Regioselective Friedel–Crafts Acylation of 1,2,3,4-Tetrahydroquinoline and Related Nitrogen Heterocycles: Effects of NH Protective Groups and Ring Size[1]

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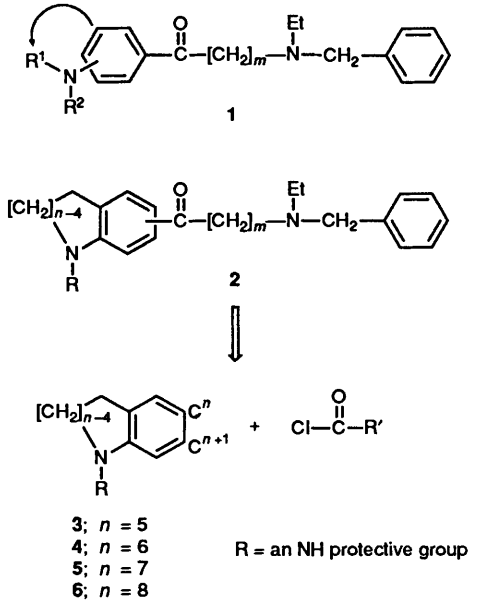
Regioselectivity of the Friedel–Crafts acylation of the following nitrogen heterocycles was studied: 2,3-dihydro-1*H*-indoles **3**, 1,2,3,4-tetrahydroquinolines **4**, 2,3,4,5-tetrahydro-1*H*-1-benzazepines **5** and 1,2,3,4,5,6-hexahydro-1-benzazocines **6**. It was found that though the ratio of regioisomers depends on ring size, it can be controlled by changing the NH protective groups. A molecular orbital (MO) calculation of the Lewis acid co-ordinated substrates gave a rational explanation of the regioselectivity.

The Friedel–Crafts acylation of 1,2-disubstituted benzenes and related heterocycles gives, in principle, a mixture of regioisomers. This sometimes leaves the difficulty of isomer separation as well as ambiguity concerning their structure, even though various selective reactions have been reported.[2] We have encountered such problems during our studies into inhibitors of acetylcholinesterase (AChE), which are considered to be promising candidates for the treatment of senile dementia of the Alzheimer type. Therefore, in an attempt to find new types of AChE inhibitors, we became interested in the activity of heterocyclic compounds **2** which are analogues of the potent inhibitors, ω-(*N*-benzyl-*N*-ethylamino)-1-phenylalkan-1-ones **1**.[1] Compounds **2** can be synthesized by acylation of the NH-protected nitrogen heterocycles **3**–**6**, which occurred mainly *para* (C-*n*) and/or *meta* [C-(*n* + 1)] to the nitrogen atom. It has been shown that C-*n* acylation is favoured in the reaction of both 2,3-dihydro-1*H*-indoles **3** and 1,2,3,4-tetrahydroquinolines **4**;[3] however, in some reports acylation of **4** has given a mixture of C-6 and C-7 isomers.[4] No C-(*n* + 1) selective acylation has been reported. In addition, little is known about the acylation of 2,3,4,5-tetrahydro-1*H*-1-benzazepines **5** or 1,2,3,4,5,6-hexahydro-1-benzazocines **6**.[5] In our initial attempt, acylation of 1-acetyl-1,2,3,4-tetrahydroquinoline **4f** with acetyl chloride gave an approximately 1:1 mixture of C-6 and C-7 isomers,† which were difficult to separate by conventional column chromatography. Therefore, in order to prepare each regioisomer of compound **2** effectively, it seemed necessary to clarify the factors governing the regioselectivity and hence to control them. Here we report on the regioselective Friedel–Crafts reaction of the nitrogen heterocycles **3**–**6** based on the effect of NH protective groups (Scheme 1). MO calculations were also studied to obtain a rational explanation for the results.



Results and Discussion

In a typical acylation procedure, reactions were carried out by refluxing a mixture of substrate (1.0 mol equiv.) and AcCl (1.1 mol equiv.) in the presence of $AlCl_3$ (2.3 mol equiv.) in CS_2 for 8 h. Chromatographic removal of the unchanged substrate from the reaction mixture and subsequent acid or alkaline hydrolysis gave a mixture of regioisomers whose ratio was measured from ^1H NMR spectra (see Tables 2 and 3). Yields were not optimized. The assignment of regiochemistries was based on ^1H and ^{13}C NMR spectral data (including HCOSY, DEPT and HETCOR measurements) as well as UV spectral investigations (Table 1). Typical features are as follows: (a) Chemical shifts of (*n* + 2)-H on C-*n* acylation products **7a**–**9a** are 6.40–6.67, which are the highest values found among the aromatic protons and correspond to 3′-Hs of 4′-aminoacetophenone;[6] (b) C–H long-range correlations through two or three bonds were observed (*J* values were 8 or 12 Hz), for example in the case of 8-acetyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine **13a**, between C-9a and 5-H as well as between C-9a and 6-H; (c) UV absorptions of 323–342 nm for C-*n* acylation products **7**–**9** and 237–246 nm for C-(*n* + 1) acylation products **11**–**14** correspond to those of 4′-aminoacetophenones and 3′-aminoacetophenones, respectively.[7]

Acylation of 1-acetyl-1,2,3,4-tetrahydroquinoline **4f** was initially examined under various conditions. Some results are given in Table 2. Among the Lewis acids tested, $AlCl_3$ gave the most satisfactory yield. The ratio of the C-6 isomer **8a** to the C-7 isomer **12a** was 51:49. With other Lewis acids ($TiCl_4$,

† The reaction was performed under a typical acylation procedure which is described in the Results and Discussion section.

