Ring Expansion of Nitrogen-containing Chloromethylheteroalicycles *via* Aziridinium Intermediates

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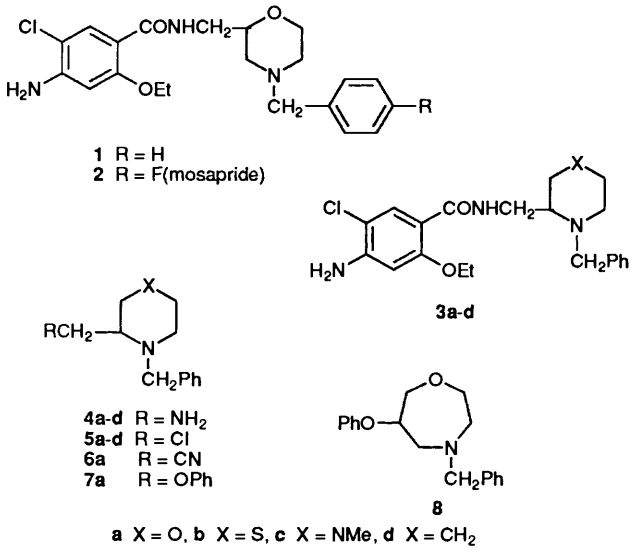
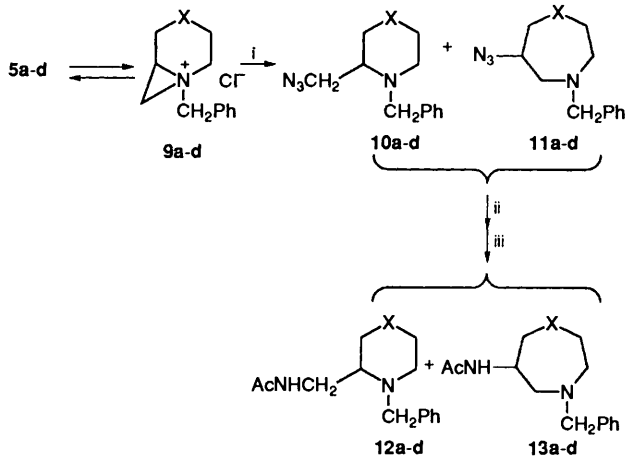
The nucleophilic reaction of NaN_3 with the chloromethylheteroalicycles, 4-benzyl-3-chloromethyl-morpholine **5a**, -tetrahydro-4*H*-1,4-thiazine **5b**, -1-methylpiperazine **5c** and 1-benzyl-2-chloromethylpiperidine **5d**, gave the ring-expanded compounds 6-azido-4-benzylhexahydro-1,4-oxazepine **11a** and its analogues **11b–d** along with the normally substituted compounds 3-azidomethyl-4-benzylmorpholine **10a** and its analogues **10b–d** in varying ratios. LUMO frontier electron densities of the reaction centres indicated that the reaction proceeded *via* the aziridinium intermediate **9** and accounted for the predominance of the reaction product **10** or **11**.

Our previous paper[1] reported the synthesis of 4-amino-*N*-[(4-benzylmorpholin-2-yl)methyl]-5-chloro-2-ethoxybenzamide **1** as a potential gastroprokinetic agent. Further modifications of the benzoyl moiety[1,2] and the *N*-benzyl group[3,4] of **1** led to the finding that 4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)morpholin-2-yl]methyl}benzamide (**2**, mosapride) shows potent gastroprokinetic activity without dopamine D_2 receptor antagonistic action; mosapride is currently under clinical study. In order to gain further insight into the structure–activity relationships of a series of 4-amino-5-chloro-2-ethoxybenzamide derivatives, we initially planned a synthesis of the benzamide derivatives **3a–d** substituted regioisomerically by *N*-benzyl six-membered heteroalicycles, starting with the chloromethylheteroalicycles **5a–d** available easily, *via* the aminomethyl derivatives **4a–d**.



Brown *et al.*[5] had reported that the reaction of 4-benzyl-3-chloromethylmorpholine **5a** with cyanide anion as a strong nucleophile gave exclusively 4-benzyl-3-cyanomethylmorpholine **6a**, whereas the reaction with the weakly nucleophilic phenoxide anion afforded 4-benzyl-6-phenoxyhexahydro-1,4-oxazepine **8** and 4-benzyl-3-(phenoxymethyl)morpholine **7a** *via* the postulated aziridinium intermediate **9a**. We hence expected that the reaction of **5a–d** with NaN_3 which was considered a strong nucleophile, followed by reduction of the resulted azide, would give the desired amines **4a–d**. An attempted reaction of 4-benzyl-3-chloromethylmorpholine **5a** with NaN_3 resulted, however, in the concomitant formation of a ring-expanded hexahydro-1,4-oxazepine derivative **11a** along with the expected 3-azidomethyl-4-benzylmorpholine **10a** (Scheme 1).



