Regioselective Friedel–Crafts Acylation of 2,3,4,5-Tetrahydro-1*H*-2-benzazepine and Related Nitrogen Heterocycles[1]

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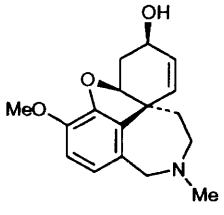
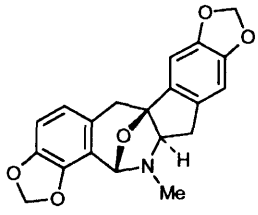
It is revealed that NH-protected 2,3,4,5-tetrahydro-1*H*-2-benzazepine **4** is acylated on C-8 with greater than 95% regioselectivity. This regioselectivity has been applied to the synthesis of 3-(1-benzylpiperidin-4-yl)-1-(2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-yl)propan-1-one **3a**, an inhibitor of acetylcholinesterase (AChE). The regioselectivities of the acylation of the following nitrogen heterocycles have also been studied: 4-formyl-2,3,4,5-tetrahydro-1,4-benzoxazepine **6**, 2,3,4,5-tetrahydro-1*H*-2-benzazepin-3-one **7**, 2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-one **8**, 7,11b,12,13-tetrahydro-5*H*-isoindolo[2,1-*b*][2]benzazepin-7-one **9** and 6,7,9,13b-tetrahydro-5*H*-isoindolo[1,2-*a*][2]benzazepin-9-one **10**. A molecular orbital (MO) calculation on the Lewis acid coordinated substrates has been used for predicting regioselectivity.

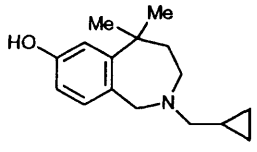
2-Benzazepine derivatives have been of considerable medicinal interest, partly because the skeleton is a component of Amaryllydaceae alkaloids such as galanthamine as well as of Ribasine alkaloids represented by ribasine.[2] Many 2-benzazepine derivatives have been reported to possess interesting biological activities. For example, 2-cyclopropylmethyl-7-hydroxy-5,5-dimethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine **1**,



galanthamine



ribasine



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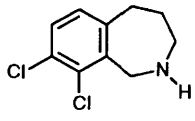

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which is a simplified analogue of these alkaloids, exhibited analgesic activity.[3] LY 134046 **2** has been extensively studied as an inhibitor of the enzyme phenylmethanolamine *N*-methyltransferase.[4] The chemistry of 2-benzazepines, in general, has long been focused on ring formation by ring closures or ring expansions such as Beckmann and Schmidt rearrangements (Scheme 1).[5] Most substituted 2-benzazepines with biological activities have been prepared from benzene precursors bearing the desired substituents; however, to our knowledge, there are no reports on direct electrophilic substitutions including halogenation, nitration and Friedel–Crafts reaction.

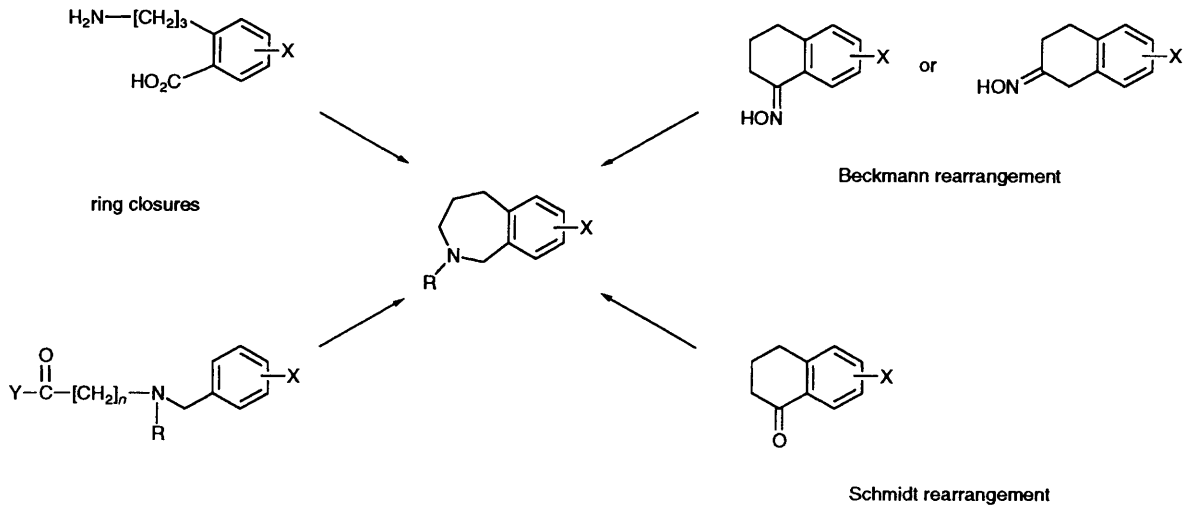
During our studies into acetylcholinesterase (AChE) inhibitors, we became interested in the biological activity of the 2-benzazepine derivative **3**, an isomer of TAK-147 which is a central selective inhibitor of AChE.[1] Compound **3** can be synthesized by Friedel–Crafts acylation of the NH-protected 2,3,4,5-tetrahydro-1*H*-2-benzazepine **4** with the acid chloride **5**, although its regioselectivity has not been reported. Therefore, it became necessary to clarify the regioselectivity in order to prepare the targeted compound **3**. In addition, because little is known about direct electrophilic substitution of similar nitrogen heterocycles,[6] we were also interested in the regioselectivity of acylation of the following compounds: 4-formyl-2,3,4,5-tetrahydro-1,4-benzoxazepine **6**, 2,3,4,5-tetrahydro-1*H*-2-benzazepin-3-one **7**, 2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-one **8**, 7,11b,12,13-tetrahydro-5*H*-isoindolo[2,1-*b*][2]benzazepin-7-one **9** and 6,7,9,13b-tetrahydro-5*H*-isoindolo[1,2-*a*]-[2]benzazepin-9-one **10**. In this paper, we report on the regioselective Friedel–Crafts reaction of the nitrogen heterocycles **4**, **6**–**10**. For the rational prediction of the regioselectivity,† we used MO calculations on the Lewis acid coordinated substrates, which have been shown to be effective in a previous study.[7]

