Azabenzocycloheptenones. Part 20. Synthesis and utilisation of 4-amino-1,2,3,4-tetrahydro-1(1*H*)-benzazepines

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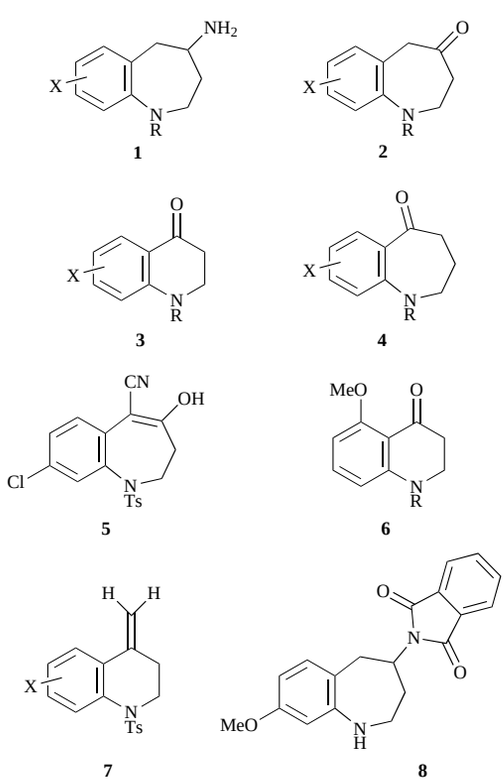
1,2,3,4-Tetrahydro-6- and -7-methoxy-4-oxo-1-(*p*-tolylsulfonyl)quinolines 3 (R = tosyl, X = 6- and 7-OMe) and 1-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-7-methoxy-4-oxoquinoline 3 (R = CH_2CO_2Et, X = 7-OMe) have been ring-expanded in two steps to 2,3,4,5-tetrahydro-7- and -8-methoxy-4-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepines 2 (R = tosyl, X = 7- and -8-OMe) and 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-8-methoxy-4-oxo-1*H*-1-benzazepine 2 (R = CH_2CO_2Et, X = 8-OMe). Reduction of the oximes gives 4-amino-2,3,4,5-tetrahydro-7-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 1 (R = tosyl, X = 7-OMe), 4-amino-2,3,4,5-tetrahydro-8-methoxy-1*H*-1-benzazepine 1 (R = H, X = 8-OMe) and 4-amino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-8-methoxy-1*H*-1-benzazepine 1 (R = CH_2CO_2Et, X = 8-OMe). From these, several N-substituted and N,N-disubstituted compounds have been obtained and 3-amino-2,3,4,5-tetrahydro-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 12 (X = NH_2, Y = H) has been made by similar means. Two routes are described to 2,3,4,5-tetrahydro-8-methoxy-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 13 (R^1 = tosyl, R^2 = H) which is converted to 2,3,4,5-tetrahydro-8-methoxy-4-methoxyimino-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 17 (R = Me) and thence to 5-[2-(ethoxycarbonyl)ethynyl]-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-methoxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 18 (R = C≡CCO_2Et) and 5-[2-(ethoxycarbonyl)ethyl]-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-methoxyimino-1-(*p*-tolylsulfonyl)-1*H*-benzazepine 18 [R = $(CH_2)_2CO_2Et$]. Reduction of oximino ketone 17 (R = H) in two steps gives both *cis*- and *trans*-4-acetamido-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepines 22 and 21 which are separately deacetylated and cyclised with ethyl chloroacetate to *cis*- and *trans*-2,3,4,4a,5,6,7,11b-octahydro-9-methoxy-3-oxo-7-(*p*-tolylsulfonyl)-[1,4]oxazino[3,2-*d*][1]benzazepine 26 and 25. By similar methodology *cis*- and *trans*-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-propionamido-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepines 28 and 27 have been obtained, separated and the latter reduced to *trans*-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-(*n*-propylamino)-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 29. In three steps the latter is converted to *trans*-2,3,4,4a,5,6,7,11b-octahydro-9-methoxy-4-(*n*-propyl)-7-(*p*-tolylsulfonyl)[1,4]oxazino[3,2-*d*][1]benzazepine 33.

In several papers of this series we have pioneered the syntheses and explored the chemistry of 1-benzazepine derivatives.[1–10] These have included some studies on annelation,[1] substitution[9] and bridging[10] reactions. We have now developed these themes further and in connection with constrained β-phenylethylamine structures,[11,12] it has now become of interest to gain access to 4-amino-2,3,4,5-tetrahydro-1-benzazepine intermediates **1** and related systems which allow access to tricyclic structures.

The Wittig–Prévost protocol[13,14] for conversion of α-tetralones into benzosuberan-6-ones‡ has expedited introduction of amino functionality[11,12] to the 6-position of the latter ring system. Accordingly it appeared promising to apply a similar approach to tetrahydro-1-benzazepin-4-ones **2** potentially available from tetrahydroquinolin-4-ones **3**. In this paper we address this question and also describe refinement of a more established method which hinges on α-oximation of tetrahydro-1-benzazepin-5-ones **4**.



Discussion

Although originally[13] we described the synthesis of the 1-benzazepine derivative **5** by the Wittig–Prévost approach, the enolic nature of the product makes it unsuitable for general use. Accordingly we have concentrated attention on methylenation

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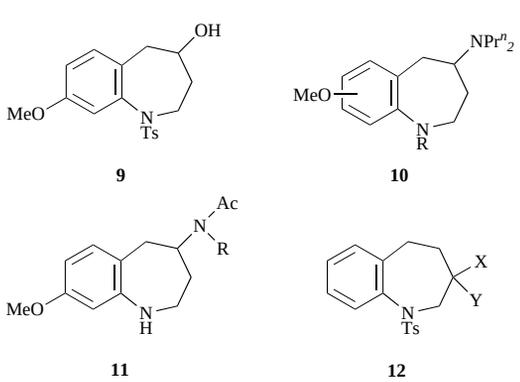
rather than cyanomethylenation in the Wittig step. Thus in the ring-expansion step (Prévost) the ultimate 5-carbon atom of the benzazepine is unsubstituted: we also stress that by contrast with the original hot anhydrous alcoholic conditions for this reaction, we have discovered it is advantageous to use aqueous alcohol at room temperature. The substrate 1-(*p*-tolylsulfonyl)-7-methoxy-4-oxo-1,2,3,4-tetrahydroquinoline **3** [R = tosyl (*p*-tolylsulfonyl) X = 7-OMe][15] was chosen and was obtained as described by Speckamp[15b] *et al.*

Interestingly, the latter ascribed the appearance of two different melting solids (mp 104–106 and 115–119 °C) to polymorphism: however, on chromatographic separation we were able to isolate the isomers **3** (R = tosyl, X = 7-OMe, mp 116–117 °C) and **6** (R = tosyl, mp 154 °C). This can be explained as the result of an intramolecular Friedel–Crafts cyclisation giving both substitution *para* and *ortho* to the methoxy group as had been previously suggested.[15a] Other workers have opined that only one isomer is found from this reaction.[16] To obtain the ketone **3** (R = H, X = 7-OMe)[15b] the corresponding amino acid was cyclised in polyphosphoric acid (PPA);[17a,b] again the isomer **6** (R = H)[17c] was also isolated.

Methylenation of the quinolone **3** (R = tosyl, X = 7-OMe) using $Ph_3P^+CH_3I^-$–Bu″Li gave the *exo*-methylene compound **7** (X = 7-OMe) in 38% yield. Many variations were explored including $Ph_3P^+CH_3Br^-$–Bu″Li, $Ph_3P^+CH_3I^-$–NaH–DMSO, Zn–CH_2I_2–$TiCl_4$,[18] the Tebbe reagent[19] and zirconocene dichloride–Zn–CH_2I_2:[20] none was an improvement. Reaction of **7** (X = 7-OMe) with silver nitrate–iodine (2:1) in THF–H_2O–MeOH (2:1:1) for 30 min at room temperature gave the ketone **2** (R = tosyl, X = 8-OMe) in 92% yield. In similar fashion methylenation of quinolone **3** (R = tosyl, X = 6-OMe)[21,22] gave the alkene **7** (R = tosyl, X = 6-OMe) (44%) which was converted as before to the ketone **2** (R = tosyl, X = 7-OMe) (77%). Protection of the nitrogen atom as a sulfonamide is not essential for this series of reactions; the tertiary amino keto ester **3** (R = CH_2CO_2Et, X = 7-OMe) could be methylenated, also in poor (36%) yield, and then expanded to give ketone **2** (R = CH_2CO_2Et, X = 8-OMe) which was substantially less stable than the *N*-sulfonamido ketones.

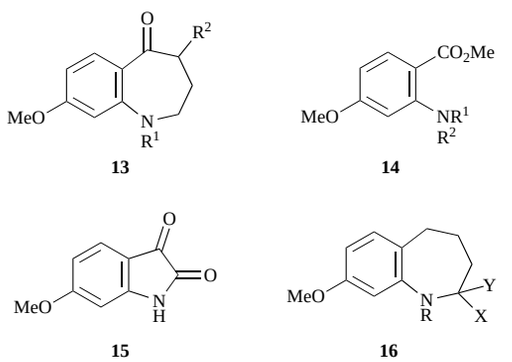
The ketones **2** were converted to oximes and reduced to the required amines **1**. $LiAlH_4$ caused detosylation as well as reduction of the oxime of **2** (R = tosyl, X = 8-OMe) giving the diamine **1** (R = H, X = 8-OMe), while the same treatment merely reduced the oxime of ketone **2** (R = tosyl, X = 7-OMe) to the compound **1** (R = tosyl, X = 7-OMe). The primary amino group in diamine **1** (R = H, X = 8-OMe) can be protected as a phthalimido derivative **8**. Reduction of the oxime of ketone **2** (R = CH_2CO_2Et, X = 8-OMe) gave the unstable amino ester **1** (R = CH_2CO_2Et, X = 8-OMe).

Unlike the corresponding carbocyclic analogue,[12] the ketone **2** (R = tosyl, X = 8-OMe) failed to form an enamine with di-*n*-propylamine, neither could it be aminated on treatment with sodium triacetoxyborohydride and *n*-propylamine, the product being the alcohol **9**. On the other hand the 4-amino-1,2,3,4-tetrahydrobenzazepines **1** could be bis-N-alkylated with sodium triacetoxyborohydride and propanal in acetic acid to give **10** (R = H, X = 8-OMe) and **10** (R = tosyl, X = 7-OMe). Diamine **1** (R = H, X = 8-OMe) was selectively acetylated to **11** (R = H) which, unexpectedly, was alkylated by ethyl bromoacetate and Hunig's base to yield **11** (R = CH_2CO_2Et). Incidentally it is possible to introduce an amino group at the 3-position of the 1-benzazepine system by methodology analogous to the above. Thus the ketone **12** (X, Y = O)[5] was converted to the oxime **12** (X, Y = NOH) which could be reduced by Raney nickel[23] to the amine **12** (X = H, Y = NH_2).



9 **10** **11** **12**

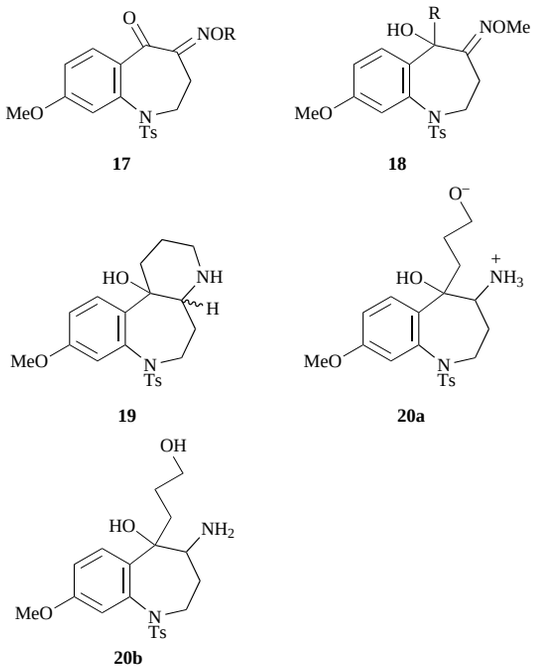
The previously unknown[24] methoxybenzazepinone **13** (R^1 = tosyl, R^2 = H) was required for the next stage of the work; two syntheses have now been developed. Firstly methoxyanthranilate **14** (R^1 = R^2 = H) can be obtained from *m*-anisidine *via* the isatin **15** (*cf.* ref. 25) using adaptations of the literature methods.[26] In particular it was essential to use PPA in the cyclisation leading to isatin **15**; sulfuric acid caused significant demethylation. The *N*-tosylanthranilate **14** (R^1 = tosyl, R^2 = H) was alkylated with ethyl 4-bromobutyrate according to precedents[2,27] and cyclised to keto ester **13** (R^1 = tosyl, R^2 = CO_2Et) which was decarboxylated to tosyl ketone **13** (R^1 = tosyl, R^2 = H) (see Experimental section). The second synthesis proceeded from 7-methoxy-α-tetralone by Beckmann rearrangement of the *O*-tosyl oxime[28] which yielded exclusively the lactam **16** (X, Y = O, R = H).[29] Reduction of the latter with $LiAlH_4$ gave the amine **16** (X = Y = R = H)[30] which could be acetylated to **16** (R = Ac, X = Y = H) or tosylated to **16** (R = tosyl, X = Y = H) all in good yield. Oxidation[31] of either of these gave the ketones **13** (R^1 = tosyl, R^2 = H or R^1 = Ac, R^2 = H) in moderate yield (see Experimental section). Either synthesis is satisfactory for large scale work.