Table 1 ^{1}H NMR chemical shifts, observed C–H long-range correlations, and UV spectra of acylated nitrogen heterocycles **7a–9a, 11a–14a**

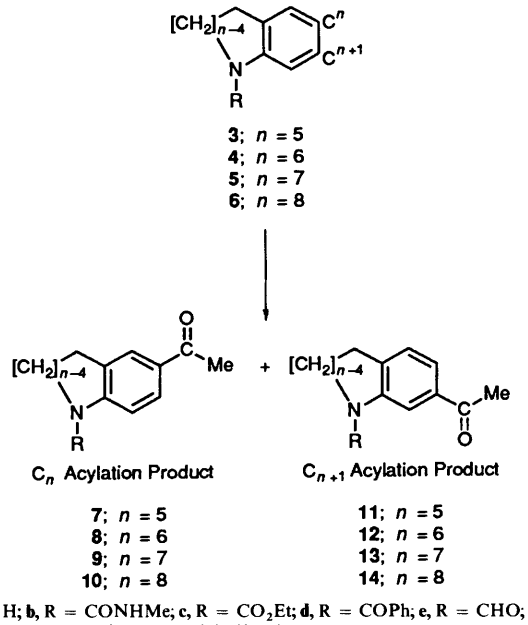
Compound	n	^{1}H NMR chemical shifts (δ_H)					C–H long-range correlations[a] (*J*-value used)	UV (λ/nm) (ε/dm^3 mol^{-1} cm^{-1})
		$(n-1)-H$	n-H		$(n+1)-H$	$(-n+2)-H$ Ac		
7a	5	7.67–7.78			7.67–7.78	6.55 2.50	C-5 and 7-H (12 Hz) C-7a and 6-H (12 Hz)	337 (16 440)
8a	6	7.57–7.65			7.57–7.65	6.39 2.47	C-6 and 8-H (12 Hz)	342 (24 670)
9a	7	7.71			7.63	6.67 2.51	C-5a and 5-H (8 Hz)[b] C-5a and 9-H (8 Hz)	323 (12 600)
11a	5	7.16	7.32			7.19 2.54	C-3a and 3-H (12 Hz)[b]	239 (19 100)
12a	6	7.00	7.17			7.05 2.52	C-4a and 8-H (8 and 12 Hz) C-8a and 5-H (8 and 12 Hz)	245 (23 200)
13a	7	7.17	7.40			7.34 2.55	C-9a and 5-H (8 Hz) C-9a and 6-H (8 Hz)	237 (22 600)
14a	8	7.13	7.43–7.52			7.43–7.52 2.56	C-9 and 7-H (8 Hz) C-10a and 7-H (8 Hz)	246 (16 730)

[a] Three-bond coupling. [b] Two-bond coupling.

Table 2 The Friedel–Crafts acylation of 1-acetyl-1,2,3,4-tetrahydroquinoline **4f**

Entry	Lewis acid (mol equiv.)	Solvent	Yield[a] (%)	Product ratio[b] **8a**:**12a**
1	$AlCl_3$ (2.3)	CS_2	64	51:49
2[c]	$AlCl_3$ (1.1)	CS_2	trace	
3	$AlCl_3$ (4.6)	CS_2	65	63:37
4	$AlCl_3$ (2.3)	$ClCH_2CH_2Cl$	58	44:56

[a] Total isolated yield after hydrolysis. [b] The ratio was determined from the integration ratio of the aromatic protons in the ^{1}H NMR spectra, as follows: 6.40 (8-H; **8a**) and 7.17 (6-H; **12a**). [c] In this run, substrate **4f** was added to a mixture of $AlCl_3$ and AcCl.



a, R = H; **b**, R = CONHMe; **c**, R = CO_2Et; **d**, R = COPh; **e**, R = CHO; **f**, R = Ac; **g**, R = $COCF_3$; **h**, R = *p*-tolylsulfonyl

Scheme 1 *Reagents:* $AlCl_3$, Lewis acid

$SnCl_4$, BF_3·OEt_2, $ZnCl_2$, $EtAlCl_2$), only trace amounts of products were detected by TLC. More than 2 mole equivalents of $AlCl_3$ were necessary for the reaction and the use of 4.6 mole equivalents of $AlCl_3$ slightly increased the amount of C-6 acylation product **8a** (entries 2 and 3). As solvent, CS_2 gave a better yield than did 1,2-dichloroethane, though the ratio of products was slightly different (entry 4). Attempted reaction using other solvents (nitrobenzene, nitromethane, dichloromethane) resulted in a trace amount of products. No significant change of regioselectivity was observed by variation of either the amount or type of Lewis acid or of the solvent.

Subsequently, we studied the effects of NH protective groups (R). The results summarized in Table 3 demonstrate that the regioselectivity depended greatly upon the nature of R. For instance, CONHMe and CO_2Et groups gave predominantly C-6 acylation product (entries 5 and 6). In contrast, a $COCF_3$ group favours C-7 acylation (entry 9). Acylation with acetic anhydride showed a similar tendency (entries 10 and 11). In the acylation of other substrates with different ring sizes (n = 5, 7 and 8), similar changes of selectivity were observed by variation of R (entries 12–20); however, the orientation tended to depend on the ring size (n): Acylation of 1-acetyl-2,3-dihydro-1*H*-indole **3f** gave C-5 acylation product predominantly (entry 13) as reported earlier, whereas acylation is favoured on C-(n + 1) positions with 1-acetyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine **5f** and 1-acetyl-1,2,3,4,5,6-hexahydro-1-benzazocine **6f** (entries 17 and 20).