Results and Discussion

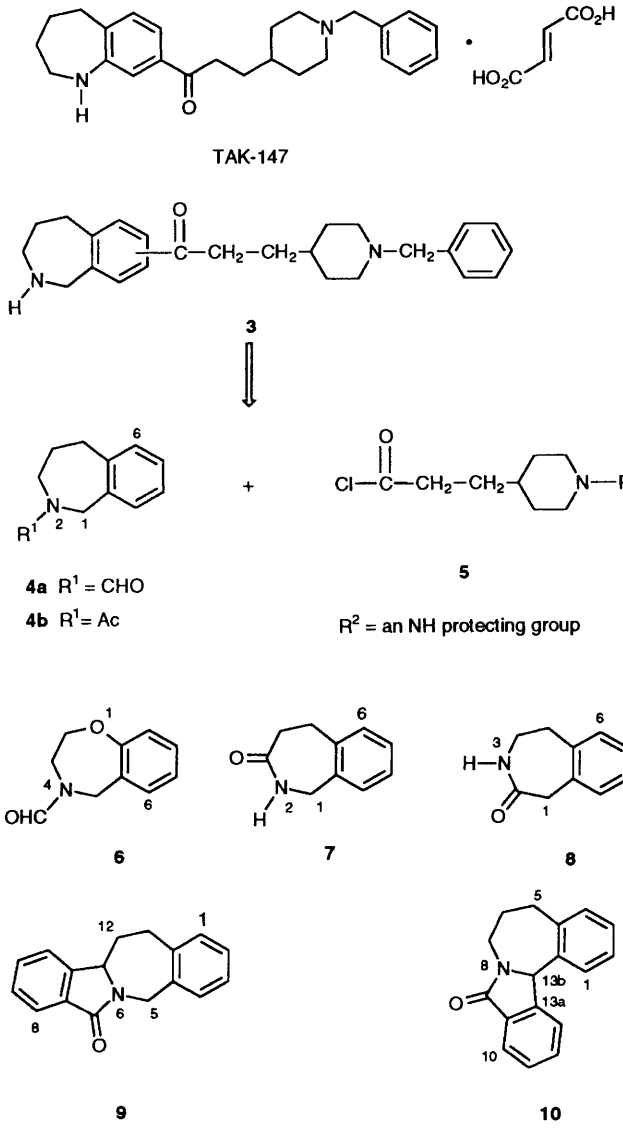
MO calculations on 2-formyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine **4a** were initially carried out by the MNDO-PM3 method according to a previous report.[7] We first determined the most stable structure of $AlCl_3$-coordinated substrate **4a** and its MOs were calculated. As reported previously, we focused our attention on the highest MOs where aromatic carbons C-6–C-9 were considered to be reactive because at least one of their electron densities was greater than those of any of the other atoms in the substrate–$AlCl_3$ complex. Table 1 shows that the highest electron density was on C-8, which seems to indicate fairly high regioselectivity on C-8.

Subsequently, acylation of compound **4a** was carried out by stirring a mixture of compound **4a** (1.0 mol equiv.) and AcCl (1.1 mol equiv.) in the presence of $AlCl_3$ (2.3 mol equiv.) in 1,2-dichloroethane at 50 °C for 4 h. Acid hydrolysis of the acylation

† For a simple analogy, NH-protected 1,2,3,4-tetrahydroisoquinoline may be considered as a six-membered analogue of 2-benzazepine **4**: nitration and sulfonylation are reported to occur on C-7 of 1,2,3,4-tetrahydroisoquinoline.[6c,d] This analogy may suggest that acylation should be favoured on C-8 of **4**. However, this seemed insufficient to us as a rational prediction, because we have found that regioselectivity greatly depends on ring size in the acylation of similar nitrogen heterocycles.[7]



Scheme 1

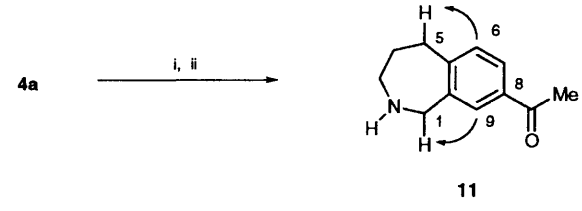


adduct gave 8-acetyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine **11** in 92% yield from **4a** (Scheme 2). Because no sign of other regioisomers was observed in the ^{1}H and ^{13}C NMR spectra of the crude product, the regioselectivity was determined to be over 95%. The regiochemical assignment was based on ^{1}H and

Table 1 Electron densities of MOs of $AlCl_3$-coordinated substrates **4a**, **4b**, **6**, **7** and **8**[a]

Substrate	C-6	C-7	C-8	C-9
4a	0.087 57	0.058 05	0.287 77	0.072 89
4b	0.069 48	0.032 18	0.196 61	0.058 94
6	0.065 33	0.267 56	0.035 91	0.113 93
7	0.054 77	0.044 34	0.197 84	0.044 60
8	0.039 68	0.039 51	0.158 60	0.035 87

[a] The highest MOs were where aromatic carbons C-6–C-9 were considered to be reactive because at least one of their electron densities was greater than that of any of the atoms in the substrate–$AlCl_3$ complex.



Scheme 2 *Reagents:* i, AcCl (1.1 equiv.), $AlCl_3$ (2.3 equiv.); ii, conc. HCl–MeOH. Arrows in formula **11** represent typical C–H long-range correlations through three bonds (*J* 8 Hz) observed in the HETCOR experiments.

^{13}C NMR spectral data (including HETCOR measurements): C–H long-range correlations through three bonds were observed (*J* 8 Hz) between C-9 and 1-H as well as between C-6 and 5-H. The structure was further confirmed by X-ray crystallographic analysis of **11**·HBr salt (Fig. 1).

From the above finding it seemed reasonable to expect high regioselectivities on C-7 of 1,4-benzoxazepine **6** and on C-8 of 2-benzazepin-3-one **7**. These were rationalized by MO calculations (Table 1) and confirmed by experiments (Scheme 3): compounds **12** and **13a** were prepared as single regioisomers from substrates **6** and **7**, respectively. In the case of 3-benzazepin-2-one **8**, acylation occurred at the C-8 position as predicted by calculation, yielding compound **14a**. We next turned our interest to the reaction of tetracyclic 2-benzazepine analogous **9** and **10**. Regardless of the different positions of condensation, MO calculations showed that the highest electron density was distributed on the carbons which correspond to C-8 of 2-benzazepine **4** (Table 2). Compounds **15a** and **16a** were actually obtained as single isomers from substrates **9** and **10**, respectively (Scheme 3). Similarly, reaction