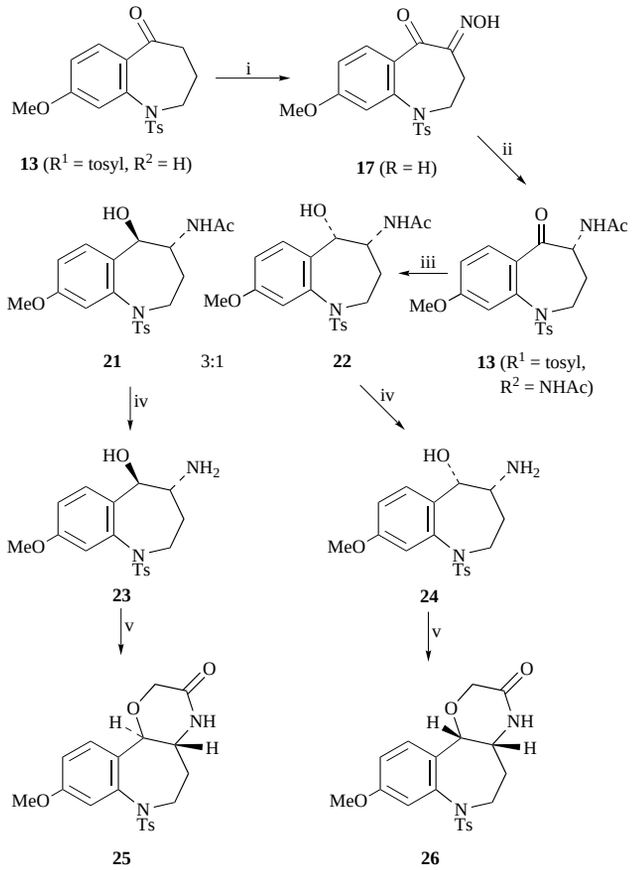
13 **14** **15** **16**

α-Oximation[32,33] of the tosyl ketone **13** (R^1 = tosyl, R^2 = H) proceeded efficiently to compound **17** (R = H) which can be methylated to **17** (R = Me). In order to make progress towards a pyridobenzazepine ring system, it was necessary to introduce a 3-carbon unit to C-5 of the benzazepine ring: this was achieved using the lithium derivative of ethyl propiolate[12,34] (LiC≡CCO_2Et) which provided compound **18** (R = C≡CCO_2Et). Catalytic reduction of the latter led to **18** (R = $CH_2CH_2CO_2Et$) but further progress was not possible since treatment of **18** (R = $CH_2CH_2CO_2Et$) with borane–THF gave an unexpected polar substance $C_{21}H_{28}N_2O_5S$. Although the originally expected structure **19** ($C_{21}H_{26}N_2O_4S$) was supported by mass spectroscopy (*m*/*z* 402), elemental analysis points to a formula containing an extra two hydrogen atoms and one oxygen atom (*i.e.* 402≡M − H_2O). Structure **20** (**a** or **b**) is a tentative assignment.

By contrast, reductions of the unmethylated oximino ketone **17** (R = H) proceeded normally. Thus catalytic hydrogenation in the presence of acetic anhydride gave rise to the acetylamino ketone **13** (R^1 = tosyl, R^2 = $NHCOCH_3$) which could be reduced by sodium borohydride to a separable mixture of two diastereomeric *N*-acetylamino alcohols (**21** and **22**) (Scheme 1). The latter were individually deacetylated and cyclised to the *trans*- and *cis*-oxazinobenzazepines **25** and **26**, which are mem-



bers of a previously unknown ring system (Scheme 1). To obtain N-substituted examples, it proved advantageous to proceed as shown in Scheme 2. In this approach the *N*-protecting group was introduced at an early stage and reduction with borane (**27** ⟶ **29**, **28** ⟶ **30**) caused no problems. However, insufficient quantities of the *cis*-isomer **30** precluded continuation of the synthesis of the *cis*-analogue of **33**. The latter, however, was obtained in fair yield.



Scheme 1 *Reagents and conditions:* i, $C_5H_{11}ONO$, Et_2O, HCl(g); ii, H_2, Pd/C, Ac_2O, THF; iii, $NaBH_4$, EtOH, room temp.; iv, NaOH, EtOH, heat; v, NaH, $ClCH_2CO_2Et$, $PhCH_3$, 80 °C

Experimental

For general remarks see *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2545. ^{1}H NMR spectra were recorded at 250.13 MHz unless otherwise stated.

1,2,3,4-Tetrahydro-7-methoxy-4-oxo-1-(*p*-tolylsulfonyl)quinoline[15] 3 (R = tosyl, X = 7-OMe)

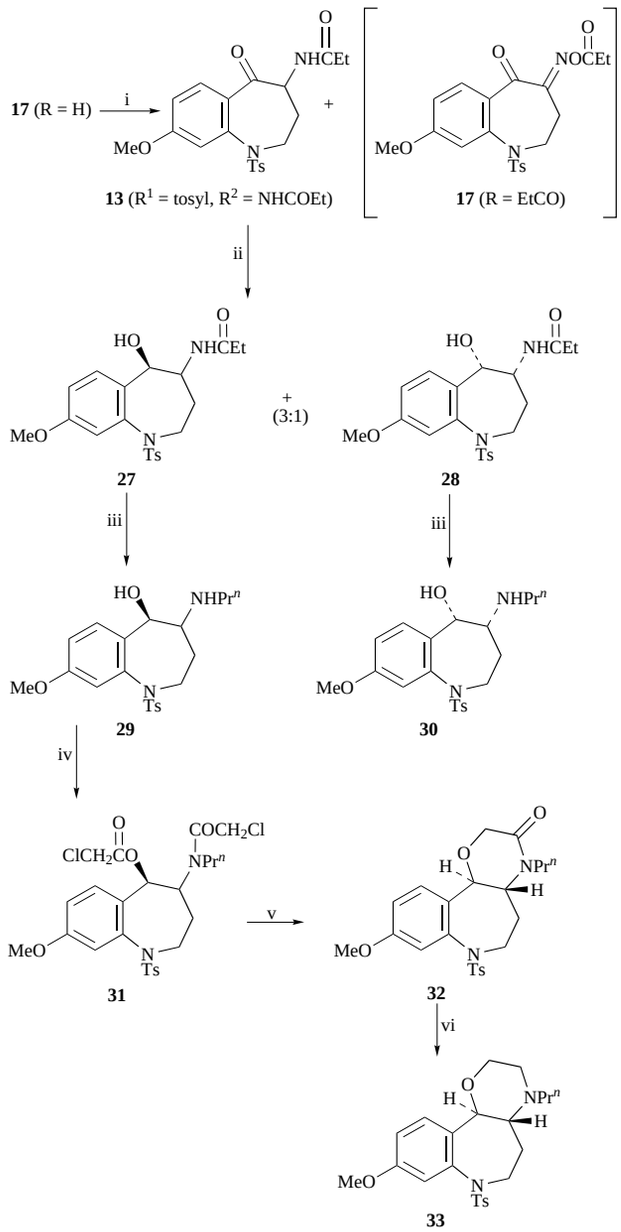
To a stirred suspension of *N*-(*m*-methoxyphenyl)-*N*-(*p*-tolylsulfonyl)-3-aminopropanoic acid (100 g, 0.28 mol) in dry benzene (250 cm^3) at 0 °C, was added in portions, phosphorous pentachloride (59 g, 0.29 mol). After the addition was complete, the resulting suspension was heated until the evolution of HCl gas ceased (5 h). The dark solution was cooled and stannic chloride (70 cm^3, 0.61 mol) in dry benzene (100 cm^3) was added at such a rate that the temperature did not exceed 5 °C. The resulting dark suspension was stirred at room temperature overnight, whereupon diethyl ether (500 cm^3) and hydrochloric acid (500 cm^3; 5 M) were added and the suspension was stirred for a further 2 h. The organic layer was separated and washed successively with water (200 cm^3), aqueous potassium hydroxide (200 cm^3; 2 M) and water again (200 cm^3), then dried and the solvent was removed *in vacuo* to give a solid. Recrystallisation from ethanol gave the title compound as white crystals (51 g, 53%), mp 116–117 °C (lit.,[15b] 115–117 °C) (Found: C, 61.8; H, 5.15; N, 4.15; S, 9.55. Calc. for $C_{17}H_{17}NO_4S$: C, 61.6; H, 5.15; N, 4.2; S, 9.65%); ν_{max}(Nujol)/cm^{-1} 1675 (C=O) and 1600 (C=C); δ_H 7.85 (1H, d, aryl), 7.5 (2H, d, aryl), 7.35 (1H, d, aryl), 7.2 (2H, d, aryl), 6.75 (1H, dd, aryl), 4.15 (2H, t, CH_2), 3.9 (3H, s, OCH_3) and 2.3 (5H, t + s, CH_2 + CH_3 tosyl). Chromatography (Al_2O_3–Et_2O) of the mother liquors gave 1,2,3,4-tetrahydro-5-methoxy-4-oxo-1-(*p*-tolylsulfonyl)quinoline **6** (8.1 g, 5%), mp 154 °C (Found: C, 61.4; H, 5.1; N, 4.1; S, 9.4. $C_{17}H_{18}NO_4S$ requires C, 61.6; H, 5.15; N, 4.25; S, 9.65%); ν_{max}(Nujol)/cm^{-1} 1670 (C=O), 1600 (C=C); δ_H 7.6–7.3 (4H, m, aryl), 7.3–7.1 (2H, d, aryl), 6.8 (1H, dd, aryl), 4.1 (2H, t, CH_2), 3.85 (3H, s, OCH_3) and 2.35 (5H, t + s, CH_3 tosyl, CH_2).

1,2,3,4-Tetrahydro-7-methoxy-4-methylene-1-(*p*-tolylsulfonyl)-quinoline 7 (X = 7-OMe)

To a stirred solution of methyltriphenylphosphonium iodide (12.2 g, 30.2 mmol) in dry THF (120 cm^3) at 0 °C under nitrogen, was added *n*-butyllithium (19 cm^3, 30.4 mmol; 1.6 M solution in hexanes), and the suspension was stirred for 30 min. To the resulting deep red solution was added a solution of the ketone **3** (R = tosyl, X = 7-OMe) (10 g, 30.2 mmol) in dry THF (50 cm^3) dropwise and the mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue was taken up in dichloromethane (150 cm^3) and washed with water (4 × 150 cm^3). The organic layer was then dried and the solvent was removed *in vacuo* to give a gum. Flash chromatography (triethylamine–diethyl ether–hexane 1:80:19) gave the product as a white solid (3.79 g, 38%), mp 112–113 °C (Found: C, 66.1; H, 6.1; N, 4.15; S, 9.8. $C_{18}H_{19}NO_3S$ requires C, 65.65; H, 5.8; N, 4.2; S, 9.7%); ν_{max}(Nujol)/cm^{-1} 1605 (C=C); δ_H(90 MHz) 7.6–7.1 (16H, m, aryl), 6.6 (1H, dd, aryl), 5.35 (1H, s, vinyl), 4.65 (1H, s, vinyl), 3.75–3.7 (5H, s + t, OCH_3 + CH_2) and 2.4–2.3 (5H, s + t, CH_3 tosyl + CH_2).

2,3,4,5-Tetrahydro-8-methoxy-4-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 2 (R = tosyl, X = 8-OMe)

Silver nitrate (1.96 g, 10 mmol) was dissolved in methanol (10 cm^3) and water (10 cm^3) at room temperature. To this vigorously stirred solution was added the alkene **7** (X = 7-OMe) (1.88 g, 5 mmol) in THF (20 cm^3) in one portion followed immediately by iodine (1.45 g, 5 mmol) in one portion. The resulting yellow suspension was stirred at room temperature for 30 min after which the precipitated silver iodide was filtered off. The filtrate was concentrated *in vacuo* and the residue was taken up



Scheme 2 *Reagents and conditions:* i, H_2, Pd/C, $(CH_3CH_2CO)_2O$, THF; ii, $NaBH_4$, EtOH, room temp., 1 h; iii, BH_3–THF, room temp., 3 h; iv, $ClCH_2COCl$, NaOH, $Cl(CH_2)_2Cl$–H_2O; v, KOH, EtOH, room temp., 16 h; vi, BH_3–THF, room temp., 12 h

in chloroform (100 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3) and brine (50 cm^3). The organic phase was then dried and the solvent was removed *in vacuo* to give a pale yellow oil. Flash chromatography (ethyl acetate–hexane, 20:80) gave the title compound as a viscous clear oil (1.58 g, 92%) (Found: C, 62.4; H, 5.45; N, 3.9; S, 9.3. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.05; S, 9.3%); ν_{max}(liquid film)/cm^{-1} 1708 (C=O) and 1600 (C=C); δ_H(90 MHz) 7.65 (2H, d, aryl), 7.4 (2H, d, aryl), 7.1–6.75 (3H, m, aryl), 3.9 (2H, t, CH_2), 3.75 (3H, s, OCH_3), 3.25 (2H, s, CH_2), 2.65 (2H, t, CH_2) and 2.45 (3H, s, CH_3 tosyl).

1,2,3,4-Tetrahydro-6-methoxy-4-methylene-1-(*p*-tolylsulfonyl)-quinoline 7 (X = 6-OMe)

To a stirred suspension of methyltriphenylphosphonium iodide (12.2 g, 32.2 mmol) in dry THF (150 cm^3) at 0 °C under nitrogen, was added dropwise *n*-butyllithium (19 cm^3, 30.4 mmol; 1.6 M solution in hexanes) and the suspension was stirred for 30 min. To the resulting deep red solution was added a solution of the ketone[22] **3** (R = tosyl, X = 6-OMe) (10 g, 30.2 mmol) in dry THF (100 cm^3) dropwise and the mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue was taken up in dichloromethane (200 cm^3) and washed with water (4 × 150 cm^3). The organic layer was then dried and the solvent was removed *in vacuo* to give an oil. Flash chromatography (triethylamine–ethyl acetate–hexane, 1:20:79) gave the title compound as a white solid (4.37 g, 44%), mp 119–120 °C (Found: C, 66.0; H, 5.9; N, 4.4; S, 9.8. $C_{18}H_{19}NO_3S$ requires C, 65.65; H, 5.8; N, 4.2; S, 9.7%); ν_{max}(Nujol)/cm^{-1} 1605 (C=C); δ_H 7.75 (1H, m, aryl), 7.45 (2H, d, aryl), 7.3 (2H, d, aryl), 6.9 (1H, d, aryl), 6.85 (1H, dd, aryl), 5.4 (1H, s, vinyl), 4.7 (1H, s, vinyl), 3.9–3.8 (5H, s + t, OCH_3 + CH_2), 2.35 (3H, s, CH_3 tosyl) and 2.3 (2H, t, CH_2).

2,3,4,5-Tetrahydro-7-methoxy-4-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 2 (R = tosyl, X = 7-OMe)

Silver nitrate (3.2 g, 18.9 mmol) was dissolved in methanol (20 cm^3) and water (20 cm^3) at room temperature. To this vigorously stirred solution was added the alkene **7** (X = 6-OMe) (3.1 g, 9.4 mmol) in THF (40 cm^3) in one portion followed immediately by iodine (2.4 g, 9.4 mmol) in one portion. The resulting yellow suspension was stirred at room temperature for 30 min after which the precipitated silver iodide was filtered off. The filtrate was concentrated *in vacuo* and the residue was taken up in dichloromethane (150 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3), dilute aqueous sodium metabisulfite (50 cm^3), water (2 × 50 cm^3) and brine (50 cm^3). The organic phase was then dried and evaporated *in vacuo* to give an oil. Flash chromatography (ethyl acetate–hexane, 20:80) gave the title compound as a white solid (2.51 g, 77%), mp 107–109 °C (Found: C, 62.4; H, 5.6; N, 4.1; S, 9.4. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.05; S, 9.3%); ν_{max}(liquid film)/cm^{-1} 1710 (C=O) and 1600 (C=C); δ_H 7.6 (2H, d, aryl), 7.4 (2H, d, aryl), 7.2 (1H, m, aryl), 6.75 (1H, dd, aryl), 6.7 (1H, d, aryl), 3.9 (2H, t, CH_2), 3.8 (3H, s, OCH_3), 3.2 (2H, s, CH_2), 2.65 (2H, t, CH_2) and 2.4 (3H, s, CH_3 tosyl).