The above regioselectivity can be explained classically by combining the conformational differences of the substrates and the electronic characters of the acylamino groups (NR). Conformational differences caused by ring size (n) affect the resonance contribution of NR. A near planar conformation of compound **3f** (n = 5) is suitable for resonance activation, which induces C-5 acylation. However, almost no resonance contribution is expected with substrates **5f** (n = 7) and **6f** (n = 8) because of the lack of conjugation between the acylamino groups and the benzene rings caused by their twisted conformation.[8] Consequently, C-n carbons are relatively deactivated, which increases the ratio of C-(n + 1) acylation products. Within substrates of the same ring size, on the other hand, field effects (F)[9] of the acylamino groups seem to dominate the regioselectivity; compare the ratios of **8**:**12** (NR, F-values as NHR[9]), 98:2 (NCONHMe, 0.04), 96:4 (NCO_2Et, 0.14), 79:21 (NCOPh, 0.09), 68:32 (NCHO, 0.25), 51:49 (NAc, 0.28) and 20:80 ($NCOCF_3$, 0.36). These explanations, although they seem reasonable, lack the evaluation of the effect of Lewis acid, which must co-ordinate to substrates, thus affecting the regioselectivity.

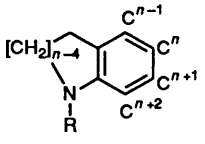
The orientation of Friedel–Crafts acylation can be explained in terms of the Frontier Molecular Orbital theory.[10] For a more rational explanation of the observed regioselectivity, we carried out MO calculation of substrates **3f**, **4c**, **4f**, **4g**, **5f** and **6f**. The HOMO distribution on aromatic carbons C-(n − 1)–C-(n + 2) summarized in Table 4 shows that electrons were usually distributed on C-n carbons, which was contrary to the experimental findings (entries 1, 17 and 20). We next calculated $AlCl_3$-co-ordinated substrates. In the Diels–Alder reaction, it is

Table 3 Effects of NH protective groups (R) and ring size (n) on acylation of nitrogen heterocycles **3–6**

Entry	Substrate	n	R	Yield[a] (%)	Product ratio[b] C-n acylation : C-(n + 1) acylation
5[c]	**4b**	6	CONHMe	96	>98 (**8b**)[c]: <2 (**12b**)[c]
6	**4c**	6	CO_2Et	94	96 (**8a**)[d]:4 (**12a**)[d]
7	**4d**	6	COPh	66	79 (**8a**)[d]:21 (**12a**)[d]
8	**4e**	6	CHO	86	68 (**8a**)[d]:32 (**12a**)[d]
9	**4g**	6	$COCF_3$	17	14 (**8a**)[d]:72 (**12a**)[d]:14[e]
10[f]	**4c**	6	CO_2Et	97	97 (**8a**)[d]:3 (**12a**)[d]
11[f]	**4g**	6	$COCF_3$	13	10 (**8a**)[d]:87 (**12a**)[d]:3[e]
12	**3c**	5	CO_2Et	81	>98 (**7a**):0 (**11a**): <2[e]
13	**3f**	5	Ac	83	94 (**7a**):6 (**11a**)
14	**3g**	5	$COCF_3$	11	59 (**7a**):41 (**11a**)
15[c]	**5b**	7	CONHMe	98	87 (**9b**)[c]:13 (**13b**)[c]
16	**5c**	7	CO_2Et	97	9 (**9a**):71 (**13a**):20[e]
17	**5f**	7	Ac	30	6 (**9a**):94 (**13a**)
18[c]	**6b**	8	CONHMe	96	13 (**10b**)[c]:87 (**14b**)[c]
19	**6c**	8	CO_2Et	81	<2 (**10a**): >98 (**14a**)
20	**6f**	8	Ac	29	<2 (**10a**): >98 (**14a**)
21[g]	**4h**	6	Ts[h]	70	97 (**8a**)[d]:3 (**12a**)[d]
22[g]	**5h**	7	Ts[h]	10	95 (**9a**):5 (**13a**)
23	**4h**	6	Ts[h]	58	91 (**8a**)[d]:9 (**12a**)[d]
24	**5h**	7	Ts[h]	41	59 (**9a**):41 (**13a**)

[a] Total isolated yield after hydrolysis. [b] The ratio was determined from the integration ratio of the aromatic protons in the ^1H NMR spectra, as follows: 6.55 (7-H; **7a**), 7.29 (5-H; **11a**); 6.68 (9-H; **9a**), 7.17 (6-H; **13a**); 7.13 (7-H; **14a**). [c] The yield and ratio were determined as a mixture of ureas (R = CONHMe). The chemical shifts of protons used to determine the ratio are as follows: 7.44 (8-H; **8b**), 7.96 (8-H; **12b**); 7.31 (9-H; **9b**), 7.38 (6-H; **13b**); 2.63 [CO*Me*; **10b** (tentative assignment)], 2.60 (CO*Me*; **14b**). [d] The ratio was determined from the integral ratio of 8-H (**8a**) and 5-H (**12a**); see footnote *b* in Table 2. [e] C-(n − 1) or C-(n + 2) acylation product, which has not been isolated or identified. [f] In this run, Ac_2O was employed as an acylating agent and 3.5 mol equiv. of $AlCl_3$ were used. [g] In this run, substrate was added to a mixture of AcCl (1.1 mol equiv.) and $AlCl_3$ (1.1 mol equiv.) in 1,2-dichloroethane–CS_2 (2 cm^3; 1:1). [h] Ts = *p*-tolylsulfonyl.

Table 4 Electron densities of the HOMO of substrates **3f**, **4c**, **4f**, **4g**, **4h**, **5f**, **5h** and **6f**



Substrate	n	R	C-(n − 1)	C-n	C-(n + 1)	C-(n + 2)
3f	5	Ac	0.0173	0.3198	0.0614	0.1706
4c	6	CO_2Et	0.0285	0.3249	0.0823	0.1174
4f	6	Ac	0.0268	0.3217	0.0808	0.1184
4g	6	$COCF_3$	0.0220	0.3601	0.1376	0.0818
5f	7	Ac	0.0336	0.2825	0.0878	0.0860
6f	8	Ac	0.0047	0.0197	0.0252	0.0300
4h	6	Ts[a]	0.0308	0.3719	0.0735	0.1684
5h	7	Ts[a]	0.0148	0.3911	0.1826	0.0732

[a] Ts = *p*-tolylsulfonyl.