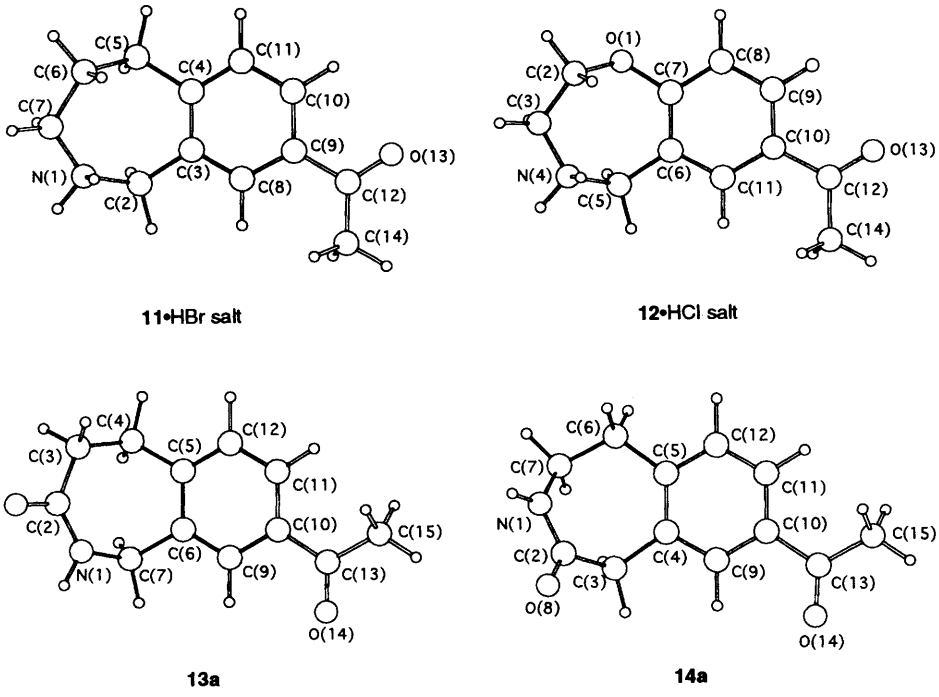


Fig. 1 X-Ray molecular structures of compounds **11**•HBr salt, **12**•HCl salt, **13a** and **14a**

Table 2 Electron densities of MOs of $AlCl_3$-coordinated substrates **9** and **10**[a]

Substrate	C-1	C-2	C-3	C-4
9	0.056 39	0.080 65	0.265 42	0.049 92
10	0.022 58	0.112 49	0.022 27	0.037 66

[a] The highest MOs were where aromatic carbons C-1–C-4 were considered to be reactive because at least one of their electron densities was greater than that of any of the other atoms in the substrate–$AlCl_3$ complex.

with 3-chloropropionyl chloride as the acylating agent proceeded regioselectively: compounds **13b**, **14b**, **15b** and **16b** were obtained in good to high yields (Scheme 3). The structures of acylation products **12**–**16** were determined by ^1H and ^{13}C NMR studies and/or by X-ray crystallographic analyses. Satisfactory C–H long-range correlations were observed for the acylation products **13**–**16** (see Experimental section). Crystal structures of compounds **12**•HCl salt, **13a** and **14a** are shown in Fig. 1.

Finally, we applied these findings to the synthesis of the AChE inhibitor **3**, which is outlined in Scheme 4. The starting acid **18** was prepared from 3-(1-acetylpiperidin-4-yl)propionic acid **17**[8] by sequential hydrolysis and Schotten–Baumann acylation with methyl chlorocarbonate. The acid chloride derived from the acid **18** was allowed to react with 2-acetyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine **4b** in the presence of 3.3 equiv. of $AlCl_3$ to afford the acylation adduct **19**; C-8 selective acylation was expected from the MO calculation of $AlCl_3$-coordinated substrate **4b** (Table 1).* Deprotection of the piperidine nitrogen of adduct **19** was performed by treatment with iodotrimethylsilane to give compound **20**. Treatment of compound **20** with benzyl bromide followed by acid hydrolysis yielded 3-(1-benzylpiperidin-4-yl)-1-(2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-yl)propan-1-one **3a**. The structure of compound **3a** was assigned by the observation of a C–H long-range correlation (*J* 8 Hz) through three bonds between C-9 and 1-H.

In conclusion, this study revealed that NH-protected 2,3,4,5-tetrahydro-1*H*-2-benzazepine **4** is acylated on the C-8 position with greater than 95% regioselectivity. This reaction was applied to the synthesis of 3-(1-benzylpiperidin-4-yl)-1-(2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-yl)propan-1-one **3a**, which was found to be a potent AChE inhibitor.† The regioselectivity of the acylation of related nitrogen heterocycles **6**–**10** was also clarified. During the study, MO calculations on the Lewis acid coordinated substrates were effectively used for predicting regioselectivity.

Experimental

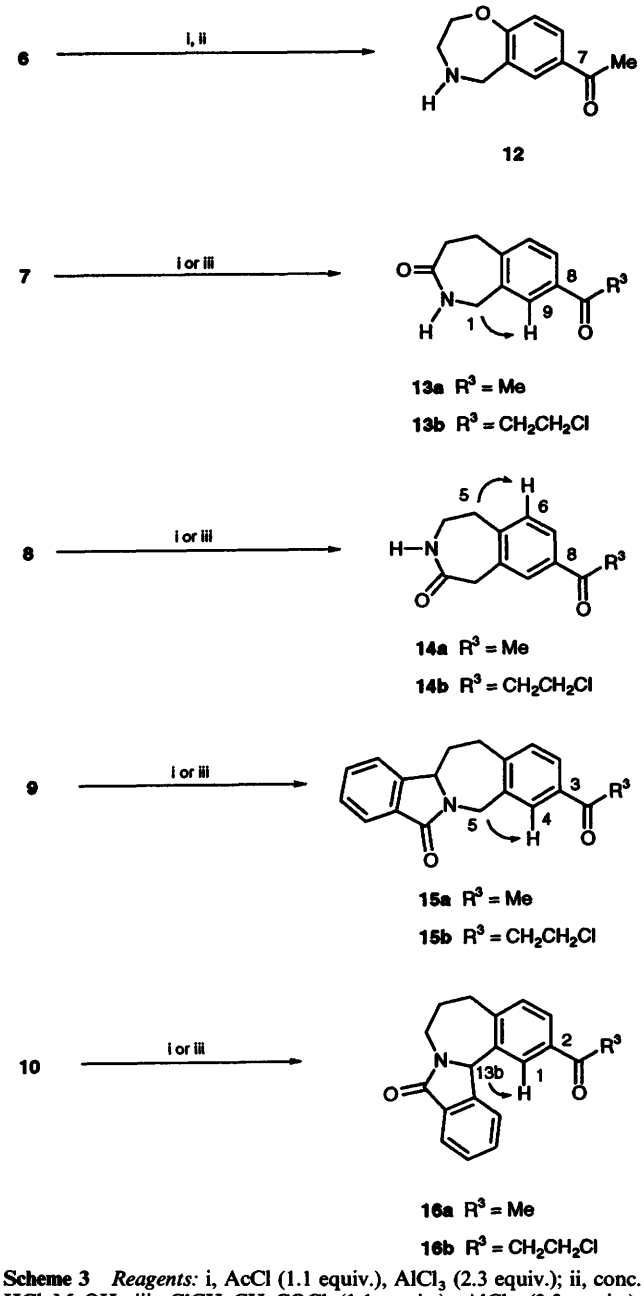
M.p.s were determined on a Yanagimoto micro m.p. apparatus and are uncorrected. IR spectra were taken on a Jasco IR-810 spectrophotometer. ^1H (200 MHz) and ^{13}C (50.29 MHz) NMR spectra were recorded on a Varian GEMINI-200 NMR spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. *J* Values are given in Hz. Column chromatography was performed with Merck silica gel 60 (0.063–0.200 mm, 70–230 mesh) and TLC with Merck silica gel 60 F_{254}. MO calculations were carried out by the MNDO-PM3 method with MOPAC ver 6.00.[9]