2,3,4,5-Tetrahydro-4-hydroxy-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 9

Procedure (a). Sodium triacetoxyborohydride (2.04 g, 9.64 mmol) was added in portions to a stirred solution of ketone **2** (R = tosyl, X = 8-OMe) (2 g, 5.8 mmol) and *n*-propylamine (0.69 g, 11.6 mmol) in 1,2-dichloroethane (25 cm^3) and acetic acid (0.5 cm^3) at 0–5 °C under nitrogen. The resulting suspension was stirred at room temperature for 16 h whereupon aqueous sodium hydroxide (30 cm^3; 2 M) was added cautiously over 30 min. The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 30 cm^3). The combined organic layers were dried and the solvent was removed *in vacuo* to give a brown oil. Flash chromatography (ethyl acetate–hexane, 80:20) gave unreacted starting material (0.74 g, 37%) (identified by TLC and ^1H NMR spectral comparison with an authentic sample), and the title compound as a viscous clear oil (0.62 g, 49%).

Procedure (b). To a stirred solution of ketone **2** (R = tosyl, X = 8-OMe) (0.6 g, 1.7 mmol) in ethanol (20 cm^3) at room temperature under nitrogen, was added sodium borohydride (0.08 g, 2.03 mmol) in one portion. The resulting suspension was stirred for 3 h and acetic acid (1 cm^3) and water (100 cm^3) were added. The mixture was extracted with dichloromethane (4 × 50 cm^3) and the combined organic extracts were dried and evaporated *in vacuo* to give an oil. Flash chromatography gave the title compound as an oil (0.42 g, 70%) This product was identical (TLC, IR and ^1H NMR spectroscopy) to the product obtained by procedure (a) (Found: C, 62.1; H, 6.3; N, 3.9; S, 9.3. $C_{18}H_{21}NO_4S$ requires C, 62.2; H, 6.05; N, 4.0; S, 9.2%); ν_{max}(liquid film)/cm^{-1} 3560–3200 (br, OH) and 1605 (C=C); δ_H 7.65 (2H, d, aryl), 7.15 (2H, d, aryl), 7.0 (1H, d, aryl), 6.75 (1H, d, aryl), 6.7 (1H, dd, aryl), 3.9 (2H, br, CH_2), 3.8 (3H, s, OCH_3), 3.7 (1H, br, C*H*OH), 2.5 (2H, m, CH_2), 2.4 (3H, s, CH_3 tosyl) and 1.9–1.7 (3H, br, CH_2 + exch., CHO*H*).

2,3,4,5-Tetrahydro-4-hydroxyimino-8-methoxy-1-(*p*-tolyl-sulfonyl)-1*H*-1-benzazepine (oxime of 2; R = tosyl, X = 8-OMe)
A mixture of the ketone (4.1 g, 12 mmol), hydroxylamine hydrochloride (1.25 g, 18 mmol) and pyridine (2 cm^3) in ethanol (20 cm^3) was heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and then poured into chloroform (100 cm^3). The organic phase was washed with hydrochloric acid (2 × 50 cm^3, 2 M) and water (2 × 50 cm^3), then dried and the solvent was removed *in vacuo* to give a gum. Trituration with diethyl ether gave a solid which was recrystallised from ethanol to give the title compound as colourless needles (4.0 g, 96%), mp 136–137 °C (Found: C, 60.1; H, 5.7; N, 7.7; S, 8.9. $C_{18}H_{20}N_2O_4S$ requires C, 60.0; H, 5.6; N, 7.8; S, 8.9%); ν_{max}(Nujol)/cm^{-1} 3450–3250 (oxime OH) and 1600 (C=C); δ_H 8.1 (1H, br, exch., =NOH), 7.4 (2H, m, aryl), 7.3 (2H, m, aryl), 7.2–7.0 (1H, m, aryl), 6.8 (2H, m, aryl), 3.9 (2H, m, CH_2), 3.7 (3H, s, OCH_3), 3.4 + 3.1 (2H, 2 × s, CH_2 benzylic *E* + *Z*), 2.9 + 2.5 (2H, 2 × t, CH_2 *E* + *Z*) and 2.4 (3H, s, CH_3 tosyl).

4-Amino-2,3,4,5-tetrahydro-8-methoxy-1*H*-1-benzazepine 1 (R = H, X = 8-OMe)
To a solution of the oxime (prepared above) (1.0 g, 2.78 mmol) in dry THF (20 cm^3) at room temperature under nitrogen, was added lithium aluminium hydride (12.6 cm^3, 12.6 mmol; 1.0 M solution in THF). After the initial vigorous effervescence had subsided, the resulting yellow solution was heated at reflux for 18 h during which time the reaction mixture became deep red: it was cooled to 0 °C, and excess hydride was destroyed by the cautious addition of 'wet' diethyl ether (10 cm^3). The mixture was diluted with ethanol (50 cm^3) and the inorganic material was filtered off. The filtrate was dried and the solvent was removed *in vacuo* to give an oil. Flash chromatography (dichloromethane–ethanol–ammonia, 50:8:1) gave the title compound as an off-white solid (0.26 g, 49%), mp 98–99 °C (Found: C, 68.5; H, 8.2; N, 14.5. $C_{11}H_{16}N_2O$ requires C, 68.75; H, 8.3; N, 14.6%); ν_{max}(Nujol)/cm^{-1} 3340, 3250 (N–H + NH_2) and 1610 (C=C); δ_H 7.0 (1H, d, aryl), 6.4 (1H, dd, aryl), 6.3 (1H, d, aryl), 3.8 (3H, s, OCH_3), 3.2–3.1 (1H, qd, C*H*NH_2), 3.1–2.9 (2H, m, CH_2), 2.8 (2H, d, CH_2), 2.0 (1H, m, CH_2), 1.9 (1H, m, CH_2) and 1.85–1.5 (3H, br, exch., NH + NH_2).

2,3,4,5-Tetrahydro-8-methoxy-4-di-*n*-propylamino-1*H*-benzazepine 10 (R = H, X = 8-OMe)
Sodium triacetoxyborohydride (0.495 g, 2.3 mmol) was added in portions to a stirred mixture of amine **1** (R = H, X = 8-OMe) (0.14 g, 0.73 mmol), propanal (0.157 g, 2.7 mmol) and glacial acetic acid (0.15 g, 2.5 mmol) in 1,2-dichloroethane (60 cm^3) at room temperature under nitrogen. The resulting suspension was stirred for 3 h and then treated with dichloromethane (30 cm^3) and aqueous sodium hydroxide (30 cm^3; 2 M). The mixture was stirred vigorously for 30 min and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 30 cm^3) and the pooled organic layers were washed with water (2 × 50 cm^3), dried and evaporated *in vacuo* to give an oil (0.24 g, 38%) which was taken up in ethanol (10 cm^3) and treated with ethereal hydrogen chloride. The solvent was removed *in vacuo* and the residue was crystallised from ethyl acetate–hexane to give the title compound as the hygroscopic dihydrochloride salt, mp 125–127 °C (Found: C, 58.5; H, 8.7; N, 8.35; Cl, 20.4. $C_{17}H_{28}N_2O$·2HCl requires C, 58.4; H, 8.6; N, 8.0; Cl, 20.3%); ν_{max}(Nujol)/cm^{-1} 3320 (NH) and 1610 (C=C); δ_H(free-base) 7.4 (1H, d, aryl), 7.1 (1H, dd, aryl), 6.9 (1H, d, aryl), 3.8 (3H, s, OCH_3), 3.1 (2H, m, CH_2), 3.0–2.7 (7H, m, 2 × CH_2 + CH_2 + CHN), 2.1–2.0 (2H, m, CH_2), 1.85–1.6 (5H, m, 2 × CH_2 + exch., NH) and 1.2 (6H, t, 2 × CH_3).

2,3,4,5-Tetrahydro-4-hydroxyimino-7-methoxy-1-(*p*-tolyl-sulfonyl)-1*H*-1-benzazepine (oxime of 2; R = tosyl, X = 7-OMe)
A solution of the ketone (1.0 g, 2.9 mmol), hydroxylamine hydrochloride (0.3 g, 4.35 mmol) and pyridine (0.5 cm^3) in ethanol (20 cm^3) was heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and was then poured into chloroform (100 cm^3). The organic phase was washed with hydrochloric acid (2 × 50 cm^3) and water (2 × 50 cm^3) then dried and the solvent was removed *in vacuo* to give a gum. Trituration with diethyl ether gave an off-white solid which was recrystallised from ethanol to afford the title compound as colourless crystals (0.95 g, 91%), mp 131–133 °C (Found: C, 60.1; H, 5.7; N, 7.7; S, 8.6. $C_{18}H_{20}N_2O_4S$ requires C, 60.0; H, 5.55; N, 7.8; S, 8.9%); ν_{max}(Nujol)/cm^{-1} 3450–3200 (OH, oxime) and 1600 (C=C); δ_H 8.2 (1H, br, exch., =NOH), 7.6 (2H, d, aryl), 7.2 (2H, d, aryl), 7.1 (1H, dd, aryl), 6.8 (2H, m, aryl), 3.9–3.7 (5H, t + s, CH_2 + OCH_3), 3.4 + 3.1 (2H, 2 × s, CH_2 benzylic *E* + *Z*), 2.9 + 2.6 (2H, 2 × t, CH_2 *E* + *Z*) and 2.4 (3H, s, CH_3 tosyl).

4-Amino-2,3,4,5-tetrahydro-7-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 1 (R = tosyl, X = 7-OMe)
To a stirred solution of the oxime (prepared above) (0.9 g, 2.5 mmol) in dry THF (20 cm^3) at room temperature under nitrogen was added dropwise a solution of lithium aluminium hydride (14 cm^3, 14 mmol; 1.0 M solution in THF). The resulting mixture was heated at reflux for 18 h and then cooled to 0 °C. Excess hydride was destroyed by the addition of 'wet' diethyl ether (10 cm^3). The inorganic salts were filtered off and the filtrate was diluted with diethyl ether (20 cm^3). The organic phase was washed with water (30 cm^3), dried and the solvent was removed *in vacuo* to give an oil. Flash chromatography (dichloromethane–ethanol–ammonia, 100:8:1) afforded the title compound as an unstable viscous oil (0.48 g, 56%); ν_{max}-(liquid film)/cm^{-1} 3340, 3250 (NH_2) and 1610 (C=C); δ_H 7.8 (1H, d, aryl), 7.5 (2H, d, aryl), 7.3 (1H, d, aryl), 7.2 (2H, d, aryl), 6.75 (1H, dd, aryl), 3.95 (1H, m, CH_2), 3.8 (3H, s, OCH_3), 3.5 (1H, m, CH_2), 3.2–3.1 (1H, qd, CHN), 2.5 (2H, m, CH_2), 2.45 (3H, s, CH_3 tosyl) and 2.0–1.7 (4H, br, CH_2 + exch., NH_2). An accurate elemental analysis could not be obtained.

2,3,4,5-Tetrahydro-7-methoxy-4-di-*n*-propylamino-1-(*p*-tolyl-sulfonyl)-1*H*-1-benzazepine 10 (R = tosyl, X = 7-OMe)
Sodium triacetoxyborohydride (0.2 g, 0.96 mmol) was added in portions to a stirred mixture of amine **1** (R = tosyl, X = 7-OMe) (0.11 g, 0.3 mmol), propanal (0.06 g, 1.03 mmol) and glacial acetic acid (2 drops) in 1,2-dichloroethane (15 cm^3) at room temperature under nitrogen. The mixture was stirred for 3 h and then treated with dichloromethane (20 cm^3) and aqueous sodium hydroxide (15 cm^3; 2 M). The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 30 cm^3). The pooled organic layers were washed with water (2 × 50 cm^3), then dried and the solvent was removed *in vacuo* to give a pale yellow oil (0.09 g, 38%). This oil was taken up in ethanol (5 cm^3) and treated with ethereal hydrogen chloride. The solvent was removed *in vacuo* and the residue was crystallised from diethyl ether–hexane to give the title compound as the hygroscopic dihydrochloride salt, mp 118–120 °C (Found: C, 57.7; H, 7.55; N, 5.5; S, 6.3; Cl, 14.3. $C_{24}H_{34}N_2O_3S$·2HCl requires C, 57.3; H, 7.2; N, 5.6; S, 6.4; Cl, 14.1%); ν_{max}(Nujol)/cm^{-1} 1610 (C=C); δ_H(Free-base) 7.6 (2H, d, aryl), 7.4 (2H, d, aryl), 7.05–6.95 (2H, m, aryl), 6.8 (1H, dd, aryl), 4.05 (1H, m, CH_2), 3.8 (3H, s, OCH_3), 3.6 (1H, m, CH_2), 3.05–2.6 (7H, m, CHN + 2 × CH_2 + CH_2), 2.45 (3H, s, CH_3 tosyl), 2.0–1.8 (6H, m, 2 × CH_2 + CH_2) and 1.1–1.0 (6H, t, 2 × CH_3).

2,3,4,5-Tetrahydro-8-methoxy-4-phthalimido-1*H*-1-benzazepine 8
4-Amino-2,3,4,5-tetrahydro-8-methoxy-1*H*-1-benzazepine (10 mg, 5.2×10^{-5} mol) *N*-ethoxycarbonyl phthalimide (11 mg, 5.2×10^{-5} mol) and triethylamine (0.1 cm^3) in THF (10 cm^3) were heated at reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent was removed under

reduced pressure. The residue was dissolved in dichloromethane and washed with 10% aqueous sodium hydrogen carbonate. The organics were dried over sodium sulfate and concentrated under reduced pressure to yield the desired product, mp 145–147 °C (Found: M^+, 322.1248. $C_{19}H_{18}N_2O_3$ requires *M*, 322.1311); δ_H 7.9 (4H, m, aryl), 7.0 (1H, d, *J* 8.2, aryl), 6.4 (1H, dd, *J* 8.3, 2.2, aryl), 6.3 (1H, d, *J* 2, aryl), 3.7 (3H, s, OCH_3), 3.4 (1H, m, CHNP), 2.9 (2H, m, CH_2), 2.7 (2H, m, CH_2), 1.9 (2H, m, CH_2) and 1.2 (1H, m, NH).

