H, t, $CO_2CH_2CH_3$); δ_C 174.0 ($CO_2CH_2CH_3$), 161.2 (C=$NOCH_3$), 152.3 ($ArOCH_3$, *ipso*), 146.5 ($ArOCH_3$, *ipso*), 135.3, 132.6, 122.4, 109.8 (aryl), 78.0 [ArC(OH)CH_2], 62.1 ($ArOCH_3$), 61.2 ($ArOCH_3$), 60.6 ($CO_2CH_2CH_3$), 55.8 (=$NOCH_3$), 34.2 (CH_2CO_2), 29.3 ($CH_2CH_2CO_2$), 24.9 (ArCH_2), 24.8 (N=CCH_2), 24.2 ($ArCH_2CH_2$) and 14.4 ($CO_2CH_2CH_3$).

6,7,8,9-Tetrahydro-1,2-dimethoxy-6-propionamido-5*H*-benzo-[7]annulen-5-one 22

A mixture of compound **19** (R = H) (1 g, 4.02 mmol), propionic anhydride (5.22 g, 40.15 mmol) and 10% palladium on charcoal catalyst (0.2 g) was hydrogenated at room temperature overnight at an initial hydrogen pressure of 45 psi. The catalyst was then removed by filtration and the filtrate was concentrated *in vacuo* to give an oil. Flash chromatography (60% ethyl acetate–hexane) afforded the title compound as a white crystalline solid (0.78 g, 66%), mp 127–129 °C (Found: C, 65.9; H, 7.2; N, 4.75%; M^+, 291.1478. $C_{16}H_{21}NO_4$ requires: C, 66.0; H, 7.3; N, 4.8%; *M*, 291.1471); ν_{max}(Nujol)/cm^{-1} 1705 (C=O), 1680 (C=O, amide) and 1610 (C=C); δ_H 7.7 (1H, d, aryl), 6.85 (1H, d, aryl), 6.7 (1H, d, *J* 6.7, exch., NHCO), 5.0–4.95 (1H, m, C*H*NHCO), 3.9 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.5–3.4 (1H, m, CH_2), 2.85–2.8 (1H, m, CH_2), 2.4–2.35 (1H, m, CH_2), 2.3–2.15 (3H, q + m, $COCH_2CH_3$ + CH_2), 1.5–1.4 (2H, m, CH_2) and 1.2–1.1 (3H, t, $COCH_2CH_3$).

***cis*- and *trans*-6,7,8,9-Tetrahydro-5-hydroxy-1,2-dimethoxy-6-propionamido-5*H*-benzo[7]annulene 24 and 23 §**

To a stirred solution of compound **22** (0.55 g, 1.89 mmol) in ethanol (20 cm^3) at room temperature under nitrogen, was added sodium borohydride (0.09 g, 2.38 mmol) in portions. The resulting mixture was stirred for 1 h, whereupon acetic acid (1 cm^3) was added. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100 cm^3). The organic phase was washed with water and brine, then dried and the solvent was evaporated to give a white solid (0.52 g, 93%) which was found to consist of two components (TLC), which were separated by flash chromatography (1% ethanol–chloroform). The first component eluted from the column was the *cis*-diastereoisomer **24** as a white solid (0.13 g), mp 166–167 °C (Found: C, 65.6; H, 7.95; N, 4.2%; M^+, 293.1632. $C_{16}H_{23}NO_4$ requires: C, 65.5; H, 7.85; N, 4.8%; *M*, 293.1627); ν_{max}(Nujol)/cm^{-1} 3360 (OH), 3250 (NH) and 1685 (C=O, amide); δ_H 7.15 (1H, d, aryl), 6.75 (1H, d, aryl), 5.55–5.45 (1H, br, exch., OH), 4.7 (1H, d, *J* 1, C*H*OH), 4.1–4.0 (1H, m, C*H*NHCO), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.15–3.1 (1H, m, CH_2), 2.75–2.7 (1H, m, CH_2), 2.2–2.15 (2H, q, $COCH_2CH_3$), 2.1–2.0 (1H, m, CH_2), 1.7–1.6 (3H, m, 1 × CH_2 + CH_2) and 1.2–1.1 (3H, t, $COCH_2CH_3$). This was followed from the column by the *trans*-diastereoisomer **23** as a white solid (0.37 g), mp 158–159 °C (Found: C, 65.3;H, 7.6; N, 4.55%; M^+, 293.1625. $C_{16}H_{23}NO_4$ requires: C, 65.5; H, 7.85; N, 4.8%; *M*, 293.1627); δ_H 7.15 (1H, d, aryl), 6.75 (1H, d, aryl), 5.6–5.5 (1H, br, exch., OH), 4.65 (1H, d, *J* 7.2, C*H*OH), 4.15–4.05 (1H, m, C*H*NHCO), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.2–3.1 (1H, m, CH_2), 2.7–2.6 (1H, m, CH_2), 2.2–2.0 (3H, q, m, $COCH_2CH_3$ + 1 × CH_2), 1.75–1.6 (3H, m, CH_2 + 1 × CH_2), 1.1–1.0 (3H, t, $COCH_2CH_3$). The amide proton of both **23** and **24** ($NHCOCH_2CH_3$) was not observed at 250 MHz.