known that Lewis acid co-ordination shows a drastic effect on regioselectivity, which is rationally explained by calculation of Lewis acid-co-ordinated dienophiles.[11] However, in the Friedel–Crafts reaction, no detailed MO study of such substrates has been reported. In our study, the most stable structures of $AlCl_3$-co-ordinated substrates were determined (Fig. 1) and then their MOs were calculated. In most calculated HOMOs, electrons were distributed on one of the chlorine atoms of $AlCl_3$. The attack of an acylating agent on the chlorine atom would produce an unreactive complex, which might dissociate to the starting substrate and the acylating agent. Therefore, we focused our attention on lower MOs where aromatic carbons C-(n − 1)–C-(n + 2) were considered to be reactive because at least one of their electron densities was

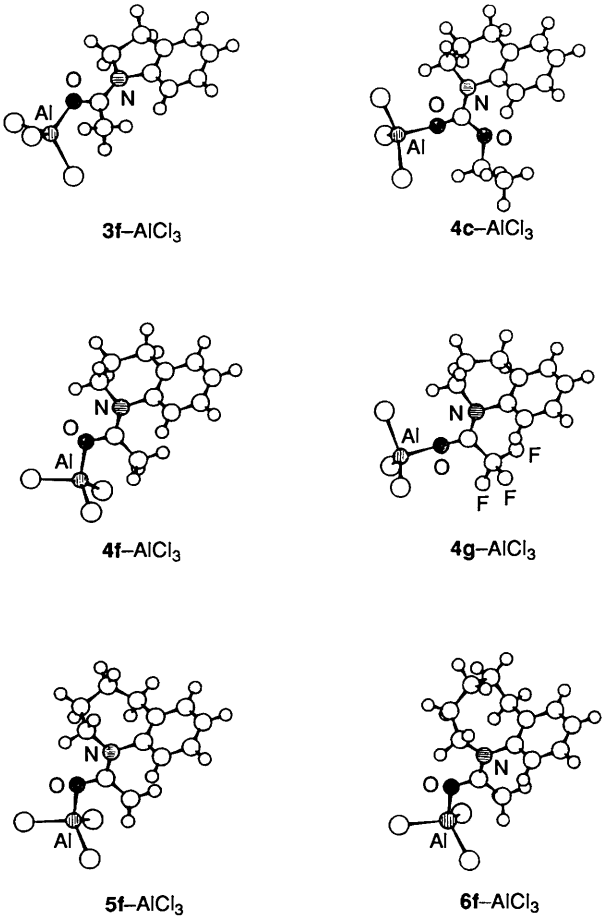
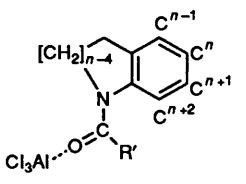


Fig. 1 The most stable structures of $AlCl_3$-co-ordinated substrates **3f**, **4c**, **4d**, **4g**, **5f** and **6f**

Table 5 Electron densities of the MOs of $AlCl_3$-co-ordinated substrates **3f**, **4c**, **4f**, **4g**, **4h**, **5f**, **5h** and **6f**[a]



Substrate	*n*	COR′	C-(*n* − 1)	C-*n*	C-(*n* + 1)	C-(*n* + 2)
3f	5	Ac	0.0029	0.2520	0.1481	0.0352
4c	6	CO_2Et	0.0098	0.3092	0.1600	0.0458
4f	6	Ac	0.0017	0.2728	0.2766	0.0037
4g	6	$COCF_3$	0.0094	0.1449	0.2026	0.0045
5f	7	Ac	0.0527	0.2264	0.4999	0.0454
6f	8	Ac	0.2408	0.0721	0.5864	0.2269
4h	6	Ts[b]	0.0187	0.4017	0.1825	0.0583
5h	7	Ts[b]	0.0025	0.2960	0.3095	0.0040

[a] The highest MOs were where aromatic carbons C-(*n* − 1)–C-(*n* + 2) were considered to be reactive because at least one of their electron densities was greater than that of any other atom in the substrate–$AlCl_3$ complex. [b] Ts = *p*-tolylsulfonyl.

greater than those of any other atoms in the substrate–$AlCl_3$ complex. By selecting the highest MOs we were able to explain the observed regioselectivity. The data shown in Table 5 agreed well with the experimental findings. We think it is necessary to investigate the validity of this discussion by predicting and examining the regioselectivity of acylation of other heterocyclic substrates.

The results of the MO calculations shown in Table 4 suggested to us that it might be interesting to investigate a *p*-tolylsulfonyl (tosyl) group as NH protective group (R). Since sulfonyl groups do not require Lewis acid co-ordination during the reaction,[12] selective C-*n* acylation might be expected regardless of ring size, as calculated in Table 4. Actually, acylation of *N*-tosyl compounds **4h** or **5h** with 1.1 mole equivalents of $AlCl_3$ afforded a >95:<5 ratio of isomers favouring C-*n* acylation products as anticipated (entries 21 and 22). The use of 2.3 mole equivalents of $AlCl_3$ reduced the ratio of C-*n* acylation, which was also rationalized by our calculations (Table 5). Unfortunately, attempted acylation of *N*-tosylated 1,2,3,4,5,6-hexahydro-1-benzazocine **6h** only resulted in a trace amount of product.

In conclusion, we have shown that although regioselectivity of acylation is dependent upon ring size, it can be controlled by changing the NH protective groups. MO calculation of the substrate with Lewis acid co-ordination gave a rational explanation of the obtained regioselectivity and might be useful for predicting regioselectivity, though further investigation is necessary to show its validity. We should also note that some synthetic problems remain to be solved, namely satisfactory C-6 selectivity in acylation of 2,3-dihydro-1*H*-indoles **3** and regioselective C-8 acylation of 1,2,3,4,5,6-hexahydro-1-benzazocines **6**. An application of the above methodology to the regioselective preparation of heterocyclic compounds **2** as well as an investigation into their biological activities are now being undertaken.