Hydrolysis of methyl *N*-(*m*-methoxyphenyl)-3-aminopropanoate

To a stirred solution of the ester[15b] (100 g, 0.447 mol) in ethanol (450 cm^3) was slowly added aqueous sodium hydroxide (18 g, 0.477 mol in 115 cm^3 water). The solution was heated gently (never refluxing) until TLC indicated absence of the ester. The ethanol was removed and the aqueous layer was acidified (pH 4) with 2 M hydrochloric acid. The reaction mixture was then extracted with chloroform, the extracts combined and washed with brine, dried over sodium sulfate and the solution was removed under reduced pressure to yield a brown oil. This was taken to the next stage without further purification; it was assumed to be N-(m-*methoxyphenyl*)-3-*aminopropanoic acid*.[17b]

1,2,3,4-Tetrahydro-7-methoxy-4-oxoquinoline 3 (R = H, X = 7-OMe)

To the stirred crude acid (from above) (40 g, 0.2 mol) at room temperature, polyphosphoric acid[17] (85%, 400 g) was added. The reaction was stirred at room temperature for 0.5 h and then to 60 °C over 0.5 h and further at 60 °C overnight. The temperature was raised to 70–80 °C for 2 h and then 100 °C for 1 h. The reaction mixture was then poured onto ice, basified with ammonia to pH 8–9. The solid precipitate formed was removed by filtration, dried and recrystallised from ethanol to yield the desired product (22 g, 61%), mp 134–136 °C (lit.,[15b] mp 139–140 °C) (lit.,[17b] mp 137–138 °C); ν_{max}/cm^{-1} 3361 (NH) (Found: C, 67.6; H, 6.2; N, 7.8%; M^+, 177.0726. Calc. for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.2; N, 7.9%; *M*, 177.0786); δ_H(*cf.*[17b]) 7.8–7.7 (1H, d, aryl), 6.3 (1H, dd, aryl), 6.0 (1H, d, aryl), 4.5 (1H, br, NH), 3.8 (3H, s, CH_3), 3.5–3.4 (2H, td, CH_2), 2.6 (2H, t, CH_2); δ_C 37.9 (CH_2), 42.5 (CH_2), 55.5 (OCH_3), 98.1 (aryl), 106.9 (aryl), 113.9 (aryl), 129.9 (aryl), 154.2 (aryl), 165.5 (aryl) and 192.5 (C=O).

1,2,3,4-Tetrahydro-5-methoxy-4-oxoquinoline 6 (R = H)[17c]

The aqueous layer from the above reaction was extracted with dichloromethane. The solvent was dried and removed under reduced pressure to yield a yellow solid (3.6 g, 10%), mp 176–178 °C (lit.,[17c] mp 183–184 °C) (Found: C, 67.8; H, 6.3; N, 7.8. Calc. for $C_{10}H_{11}NO_2$: C, 67.7; H, 6.2; N, 7.9%); δ_H 2.7 (2H, m, CH_2), 3.25 (2H, m, CH_2), 3.8 (3H, s, OCH_3), 6.3 (2H, m, aryl) and 7.2 (1H, m, aryl).

Ethyl (1,2,3,4-tetrahydro-7-methoxy-4-oxo-1-quinolyl)acetate 3 (R = CH_2CO_2Et, X = 7-OMe)

Under nitrogen, the ketone **3** (R = tosyl, X = 7-OMe) (5 g, 28 mmol), dry toluene (50 cm^3), Hunig's base (13 cm^3) and ethyl bromoacetate (5 cm^3) were heated together to 90 °C for 90 h. The reaction was cooled and the solid formed was filtered off. The aqueous layer was extracted with chloroform and the combined organics were washed with water, dried over sodium sulfate and the solvent was removed to yield a brown oil which crystallised on standing. The crystals were combined and recrystallisation from ethanol yielded the desired product (3.72 g, 51%), mp 92–94 °C (Found: C, 63.6; H, 6.3; N, 5.2%; M^+, 263.1165. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%; *M*, 263.1152); ν_{max}/cm^{-1} 1753 (C=O); δ_H 8.1–8.0 (1H, d, aryl), 6.5 (1H, dd, aryl), 6.1 (1H, d, aryl), 4.4–4.2 (2H, q, CH_2), 4.1 (2H, s, CH_2), 3.8 (3H, s, OCH_3), 3.7 (2H, t, CH_2), 2.9–2.8 (2H, t, CH_2) and 1.5–1.4 (3H, t, CH_3).

Ethyl (1,2,3,4-tetrahydro-7-methoxy-4-methylene-1-quinolyl)-acetate 7 (X = 7-OMe, CH_2CO_2Et for Ts)

To a solution of ethyl (1,2,3,4-tetrahydro-7-methoxy-4-oxo-1-quinolyl)acetate (0.5 g, 1.9 mmol) in THF cooled to 0 °C was added Tebbe reagent[19] (6 cm^3; 0.5 M). After 30 min, diethyl ether (20 cm^3) was added followed by the addition of 5–10 drops of aqueous NaOH (0.1 M) while stirring to destroy active aluminium compounds. The reaction mixture was then dried over sodium sulfate, filtered through Kieselguhr and concentrated *in vacuo* to yield a brown oil. Flash column chromatography [SiO_2 (pretreated with ammonia to prevent isomerisation), dichloromethane] yielded the desired product (0.13 g, 27%) and starting material (0.21 g, 42%) (Found: M^+, 261.1317. $C_{15}H_{19}NO_3$ requires *M*, 261.1359); ν_{max}/cm^{-1} 1753 (C=O), 1625 (C=C); δ_H 7.4 (1H, d, *J* 8.6, aryl), 6.3–6.2 (1H, dd, *J* 2.4, 8.6, aryl), 6.06 (1H, d, *J* 2.7, aryl), 5.26 (1H, s, vinyl), 4.68 (1H, s, vinyl), 4.2–4.0 (2H, m, CH_2CH_3), 3.9 (2H, s, CH_2CO_2), 3.7 (3H, s, OCH_3), 3.4 (2H, t, *J* 6.2, CH_2), 2.6 (2H, t, *J* 6.1), 1.3 (3H, m, CH_3).

Ethyl (2,3,4,5-tetrahydro-8-methoxy-4-oxo-1*H*-1-benzazepin-1-yl)acetate 2 (R = CH_2CO_2Et, X = 8-OMe)

Silver nitrate (2.2 g, 0.013 mol), methanol (24 cm^3) and water (24 cm^3) were stirred vigorously. Ethyl (1,2,3,4-tetrahydro-7-methoxy-4-methylene-1-quinolyl)acetate (1.7 g, 6.5 mmol) in tetrahydrofuran (38 cm^3) was added immediately followed by the addition of iodine (1.6 g, 6.5 mmol) all at once. After being stirred at room temperature for 1 h, the reaction was filtered and the solvent evaporated. The residue was dissolved in chloroform, washed with aqueous sodium hydrogen carbonate, dilute aqueous sodium metabisulfite, dried and the solvent removed to yield a clear oil (1.2 g, 66%) (Found: M^+, 277.1507. $C_{15}H_{19}NO_4$ requires *M*, 277.1577). Instability of this product prevented acquisition of satisfactory data.

4-Acetamido-2,3,4,5-tetrahydro-8-methoxy-1*H*-1-benzazepine 11 (R = H)

Acetyl chloride (0.075 cm^3, 1.05 mmol) in dry THF (5 cm^3) was added, in one portion, to a stirred solution of 4-amino-2,3,4,5-tetrahydro-8-methoxy-1(1*H*)-benzazepine **1** (R = H, X = 8-OMe, 0.2 g, 1.05 mmol) and trimethylamine (0.15 cm^3, 1.05 mmol) in dry THF (15 cm^3), and the resulting suspension stirred at −78 °C for 0.5 h. The reaction mixture was stirred for a further 2 h at room temperature, dilute hydrochloric acid (2 M, 100 cm^3) was added and the mixture washed with chloroform. The aqueous layer was basified (2 M NaOH) and extracted with chloroform. The chloroform extracts were dried and the solvent removed *in vacuo* to give a brown oil. Flash chromatography [SiO_2–dichloromethane–ethanol–ammonia (DEA), 300 : 8 : 1] and trituration with diethyl ether gave the product as a white solid (0.2 g, 81%), mp 139–141 °C (Found: C, 66.1; H, 7.7; N, 11.6. $C_{13}H_{18}N_2O_2$ requires C, 66.55; H, 7.75; N, 11.95%); ν_{max}(Nujol)/cm^{-1} 3330 (NH), 3240 (NH), 1600 (C=C); δ_H 7.05 (1H, d, aryl), 6.45 (1H, dd, aryl), 6.3 (1H, d, aryl), 5.45 (1H, br, exch., NH amine), 4.25 (1H, m, >C*H*NHAc), 3.8 (3H, s, OMe), 3.25–2.95 (3H, m, CH_2, + CH benzylic), 2.8 (1H, dd, CH benzylic), 2.0 (5H, m + s, CH_2, $NHCOCH_3$) and 1.8–1.45 (1H, br, exch., NH amide).

4-(*N*-Acetyl-*N*-ethoxycarbonylmethylamino)-2,3,4,5-tetrahydro-8-methoxy-1*H*-benzazepine 11 (R = CH_2CO_2Et)

4-Acetamido-2,3,4,5-tetrahydro-8-methoxy-1*H*-1-benzazepine **11** (R = H, 0.42 g, 1.8 mmol), ethyl bromoacetate (0.24 cm^3, 2.16 mmol) and *N*,*N*-diisopropylethylamine (0.63 cm^3, 3.6 mmol) were heated together in toluene at 110 °C for 16 h under nitrogen. The cooled reaction mixture was poured onto chloroform (100 cm^3) and washed with dilute hydrochloric acid, dried and the solvent removed *in vacuo* to give a brown oil. Flash chromatography (SiO_2–DEA 300 : 8 : 1) gave a white solid (0.485 g, 84%), mp 134–135 °C (Found: C, 63.6; H, 7.8; N, 8.5. $C_{17}H_{24}N_2O_4$ requires C, 63.7; H, 7.55; N, 8.75%); $\nu_{max}(CHCl_3)$/cm^{-1} 3320 (NH, amide), 1730 (C=O, ester), 1640 (C=O, amide); δ_H 7.0 (1H, d, aryl), 6.45 (1H, dd, aryl), 6.3 (1H, d, aryl), 5.95

(1H, br, exch., NH), 4.4–4.2 (3H, q + m, >C*H*NH, CO_2CH_2-CH_3), 4.0 (2H, dd, *J* 20, CH_2CO_2Et), 3.8 (3H, s, OCH_3), 3.3–3.0 (3H, m, CH_2, CH benzylic), 2.85 (1H, dd, CH benzylic), 1.95 (5H, m + s, CH_2, $NRCOCH_3$) and 1.3 (3H, t, $CO_2CH_2CH_3$).

2,3,4,5-Tetrahydro-3-hydroxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 12 (X, Y = NOH)

2,3,4,5-Tetrahydro-3-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine (**12**; X, Y = O, 2 g, 6.35 mmol),[5] hydroxylamine hydrochloride (0.67 g, 9.53 mmol) and pyridine (1.2 cm^3) were refluxed together in ethanol (20 cm^3) for 2 h. The reaction mixture was poured into chloroform (100 cm^3) and washed with dilute hydrochloric acid. The chloroform extracts were dried and the solvent removed *in vacuo* to give an oil which solidified on standing. Recrystallisation from ethanol gave the title product as white crystals (1.8 g, 86%), mp 186 °C (decomp.) (Found: C, 61.3; H, 5.1; N, 8.3; S, 9.6. $C_{17}H_{18}N_2O_3S$ requires C, 61.8; H, 5.5; N, 8.5; S, 9.7%); ν_{max}(Nujol)/cm^{-1} 3250 (OH), 1600 (C=C); δ_H 8.0–7.0 (9H, m, aryl, OH exch.), 4.65 + 4.35 (2H, 2s, CH_2, *E* + *Z*) and 2.7–2.05 (7H, m, CH_3, tosyl, 2 × CH_2).

3-Amino-2,3,4,5-tetrahydro-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 12 (X = NH_2, Y = H)

To 2,3,4,5-tetrahydro-3-hydroxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine **12** (X, Y = NOH) (1.5 g, 4.5 mmol), ethanol (30 cm^3) and aqueous sodium hydroxide (4 M; 30 cm^3) was added Raney nickel alloy (2.25 g, 1:1 Ni/Al), in one portion, at room temperature. The resulting suspension was stirred for 1 h after which the nickel was collected by filtration (**CAUTION**: pyrophoric). The filtrate was concentrated *in vacuo*, extracted with chloroform (100 cm^3), dried and the solvent removed *in vacuo* to give an oil. Flash chromatography (SiO_2–DEA 300:8:1) gave the title product as a clear oil (0.87 g, 62%) (Found: C, 64.4; H, 6.05; N, 8.6; S, 9.55. $C_{17}H_{20}N_2O_2S$ requires C, 64.55; H, 6.35; N, 8.85; S, 10.15%); ν_{max}(film)/cm^{-1} 3360 (NH_2), 1600 (C=C); δ_H 7.65 (2H, d, aryl), 7.3–7.05 (6H, m, aryl), 4.2 (1H, d, CH_2), 3.2 (1H, m, CH_2), 2.9 (1H, m, >C*H*NH_2), 2.7–2.4 (5H, m + s, CH_2, CH_3 tosyl), 2.05 (1H, m, CH_2), 1.3 (1H, m, CH_2) and 1.45 (2H, s, exch., NH_2).

1,2,3,4-Tetrahydro-7-methoxy-1-hydroxyiminonaphthalene[28]

7-Methoxy-1-tetralone (100 g, 0.568 mol), sodium hydroxide (120 g, 3 mol), hydroxylamine hydrochloride (96.2 g, 1.38 mol) and ethanol (100 cm^3) were heated at reflux for 2 h. The mixture was then allowed to cool to room temperature and water (3000 cm^3) was added. The mixture was extracted with dichloromethane (4 × 500 cm^3), the combined organic layers were dried and the solvent was removed *in vacuo* to give the title compound as an off-white solid (96.96 g, 89%). Recrystallisation was from light petroleum (60–80 °C), mp 86–88 °C (lit.,[28] mp 87–88 °C) (Found: C, 69.15; H, 7.3; N, 7.3. Calc. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; N, 7.3%); ν_{max}(Nujol)/cm^{-1} 3360 (OH, oxime) and 1620 (C=C); δ_H(90 MHz) 7.7 (1H, s, exch., NO*H*), 7.45 (1H, d, aryl), 7.0 (2H, m, aryl), 3.8 (3H, s, OCH_3), 2.8–2.7 (4H, m, 2 × CH_2) and 1.85 (2H, m, CH_2).

1,2,3,4-Tetrahydro-7-methoxy-1-(*p*-tolylsulfonyloxyimino)-naphthalene[28]

To the oxime of 7-methoxy-1-tetralone (96.9 g, 0.507 mol) in acetone (250 cm^3) at 0 °C, was added dropwise aqueous potassium hydroxide (500 cm^3; 10%). When the addition was complete, a solution of toluene-*p*-sulfonyl chloride (98.43 g, 0.517 mol) in acetone (300 cm^3) was added dropwise. The resulting mixture was stirred at room temperature for 3 h. The solid was filtered off, washed with water (500 cm^3) and dried in air to give the title compound as an off-white solid (182.6 g, 97%), purified by recrystallisation from ethanol, mp 130–132 °C (lit.,[28] mp 130–131 °C) (Found: C, 62.9; H, 6.0; N, 4.1; S, 9.2. Calc. for $C_{18}H_{19}NO_4S$: C, 62.6; H, 5.5; N, 4.05; S, 9.3%); ν_{max}(Nujol)/cm^{-1} 1620 (C=C); δ_H(90 MHz) 7.85 (2H, d, aryl), 7.3–7.1 (5H, m, aryl), 3.8 (3H, s, OCH_3), 2.85–2.7 (4H, m, 2 × CH_2), 2.4 (3H, s, CH_3 tosyl) and 1.8 (2H, m, CH_2).