Substrates.—2,3,4,5-Tetrahydro-1*H*-2-benzazepin-3-one **7**,[10] 2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-one **8**[11] and 6,7,9,13b-tetrahydro-5*H*-isoindolo[1,2-*a*][2]benzazepin-9-one **10**[12] were prepared by previously reported methods. 7,11b,12,13-Tetrahydro-5*H*-isoindolo[2,1-*b*][2]benzazepin-7-one **9** was prepared by Wolff–Kishner reduction of 7,11b,12,13-tetrahydro-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione.[13] Substrates **4a**, **4b** and **6** were prepared by normal procedures.[14]

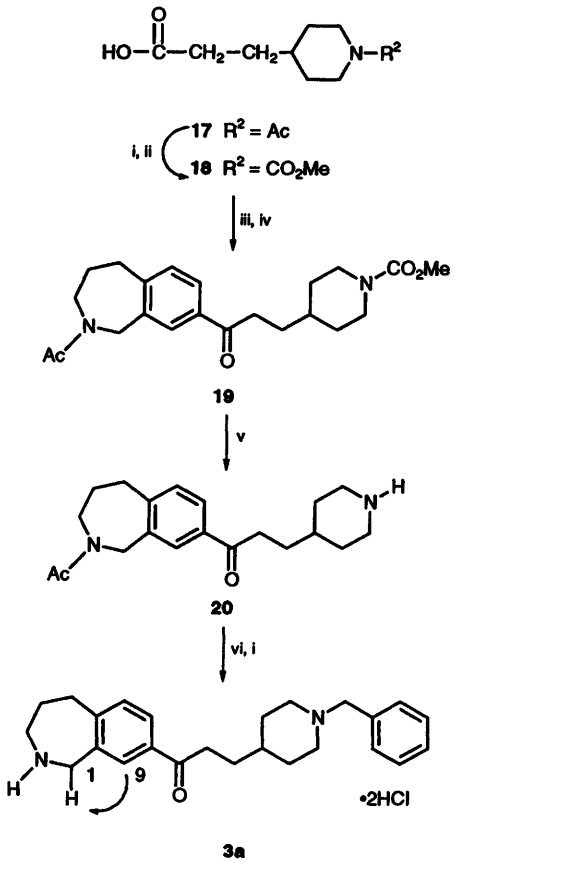
2,3,4,5-*Tetrahydro*-1H-2-*benzazepine*-2-*carbaldehyde* **4a**. Powder, m.p. 59–60 °C (from hexane–diethyl ether) (Found: C, 75.2; H, 7.3; N, 7.9. $C_{11}H_{13}NO$ requires C, 75.40; H, 7.48; N,

* The intermediates **18** and **19** gave complicated NMR spectra because of the existence of s-*cis* and s-*trans* isomers; accordingly, the regiochemistry of Friedel–Crafts acylation was determined from spectral studies of compound **3a**.

† The biological activity of compound **3a** will be reported elsewhere.



Scheme 3 *Reagents:* i, AcCl (1.1 equiv.), $AlCl_3$ (2.3 equiv.); ii, conc. HCl–MeOH; iii, $ClCH_2CH_2COCl$ (1.1 equiv.), $AlCl_3$ (2.3 equiv.). Arrows in formulae **13–16** represent typical C–H long-range correlations through three bonds (*J* 8 Hz) observed in the HETCOR experiments.



Scheme 4 *Reagents:* i, conc. HCl; ii, $ClCO_2Me$; iii, $SOCl_2$; iv, **4b**, $AlCl_3$ (3.3 equiv.); v, Me_3SiI; vi, $PhCH_2Br$, K_2CO_3. The arrow in formula **3a** represents typical C–H long-range correlation through three bonds (*J* 8 Hz) observed in the HETCOR experiments.

7.99%); ν_{max}(KBr)/cm^{-1} 1656 (CON); δ_H 1.75–1.89 (2 H, m), 2.94–3.03 (2 H, m), 3.64 and 3.81 (2 H, each t, *J* 5.5), 4.44 and 4.54 (2 H, each s), 7.10–7.39 (4 H, m) and 8.00 and 8.12 (1 H, each s).

1-(2,3,4,5-*Tetrahydro*-1H-2-*benzazepin*-2-*yl*)*ethanone* **4b**. Oil; ν_{max}(film)/cm^{-1} 1636 (CON); δ_H 1.75–1.88 (2 H, m), 2.04 and 2.11 (3 H, each s), 2.97 (2 H, t, *J* 5.7), 3.70 and 3.86 (2 H, each t, *J* 5.6), 4.48 and 4.56 (2 H, each s) and 7.10–7.40 (4 H, m).

2,3,4,5-*Tetrahydro*-1,4-*benzoxazepine*-4-*carbaldehyde* **6**. Oil; ν_{max}(film)/cm^{-1} 1667 (CON); δ_H 3.70–3.79 and 3.88–3.96 (2 H, each m), 4.02–4.14 (2 H, m), 4.47 and 4.60 (2 H, each s), 7.00–7.38 (4 H, m) and 8.06 and 8.19 (1 H, each s).

7,11b,12,13-*Tetrahydro*-5H-*isoindolo*[2,1-b][2]*benzazepin*-7-*one* **9**. Wolff–Kishner reduction of 7,11b,12,13-tetrahydro-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione [13] by the procedure of Huang-Minlon [15] gave compound **9** in 75% yield. Pale yellow fine needles, m.p. 170–171 °C (from ethyl acetate–diethyl ether) (Found: C, 81.6; H, 6.0; N, 5.5. $C_{17}H_{15}NO$ requires C, 81.90; H, 6.06; N, 5.62%); ν_{max}(KBr)/cm^{-1} 1685 (CON); δ_H 1.36–1.56 (1 H, m), 2.54–2.67 (1 H, m), 3.00 (1 H, ddd, *J* 1.8, 7.4 and 14.6), 3.16–3.31 (1 H, m), 4.42 (1 H, d, *J* 14.6), 4.68 (1 H, dd, *J* 3.6 and 11.4), 5.27 (1 H, d, *J* 14.6), 7.10–7.23 (3 H, m), 7.37–7.56 (4 H, m) and 7.81 (1 H, dd, *J* 1.4 and 7.0).