Experimental

M.p.s were determined on a Yanagimoto micro m.p. apparatus and are uncorrected. IR spectra were taken on a Hitachi 260-10 spectrophotometer. UV spectra were measured on a Hitachi U-3210 spectrophotometer. ^1H (200 MHz) and ^{13}C (50.29 MHz) NMR spectra were recorded on a Varian Gemini 200 FT NMR spectrometer for solutions 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 PM_3 method with MOPAC ver 6.00.[13]

Substrates.—1-Ethoxycarbonyl-2,3-dihydro-1*H*-indole **3c**,[14] 1-acetyl-2,3-dihydro-1*H*-indole **3f**,[15] 1-trifluoroacetyl-2,3-dihydro-1*H*-indole**3g**,[16] 1-methylcarbamoyl-1,2,3,4-tetrahydroquinoline **4b**,[17] 1-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline **4c**,[18] 1-benzoyl-1,2,3,4-tetrahydroquinoline **4d**,[15a,19] 1-formyl-1,2,3,4-tetrahydroquinoline **4e**,[20] 1-acetyl-1,2,3,4-tetrahydroquinoline **4f**,[15a,21] 1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline **4g**,[22] and 1-acetyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine **5f**[5] were prepared by previously reported methods. Other substrates **4h**, **5b**, **5c**, **5h**, **6b**, **6c**, **6f** and **6h** prepared by common procedures[23] were as follows:

1-(*p-Tolylsulfonyl*)-1,2,3,4-*tetrahydroquinoline* **4h**: plates, m.p. 93–94 °C (from diethyl ether–hexane) (Found: C, 66.8; H, 6.0; N, 4.8. $C_{16}H_{17}NO_2S$ requires C, 66.87; H, 5.96; N, 4.87%); ν_{max}(KBr)/cm^{-1} 1340 and 1161 (SO_2); δ_H 1.64 (2 H, tt, *J* 6.0, 6.8), 2.38 (3 H, s), 2.48 (2 H, t, *J* 6.8), 3.80 (2 H, t, *J* 6.0), 6.96–7.25 (5 H, m), 7.48 (2 H, d, *J* 8.3) and 7.79 (1 H, d, *J* 8.0).

1-*Methylcarbamoyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **5b**: cubes, m.p. 104–109 °C (from diethyl ether–hexane) (Found: C, 70.5; H, 7.9; N, 13.7. $C_{12}H_{16}N_2O$ requires C, 70.56; H, 7.89; N, 13.71%); ν_{max}(KBr)/cm^{-1} 3358 (NH) and 1642 (C=O); δ_H 1.15–2.00 (4 H, m), 2.48–3.83 (6 H, m), 4.10–4.85 (2 H, m) and 7.17–7.30 (4 H, m).

1-*Ethoxycarbonyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **5c**: oil (Found: C, 71.0; H, 7.7; N, 6.2. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39%); ν_{max}(neat)/cm^{-1} 1703 (C=O); δ_H 1.05–2.03 (7 H, m), 2.55–2.87 (3 H, m), 3.35–4.64 (3 H, m) and 7.16 (4 H, s).

1-(*p-Tolylsulfonyl*)-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **5h**: cubes, m.p. 92–93 °C (from CH_2Cl_2–diethyl ether) (Found: C, 67.6; H, 6.5; N, 4.8. $C_{17}H_{19}NO_2S$ requires C, 67.74; H, 6.35; N, 4.65%); ν_{max}(KBr)/cm^{-1} 1340 and 1153 (SO_2); δ_H 1.43–1.87 (4 H, m), 2.32–2.47 (5 H, m), 3.68 (2 H, br), 7.07–7.34 (6 H, m) and 7.61 (2 H, d, *J* 8.1).

1-*Methylcarbamoyl*-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **6b**: cubes, m.p. 99–101 °C (from diethyl ether) (Found: C, 71.3; H, 8.4; N, 12.8. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31; N, 12.83%); ν_{max}(KBr)/cm^{-1} 3342 (NH) and 1639 (C=O); δ_H 1.17–2.03 (6 H, m), 2.50–2.96 (6 H, m), 3.92 (1 H, br), 4.54–4.73 (1 H, m) and 7.10–7.43 (4 H, m).

1-*Ethoxycarbonyl*-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **6c**: oil (Found: C, 71.9; H, 8.2; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%); ν_{max}(KBr)/cm^{-1} 1702 (C=O); δ_H 1.07–1.98 (9 H, m), 2.56–2.74 (2 H, m), 2.86–3.12 (1 H, m), 3.96–4.51 (3 H, m) and 7.03–7.40 (4 H, m).

1-*Acetyl*-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **6f**: cubes, m.p. 49–51 °C (from hexane) (Found: C, 76.7; H, 8.4. N, 6.8. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N, 6.89%); ν_{max}(KBr)/cm^{-1} 1652 (C=O); δ_H 1.26–1.97 (9 H, m), 2.59–2.68 (2 H, m), 2.76 (1 H, ddd, *J* 2.8, 7.2 and 13.2), 4.76 (1 H, ddd, *J* 3.3, 8.2 and 13.2), 7.06–7.13 (1 H, m) and 7.22–7.34 (3 H, m).

1-(*p-Tolylsulfonyl*)-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **6h**: needles, m.p. 135–136 °C (from CH_2Cl_2–diethyl ether) (Found: C, 68.45; H, 6.7; N, 4.6. $C_{18}H_{21}NO_2S$ requires C, 68.54; H, 6.71; N, 4.44%); ν_{max}(KBr)/cm^{-1} 1343 and 1154 (SO_2); δ_H 1.20–1.90 (6 H, m), 2.46 (3 H, s), 2.70–4.00 (3 H, m), 6.59 (1 H, d, *J* 7.7), 7.02–7.15 (1 H, m), 7.22–7.28 (3 H, m), 7.31 (2 H, d, *J* 8.0) and 7.70 (2 H, d, *J* 8.0).