2,3,4,5-Tetrahydro-8-methoxy-2-oxo-1*H*-1-benzazepine 16 (R = H, X, Y = O)[28,29]

A suspension of the oxime tosylate (64.4 g, 0.187 mol) in glacial acetic acid (1000 cm^3) and water (800 cm^3) was stirred at 60 °C overnight, during which time the solid dissolved. The solution was allowed to cool and the solvent was removed *in vacuo* to give a brown oil which was cooled (0 °C), and aqueous sodium hydrogen carbonate (1000 cm^3; 2 M) was added with stirring. The precipitated solid was filtered and dried in air (28.07 g, 78%), mp 128–130 °C (lit.,[29] mp 129–131 °C) (Found: C, 68.8; H, 6.8; N, 7.3. Calc. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; N, 7.3%); ν_{max}(Nujol)/cm^{-1} 3210 (NH) and 1685 (C=O); δ_H(90 MHz), 8.65 (1H, s, exch., NH), 7.1 (1H, d, aryl), 6.7–6.65 (1H, dd, aryl), 6.6 (1H, d, aryl), 3.8 (3H, s, OCH_3), 2.75–2.7 (2H, t, CH_2), 2.4–2.3 (2H, t, CH_2) and 2.25–2.15 (2H, m, CH_2).

2,3,4,5-Tetrahydro-8-methoxy-1*H*-1-benzazepine 16 (R = X = Y = H)

To a suspension of lithium aluminium hydride (16 g, 0.42 mol) in dry THF (400 cm^3) at 0 °C under nitrogen, was added dropwise a solution of lactam **16** (R = H, X, Y = O)[29] (16 g, 0.084 mol) in dry THF (100 cm^3). The resulting suspension was heated at reflux for 3 h and then cooled to 0 °C. Excess hydride was destroyed by the cautious addition of ethanol (50 cm^3) followed by saturated aqueous sodium sulfate (150 cm^3). The inorganic salts were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was taken up in diethyl ether (200 cm^3) and washed with water and brine, then dried and the solvent was removed *in vacuo* to give a brown oil (11.33 g, 86%) which was used without further purification. The *N*-acetate made in the usual way (pyridine, acetyl chloride, diethyl ether, 0 °C) had mp 62–64 °C.

2,3,4,5-Tetrahydro-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 16 (R = tosyl, X = Y = H)

To a cooled (0 °C) solution of compound **16** (R = X = Y = H)[30] (8.5 g, 48 mmol) in pyridine (30 cm^3) was added toluene-*p*-sulfonyl chloride (9.29 g, 48 mmol) in portions. The resulting deep red mixture was stirred at room temperature for 3 h, whereupon ice-cooled water (50 cm^3) and dilute hydrochloric acid (50 cm^3) were added. The mixture was extracted with diethyl ether (4 × 100 cm^3) and the combined organic extracts were washed with water, then dried and the solvent was removed *in vacuo* to give a red oil which solidified on standing to a yellow solid (15.25 g, 96%) which was chromatographed (Al_2O_3, diethyl ether–light petroleum, 1:5) giving colourless crystals, mp 82–83 °C (softens 52–54 °C) (Found: C, 65.25; H, 6.45; N, 4.15; S, 9.65%; M^+, 331.1252. $C_{18}H_{21}NO_3S$ requires C, 65.25; H, 6.4; N, 4.25; S, 9.65%; *M*, 331.1242).

2,3,4,5-Tetrahydro-8-methoxy-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 4 (R = tosyl, X = 8-OMe)

To a cooled (0 °C) solution of compound **16** (R = tosyl, X = Y = H) (13.3 g, 40.2 mmol) and acetic acid (100 cm^3) was added a solution of chromium trioxide (18.94 g, 189 mmol) in acetic acid (132 cm^3) and water (50 cm^3) dropwise over 3 h.[31] The resulting dark green mixture was stirred at room temperature overnight and then cooled to 0 °C. Aqueous sodium hydroxide (200 cm^3; 10%) was added dropwise and the solution was stirred for 1 h and then extracted with dichloromethane (4 × 250 cm^3). The combined organic extracts were washed with water (2 × 250 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give a green oil. Chromatography on alumina (ethyl acetate–hexane, 30:70) gave a yellow solid (11.84 g) which was recrystallised from propan-2-ol to give the title compound as colourless crystals (10.26 g, 74%), mp 86–88 °C (Found: C, 62.5; H, 5.6; N, 4.1; S, 9.4. $C_{18}H_{19}NO_4S$ requires C,

62.6; H, 5.5; N, 4.05; S, 9.3%); ν_{max}(Nujol)/cm^{-1} 1708 (C=O), 1605 (C=C); δ_H 7.7 (1H, d, aryl), 7.6 (2H, d, aryl), 7.3 (2H, d, aryl), 6.9 (1H, d, aryl), 6.85–6.8 (1H, dd, aryl), 3.85–3.8 (5H, t + s, CH_2 + OCH_3), 2.45–2.35 (5H, s + t, tosyl + CH_2) and 2.0–1.9 (2H, m, CH_2). *N*-Acetyl-2,3,4,5-tetrahydro-8-methoxy-5-oxo-1*H*-1-benzazepine **4** (R = Ac, X = 8-OMe) was obtained similarly[31] and had mp 76–78 °C (Found: C, 67.0; H, 6.6; N, 5.95. $C_{13}H_{15}NO_3$ requires C, 66.95; H, 6.5; N, 6.0%); ν_{max}(Nujol)/cm^{-1} 1660, 1600 and 1580; δ_H 7.9 (1H, d, aryl), 6.94 (1H, dd, aryl), 6.7 (1H, d, aryl), 3.87 (3H, s, OMe), 2.61 (2H, m, CH_2), 1.90–1.97 (5H, m, CH_2 + CH_3, CO) and 1.48–1.5 (2H, m, CH_2).

2-Hydroxyimino-3′-methoxyacetanilide (*cf.* ref. 26)

To trichloroacetaldehyde hydrate (90 g, 0.54 mol) in water (1200 cm^3) was added in order: anhydrous sodium sulfate (568 g) in water (750 cm^3), a solution of *m*-anisidine (61.5 g, 0.5 mol) in water (300 cm^3) containing concentrated hydrochloric acid (43 cm^3) and finally hydroxylamine hydrochloride (110 g, 1.58 mol) in water (500 cm^3). The mixture was slowly heated with stirring, until vigorous boiling commenced after about 45 min. After 1 or 2 min boiling, the reaction was complete, and the contents of the flask were cooled immediately. The brown solid that separated was filtered and dried to yield 84 g, which was used without further purification.

6-Methoxyisatin 15

Method (a). 2-Hydroxyimino-3′-methoxyacetanilide (20 g) was added with stirring to concentrated sulfuric acid (100 cm^3) at 50 °C. The rate of addition was such that the temperature did not rise above 70 °C. After the addition was complete the reaction mixture was heated to 80 °C for 10 min, then cooled to room temperature and poured onto 1 l of ice. The chloroform extracts were dried and evaporated *in vacuo* to yield bright orange crystals, which recrystallised from acetone–light petroleum to give 0.65 g of **15** (mp 154–157 °C) (Found: C, 60.8; H, 3.85; N, 7.9%; M^+, 177.0425. $C_9H_7NO_3$ requires C, 61.0; H, 4.0; N, 7.9%; *M*, 177.0426); ν_{max}/cm^{-1} 3240 (NH amide), 1620 [shoulder at 1640 (C=O)], 1600 (C=C); δ_H 7.6–7.4 (1H, d, aryl), 7.2–7.0 (1H, dd, aryl), 7.95 (1H, d, aryl), 3.9 (3H, s, OMe) and 10.95 (1H, br, exch., NH).

Method (b). 2-Hydroxyimino-3′-methoxyacetanilide (40 g) was added with stirring to polyphosphoric acid (400 g) at 50 °C in the same manner as for method (a). After 10 min stirring at 80 °C the mixture was immediately poured onto a large excess of ice and the solid filtered off. The dried solid was purified by reprecipitation with dilute hydrochloric acid from dilute aqueous sodium hydroxide to yield 24 g of **15** (66%), identical to that found in method (a).

4-Methoxyanthranilic acid 14 (R^1 = R^2 = H, CO_2H for CO_2Me)

6-Methoxyisatin (5 g, 0.03 mol) was dissolved in water (150 cm^3) containing sodium hydroxide (8 g, 0.2 mol). To this solution at 25–30 °C was added dropwise 30% w/v aqueous hydrogen peroxide (8 cm^3) in water (70 cm^3). When the addition was complete the reaction mixture was stirred at room temperature for 24 h. Neutralisation with dilute hydrochloric acid, followed by filtration yielded the product as an off-white solid (3.98 g, 78%). Identified by comparison with a genuine sample (mp 174–176 °C, IR, NMR spectroscopy, TLC) prepared by the literature method.[35]

Ethyl 4-methoxyanthranilate 14 (R^1 = R^2 = H, CO_2Et for CO_2Me)

4-Methoxyanthranilic acid (1 g, 6 mmol) was refluxed in ethanol (50 cm^3), saturated with dry hydrogen chloride gas, overnight. The reaction mixture was poured onto an excess of aqueous sodium hydrogen carbonate and the ethanol evaporated *in vacuo*. The chloroform extracts were dried, and evaporated *in vacuo* to yield a light purple oil which crystallised on standing. Recrystallisation from diethyl ether–light petroleum gave light purple needles (0.624 g, 52%), mp 67–68 °C (Found: C, 61.3; H, 6.75; N, 6.9%, M^+, 195.0895. $C_{10}H_{13}NO_3$ requires C, 61.55; N, 7.2; H, 6.65%; *M*, 195.0895); ν_{max}(TCE)/cm^{-1} 3500, 3360 (NH), 1680 (C=O ester); δ_H 7.8 (1H, s, aryl), 6.2 (1H, dd, aryl), 6.1 (1H, d, aryl), 5.7 (2H, br, exch., NH), 4.3 (2H, q, CH_2CH_3), 3.75 (3H, s, OMe) and 1.3 (3H, t, CH_2CH_3).

Ethyl 4-methoxy-*N*-(*p*-tolylsulfonyl)anthranilate 14 (R^1 = H, R^2 = tosyl, CO_2Et for CO_2Me)

To a solution of ethyl 4-methoxyanthranilate (4.3 g, 0.022 mol) in dry pyridine (30 cm^3) was added toluene-*p*-sulfonyl chloride (5.5 g, 0.029 mol). The resulting mixture was stirred at 90 °C for 6 h and cooled to room temperature overnight. The reaction mixture was then poured onto ice and concentrated hydrochloric acid (6:1). The solid was filtered and recrystallised from methanol to give white needles (5.8 g, 78%), mp 144–146 °C (Found: C, 58.2; H, 5.4; N, 3.95%; M^+, 349.0971. $C_{17}H_{19}NO_5S$ requires C, 58.45; H, 5.5; N, 4.0%; *M*, 349.0984); ν_{max}(TCE)/cm^{-1} 1660 (C=O ester), 1600 (C=C); δ_H 7.8 (3H, m, aryl), 7.3 (3H, m, aryl), 6.5 (1H, dd, aryl), 4.3 (2H, q, CH_2CH_3), 3.8 (3H, s, OCH_3), 2.35 (3H, s, CH_3 tosyl), 1.35 (3H, t, CH_2CH_3) and 10.95 (1H, br, exch., NH).

Methyl 4-methoxyanthranilate 14 (R^1 = R^2 = H)

Method (a). 4-Methoxyanthranilic acid (10 g, 60 mmol) was refluxed for 18 h in methanol (80 cm^3) containing boron trifluoride–methanol complex (19.6 cm^3, 180 mmol). The methanol was evaporated *in vacuo* to yield a dark solid which was treated with saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The extracts were dried and evaporated *in vacuo* to yield a dark oil. Kugelrohr distillation yielded two products, the fraction boiling at 100 °C, at 0.02 mbar (3.1 g) was identified as *m*-anisidine by comparison with a genuine sample (IR and NMR spectroscopy, bp, TLC). The second fraction yielded the title product as a pale yellow oil which slowly solidified on standing (bp 150 °C at 0.02 mmHg, 0.56 g, 5%), mp 73–75 °C (Found: C, 60.0; H, 6.4; N, 7.8%; M^+, 181.0726. $C_9H_{11}NO_3$ requires C, 59.7; H, 6.1; N, 7.7%; *M*, 181.0739); ν_{max}(TCE)/cm^{-1} 3490, 3380 (NH_2), 1680 (C=O, ester); δ_H 7.8 (1H, d, aryl), 6.2 (2H, m, aryl), 5.8–5.2 (2H, br, exch., NH_2), 3.85 (3H, s, OMe, ester) and 3.8 (3H, s, OMe, aryl).

Method (b). 4-Methoxyanthranilic acid (5 g, 30 mmol) was refluxed for 24 h with thionyl chloride (15.5 cm^3, 210 mmol), in dry dichloromethane (30 cm^3). The reaction mixture was evaporated *in vacuo* to yield the intermediate acid chloride as a dark oil. To this oil in dry dichloromethane (20 cm^3) was added dry methanol (20 cm^3) and the resulting solution stirred for 1 h at room temperature. The solvents were removed *in vacuo* and the resulting oil treated with saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The chloroform extracts were dried and the solvent removed *in vacuo* to yield a dark solid. Column chromatography yielded the title product as an off-white solid (3.8 g, 70%), identified by comparison with the product from method (a) above (IR and NMR spectroscopy, TLC).

Methyl 4-methoxy-*N*-(*p*-tolylsulfonyl)anthranilate 14 (R^1 = H, R^2 = tosyl)

Toluene-*p*-sulfonyl chloride (14.9 g, 78 mmol) was added in portions to a stirred solution of methyl 4-methoxyanthranilate (9.33 g, 52 mmol) in dry pyridine (30 cm^3). The resulting yellow solution was stirred overnight at room temperature and then poured into ice and concentrated hydrochloric acid (6:1). The resulting white solid was filtered off and recrystallised from methanol to yield the title product as white needles (16.2 g, 94%), mp 104–105 °C (Found: C, 57.1; H, 5.0; N, 4.1; S, 9.4%; M^+, 335.0816. $C_{16}H_{17}NO_5S$ requires C, 57.3; H, 5.1; N, 4.2; S, 9.6%; *M*, 335.0827); ν_{max}(TCE)/cm^{-1} 1675 (C=O ester), 1600

(C=C); δ_H 7.8 (3H, m, aryl), 7.3 (3H, m, aryl), 6.55 (1H, dd, aryl), 3.85 (3H, s, OMe ester), 3.8 (3H, s, OMe aryl), 2.35 (3H, s, CH_3 tosyl) and 10.9 (1H, br, exch., NH).