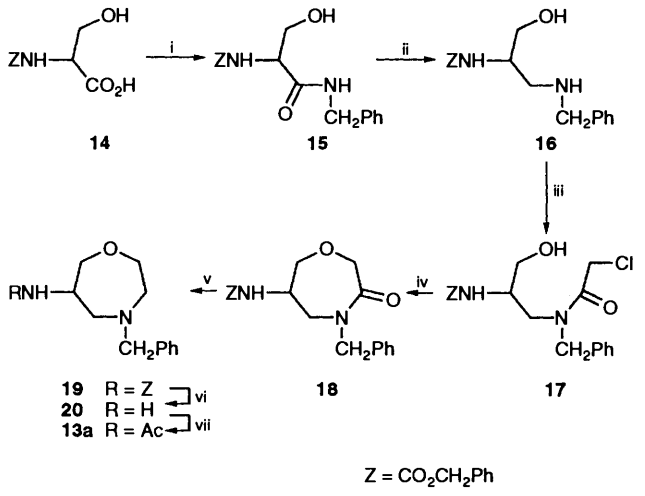
Scheme 1 *Reagents:* i, NaN_3; ii, $Na[AlH_2(OCH_2CH_2OCH_3)_2]$; iii, Ac_2O

An interest in such ring expansions led us to an extensive study of nucleophilic reactions of azide anions with the six-membered heteroalicycles **5a–d** (X = O, S, NMe and CH_2) containing a chloromethyl group at the position adjacent to a nitrogen atom. This is the primary subject of the present paper, in which we also discuss the control of the reaction in terms of frontier electron densities of the reaction centres.

The reaction of **5a** with NaN_3 in acetonitrile afforded an inseparable mixture of products **10a** and **11a** (Scheme 1) for which retention times of 6.6 and 7.9 min, respectively, were observed, in an approximately 7:3 ratio by high performance liquid chromatography (HPLC). The mixture of products **10a** and **11a** was reduced with sodium bis(2-methoxyethoxy)-aluminium hydride, followed by acetylation with Ac_2O, to afford a mixture of the acetylamino derivatives **12a** and **13a**. The mixture was separated into the more polar compound **12a** (57%) and the less polar compound **13a** (24%), by medium-pressure column chromatography on silica gel. The structures of **12a** and **13a** were assigned as 3-(acetylamino)methyl-

4-benzylmorpholine and 6-acetylamino-4-benzylhexahydro-1,4-oxazepine, respectively, by the evidence described later. Accordingly, the initial products **10a** and **11a** were the morpholine and hexahydro-1,4-oxazepine analogues, respectively.

The MS spectra of **12a** and **13a** showed fragment peaks at *m/z* 176 ($M^+ - 72$) and 189 ($M^+ - 59$) attributable to 4-benzylmorpholine and 4-benzylhexahydro-1,4-oxazepine moieties, respectively. The ^1H NMR spectrum of **12a**, similar to that of the starting material **5a**, verified the presence of a morpholine ring and a methylene appendage at the side chain. In the ^1H NMR spectrum of **13a**, the C-6 methine proton signal was observed at δ 4.10 as a distinctive multiplet signal like that of **8** appearing at δ 4.48. Confirmation of the assigned structure of **13a** was provided by the alternative synthesis from commercially available *N*-benzyloxycarbonyl-DL-serine **14** (Scheme 2). Thus,



Scheme 2 *Reagents:* i, $PhCH_2NH_2$, $EtN{=}C{=}N(CH_2)_3NMe_2{\cdot}HCl$; ii, $BH_3{\cdot}THF$; iii, $ClCOCH_2Cl$, Et_3N; iv, Bu^{t}OK; v, $BH_3{\cdot}THF$; vi, HBr; vii, Ac_2O