Typical Procedure for Friedel–Crafts Acylation.—Acetyl chloride (78 mm^3, 1.1 mmol) was added dropwise to a mixture of compound **4f** (175 mg, 1.0 mmol) and $AlCl_3$ (308 mg, 2.3

mmol) in CS_2 (2.0 cm^3). The resulting mixture was refluxed for 8 h, quenched with ice–water, and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and the solvent was evaporated to give a residue. Unchanged **4f** was removed by column chromatography on silica gel (6.0 g) and elution with dichloromethane–EtOAc (10:1; v/v), giving a mixture of regioisomers. A solution of the mixture and conc. HCl (10 cm^3) was refluxed for 16 h. After evaporation of conc. HCl, the residue was taken up in water, and the 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 mixture of products **8a** and **12a**. The ratio of the regioisomers was determined from the ^1H NMR spectrum of the residue.

The pure compounds **7–14** were obtained by recrystallization. Reference compounds **12b** and **13b** were prepared by reaction of the parent compounds **12a** and **13a** with methyl isocyanate in the presence of Et_3N.

5-*Acetyl*-2,3-*dihydro*-1H-*indole* **7a**: cubes, m.p. 74–75 °C (from diethyl ether–hexane) (lit.,[15c] 76–77 °C) (Found: C, 74.3; H, 7.0; N, 8.6. Calc. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%); ν_{max}(KBr)/cm^{-1} 3314 (NH) and 1647 (C=O); λ_{max}(MeOH)/nm 241 (ε 5770) and 337 (16 440); δ_H 2.50 (3 H, s, Me), 3.08 (2 H, t, *J* 8.6, 3-H_2), 3.68 (2 H, t, *J* 8.6, 2-H_2), 4.20 (1 H, br, NH), 6.55 (1 H, d, *J* 8.1, 7-H) and 7.67–7.78 (2 H, m, 4- and 6-H); δ_C 26.23 (Me), 28.79 (C-3), 47.34 (C-2), 107.29 (C-7), 125.43 (C-4), 128.25 [C-5(3a)], 129.23 [C-3a(5)], 130.73 (C-6), 156.73 (C-7a) and 197.04 (CO).

6-*Acetyl*-2,3-*dihydro*-1H-*indole* **11a**: needles, m.p. 71–72 °C (from diethyl ether–hexane) (Found: C, 74.6; H, 7.0; N, 8.7. $C_{10}H_{11}NO$ requires C, 74.51; H, 6.88; N, 8.69%); ν_{max}(KBr)/cm^{-1} 3318 (NH) and 1668 (C=O); λ_{max}(MeOH)/nm 239 (ε 19 100) and 338 (5500); δ_H 2.54 (3 H, s, Me), 3.07 (2 H, t, *J* 8.5, 3-H_2), 3.61 (2 H, t, *J* 8.5, 2-H_2), ~4.0 (1 H, br, NH), 7.16 (1 H, d, *J* 7.6, 4-H), 7.19 (1 H, d, *J* 1.5, 7-H) and 7.32 (1 H, dd, *J* 1.5 and 7.6, 5-H); δ_C 26.70 (Me), 29.83 (C-3), 47.38 (C-2), 107.84 (C-7), 120.09 (C-5), 124.30 (C-4), 135.31 (C-3a), 137.03 (C-6), 152.06 (C-7a) and 198.17 (CO).

6-*Acetyl*-1,2,3,4-*tetrahydroquinoline* **8a**: pale yellow cubes, m.p. 104–105 °C (from diethyl ether) (Found: C, 75.2; H, 7.4; N, 8.0. $C_{11}H_{13}NO$ requires C, 75.40; H, 7.48; N, 7.99%); ν_{max}(KBr)/cm^{-1} 3338 (NH) and 1643 (C=O); λ_{max}(MeOH)/nm 245 (ε 5870) and 342 (24 670); δ_H 1.94 (2 H, tt, *J* 5.5 and 6.4, 3-H_2), 2.47 (3 H, s, Me), 2.78 (2 H, t, *J* 6.4, 4-H_2), 3.37 (2 H, t, *J* 5.5, 2-H_2), 4.41 (1 H, br, NH), 6.39 (1 H, d, *J* 9.2, 8-H) and 7.57–7.65 (2 H, m, 5- and 7-H); δ_C 21.40 (C-3), 26.00 (Me), 27.08 (C-4), 41.80 (C-2), 112.81 (C-8), 120.07 (C-4a), 126.10 (C-6), 128.96 [C-7(5)], 130.82 [C-5(7)], 149.72 (C-8a) and 197.04 (CO).

6-*Acetyl*-1-*methylcarbamoyl*-1,2,3,4-*tetrahydroquinoline* **8b**: needles, m.p. 134–135 °C (from CH_2Cl_2–hexane) (Found: C, 67.0; H, 6.9; N, 11.85. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%); ν_{max}(KBr)/cm^{-1} 3316 (NH), 1678 and 1648 (C=O); λ_{max}(MeOH)/nm 307 (ε 16 790); δ_H 1.95 (2 H, tt, *J* 6.2 and 6.4, 3-H_2), 2.57 (3 H, s, COMe), 2.80 (2 H, t, *J* 6.4, 4-H_2), 2.88 (3 H, d, *J* 4.7, NMe), 3.76 (2 H, t, *J* 6.2, 2-H_2), 5.11 (1 H, br, NH), 7.44 (1 H, d, *J* 9.2, 8-H) and 7.72–7.80 (2 H, m, 5- and 7-H); δ_C 23.50 (C-3), 26.48 (CO*Me*), 27.57 (C-4), 27.68 (NMe), 44.48 (C-2), 122.37 (C-8), 127.45 (C-7), 129.98 (C-5), 130.97 (C-6), 132.29 (C-4a), 144.29 (C-8a), 157.47 (NCO) and 197.61 (CO).