Ethyl 4-[*N*-(2-ethoxycarbonyl-5-methoxyphenyl)-*p*-tolylsulfonamido]butyrate 14 (R^1 = $CH_2CH_2CH_2CO_2Et$, R^2 = tosyl, CO_2-Et for CO_2Me)

Ethyl 4-methoxy-*N*-toluene-*p*-sulfonylanthranilate **14** (R^1 = H, R^2 = tosyl, CO_2Et for CO_2Me) (5 g, 0.014 mol) in dry DMF (60 cm^3) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion; 0.616 g, 0.016 mol) under nitrogen. This was then stirred for 2 h at room temperature after which ethyl 4-iodobutyrate (4.1 g, 0.017 mol) in dry DMF was added dropwise. The reaction mixture was then stirred for 12 h at room temperature after which it was heated to 90 °C for 6 h. The cooled mixture was treated with methanol and poured onto an excess of water. The chloroform extracts were washed with water, dried and evaporated *in vacuo* to yield a pale yellow oil. Chromatography [EtOAc–light petroleum (60–80 °C) 3 : 7] gave an almost clear oil (5.6 g, 84%) (Found: C, 60.8; H, 6.7; N, 3.0; S, 7.15%; M^+, 463.1624. $C_{23}H_{29}NO_7S$ requires C, 59.6; H, 6.3; N, 3.0; S, 6.9%; *M*, 463.1665); ν_{max}(film)/cm^{-1} 1710 (C=O, ester), 1600 (C=C); δ_H 7.9 (1H, d, aryl), 7.6–7.1 (4H, m, aryl), 6.9 (1H, dd, aryl), 6.5 (1H, d, aryl), 4.4–3.95 (4H, dq, CH_2CH_3), 3.9–3.5 (5H, m, OCH_3, NCH_2), 2.4 (5H, m, CH_3, CH_2), 1.9 (2H, m, CH_2) and 1.3 (6H, dt, CH_2CH_3).

4-Ethoxycarbonyl-2,3,4,5-tetrahydro-8-methoxy-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 13 (R^1 = tosyl, R^2 = CO_2Et)

To a suspension of sodium hydride (3.3 g, 0.07 mol; 50% oil dispersion) in dry DMF (20 cm^3) was added dropwise methyl 4-methoxy-*N*-(*p*-tolylsulfonyl)anthranilate **14** (R^1 = H, R^2 = tosyl) (19.3 g, 0.058 mol) in dry DMF (100 cm^3) and the resulting mixture stirred at room temperature for 2 h under nitrogen. To this mixture at room temperature was added dropwise ethyl 4-iodobutyrate (15.5 g, 0.064 mol) in dry DMF (20 cm^3), and the resulting solution then stirred at 80 °C for 24 h. After cooling at room temperature a further equivalent of sodium hydride was added and after the initial effervescence had subsided the reaction mixture was heated to 80 °C for 2 h. To the cooled (ice) reaction mixture was added water (400 cm^3) and 2 M hydrochloric acid (100 cm^3). The resulting suspension was poured onto a large excess of water and the solid filtered. Recrystallisation from ethanol gave a solid (17.7 g, 74%), mp 108–110 °C (Found: C, 60.0; H, 5.5; N, 3.3; S, 7.8%; M^+, 417.1246. $C_{21}H_{23}NO_6S$ requires C, 60.4; H, 5.5; N, 3.4; S, 7.7%; *M*, 417.1245); ν_{max}(TCE)/cm^{-1} 1660 (C=O, ester), 1600 (C=C); δ_H 7.5–7.3 (3H, m, aryl), 7.3–7.15 (3H, m, aryl), 7.15–6.85 (1H, dd, aryl), 4.3–3.95 (4H, m, CH_2, CH_3CH_2), 3.85 (3H, s, OCH_3), 2.5–2.2 (5H, m, CH_3, CH_2), 1.3 (3H, t, CH_2CH_3) and 11.9 (1H, d, enolic OH).

2,3,4,5-Tetrahydro-8-methoxy-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 13 (R^1 = tosyl, R^2 = H)

The keto ester **13** (R^1 = tosyl, R^2 = CO_2Et) (21.5 g, 0.052 mol), glacial acetic acid (130 cm^3), concentrated hydrochloric acid (22 cm^3), ethanol (45 cm^3) and water (22 cm^3) were refluxed together for 24 h. The reaction mixture was cooled to room temperature, poured onto a large excess of water and extracted with dichloromethane. The extracts were dried and the solvent removed *in vacuo* to yield a pale brown oil which gave a white solid on trituration with diethyl ether. Recrystallisation from propan-2-ol gave the title compound (12.5 g, 70%), mp 86–88 °C identical to material obtained as above.

2,3,4,5-Tetrahydro-8-methoxy-5-oxo-1*H*-1-benzazepine 13 (R^1 = R^2 = H)

The tosyl ketone **13** (R^1 = tosyl, R^2 = H) (1.85 g, 5.4 mmol), concentrated sulfuric acid (10 cm^3) and glacial acetic acid (15 cm^3) were stirred together at 80 °C for 2 h. The cooled mixture was poured onto ice, basified with powdered sodium hydroxide and extracted with dichloromethane. The extracts were dried and the solvent was removed *in vacuo* to yield an off-white solid (0.78 g, 76%). Chromatography (silica gel, chloroform) gave the product as a white solid, mp 92–95 °C (Found: C, 68.75; H, 6.7; N, 7.25%; M^+, 191.0948. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.8; N, 7.3%; *M*, 191.0946); ν_{max}(TCE)/cm^{-1} 3360 (NH, amine), 1650 (C=O, ketone), 1600 (C=C); δ_H 7.75 (1H, d, aryl), 6.4 (1H, dd, aryl), 6.2 (1H, d, aryl), 4.65 (1H, br, exch., >NH), 3.8 (3H, s, OCH_3), 3.25 (2H, t, CH_2), 2.8 (2H, t, CH_2) and 2.15 (2H, q, CH_2).

2,3,4,5-Tetrahydro-8-methoxy-4-hydroxyimino-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 17 (R = H)

To a stirred solution of ketone **4** (R = tosyl, X = 8-OMe) (2 g, 5.8 mmol) in dry diethyl ether (150 cm^3) at room temperature, was added dropwise a solution of isoamyl nitrite (1.36 g, 11.6 mmol)[32,33] in dry diethyl ether (15 cm^3), whilst a continuous stream of dry hydrogen chloride gas was passed through the reaction mixture. The yellow reaction mixture was stirred for 1 h during which time a copious precipitate formed. The precipitate was filtered off and was washed with diethyl ether (50 cm^3) to give the title compound as a white powder (1.97 g, 91%), mp 212–214 °C (from ethanol) (Found: C, 57.9; H, 4.7; N, 7.2; S, 8.55%; M^+, 374.0933. $C_{18}H_{18}N_2O_5S$ requires C, 57.75; H, 4.8; N, 7.5; S, 8.55%; *M*, 374.0937); ν_{max}(Nujol)/cm^{-1} 3260 (OH, oxime), 1700 (C=O) and 1620 (C=C); δ_H(DMSO) 12.35 (1H, s, exch., =NOH), 7.7 (1H, d, aryl), 7.5 (2H, d, aryl), 7.35 (2H, d, aryl), 7.1–7.05 (1H, dd, aryl), 6.7 (1H, d, aryl), 3.9 (2H, t, CH_2), 3.8 (3H, s, OCH_3), 2.8 (2H, t, CH_2) and 2.4 (3H, s, CH_3 tosyl).

2,3,4,5-Tetrahydro-8-methoxy-4-methoxyimino-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 17 (R = Me)

To sodium hydride (0.48 g, 12 mmol; 60% dispersion in mineral oil) in dry THF (50 cm^3) at 0 °C under nitrogen, was added compound **17** (R = H) (3.6 g, 9.62 mmol) in portions. The resulting suspension was stirred at room temperature for 1 h and then cooled to 0 °C, whereupon a solution of methyl iodide (1.64 g, 11.55 mmol) in dry THF (5 cm^3) was added dropwise. When the addition was complete, the reaction mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue was taken up in ethyl acetate (100 cm^3) and washed with water (2 × 100 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give a red oil. Flash chromatography (ethyl acetate–hexane, 1 : 1) gave the title compound as an off-white solid (2.73 g, 73%), mp 144–146 °C (Found: C, 58.8; H, 5.4; N, 7.25; S, 8.15%; M^+, 388.1086. $C_{19}H_{20}N_2O_5S$ requires C, 58.8; H, 5.15; N, 7.2; S, 8.2%; *M*, 388.1093); ν_{max}(Nujol)/cm^{-1} 1700 (C=O) and 1615 (C=C); δ_H 7.8 (1H, d, aryl), 7.4 (2H, d, aryl), 7.2 (2H, d, aryl), 7.1 (1H, d, aryl), 6.9 (1H, dd, aryl), 3.95–3.8 (8H, t + s, CH_2 + 2 × OCH_3), 2.8–2.7 (2H, t, CH_2) and 2.4 (3H, s, CH_3 tosyl).

5-[2-(Ethoxycarbonyl)ethynyl]-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-methoxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 18 (R = C≡CCO_2Et)

To ethyl propiolate (0.304 g, 3.1 mmol) in dry THF (10 cm^3) at −78 °C under nitrogen, was added dropwise, n-butyllithium (2 cm^3, 3.1 mmol; 1.6 M solution in hexanes). The resulting mixture was stirred for 30 min whereupon a solution of compound **17** (R = Me) (1.0 g, 2.58 mmol) in dry THF (15 cm^3) was added dropwise, and the mixture was stirred at −78 °C for 1 h. Acetic acid (0.5 cm^3) was added and the mixture was slowly allowed to reach room temperature. Diethyl ether (25 cm^3) was added and the organic phase was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried and the solvent was removed *in vacuo* to give a red oil. Flash chromatography (ethyl acetate–hexane, 1 : 1) gave a pale yellow solid which was recrystallised from ethanol to give the title compound as white crystals (1.14 g, 91%), mp 130–131 °C (Found: C, 59.15; H, 5.4; N, 5.6; S, 6.75%; M^+, 486.1479. $C_{24}H_{26}N_2O_7S$ requires C, 59.25; H,

5.35; N, 5.75; S, 6.6%; *M*, 486.1461); ν_{max}(Nujol)/cm^{-1} 3450 (OH) and 1735 (C=O ester); δ_H 7.85 (1H, d, aryl), 7.7 (2H, d, aryl), 7.3 (2H, d, aryl), 6.9 (1H, dd, aryl), 6.75 (1H, d, aryl), 4.3 (1H, s, exch., OH), 4.25–4.2 (2H, q, $CO_2CH_2CH_3$), 3.95 (1H, m, CH_2N), 3.8 (3H, s, $ArOCH_3$), 3.75 (3H, s, $=NOCH_3$), 3.7–3.65 (1H, m, CH_2N), 3.3–3.2 (1H, m, $CH_2C=N$), 2.6–2.55 (1H, m, $CH_2C=N$), 2.4 (3H, s, CH_3 tosyl) and 1.3 (3H, t, $CO_2CH_2CH_3$); δ_C 160.6 (*C*=NOCH$_3$), 155.0 (*C*O$_2$CH$_2$CH$_3$), 153.4 (ArOCH$_3$, ipso), 143.9 (ArSO$_2$, ipso), 137.9 (aryl), 137.3 (ArCH$_3$, ipso), 130.4 (aryl), 129.7 (2 × aryl), 129.6 (aryl), 128.0 (2 × aryl), 114.5 (2 × aryl), 86.0 (O$_2$C*C*≡C), 77.6 [Ar*C*(OH)C≡], 72.4 (OCC≡*C*), 62.6 (=NOCH$_3$), 62.4 (CO$_2$*C*H$_2$CH$_3$), 55.7 (ArOCH$_3$), 47.1 (CH$_2$N), 25.5 (*C*H$_2$CH$_2$N), 21.8 (Ar*C*H$_3$) and 14.2 (CO$_2$CH$_2$*C*H$_3$).

5-[2-(Ethoxycarbonyl)ethyl]-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-methoxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 18 [R = (CH$_2$)$_2$CO$_2$Et]

Compound **18** (R = C≡CCO$_2$Et) (0.5 g, 1.03 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 removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed on alumina (ethyl acetate–hexane, 3:7) to give the title compound as a white solid (0.45 g, 90%), mp 91–92 °C (Found: C, 58.55; H, 6.3; N, 5.7; S, 6.65%; [M + H]$^+$, 491. $C_{24}H_{30}N_2O_7S$ requires C, 58.8; H, 6.1; N, 5.7; S, 6.5%; [*M* + H], 491); ν_{max}(Nujol)/cm^{-1} 3440 (OH) and 1745 (C=O ester); δ_H 7.85–7.8 (3H, m, aryl), 7.35 (2H, d, aryl), 6.85–6.8 (1H, dd, aryl), 6.55 (1H, d, aryl), 4.45 (1H, s, exch., OH), 4.2–4.15 (1H, m, CH_2N), 4.1-4.0 (2H, q, $CO_2CH_2CH_3$), 3.85 (3H, s, $ArOCH_3$), 3.7 (3H, s, $=NOCH_3$), 3.3–3.2 (1H, m, C*H*$_2$C=N), 3.15–3.05 (1H, m, CH_2N), 2.8–2.7 (1H, m, $CH_2C=N$), 2.65–2.55 (1H, m, CH_2CO_2), 2.5–2.4 (4H, s + m, CH_3 tosyl + CH_2CO_2), 2.35–2.2 (2H, m, CH_2) and 1.3–1.2 (3H, t, $CO_2CH_2CH_3$); δ_C 173.9 (*C*O$_2$CH$_2$CH$_3$), 159.4 (*C*=NOCH$_3$), 158.3 (ArOCH$_3$, ipso), 144.0 (ArSO$_2$, ipso), 139.0 (aryl), 138.4 (ArCH$_3$, ipso), 133.0 (aryl), 130.1 (2 × aryl), 129.0 (aryl), 127.5 (2 × aryl), 113.4, 112.7 (aryl), 77.0 [Ar*C*(OH)CH$_2$], 62.3 (=NOCH$_3$), 60.5 (CO$_2$*C*H$_2$CH$_3$), 55.5 (ArO*C*H$_3$), 48.5 (CH$_2$N), 34.6 (*C*H$_2$CO$_2$), 29.1 (*C*H$_2$CH$_2$CO$_2$), 25.8 (*C*H$_2$CH$_2$N), 21.8 (ArCH$_3$) and 14.4 (CO$_2$CH$_2$*C*H$_3$).