***trans*-6,7,8,9-Tetrahydro-5-hydroxy-1,2-dimethoxy-6-propylamino-5*H*-benzo[7]annulene 25 §**

To borane–THF complex (16.25 cm^3, 16.25 mmol, 1.0 M solution in THF) at 0 °C under nitrogen, was added compound **23** (0.95 g, 3.24 mmol) in dry THF (20 cm^3). When the addition was complete, the clear solution was stirred at room temperature overnight and was then cooled to 0 °C. Water (10 cm^3) was added (CAUTION) followed by hydrochloric acid (2 M, 2 cm^3). The mixture was heated at reflux for 1 h and the solvent was removed *in vacuo*. Water (10 cm^3) was added to the residue which was basified (pH 10) with solid sodium hydroxide and extracted with chloroform (4 × 50 cm^3). The combined organic layers were washed with water and brine, then dried and the solvent was removed *in vacuo* to give an oil. Flash chromatography (chloroform–ethanol–ammonia, 100:8:1) gave the title compound as a white powder (0.59 g, 65%), mp 62–64 °C (Found: C, 68.75; H, 9.0; H, 5.15%; M^+, 279.1838. $C_{16}H_{25}NO_3$ requires: C, 68.8; H, 8.95; N, 5.0%; *M*, 279.1835); ν_{max}(Nujol)/cm^{-1} 3365 (OH), 3255 (NH) and 1610 (C=C); δ_H 7.5 (1H, d, aryl), 6.8 (1H, d, aryl), 4.4 (1H, d, *J* 8.9 C*H*OH), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.45–3.35 (1H, m, CH_2), 2.8–2.75 (1H, m, C*H*NH), 2.5–2.0 (5H, m, 1 × CH_2 + 2 × CH_2), 1.6–1.4 (3H, m, 1 × CH_2 + CH_2), 1.4–1.3 (2H, br, CH_2 + NH) and 1.0–0.9 (3H, t, CH_3). The hydroxy proton at C-5 was not observed at 250 MHz.

***cis*-6,7,8,9-Tetrahydro-5-hydroxy-1,2-dimethoxy-6-propylamino-5*H*-benzo[7]annulene 26 §**

Compound **24** (0.65 g, 2.22 mmol) and borane–THF complex (11.1 cm^3, 11.1 mmol, 1.0 M solution in THF) in dry THF (20 cm^3) were reacted according to the above procedure. The crude product was purified by flash chromatography (chloroform–ethanol–ammonia, 100:8:1) to give the title compound as a white semi-solid (0.36 g, 58%) (Found: C, 68.75; H, 9.1; N, 5.05%; M^+, 279.1833. $C_{16}H_{25}NO_3$ requires: C, 68.8; H, 9.0; N, 5.0%; *M*, 279.1835); δ_H 7.15 (1H, d, aryl), 6.75 (1H, d, aryl), 4.8 (1H, d, *J* 2, C*H*OH), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.2–3.1 (1H, m, CH_2), 2.85 (1H, m, C*H*NH), 2.75–2.4 (5H, m, 1 × CH_2 + 2 × CH_2), 1.9–1.8 (2H, m, CH_2), 1.7–1.4 (3H, m, CH_2 + NH) and 0.95–0.9 (3H, t, CH_3). The hydroxy proton at C-5 was not observed at 250 MHz.