7-*Acetyl*-1,2,3,4-*tetrahydroquinoline* **12a**: plates, m.p. 50–52 °C (from hexane) (Found: C, 75.2; H, 7.4; N, 8.0. $C_{11}H_{13}NO$ requires C, 75.40; H, 7.48; N, 7.99%); ν_{max}(KBr)/cm^{-1} 3372 (NH) and 1666 (C=O); λ_{max}(MeOH)/nm 245 (ε 23 200) and 347 (2600); δ_H 1.94 (2 H, tt, *J* 5.5 and 6.4, 3-H_2), 2.52 (3 H, s, Me), 2.80 (2 H, t, *J* 6.4, 4-H_2), 3.33 (2 H, d, *J* 5.5, 2-H_2), ~3.9–4.0 (1 H, br, NH), 7.00 (1 H, d, *J* 7.7, 5-H), 7.05 (1 H, d, *J* 1.7, 8-H) and 7.17 (1 H, dd, *J* 1.7 and 7.7, 6-H); δ_C 21.62 (C-3), 26.53 (Me), 27.23 (C-4), 41.78 (C-2), 113.15 (C-8), 117.12 (C-6), 126.99 (C-4a), 129.42 (C-5), 136.05 (C-7), 144.86 (C-8a) and 198.36 (CO).

7-*Acetyl*-1-*methylcarbamoyl*-1,2,3,4-*tetrahydroquinoline* **12b**: needles, m.p. 138–139 °C (from CH_2Cl_2–diethyl ether) (Found: C, 67.1; H, 6.9; N, 12.1. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94; N, 12.06%); ν_{max}(KBr)/cm^{-1} 3352 (NH), 1675 and 1641 (C=O); λ_{max}(MeOH)/nm 243 (ε 26 600) and 316 (1600); δ_H 1.95 (2 H, tt, *J* 6.2 and 6.6, 3-H_2), 2.58 (3 H, s, COMe), 2.80 (2 H, t, *J* 6.6, 4-H_2), 2.87 (3 H, d, *J* 4.7, NMe), 3.76 (2 H, t, *J* 6.2, 2-H_2), 4.98–5.08 (1 H, br, NH), 7.24 (1 H, d, *J* 7.9, 5-H), 7.61 (1 H, dd, *J* 1.7 and 7.9, 6-H) and 7.96 (1 H, d, *J* 1.7, 8-H); δ_C 23.61 (C-3), 26.70 (CO*Me*), 27.57 (C-4), 27.73 (NH*Me*), 43.87 (C-2), 123.24 (C-8), 123.98 (C-6), 129.90 (C-5), 136.21 (C-7), 137.62 (C-4a), 140.09 (C-8a), 157.60 (NCO) and 192.07 (CO).

7-*Acetyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **9a**: viscous oil (Found: C, 76.0; H, 8.0; N, 7.35. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40%); ν_{max}(neat)/cm^{-1} 3352 (NH) and 1661 (C=O); λ_{max}(MeOH)/nm 237 (ε 8040) and 323 (12 600); δ_H 1.60–1.87 (4 H, m), 2.51 (3 H, s, Me), 2.82 (2 H, t, *J* 5.5, 5-H_2), 3.17 (2 H, t, *J* 5.5, 2-H_2), 4.20 (1 H, br, NH), 6.67 (1 H, d, *J* 8.2, 9-H), 7.63 (1 H, dd, *J* 2.1 and 8.2, 8-H) and 7.71 (1 H, d, *J* 2.2, 6-H); δ_C 26.21 (Me), 26.47 (C-4), 30.78 (C-3), 35.49 (C-5), 47.75 (C-2), 118.25 (C-9), 127.78 (C-8), 129.35 (C-7), 131.02 (C-5a), 131.93 (C-6), 155.04 (C-9a) and 196.84 (CO). Treatment of compound **9a** with methanolic HCl (1 mol equiv.) gave the *hydrochloride* as fine needles, m.p. 135–138 °C (from ethanol–diethyl ether) (Found: C, 63.8; H, 7.4; N, 6.1. $C_{12}H_{15}NO$·HCl requires C, 63.85; H, 7.14; N, 6.21%).

7-*Acetyl*-1-*methylcarbamoyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **9b**: cubes, m.p. 132–134 °C (from CH_2Cl_2–diethyl ether) (Found: C, 68.2; H, 7.3; N, 11.4. $C_{14}H_{18}N_2O_2$ requires C, 68.27; H, 7.37; N, 11.37%); ν_{max}(KBr)/cm^{-1} 3318 (NH), 1678 and 1647 (C=O); λ_{max}(MeOH)/nm 239 (ε 9300) and 282 (6400); δ_H 1.60–1.77 (2 H, m, 4-H_2), 1.79–1.95 (2 H, m, 3-H_2), 2.61 (3 H, s, COMe), 2.76 (3 H, d, *J* 4.7, NH*Me*), 2.81 (2 H, t, *J* 5.6, 5-H_2), ~3.2–3.9 (2 H, m, 2-H_2), 4.10–4.25 (1 H, br, NH), 7.31 (1 H, d, *J* 8.0, 9-H), 7.83 (1 H, dd, *J* 2.1 and 8.0, 8-H) and 7.87 (1 H, d, *J* 2.1, 6-H); δ_C 25.85 (C-4), 26.67 (CO*Me*), 27.45 (NMe), 29.52 (C-3), 34.72 (C-5), 47.24 (C-2), 127.70 (C-8), 128.23 (C-9), 130.67 (C-6), 136.19 (C-7), 142.10 (C-5a), 146.72 (C-9a), 156.29 (NCO) and 197.20 (CO).