Typical Procedure for Friedel–Crafts Acylaion.—Acetyl chloride (1.5 g, 19.1 mmol) was added dropwise to a mixture of compound **4a** (3.0 g, 17.1 mmol) and freshly powdered $AlCl_3$ (5.25 g, 39.4 mmol) in 1,2-dichloroethane (20.0 cm^3). The resulting mixture was heated at 50 °C for 4 h, quenched with ice–water and then extracted with dichloromethane. The extracts were dried (Na_2SO_4) and the solvent was evaporated to give a residue. A mixture of the residue and conc. HCl (10 cm^3) in methanol (10 cm^3) was refluxed for 2 h. After evaporation of the conc. HCl and methanol, the residue was taken up in water. The aqueous solution was made basic with 10% NaOH and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a crude product. The regioselectivity was determined from the ^{1}H and ^{13}C NMR spectra. The pure product **11** was obtained by recrystallization. In the acylation of substrates **7–10**, acid hydrolysis of the Friedel–Crafts adduct was not necessary.

1-(2,3,4,5-*Tetrahydro*-1H-2-*benzazepin*-8-*yl*)*ethanone* **11**. Powder (92%), m.p. 71–72 °C (from diethyl ether) (Found: C, 76.0; H, 8.0; N, 7.4. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40%); ν_{max}(KBr)/cm^{-1} 3336 (NH) and 1672 (CO); δ_H 1.63 (1 H, br, NH), 1.68–1.82 (2 H, m, 4-H), 2.58 (3 H, s, Me), 3.00 (2 H, t, *J* 5.5, 5-H), 3.23 (2 H, t, *J* 5.3, 3-H), 4.00 (2 H, s, 1-H), 7.25 (1 H, d,

J 8.3, 6-H) and 7.70–7.78 (2 H, m, 7-H and 9-H); δ_C 26.55 (Me), 30.55 (C-4), 36.23 (C-5), 53.55 (C-3), 55.01 (C-1), 127.40 (C-7), 128.06 (C-9), 129.55 (C-6), 135.23 (C-8), 143.27 (C-9a), 148.80 (C-5a) and 197.76 (CO); C–H long-range correlations (*J* 8) were observed between C-9 and 1-H and C-6 and 5-H. Treatment of **11** with 48% HBr (1 equiv.) gave the hydrobromide as yellow needles, m.p. 290–293 °C (from methanol) (Found: C, 53.1; H, 5.85; N, 5.15. $C_{12}H_{15}NO$·HBr requires C, 53.35; H, 5.97; N, 5.18%); ν_{max}(KBr)/cm^{-1} 2700–3000 (N^+H_2) and 1674 (CO).

1-(2,3,4,5-*Tetrahydro*-1,4-*benzoxazepin*-7-*yl*)*ethanone* **12**. Needles (82%), m.p. 81–82 °C (from CH_2Cl_2–hexane) (Found: C, 68.8; H, 6.8; N, 7.15. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32%); ν_{max}(KBr)/cm^{-1} 3296 (NH) and 1670 (CO); δ_H 1.66 (1 H, br, NH), 2.56 (3 H, s, Me), 3.25 (2 H, t, *J* 4.5, 3-H), 4.02 (2 H, s, 5-H), 4.11 (2 H, t, *J* 4.5, 2-H), 7.07 (1 H, d, *J* 8.6, 9-H) and 7.75–7.82 (2 H, m, 6-H and 8-H); δ_C 26.33 (Me), 51.70 (C-3), 52.87 (C-5), 75.15 (C-2), 121.29 (C-9), 129.22 (C-8), 130.09 (C-6), 132.53 (C-7), 134.79 (C-5a), 164.31 (C-9a) and 197.25 (CO). Treatment of **12** with methanolic HCl (1 equiv.) gave the hydrochloride as colourless needles, m.p. 263–266 °C (from methanol) (Found: C, 57.85; H, 6.15; N, 6.15. $C_{11}H_{13}NO_2$·HCl requires C, 58.03; H, 6.20; N, 6.15%); ν_{max}(KBr)/cm^{-1} 2600–3000 (N^+H_2) and 1671 (CO).

8-*Acetyl*-2,3,4,5-*tetrahydro*-1H-2-*benzazepin*-3-*one* **13a**. Needles (88%), m.p. 182–184 °C (from CH_2Cl_2–diethyl ether) (Found: C, 70.65; H, 6.4; N, 6.8. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%); ν_{max}(KBr)/cm^{-1} 3180 (NH), 1686 (CO) and 1655 (CON); δ_H 2.60 (3 H, s, Me), 2.85 (2 H, t, *J* 6.6, 4-H), 3.18 (2 H, t, *J* 6.6, 5-H), 4.44 (2 H, d, *J* 5.5, 1-H), 6.35 (1 H, br, NH), 7.30 (1 H, d, *J* 8.0, 6-H), 7.74 (1 H, d, *J* 2.2, 9-H) and 7.84 (1 H, dd, *J* 2.2 and 8.0, 7-H); δ_C 26.36 (Me), 28.47 (C-5), 33.64 (C-4), 45.36 (C-1), 128.20 [C-7 (C-9)], 128.27 [C-9 (C-7)], 130.06 (C-6), 135.48 (C-8), 136.68 (C-9a), 144.69 (C-5a), 175.70 (C-3) and 197.72 (*C*OMe); a C–H long-range correlation (*J* 8) was observed between C-1 and 9-H.

8-(3-*Chloro*-1-*oxopropyl*)-2,3,4,5-*tetrahydro*-1H-2-*benzazepin*-3-*one* **13b**. Needles (63%), m.p. 123–125 °C (from CH_2Cl_2–diethyl ether) (Found: C, 61.7; H, 5.7; N, 5.3. $C_{13}H_{14}ClNO_2$ requires C, 62.03; H, 5.61; N, 5.56%); ν_{max}(KBr)/cm^{-1} 3202 (NH), 1694 and 1677 (CO and CON); δ_H 2.79–2.88 (2 H, m, 4-H), 3.13–3.23 (2 H, m, 5-H), 3.43 (2 H, t, *J* 6.8, $COCH_2$), 3.92 (2 H, t, *J* 6.8, CH_2Cl), 4.44 (2 H, d, *J* 5.6, 1-H), 6.58 (1 H, br, NH), 7.31 (1 H, d, *J* 8.0, 6-H), 7.74 (1 H, d, *J* 1.9, 9-H) and 7.83 (1 H, dd, *J* 1.9 and 8.0, 7-H); δ_C 28.77 (C-5), 33.79 (C-4), 38.70 (CH_2Cl), 41.25 ($COCH_2$), 45.62 (C-1), 127.95 [C-7 (C-9)], 128.02 [C-9 (C-7)], 130.20 (C-6), 134.79 (C-8), 136.75 (C-9a), 145.09 (C-5a), 175.37 (C-3) and 196.01 ($COCH_2$); a C–H long-range correlation (*J* 8) was observed between C-1 and 9-H.