***trans*-6-[Chloroacetyl(propyl)amino]-5-chloroacetoxy-6,7,8,9-tetrahydro-1,2-dimethoxy-5*H*-benzo[7]annulene 27 §**

To compound **25** (0.46 g, 1.65 mmol) in 1,2-dichloroethane (10 cm^3) at room temperature was added a solution of sodium hydroxide (0.086 g, 2.15 mmol) in water (5 cm^3). The resulting mixture was stirred vigorously for 15 min and was then cooled to 0 °C, whereupon a solution of chloroacetyl chloride (0.25 g, 2.21 mmol) in 1,2-dichloroethane (3 cm^3) was added dropwise. The resulting mixture was stirred at room temperature overnight and then the phases were separated. The organic phase was washed with dilute hydrochloric acid (5 cm^3), water (10 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give a white solid which was recrystallised from toluene to give the title compound as colourless crystals (0.385 g, 54%), mp 154–155 °C [Found: C, 55.7; H, 6.95; N, 3.2: Cl, 16.5%; M^+ (−HCl), 395.1495. $C_{20}H_{27}NO_5Cl_2$ requires: C, 55.5; H, 6.25; N, 3.25; Cl, 16.4%; *M* (−HCl), 395.1500]; ν_{max}(Nujol)/cm^{-1} 1765 (C=O, ester), 1660 (C=O, amide) and 1610 (C=C); δ_H 7.05 (1H, d, aryl), 6.75 (1H, d, aryl), 6.2 (1H, d, *J* 8, CHOCO), 4.5–4.35 (2H, m, $OCOCH_2Cl$), 3.9–3.65 (9H, 2 × s + m, 2 × OCH_3 + CHN + $COCH_2Cl$), 3.1 (1H, m, CH_2), 3.0–2.9 (2H, m, CH_2), 2.85–2.8 (1H, m, CH_2), 2.1–1.9 (4H, m, 2 × CH_2), 1.5–1.4 (2H, m, CH_2) and 1.0 (3H, t, CH_3).

***trans*-2,3,4,4a,5,6,7,11b-Octahydro-8,9-dimethoxy-4-propylbenzo[6,7]cyclohept[1,2-*b*][1,4]oxazin-3-one 28 ¶**

To a stirred solution of potassium hydroxide (0.089 g, 1.59 mmol) in ethanol (10 cm^3) at room temperature, was added compound **27** (0.23 g, 0.53 mmol) in portions. The resulting suspension was stirred for 16 h whereupon the solvent was removed *in vacuo*. The residue was taken up in chloroform (20 cm^3) and the organic phase was washed with dilute hydrochloric acid (5 cm^3), water (2 × 10 cm^3) and brine, then dried and the solvent was evaporated to give a white solid. Recrystallisation from toluene gave the title compound as white crystals (0.15 g, 89%), mp 137–139 °C (Found: C, 67.4; H, 7.7; N, 4.15%; M^+, 319.1802. $C_{18}H_{25}NO_4$ requires: C, 67.7; H, 7.8; N, 4.4%; *M*, 319.1784); ν_{max}(Nujol)/cm^{-1} 1680 (C=O, lactam) and 1610

§ The terms *cis* and *trans* refer to the relative stereochemistry of the groups at the 5- and 6-positions.

¶ The terms *cis* and *trans* refer to the steric relationship at the bridgeheads between the cycloheptane and oxazine rings.

(C=C); δ_H 7.35 (1H, d, aryl), 6.8 (1H, d, aryl), 4.6 (1H, d, *J* 9.3, CHO), 4.5–4.4 (1H, d, *J* 15.9, OCH_2CO), 4.15–4.0 (1H, d, *J* 15.9, OCH_2CO), 3.85 (3H, s, OCH_3), 3.75–3.6 (4H, s + m, OCH_3 + CHN), 3.5–3.4 (1H, m, CH_2), 3.25–3.15 (1H, m, CH_2), 3.1–3.0 (1H, m, CH_2), 2.5–2.1 (3H, m, 1 × CH_2 + CH_2), 1.7–1.2 (4H, m, 2 × CH_2) and 0.9–0.85 (3H, t, CH_3).

***trans*-2,3,4,4a,5,6,7,11b-Octahydro-8,9-dimethoxy-4-propylbenzo[6,7]cyclohept[1,2-*b*][1,4]oxazine 29 ¶**

To a suspension of lithium aluminium hydride (0.031 g, 0.817 mmol) in dry THF (5 cm^3) at 0 °C under nitrogen, was added dropwise a solution of compound **28** (0.1 g, 0.313 mmol) in dry THF (5 cm^3). The resulting suspension was heated at reflux for 2 h and was then cooled to 0 °C. Isopropyl alcohol (1 cm^3) was added carefully followed by saturated aqueous sodium sulfate (4 cm^3). The precipitated inorganic salts were collected and the filtrate was concentrated *in vacuo*. The residue was taken up in ether (20 cm^3) and the organic phase was washed with water (10 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give an oil. Flash chromatography (2% ethanol–chloroform) afforded the title compound as an off-white solid (0.069 g, 72%), mp 119–120 °C (Found: C, 70.5; H, 8.6; N, 4.35%; M^+, 305.2004. $C_{18}H_{27}NO_3$ requires: C, 70.8; H, 8.85; N, 4.6%; *M*, 305.1991); ν_{max}(Nujol)/cm^{-1} 1610 (C=C); δ_H 7.35 (1H, d, aryl), 6.8 (1H, d, aryl), 4.5 (1H, d, *J* 8.8, CHO), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.5–3.4 (2H, m, OCH_2), 2.9–2.4 (7H, m, CHN + 3 × CH_2), 2.15–2.0 (2H, m, CH_2), 1.55–1.25 (4H, m, 2 × CH_2) and 0.9–0.8 (3H, t, CH_3).

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