8-*Acetyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **13a**: . pale yellow cubes, m.p. 88–89 °C (from diethyl ether–hexane) (Found: C, 76.0; H, 8.0; N, 7.3. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40%); ν_{max}(KBr)/cm^{-1} 3358 (NH) and 1677 (C=O); λ_{max}(MeOH)/nm 237 (ε 22 600) and 321 (1800); δ_H 1.55–1.73 (2 H, m), 1.74–1.89 (2 H, m), 2.55 (3 H, s, COMe), 2.81 (2 H, t, *J* 5.5, 5-H_2), 3.06 (2 H, t, *J* 5.5, 2-H_2), 3.92 (1 H, br, NH), 7.17 (1 H, d, *J* 7.7, 6-H), 7.34 (1 H, d, *J* 1.7, 9-H) and 7.40 (1 H, dd, *J* 1.7 and 7.7, 7-H); δ_C 26.62 (Me and C-4), 31.74 (C-3), 36.15 (C-5), 48.89 (C-2), 118.99 (C-9), 121.61 (C-7), 131.29 (C-6), 136.31 (C-8), 139.81 (C-5a), 151.11 (C-9a) and 198.51 (CO).

8-*Acetyl*-1-*methylcarbamoyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* **13b**: needles, m.p. 184–185 °C (from CH_2Cl_2–diethyl ether) (Found: C, 68.25; H, 7.5; N, 11.5. $C_{14}H_{18}N_2O_2$ requires C, 68.27; H, 7.37; N, 11.37%); ν_{max}(KBr)/cm^{-1} 3310 (NH), 1675 and 1645 (C=O); λ_{max}(MeOH)/nm 246 (ε 15 860); δ_H 1.35–2.05 (4 H, m), 2.59 (3 H, s, COMe), 2.73–2.88 (6 H, m), 4.07–4.20 (1 H, m), 4.25–4.90 (1 H, br), 7.38 (1 H, d, *J* 8.4, 6-H) and 7.78–7.87 (2 H, m, 7- and 9-H); δ_C 25.89 (C-4), 26.72 (CO*Me*), 27.57 (NMe), 29.63 (C-3), 34.77 (C-5), 47.42 (C-2), 128.18 [C-7(9)], 128.46 [C-9(7)], 131.33 (C-6), 137.26 (C-8), 143.00 (C-9a), 148.15 (C-5a), 156.98 (NCO) and 197.48 (CO).

9-*Acetyl*-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **14a**: pale yellow needles, m.p. 51–52 °C (from diethyl ether–hexane) (Found: C, 76.6; H, 8.5; N, 6.9. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N, 6.89%); ν_{max}(KBr)/cm^{-1} 3396 (NH) and 1685 (C=O); λ_{max}-

(MeOH)/nm 246 (ε 16 730); δ_H 1.42–1.65 (4 H, m, 3- and 4-H_2), 1.69–1.85 (2 H, m, 5-H_2), 2.56 (3 H, s, Me), 2.92 (2 H, t, *J* 6.4, 6-H_2), ~3.1 (1 H, br, NH), 3.28 (2 H, br t, *J* 5.5, 2-H_2), 7.13 (1 H, d, *J* 7.4, 7-H) and 7.43–7.52 (2 H, m, 8- and 10-H); δ_C 24.74 (C-4), 26.65 (Me), 29.21 (C-3), 30.87 (C-5), 32.17 (C-6), 50.57 (C-2), 121.94 (C-9), 122.53 (C-8), 131.31 (C-7), 136.81 (C-9), 140.10 (C-6a), 148.57 (C-10a) and 198.60 (CO).

9-*Acetyl*-1-*methylcarbamoyl*-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **14b**: cubes, m.p. 149–151 °C (from CH_2Cl_2–diethyl ether) (Found: C, 69.2; H, 7.65; N, 10.8. $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.74; N, 10.76%); ν_{max}(KBr)/cm^{-1} 3404 (NH), 1677 and 1652 (C=O); λ_{max}(MeOH)/nm 250 (ε 14 500); δ_H 1.16–2.04 (6 H, m), 2.47–2.98 (9 H, m), 3.80–3.92 (1 H, m), 4.64 (1 H, br), 7.41 (1 H, d, *J* 8.0, 10-H), 7.76 (1 H, d, *J* 1.8, 7-H) and 7.92 (1 H, dd, *J* 1.8 and 8.0, 9-H); δ_C 26.31 [C-4(3)], 26.69 (CO*Me*), 27.02 [C-3(4)], 27.62 (NMe), 31.23 (C-6), 31.52 (C-5), 50.68 (C-2), 129.22 [C-8(10)], 129.27 [C-10(8)], 131.35 (C-7), 137.95 (C-9), 141.08 (C-10a), 149.83 (C-6a), 157.86 (NCO) and 197.42 (CO).

1,9-*Diacetyl*-1,2,3,4,5,6-*hexahydro*-1-*benzazocine* **14f**: cubes, m.p. 89–90 °C (from CH_2Cl_2–diethyl ether) (Found: C, 73.3; H, 7.8; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%); ν_{max}(KBr)/cm^{-1} 1686 and 1651 (C=O); λ_{max}(MeOH)/nm 251 (ε 14 500); δ_H 1.24–2.02 (9 H, m), 2.61 (3 H, s, CO*Me*), 2.64–2.88 (3 H, m), 4.79 (1 H, ddd, *J* 3.4, 8.3 and 13.4, 2-H), 7.39 (1 H, d, *J* 7.9, 7-H), 7.72 (1 H, d, *J* 1.8, 10-H) and 7.90 (1 H, dd, *J* 1.8 and 7.9, 8-H); δ_C 22.56 (NCO*Me*), 26.17 [C-4(3)], 26.35 [C-3(4)], 26.57 (Me), 31.05 [C-6(5)], 31.15 [C-5(6)], 50.08 (C-2), 127.53 (C-10), 128.77 (C-8), 130.66 (C-7), 137.29 (C-9), 142.38 (C-10a), 147.37 (C-6a), 170.01 (NCO) and 197.76 (CO).

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