8-*Acetyl*-2,3,4,5-*tetrahydro*-1H-3-*benzazepin*-2-*one* **14a**. Needles (95%), m.p. 203–204 °C (from CH_2Cl_2–diethyl ether) (Found: C, 70.7; H, 6.3; N, 6.7. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%); ν_{max}(KBr)/cm^{-1} 3206 (NH) and 1673 (CO and CON); δ_H 2.58 (3 H, s, Me), 3.19 (2 H, t, *J* 6.0, 5-H), 3.62 (2 H, dt, *J* 5.5 and 6.0, 4-H), 3.92 (2 H, s, 1-H), 6.10 (1 H, br, NH), 7.22 (1 H, d, *J* 7.7, 6-H), 7.74 (1 H, d, *J* 2.2, 9-H) and 7.79 (1 H, dd, *J* 2.2 and 7.7, 7-H); δ_C 26.61 (Me), 33.74 (C-5), 40.64 (C-4), 42.47 (C-1), 127.06 (C-7), 130.52 (C-6), 130.66 (C-9), 132.10 (C-9a), 135.76 (C-8), 142.42 (C-5a), 173.52 (C-2) and 197.48 (*C*OMe); a C–H long-range correlation (*J* 8) was observed between C-5 and 6-H.

8-(3-*Chloro*-1-*oxopropyl*)-2,3,4,5-*tetrahydro*-1H-3-*benzazepin*-2-*one* **14b**. Needles (67%), m.p. 203–204 °C (from CH_2Cl_2–diethyl ether) (Found: C, 61.9; H, 5.6; N, 5.7. $C_{13}H_{14}ClNO_2$ requires C, 62.03; H, 5.61; N, 5.56%); ν_{max}(KBr)/cm^{-1} 3224 (NH) and 1673 (CO and CON); δ_H 3.15 (2 H, t, *J* 6.0, 5-H), 3.42 (2 H, t, *J* 6.8, $COCH_2$), 3.64 (2 H, dt, *J* 5.2 and 6.0, 4-H), 3.87–3.96 [4 H, m, CH_2Cl and 1-H, peak of 1-H at 3.91 (s)], 6.90 (1 H, br, NH), 7.23 (1 H, d, *J* 7.7, 6-H), 7.73 (1 H, d, *J* 1.8, 9-H) and 7.78 (1 H, dd, *J* 1.8 and 7.7, 7-H); δ_C 33.82 (C-5), 38.70 (CH_2Cl), 40.62 (C-4), 41.23 ($COCH_2$), 42.45 (C-1), 126.85 (C-7), 130.34 (C-9), 130.70 (C-6), 132.35 (C-9a), 135.02 (C-8), 142.94 (C-5a), 173.33 (C-2) and 196.07 ($COCH_2$); a C–H long-range correlation (*J* 8) was observed between C-9 and 1-H.

3-*Acetyl*-7,11b,12,13-*tetrahydro*-5H-*isoindolo*[2,1-b][2]*benzazepin*-7-*one* **15a**. Cubes (65%), m.p. 162–163 °C (from CH_2Cl_2–diethyl ether) (Found: C, 78.5; H, 5.8; N, 4.7. $C_{19}H_{17}NO_2$ requires C, 78.33; H, 5.88; N, 4.81%); ν_{max}(KBr)/cm^{-1} 1682 (CO and CON); δ_H 1.36–1.57 (1 H, m, 1 H of 12-H_2), 2.55–2.72 [4 H, m, 1 H of 12-H_2 and Me (peak at 2.61)], 2.98–3.36 (2 H, m, 13-H), 4.46 (1 H, d, *J* 15.0, 1 H of 5-H_2), 4.73 (1 H, dd, *J* 3.7 and 11.2, 11b-H), 5.37 (1 H, d, *J* 15.0, 1 H of 5-H_2), 7.25 (1 H, d, *J* 7.3, 1-H), 7.38–7.58 (3-H, m), 7.78–7.84 (2 H, m) and 8.02 (1 H, d, *J* 1.7, 4-H); δ_C 26.58 (Me), 32.70 [C-13 (C-12)], 33.17 [C-12 (C-13)], 45.44 (C-5), 63.74 (C-11b), 121.58, 123.58 (C-8), 127.84 (C-2), 128.16, 128.89 (C-4), 129.91 (C-1), 131.48, 131.77 [C-7a (C-11a)], 135.77 (C-3), 137.37 (C-4a), 145.09 [C-11a (C-7a)], 146.80 (C-13a), 166.67 (C-7) and 197.39 (*C*OMe); a C-H long-range correlation (*J* 8) was observed between C-5 and 4-H.

3-(3-*Chloro*-1-*oxopropyl*)-7,11b,12,13-*tetrahydro*-5-H-*isoindolo*[2,1-b][2]*benzazepin*-7-*one* **15b**. Cubes (85%), m.p. 139–142 °C (from CH_2Cl_2–diethyl ether) (Found: C, 70.7; H, 5.4; N, 4.1. $C_{20}H_{18}ClNO_2$ requires C, 70.69; H, 5.34; N, 4.12%); ν_{max}(KBr)/cm^{-1} 1683 (CO and CON); δ_H 1.36–1.58 (1 H, m, 1 H of 12-H_2), 2.57–2.72 (1 H, m, 1 H of 12-H_2), 2.98–3.37 (2 H, m, 13-H), 3.46 (2 H, t, *J* 7.0, $COCH_2$), 3.92 (2 H, t, *J* 7.0, CH_2Cl), 4.46 (1 H, d, *J* 14.9, 1 H of 5-H_2), 4.73 (1 H, dd, *J* 3.7 and 11.0, 11b-H), 5.36 (1 H, d, *J* 14.9, 1 H of 5-H_2), 7.26 (1 H, d, *J* 7.8, 1-H), 7.38–7.59 (3 H, m), 7.77–7.84 (2 H, m) and 8.01 (1 H, d, *J* 1.5, 4-H); δ_C 32.83 [C-13 (C-12)], 33.25 [C-12 (C-13)], 38.70 (CH_2Cl), 41.33 ($COCH_2$), 45.57 (C-5), 63.92 (C-11b), 121.66, 123.86 (C-8), 127.85 (C-2), 128.35, 128.68 (C-4), 130.19 (C-1), 131.66, 131.79 [C-7a (C-11a)], 135.15 (C-3), 137.66 (C-4a), 145.18 [C-11a (C-7a)], 147.38 (C-13a), 166.92 (C-7) and 196.07 ($COCH_2$); a C–H long-range correlation (*J* 8) was observed between C-5 and 4-H.