Diborane reduction of 5-[2-(ethoxycarbonyl)ethyl]-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-4-methoxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 18 [R = (CH$_2$)$_2$CO$_2$Et]

To a cooled (0 °C) solution of the title compound (0.27 g, 0.55 mmol) in dry THF (10 cm^3) under nitrogen, was added dropwise borane–THF complex (2.8 cm^3, 2.8 mmol; 1.0 M solution in THF). After the initial vigorous effervescence had subsided, the clear solution was stirred at room temperature for 12 h. The mixture was then cooled to 0 °C and excess hydride was destroyed by the cautious addition of water (5 cm^3). Hydrochloric acid (5 cm^3; 5 M) was added and the mixture was heated at reflux for 1 h. The solvent was removed *in vacuo* and water (15 cm^3) was added to the residue which was basified (pH 10) with solid sodium hydroxide. The mixture was extracted with chloroform (4 × 50 cm^3) and the combined organic layers were washed with water and brine, then dried and the solvent was removed *in vacuo* to give a clear oil. Flash chromatography (dichloromethane–ethanol–ammonia, 40:8:1) gave the product as a white solid (0.202 g, 88%), mp 182–183 °C. This is formulated as **20a** or **b** [Found: C, 60.0; H, 6.2; N, 6.5; S, 7.65%; M$^+$, 402.1613. $C_{21}H_{26}N_2O_5S$ requires C, 60.05; H, 6.7; N, 6.65; S, 7.65%; *M* (− H$_2$O), 402.1613]; ν_{max}(Nujol)/cm^{-1} 3300–3100 (br, OH and NH) and 1610 (C=C); δ_H 7.85 (3H, m, aryl), 7.4 (2H, d, aryl), 6.8 (1H, dd, aryl), 6.4 (1H, d, aryl), 4.3 (1H, dt, CH_2N), 3.65 (3H, s, OCH_3), 3.6–3.55 (2H, t, CH_2O), 3.1–3.05 (1H, m, CH_2N), 2.75–2.65 (2H, m, C*H*NH + C*H*$_2$), 2.5–2.4 (4H, s + m, CH_3 tosyl + C*H*$_2$), 2.0 (1H, m, CH_2), 1.9–1.7 (2H, br, exch., NH + OH), 1.6–1.5 (2H, m, CH_2) and 1.3–1.25 (1H, m, CH_2). Not all exchangeable protons could be identified.

4-Acetamido-2,3,4,5-tetrahydro-8-methoxy-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 13 (R^1 = tosyl, R^2 = NHAc)

Oxime **17** (R = H) (3.5 g, 9.36 mmol), acetic anhydride (8.5 g, 83.33 mmol) and 10% palladium on charcoal catalyst (0.1 g) in dry THF (150 cm^3) were hydrogenated at an initial hydrogen pressure of 45 psi overnight. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give an oil. Flash chromatography (ethyl acetate–hexane, 9:1) gave a white solid that was recrystallised from ethanol to give the title compound as colourless prisms (2.52 g, 67%), mp 162–164 °C (Found: C, 59.45; H, 5.7; N, 6.85; S, 8.2%; M$^+$, 402.1257. $C_{20}H_{22}N_2O_5S$ requires C, 59.7; H, 5.5; N, 7.0; S, 8.0%; *M*, 402.1250); ν_{max}(Nujol)/cm^{-1} 3350 (NH, amide), 1708 (C=O) and 1680 (C=O, amide); δ_H 7.85–7.8 (3H, m, aryl), 7.3–7.25 (3H, m, aryl), 6.8–6.75 (1H, dd, aryl), 6.55–6.5 (1H, d, *J* 6.2, exch., NHCO), 4.65–4.45 (2H, m, C*H*NHCO + CH$_2$N), 3.85 (3H, s, OCH_3), 3.4–3.35 (1H, m, CH_2N), 3.0–2.85 (1H, m, CH_2), 2.4 (3H, s, CH_3 tosyl), 2.0 (3H, s, CH_3CO) and 1.7–1.6 (1H, m, CH_2).

***cis*- and *trans*-4-Acetamido-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 22 and 21**

To compound **13** (R^1 = tosyl, R^2 = NHAc) (1.9 g, 4.73 mmol) in ethanol (50 cm^3) at room temperature under nitrogen was added sodium borohydride (0.2 g, 5.29 mmol) in portions. The resulting suspension was stirred for 1 h during which time the mixture became homogenous. Acetic acid (0.5 cm^3) was then added and the solvent was removed *in vacuo*. The residue was taken up in chloroform (100 cm^3) and was washed with water (2 × 50 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give a white solid (1.85 g, 97%). This was shown to consist of two components (TLC) which were separated by flash chromatography (ethanol–chloroform, 1:19). The first component obtained was the *cis*-diastereoisomer **22** as a white solid (0.48 g), mp 178–179 °C (Found: C, 59.3; H, 5.9; N, 6.7; S, 7.95%; M$^+$, 404.1406. $C_{20}H_{24}N_2O_5S$ requires C, 59.4; H, 5.9; N, 6.9; S, 7.9%; *M*, 404.1406); ν_{max}(Nujol)/cm^{-1} 3440–3300 (OH + NH) and 1685 (C=O, amide); δ_H 7.7 (2H, d, aryl), 7.35–7.25 (4H, m, aryl), 6.85–6.8 (1H, dd, aryl), 6.4–6.3 (1H, br, NHCO), 5.9–5.7 (1H, br, exch., OH), 4.6 (1H, d, *J* 1, C*H*OH), 4.2–4.15 (1H, m, C*H*NHCO), 4.05–3.9 (2H, m, CH_2N), 3.7 (3H, s, OCH_3), 2.45 (3H, s, CH_3 tosyl), 2.35–2.2 (1H, m, CH_2), 2.15–2.05 (1H, m, CH_2) and 2.0 (3H, s, CH_3CO). This was followed from the column by the *trans*-diastereoisomer **21** as a white solid (1.31 g), mp 155–156 °C (Found: C, 59.2; H, 5.75; N, 6.7, S, 8.0%; M$^+$, 404.1396. $C_{20}H_{24}N_2O_5S$ requires C, 59.4; H, 5.9; N, 6.9; S, 7.9%; *M*, 404.1406); ν_{max}(Nujol)/cm^{-1} 3445–3310 (OH + NH) and 1685 (C=O, amide); δ_H 7.8 (3H, m, aryl), 7.5 (1H, d, aryl), 7.3–7.25 (2H, d, aryl), 6.85–6.8 (1H, dd, aryl), 6.6 (1H, d, *J* 2.3, NHCO), 6.05–5.95 (1H, br, exch., OH), 4.55 (1H, d, *J* 8, C*H*OH), 3.95–3.8 (2H, m, C*H*NCO + C*H*$_2$), 3.7 (3H, s, OCH_3), 3.5–3.4 (1H, m, CH_2), 2.45 (3H, s, OCH_3) and 2.05–1.9 (5H, s + m, C*H*$_3$CO + C*H*$_2$).

***cis*-4-Amino-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 24**

To compound **22** (0.39 g, 0.96 mmol) in ethanol (20 cm^3) was added aqueous sodium hydroxide (25 cm^3; 3 M) and the resulting mixture was heated at reflux for 12 h and then allowed to cool. The solvent was removed *in vacuo* and water (20 cm^3) was added to the residue, which was acidified (pH 3) with concentrated hydrochloric acid. The mixture was extracted with dichloromethane (2 × 50 cm^3) and the aqueous phase was basified (pH 9) with aqueous sodium hydroxide (2 M) and then extracted with dichloromethane (4 × 50 cm^3). The combined organic layers were dried and the solvent was removed *in vacuo* to give a white solid which was recrystallised from hexane–1% ethanol to give the title compound as colourless needles (0.29 g,

83%), mp 86–87 °C (Found: C, 59.9; H, 6.0; N, 7.5; S, 8.9%; M^+, 362.1303. $C_{18}H_{22}N_2O_4S$ requires C, 59.7; H, 6.1; N, 7.7; S, 8.8%; *M*, 362.1300); ν_{max}(Nujol)/cm^{-1} 3450 (OH), 3340, 3310 (NH_2) and 1615 (C=C); δ_H 7.7 (2H, d, aryl), 7.35–7.25 (4H, m, aryl), 6.85–6.8 (1H, dd, aryl), 6.75–6.65 (1H, br, OH), 4.4 (1H, d, *J* 1, C*H*OH), 3.75–3.5 (4H, s + m, OCH_3 + CH_2), 3.15 (1H, m, CH_2), 2.6 (1H, m, C*H*NH_2), 2.45 (3H, s, CH_3 tosyl), 2.1 (1H, m, CH_2) and 1.85–1.6 (3H, br, CH_2 + exch., NH_2).

***trans*-4-Amino-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 23**

Compound **21** (0.42 g, 1.04 mmol) and aqueous sodium hydroxide (25 cm^3; 3 M) in ethanol (20 cm^3) were reacted according to the above procedure to give a white solid which was recrystallised from toluene to give the title compound as colourless needles (0.32 g, 88%), mp 129–130 °C (Found: C, 59.6; H, 6.1; N, 7.55; S, 8.75%; M^+, 362.1293. $C_{18}H_{22}N_2O_4S$ requires C, 59.7; H, 6.1; N, 7.7; S, 8.8%; *M*, 362.1300); ν_{max}(Nujol)/cm^{-1} 3450 (OH), 3350, 3315 (NH_2) and 1610 (C=C); δ_H 7.7 (2H, d, aryl), 7.6 (1H, d, aryl), 7.3–7.15 (3H, m, aryl), 6.9–6.85 (1H, dd, aryl), 6.75–6.65 (1H, br, OH), 4.25 (1H, m, CH_2), 4.2 (1H, d, *J* 8, C*H*OH), 3.7 (3H, s, OCH_3), 3.15 (1H, m, CH_2), 2.6 (1H, m, C*H*NH_2), 2.4 (3H, s, CH_3 tosyl), 2.2–2.1 (2H, exch., NH_2) and 2.0–1.85 (2H, m, CH_2).

***trans*-2,3,4,4a,5,6,7,11b-Octahydro-9-methoxy-3-oxo-7-(*p*-tolylsulfonyl)[1,4]oxazino[3,2-*d*][1]benzazepine 25**

To compound **23** (0.2 g, 0.5 mmol) in dry toluene (10 cm^3) at room temperature under nitrogen, was added sodium hydride (0.3 g, 0.75 mmol; 60% dispersion in oil). The resulting suspension was stirred for 15 min whereupon ethyl chloroacetate (0.08 g, 0.65 mmol) was added dropwise. The mixture was heated at reflux for 3 h and then allowed to cool to room temperature. Ethanol (5 drops) and water (5 cm^3) were added and the mixture was extracted with dichloromethane (4 × 30 cm^3). The combined organic layers were washed with water, dried and the solvent was removed *in vacuo* to give an orange oil. Flash chromatography (chloroform–ethanol–ammonia, 100 : 8 : 1) gave the title compound as an off white solid (0.067 g, 30%), mp 135–137 °C (Found: C, 58.9; H, 5.8; N, 6.6; S, 7.9%; M^+, 402.1241. $C_{20}H_{22}N_2O_4S$ requires C, 59.7; H, 5.5; N, 6.95; S, 7.95%; *M*, 402.1250); ν_{max}(Nujol)/cm^{-1} 3250 (NH), 1695 (C=O) and 1610 (C=C); δ_H 7.7 (2H, d, aryl), 7.55 (1H, dd, aryl), 7.3 (2H, d, aryl), 6.9–6.85 (1H, dd, aryl), 6.75 (1H, d, aryl), 6.65 (1H, s, exch., NH), 4.4 (1H, d, *J* 8, CHO), 4.35–4.3 (1H, d, *J* 16.5, OCH_2CO), 3.95 (1H, m, CHN), 3.9–3.8 (1H, d, *J* 16.5, OCH_2CO), 3.75 (3H, s, OCH_3), 3.35–3.25 (1H, m, CH_2), 3.05–2.95 (1H, m, CH_2), 2.45 (3H, s, CH_3 tosyl), 2.15–2.1 (1H, m, CH_2) and 1.9–1.85 (1H, m, CH_2).

***cis*-2,3,4,4a,5,6,7,11b-Octahydro-9-methoxy-3-oxo-7-(*p*-tolylsulfonyl)[1,4]oxazino[3,2-*d*][1]benzazepine 26**

Compound **24** (0.28 g, 0.635 mmol), sodium hydride (0.03 g, 0.75 mmol; 60% dispersion in mineral oil) and ethyl chloroacetate (0.083 g, 0.67 mmol) in dry toluene (10 cm^3) were reacted according to the above procedure. The crude product was purified by flash chromatography (dichloromethane–ethanol–ammonia, 150 : 8 : 1) to give the product as an off-white solid (0.061 g, 24%), mp 126–128 °C (Found: C, 60.0; H, 5.7; N, 6.7; S, 7.9%. $C_{20}H_{22}N_2O_5S$ requires C, 59.7; H, 5.5; N, 6.95; S, 7.95%); δ_H 7.65 (2H, d, aryl), 7.35–7.25 (2H, d, aryl), 7.15–7.1 (2H, m, aryl), 7.0 (1H, s, exch., NH), 6.8–6.75 (1H, dd, aryl), 4.5 (1H, d, *J* 1.2, CHO), 4.05–3.9 [2H, d, (*J* 16.9) + m, OCH_2-CO + CHN], 3.8 (3H, s, OCH_3), 3.65–3.55 (1H, d, *J* 16.9, OCH_2CO), 3.5–3.4 (1H, m, CH_2), 3.1–2.9 (1H, m, CH_2), 2.45 (3H, s, CH_3 tosyl), 2.05–1.95 (1H, m, CH_2) and 1.9–1.8 (1H, m, CH_2).