2-*Acetyl*-6,7,9,13b-*tetrahydro*-5H-*isoindolo*[1,2-a][2]*benzazepin*-9-*one* **16a**. Cubes (70%), m.p. 145–148 °C (from CH_2Cl_2–diethyl ether) (Found: C, 78.05; H, 6.1; N, 4.7. $C_{19}H_{17}NO_2$ requires C, 78.33; H, 5.88; N, 4.81%); ν_{max}(KBr)/cm^{-1} 1696 and 1676 (CO and CON); δ_H 1.83–2.05 (1 H, m, 1 H of 6-H_2), 2.12–2.36 (1 H, m, 1 H of 6-H_2), 2.58 (3 H, s, Me), 2.74–2.84 (2 H, m, 5-H), 3.25–3.43 (1 H, m, 1 H of 7-H_2), 4.40 (1 H, ddd, *J* 2.7 and 7.0 and 13.7, 1 H of 7-H_2), 5.80 (1 H, s, 13b-H), 7.25 (1 H, d, *J* *ca.* 8, 4-H), 7.43–7.63 (3 H, m), 7.82 (1 H, dd, *J* 1.8 and 7.7, 3-H) and 7.88–7.98 [2 H, m, 1-H and 10-H, peak of 1-H at 7.96 (d, *J* 1.8)]; δ_C 25.24 (C-6), 26.58 (Me), 31.64 (C-5), 40.92 (C-7), 65.71 (C-13b), 123.32, 124.09 (C-10), 127.18 (C-1), 128.67, 128.78, 131.00 (C-4), 131.77, 132.17, 136.06 (2 C, C-2 and C-13c), 143.56 (C-4a), 145.60, 169.00 (C-9) and 197.35 (*C*OMe); a C–H long-range correlation (*J* 8) was observed between C-13b and 1-H.

2-(3-*Chloro*-1-*oxopropyl*)-6,7,9,13b-*tetrahydro*-5H-*isoindolo*[1,2-a][2]*benzazepin*-9-*one* **16b**. Cubes (81%), m.p. 152–156 °C (from CH_2Cl_2–diethyl ether) (Found: C, 70.6; H, 5.4; N, 4.1. $C_{20}H_{18}ClNO_2$ requires C, 70.69; H, 5.34; N, 4.12%); ν_{max}(KBr)/cm^{-1} 1685 (CO and CON); δ_H 1.83–2.05 (1 H, m, 1 H of 6-H_2), 2.09–2.34 (1 H, m, 1 H of 6-H_2), 2.76–2.85 (2 H, m, 5-H), 3.26–3.45 (3 H, m, $COCH_2$ and 1 H of 7-H_2), 3.92 (2 H, t, *J* 6.7, CH_2Cl), 4.42 (1 H, ddd, *J* 2.4, 6.7 and 14.1, 1 H of 7-H_2), 5.81 (1 H, s, 13b-H), 7.27 (1 H, d, *J* 7.9, 4-H), 7.45–7.64 (3 H, m), 7.82 (1 H, dd, *J* 1.9 and 7.9, 3-H) and 7.89–7.98 [2 H, m, 1-H and 10-H, peak of 1-H at 7.96 (d, *J* 1.9)]; δ_C 25.24 (C-6), 31.82 (C-5), 38.63 (CH_2Cl), 41.10 [C-7 ($COCH_2$)], 41.21 [$COCH_2$ (C-7)], 65.56 (C-13b), 123.40, 124.16 (C-10), 127.00 (C-1), 128.31 (C-3),

Table 3 Crystallographic data of compounds **11**·HBr salt, **12**·HCl salt, **13a** and **14a**

Compound	**11**·HBr salt[a]	**12**·HCl salt[a]	**13a**[b]	**14a**[c]
Formula	$C_{12}H_{15}NO$·HBr	$C_{11}H_{13}NO_2$·HCl	$C_{12}H_{13}NO_2$	$C_{12}H_{13}NO_2$
M	270.17	227.69	203.24	203.24
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$C2/c$	$C2/c$	$P2_1/c$	$P2_1/n$
a/Å	29.474(3)	29.258(3)	4.435(2)	19.540(2)
b/Å	11.231(2)	11.024(4)	12.362(2)	12.262(2)
c/Å	7.547(3)	7.200(2)	18.697(2)	4.309(2)
β/deg	97.64(2)	99.62(2)	91.56(2)	96.15(2)
Z	8	8	4	4
D_c/g cm^{-3}	1.450	1.351	1.318	1.315
Cell volume (Å^3)	2475.8(9)	2290(1)	1024.6(6)	1026.6(4)
Radiation	Mo-Kα (λ0.7107 Å)	Mo-Kα (λ 0.7107 Å)	Cu-Kα (λ1.5418 Å)	Cu-Kα (λ1.5418 Å)
μ/cm^{-1}	34.95	3.17	7.40	7.38
Scan mode	2θ–ω	2θ–ω	2θ–ω	2θ–ω
2θ range/deg	3–50	3–50	3–120	3–120
Reflections collected	2299	2139	1596	1604
Observed [$F > 3\sigma(F)$]	1077	1255	1148	1301
Scan speed (deg min^{-1})	32	32	32	32
R	0.110[d]	0.060	0.064	0.062
R_w	0.136[d]	0.061	0.065	0.077

[a] Crystals of compounds **11**·HBr salt and **12**·HCl salt were grown from methanol. [b] Crystals of compound **13a** were grown from dichloromethane. [c] Crystals of **14a** were grown from dichloromethane–diethyl ether. [d] This high R factor may be due to insufficient volume and quality of the crystal.

128.86, 131.08 (C-4), 131.80, 132.17, 135.30 (C-2), 136.39 (C-13c), 143.42 (C-4a), 146.29, 169.00 (C-9) and 195. 97 ($COCH_2$); a C–H long-range correlation (J 8) was observed between C-13b and 1-H.

X-Ray Crystallographic Analysis.—The structures of compounds **11**, **12**, **13a** and **14a** were confirmed by X-ray analyses and their crystal data are summarized in Table 3. Intensity data were collected on a RIGAKU AFC5R diffractometer. No absorption correction was applied. The structures were solved by direct methods using the MULTAN program[16] and refined by the XTAL system.[17] The positions and anisotropic thermal parameters of non-hydrogen atoms were refined by the full-matrix least-squares method. Hydrogen atoms were placed at idealized positions (C–H = 1.09 Å, N–H = 1.0 Å) with isotropic thermal parameters of their parent non-hydrogen atoms. Hydrogen atoms were not refined but they were allowed to ride on their parent atoms during refinement cycles.

Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **11**, **12**, **13a** and **14a** have been deposited at the Cambridge Crystallographic Data Centre.*

Preparation of 3-(1-*Benzylpiperidin*-4-*yl*-1-(2,3,4,5-*tetrahydro*-1H-2-*benzazepin*-8-*yl*)*propan*-1-*one Dihydrochloride* **3a**.—A mixture of 3-(1-acetylpiperidin-4-yl)propionic acid **17** (99.6 g, 0.50 mol)[8] and conc. HCl (208 cm^3) was refluxed for 6 h, concentrated to half volume and then left to stand at 0 °C for 16 h. The resulting precipitate was collected by filtration and washed with cold ethanol. Methyl chlorocarbonate (34 cm^3, 0.44 mol) was added dropwise to a mixture of the solid, dichloromethane (360 cm^3) and NaOH (3 mol dm^{-3}; 400 cm^3) at 0 °C. The resulting mixture was stirred at room temperature for 5 h. 50% NaOH was added to the mixture to take the pH to 8 and then the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was triturated in diisopropyl ether–hexane to give 3-(1-methoxycarbonylpiperidin-4-yl)propionic acid **18** (76.5 g, 71%) as a powder, m.p. 88–90 °C (Found: C, 55.8; H, 8.0; N, 6.5. $C_{10}H_{17}NO_4$ requires C, 55.69; H, 8.01; N, 6.47%).

The acid **18** (7.5 g, 34.8 mmol) was added portionwise to $SOCl_2$ (12 cm^3, 165.2 mmol) at 0–5 °C. After being stirred for 30 min at 0–5 °C, the excess of $SOCl_2$ was evaporated to give the acid chloride (*ca.* 8.1 g) as an oil, which was used for the next step without further purification. Freshly powdered $AlCl_3$ (15.3 g, 114.7 mmol) was added portionwise to a mixture of the acid chloride (*ca.* 8.1 g) and compound **4b** (6.0 g, 31.7 mmol) in 1,2-dichloroethane (30.0 cm^3). The resulting mixture was stirred at room temperature for 16 h, quenched with ice–water, and then extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and the solvent was evaporated to give a residue. Chromatographic purification eluting with ethyl acetate–methanol (20:1) afforded 1-(2-acetyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-yl)-3-(1-methoxycarbonylpiperidine-4-yl)propan-1-one **19** (8.3 g, 68% from **4b**) as an oil; δ_H 1.03–1.97 (9 H, m), 2.05 and 2.12 (3 H, each s), 2.66–2.83 (2 H, m), 2.93–3.09 (4 H, m), 3.69 (3 H, s), 3.75 and 3.88 (2 H, each t, J 5.6), 4.03–4.26 (2 H, m), 4.56 and 4.61 (2 H, each s), 7.20–7.32 (1 H, m) and 7.74–7.96 (2 H, m).

Iodotrimethylsilane (6.5 cm^3, 45.7 mmol) was added to compound **19** (6.8 g, 17.6 mmol) in dry $CHCl_3$ (90 cm^3) at room temperature and then heated at 50 °C for 3.5 h according to the known procedure.[18] The reaction was quenched by sequential addition of methanol (7.2 cm^3), NaOH (1 mol dm^{-3}; 88 cm^3) and 10% $Na_2S_2O_3$ (88 cm^3). The resulting mixture was made basic with 10% NaOH and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and then the solvent was removed under reduced pressure to afford 1-(2-acetyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-8-yl)-3-(piperidin-4-yl)propan-1-one **20** (4.07 g, 70%) as an oil; δ_H 1.03–1.97 (9 H, m), 2.05 and 2.12 (3 H, each s), 2.26 (1 H, s), 2.59 (2 H, dt, J 2.4 and 12.0), 2.78–3.12 (6 H, m), 3.74 and 3.87 (2 H, each t, J 5.6), 4.55 and 4.61 (2 H, each s), 7.17–7.31 (1 H, m) and 7.70–7.95 (2 H, m).

Benzyl bromide (1.95 g, 11.4 mmol) was added to a suspension of compound **20** (3.8 g, 11.6 mmol) and K_2CO_3 (2.1 g, 15.2 mmol) in ethanol (75 cm^3) at 0–5 °C and the mixture was stirred at room temperature for 6 h. After evaporation of the ethanol, the residue was taken up in water and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), passed through a plug of silica gel and then the solvent was removed under reduced pressure to give an oil. A mixture of the oil and conc. HCl (25 cm^3) was refluxed for 20 h and then concentrated. The remaining residue was dissolved in water and

* For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

washed with ethyl acetate. The water layer was made basic with 10% NaOH and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), passed through a plug of silica gel and then the solvent was removed under reduced pressure to afford the free base of **3a** (3.1 g, 71% from **20**) as an oil. Treatment of the oil (2.9 g, 7.7 mmol) with methanolic HCl (4 mol dm^{-3}; 4.0 cm^3, 16.0 mmol) yielded the product **3a** (2.9 g) as a powder (from ethanol), m.p. 147–150 °C (Found: C, 65.7; H, 7.8; N, 5.9. $C_{25}H_{32}N_2O{\cdot}2HCl{\cdot}0.5H_2O$ requires C, 65.49; H, 7.69; N, 6.11%); ν_{max}(KBr)/cm^{-1} 2500–3000 (N^+H_2) and 1678 (CO); δ_H(free base) 1.18–1.44 (3 H, m), 1.58–1.76 (7 H, m), 1.84–1.97 (2 H, m), 2.82–3.04 (6 H, m), 3.22 (2 H, t, *J* 5.3), 3.49 (2 H, s), 3.99 (2 H, s, 1-H), 7.18–7.33 (6 H, m) and 7.67–7.75 (2 H, m, 7-H and 9-H); δ_C 30.54, 30.96, 32.22 (2 C), 35.43, 35.82, 36.22, 53.55, 53.80 (2 C), 55.04, 63.48, 126.84, 127.07 (C-7), 127.84 (C-9), 128.09 (2 C), 129.15 (2 C), 129.51 (C-6), 135.06 (C-8), 138.58, 143.24 (C-9a), 148.55 (C-5a) and 200.06 (CO); a C–H long-range correlation (*J* 8) was observed between C-9 and 1-H.

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