Catalytic hydrogenation of 2,3,4,5-tetrahydro-8-methoxy-4-hydroxyimino-5-oxo-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 17 (R = H) in the presence of propionic anhydride

Compound **17** (R = H) (2 g, 5.35 mmol), propionic anhydride (6.26 g, 48.15 mmol) and 10% palladium on charcoal catalyst (0.4 g) in dry THF (120 cm^3) were hydrogenated at room temperature overnight at an initial hydrogen pressure of 45 psi. Thereafter the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Flash chromatography (50% ethyl acetate–hexane) allowed the separation of two components. The minor product 2,3,4,5-tetrahydro-8-methoxy-5-oxo-4-propionyloxyimino-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine **17** (R = EtCO) was obtained as a yellow solid which was recrystallised from ethanol to give yellow platelets (0.12 g, 5%), mp 143–144 °C (Found: C, 58.4; H, 4.9; N, 6.4; S, 7.8%; M^+, 430.1195. $C_{21}H_{22}N_2O_6S$ requires C, 58.6; H, 5.1; N, 6.5; S, 7.45%; *M*, 430.1199); ν_{max}(Nujol)/cm^{-1} 1740 (C=O, ester), 1705 (C=O) and 1620 (C=C); δ_H 7.9 (2H, d, aryl), 7.5 (1H, d, aryl), 7.25–7.15 (3H, m, aryl), 6.9 (1H, dd, aryl), 4.05–4.0 (2H, t, CH_2), 3.9 (3H, s, OCH_3), 3.0 (2H, t, CH_2), 2.5–2.45 (2H, q, $COCH_2CH_3$), 2.4 (3H, s, CH_3 tosyl) and 1.25–1.2 (3H, t, $COCH_2CH_3$). The major product 2,3,4,5-tetrahydro-8-methoxy-5-oxo-4-propionamido-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine **13** (R^1 = tosyl, R^2 = NHCOEt) was obtained from the column as a white solid (1.49 g, 67%), mp 146–148 °C (Found: C, 60.2; H, 5.9; N, 6.5; S, 7.8%; M^+, 416.1419. $C_{21}H_{24}N_2O_5S$ requires C, 60.6; H, 5.8; N, 6.7; S, 7.7%; *M*, 416.1406); ν_{max}(Nujol)/cm^{-1} 3340 (NH), 1705 (C=O) and 1685 (C=O, amide); δ_H 7.85–7.8 (3H, m, aryl), 7.3–7.25 (3H, m, aryl), 6.8–6.75 (1H, dd, aryl), 6.5 (1H, d, *J* 6.2, exch., NHCOO), 4.65–4.45 (2H, m, CHNCO + CH_2N), 3.85 (3H, s, OCH_3), 3.45–3.35 (1H, m, CH_2NH), 3.0–2.85 (1H, m, CH_2), 2.4 (3H, s, CH_3 tosyl), 2.3–2.2 (2H, q, $COCH_2CH_3$), 1.7–1.6 (1H, m, CH_2) and 1.2–1.1 (3H, t, $COCH_2CH_3$).

***cis*- and *trans*-2,3,4,5-Tetrahydro-5-hydroxy-8-methoxy-4-propionamido-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 28 and 27**

To a suspension of compound **13** (R^1 = tosyl, R^2 = NHCOEt) (2.56 g, 6.12 mmol) in ethanol (60 cm^3) at room temperature under nitrogen, was added sodium borohydride (0.26 g, 6.87 mmol) in portions. The resulting suspension was stirred for 1 h, becoming homogenous during this time. Acetic acid (1 cm^3) was then added and the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (100 cm^3) and was washed with water (2 × 50 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give a white solid (2.43 g, 95%). This was found to consist of two components (TLC) which were separated by flash chromatography (ethanol–chloroform, 1 : 19). The first component eluted from the column was the *cis*-diastereoisomer **28** as a white solid (0.52 g), mp 106–108 °C [Found: C, 60.2; H, 6.45; N, 6.8; S, 7.55%; M^+ ($-H_2O$), 400.1467. $C_{21}H_{26}N_2O_5S$ requires C, 60.3; H, 6.2; N, 6.7; S, 7.65%; *M* ($-H_2O$), 400.1457]; ν_{max}(Nujol)/cm^{-1} 3375 (OH), 3330 (NH), 1705 (C=O) and 1685 (C=O, amide); δ_H 7.7 (2H, d, aryl), 7.3–7.2 (4H, m, aryl), 6.8 (1H, dd, aryl), 6.5–6.4 (1H, br, NHCO), 5.8–5.65 (1H, br, exch., OH), 4.55 (1H, d, *J* 1, C*H*OH), 4.2 (1H, m, C*H*NHCO), 4.05–3.95 (1H, m, CH_2), 3.7–3.6 (4H, s + m, OCH_3 + CH_2), 2.45 (3H, s, CH_3 tosyl), 2.3–2.15 (4H, m, 2 × CH_2) and 1.1–1.05 (3H, t, $COCH_2CH_3$). This was followed from the column by the *trans*-diastereoisomer **27** as a white solid (1.78 g), mp 120–122 °C [Found: C, 59.7; H, 6.3; N, 6.4; S, 7.6%, M^+ ($-H_2O$), 400.1439. $C_{21}H_{26}N_2O_5S$ requires C, 60.3; H, 6.2; N, 6.7; S, 7.65%; *M* ($-H_2O$), 400.1457]; ν_{max}(Nujol)/cm^{-1} 3380 (OH), 3325 (NH), 1705 (C=O) and 1680 (C=O, amide); δ_H 7.7 (2H, d, aryl), 7.5 (1H, d, aryl), 7.3–7.2 (3H, m, aryl), 6.9–6.85 (1H, dd, aryl), 6.6 (1H, br, NHCO), 5.9–5.75 (1H, br, exch., OH), 4.5 (1H, d, *J* 8, C*H*OH), 4.05–4.0 (1H, m, C*H*NHCO), 3.75–3.65 (4H, s + m, OCH_3 + CH_2), 3.5–3.45 (1H, m, CH_2), 2.45 (3H, s, CH_3 tosyl), 2.2–2.15 (2H, q, $COCH_2CH_3$), 1.95–1.85 (2H, m, CH_2) and 1.15–1.1 (3H, t, $COCH_2CH_3$).

***trans*-2,3,4,5-Tetrahydro-5-hydroxy-8-methoxy-4-(*n*-propylamino)-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 29**

To borane–THF complex (9.7 cm^3, 9.7 mmol; 1.0 M solution in THF) at 0 °C under nitrogen, was added a solution of com-

pound **27** (0.81 g, 1.94 mmol) in dry THF (10 cm^3) dropwise. The clear reaction mixture was stirred at room temperature for 3 h and then cooled to 0 °C. Water (10 cm^3) was added cautiously, followed by hydrochloric acid (3 cm^3; 5 M) and the mixture was heated at reflux for 1 h. The solvent was then removed *in vacuo* and water (10 cm^3) was added to the residue which was basified (pH 10) (solid sodium hydroxide). The mixture was extracted with chloroform (4 × 50 cm^3) and the combined organic layers were washed with water and brine, then dried and the solvent was removed *in vacuo* to give a white semi-solid. Flash chromatography (chloroform–ethanol–ammonia, 100 : 8 : 1) afforded the title compound as a white powder (0.64 g, 82%), mp 144–145 °C (Found: C, 62.4; H, 7.15; N, 6.9; S, 7.95%; M^+, 404.1774. $C_{21}H_{28}N_2O_4S$ requires C, 62.4; H, 6.9; N, 6.9; S, 7.9%; *M*, 404.1770); ν_{max}(Nujol)/cm^{-1} 3360 (OH), 3250 (NH) and 1610 (C=C); δ_H 7.7–7.6 (3H, m, aryl), 7.3–7.2 (2H, d, aryl), 6.9–6.8 (1H, dd, aryl), 6.75 (1H, d, aryl), 4.4–4.3 (1H, m, CH_2), 4.05–4.0 (1H, d, *J* 9.3, C*H*OH), 3.75 (3H, s, OCH_3), 3.2–3.1 (1H, m, CH_2), 2.75–2.7 (1H, m, C*H*NH), 2.5–2.4 (5H, s + m, CH_3 tosyl + CH_2), 2.2–2.0 (2H, br, CH_2 + NH), 1.9–1.8 (1H, m, CH_2), 1.5–1.4 (2H, m, CH_2) and 0.95–0.85 (3H, t, CH_3).

***cis*-2,3,4,5-Tetrahydro-5-hydroxy-8-methoxy-4-(*n*-propylamino)-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 30**

Compound **28** (0.25 g, 0.62 mmol) and borane–THF complex (3 cm^3, 3 mmol; 1.0 M solution in THF) in dry THF (10 cm^3) were reacted according to the above procedure to give an oil. Flash chromatography (chloroform–ethanol–ammonia, 100 : 8 : 1) afforded the title compound as a white foam (0.18 g, 72%), mp 60–62 °C (Found: C, 62.2; H, 7.05; N, 6.8; S, 8.5%; M^+, 404.1757. $C_{21}H_{28}N_2O_4S$ requires C, 62.4; H, 6.9; N, 6.9; S, 7.9%; *M*, 404.1770); δ_H 7.7–7.6 (2H, d, aryl), 7.3–7.15 (3H, m, aryl), 6.9–6.7 (2H, m, aryl), 4.2 (1H, d, *J* 1.3, C*H*OH), 3.85–3.4 (5H, s + m, OCH_3 + CH_2), 2.8 (1H, m, C*H*NH), 2.55–2.35 (5H, s + m, CH_3 tosyl + CH_2), 2.15–2.1 (1H, m, CH_2), 1.7–1.4 (4H, br, CH_2 + CH_2 + NH) and 0.9–0.85 (3H, t, CH_3). The hydroxy proton at C-5 was not observed at 250 MHz.

***trans*-4-[*N*-(Chloroacetyl)-*N*-(*n*-propyl)amino]-5-chloroacetyloxy-2,3,4,5-tetrahydro-8-methoxy-1-(*p*-tolylsulfonyl)-1*H*-1-benzazepine 31**

To a solution of compound **29** (0.5 g, 1.24 mmol) in 1,2-dichloroethane (10 cm^3) at room temperature was added a solution of sodium hydroxide (0.065 g, 1.62 mmol) in water (5 cm^3). The resulting mixture was stirred vigorously for 30 min and then cooled to 0 °C, whereupon a solution of chloroacetyl chloride (0.19 g, 1.65 mmol) in 1,2-dichloroethane (2 cm^3) was added dropwise. The 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 clear oil which crystallised upon trituration with diethyl ether to give the title compound as a white solid (0.43 g, 62%). Recrystallisation from 1% ethanol–toluene gave colourless crystals, mp 161–162 °C [Found: C, 53.9; H, 6.1; N, 5.25; S, 5.6; Cl, 12.5%; M^+ ($-C_2H_3O_2Cl$) 464.1383, 462.1381. $C_{25}H_{30}N_2O_6SCl_2$ requires C, 53.85; H, 5.4; N, 5.05; S, 5.75; Cl, 12.75%; *M* ($-C_2H_3O_2Cl$) 464.1351, 462.1380]; ν_{max}(Nujol)/cm^{-1} 1765 (C=O, ester), 1665 (C=O, amide) and 1610 (C=C); δ_H 7.8 (2H, d, aryl), 7.35–7.2 (3H, m, aryl), 6.8–6.75 (1H, dd, aryl), 6.7 (1H, d, aryl), 6.0 (1H, d, *J* 7.5, CHOCO), 4.4–4.2 (2H, m, $OCOCH_2Cl$), 4.1–4.0 (1H, m, CH_2), 3.9–3.6 (6H, s + m, OCH_3 + CHN + $COCH_2Cl$), 3.2–3.1 (1H, m, CH_2), 2.8 (2H, m, CH_2), 2.45 (3H, s, CH_3 tosyl), 2.2–2.1 (1H, m, CH_2), 1.9–1.7 (2H, m, CH_2), 1.65–1.6 (1H, m, CH_2) and 1.0 (3H, t, CH_3).

***trans*-2,3,4,4a,5,6,7,11b-Octahydro-9-methoxy-3-oxo-4-(*n*-propyl)-7-(*p*-tolylsulfonyl)[1,4]oxazino[3,2-*d*][1]benzazepine 32**

To potassium hydroxide (0.081 g, 1.45 mmol) in ethanol (5 cm^3) at room temperature, was added compound **31** (0.27 g, 0.485 mmol) in portions and the resulting suspension was stirred for 16 h. The solvent was then removed *in vacuo* and the residue was taken up in chloroform (20 cm^3). 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 an oil. Flash chromatography (chloroform–ethanol–ammonia, 100 : 8 : 1) gave the title compound as a hygroscopic white foam (0.138 g, 64%), mp 102–103 °C (Found: C, 61.5; H, 6.2; N, 6.05; S, 7.05%; M^+, 444.1727. $C_{23}H_{28}N_2O_5S$ requires C, 62.15; H, 6.3; N, 6.3; S, 7.2%; *M*, 444.1719); ν_{max}(Nujol)/cm^{-1} 1675 (C=O, lactam) and 1610 (C=C); δ_H 7.65 (2H, d, aryl), 7.5 (1H, d, aryl), 7.3–7.2 (2H, d, aryl), 6.9–6.85 (1H, dd, aryl), 6.85 (1H, d, aryl), 4.55–4.45 (1H, dt, CH_2N), 4.35–4.25 (1H, d, *J* 15.9, OCH_2CO), 3.9–3.85 (1H, d, *J* 9.3, CHO), 3.75 (3H, s, OCH_3), 3.7–3.55 [2H, d, (*J* 15.9) + m, OCH_2CO + CHN], 3.2–3.15 (1H, m, CH_2N), 3.1–2.95 (2H, m, CH_2), 2.45 (3H, s, CH_3 tosyl), 2.15–2.0 (1H, m, CH_2), 1.9–1.8 (1H, m, CH_2), 1.6–1.4 (2H, m, CH_2) and 0.9–0.85 (3H, t, CH_3).

***trans*-2,3,4,4a,5,6,7,11b-Octahydro-9-methoxy-4-(*n*-propyl)-7-(*p*-tolylsulfonyl)[1,4]oxazino[3,2-*d*][1]benzazepine 33**

To borane–THF complex (1.24 cm^3, 1.24 mmol; 1.0 M solution in THF) at 0 °C under nitrogen, was added dropwise compound **32** (0.11 g, 0.25 mmol) in dry THF (5 cm^3). The reaction mixture was stirred at room temperature overnight and was then cooled to 0 °C. Water (5 cm^3) was added with caution followed by hydrochloric acid (2 cm^3; 5 M), and the mixture was heated at reflux for 1 h. The solvent was then removed *in vacuo* and water (10 cm^3) was added to the residue which was basified (pH 9) with solid sodium hydroxide. The mixture was extracted with chloroform (4 × 30 cm^3) and the combined extracts were washed with water (2 × 30 cm^3) and brine, then dried and the solvent was removed *in vacuo* to give an oil which crystallised on standing. Recrystallisation from 2% toluene–hexane afforded the product as fluffy white needles (0.083 g, 77%), mp 146–148 °C (Found: C, 63.8; H, 6.95; N, 6.7; S, 7.35%; M^+, 430.1919. $C_{23}H_{30}N_2O_4S$ requires C, 64.2; H, 7.0; N, 6.5; S, 7.45%; *M*, 430.1926); ν_{max}(Nujol)/cm^{-1} 1615 (C=C); δ_H 7.6 (2H, d, aryl), 7.35–7.25 (3H, m, aryl), 7.0 (1H d, aryl), 6.85–6.8 (1H, dd, aryl), 4.05–4.0 (1H, m, CH_2N), 3.9–3.8 [4H, d, (*J* 9) + s, CHO + OCH_3], 3.4–3.35 (2H, m, OCH_2), 3.3–3.2 (1H, m, CH_2N), 2.7–2.5 (2H, m, CHN + CH_2), 2.45 (3H, s, CH_3 tosyl), 2.4–2.2 (2H, m, 2 × CH_2), 2.1–2.0 (2H, m, 2 × CH_2), 1.7–1.6 (1H, m, CH_2), 1.45–1.4 (2H, m, CH_2) and 0.9–0.85 (3H, t, CH_3).

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