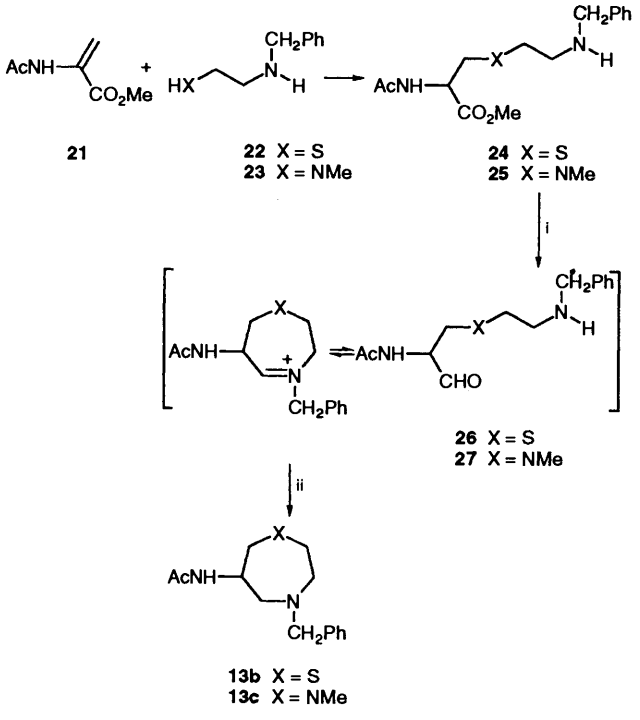
the treatment of **14** with benzylamine gave *N*-benzyl-2-(benzyloxycarbonyl)amino-3-hydroxypropionamide **15**, which was then reduced with a borane–tetrahydrofuran complex ($BH_3{\cdot}THF$) to afford **16**. The reaction of **16** with chloroacetyl chloride followed by treatment of the resulting 3-chloroacetylaminopropanol **17** with potassium *tert*-butoxide (Bu^{t}OK) gave 4-benzyl-6-(benzyloxycarbonyl)aminohexahydro-1,4-oxazepin-3-one **18**. Reduction of **18** with $BH_3{\cdot}THF$ afforded 4-benzyl-6-(benzyloxycarbonyl)aminohexahydro-1,4-oxazepine **19**. Removal of the benzyloxycarbonyl group of **19** by hydrogen bromide, followed by treatment with Ac_2O, afforded the hexahydro-1,4-oxazepine derivative **13a**. Compound **13a** thus prepared was identical in all respects with the ring-expanded product obtained previously.

Few reports have appeared on the ring expansion of six-membered heteroalicycles containing a nitrogen atom, other than the reaction reported by Brown *et al.*[5] For a better understanding of the reaction, our attention was focussed on the reactions of 4-benzyl-3-chloromethyl-tetrahydro-4*H*-1,4-thiazine **5b**, -1-methylpiperazine **5c** and 1-benzyl-2-chloromethylpiperidine **5d**, prepared by conventional methods, with NaN_3. These gave mixtures of **10b–d** and **11b–d**, respectively, in ratios determined by HPLC (Table 1). Reduction and successive acetylation of each mixture of **10b–d** and **11b–d** under the same conditions as employed previously afforded the corresponding products **12b–d** and **13b–d**. On the basis of MS and ^1H NMR spectral data, **12b–d** and **13b–d** were assigned as the normally substituted six-membered products and the ring-expanded seven-membered products, respectively. The structures of **13b–d** were confirmed by their unambiguous synthesis (Scheme 3). The treatment of methyl 2-acetylaminoacrylate **21**[6] with 2-benzylaminoethanethiol **22**[7] gave methyl 2-acetylamino-3-[2-(benzylamino)ethylsulfanyl]propionate **24**. Partial reduction of **24** with diisobutylaluminium hydride at −70 °C, followed by reductive cyclization of the resulting amino aldehyde **26** without isolation afforded the 1,4-thiazepine **13b**; the cyclization was considered to proceed *via* the imminium salt of **26**. According to the same procedure using N^1-benzyl-N^2-methylethylenediamine **23**[8] in place of **22**, the 1,4-diazepine **13c** was prepared. The azepine **13d** was obtained by treatment of the known 3-amino-1-benzylhexahydro-1*H*-azepine[9] with Ac_2O. Compounds **13b–d** thus prepared were identified with the corresponding ring-expanded products obtained from **5b–d**.

Table 1 Ratios and retention times of compounds **10a–d** and **11a–d**

Starting compound	X	Ratio[a] 10:11	Retention time[a] (min) 10	11
5a	O	68:32	6.6	7.9
5b	S	44:56	12.2	13.4
5c	NMe	85:15	8.2[b]	3.3[b]
5d	CH_2	38:62	6.6[b]	9.3[b]

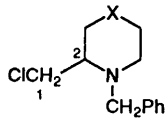
[a] Determined by HPLC analysis, using CAPCELL PAK C^{18}: 4.6 × 150 mm; 0.05% CF_3CO_2H–MeCN (90:10); flow rate 1.0 ml min^{-1} at 25 °C. [b] Eluent: 0.05% CF_3CO_2H–MeCN (85:15).



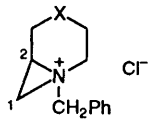
Scheme 3 *Reagents:* i, $[(CH_3)_2CHCH_2]_2AlH$; ii, $NaBH_4$

The ratio of **10** *vs.* **11** interestingly varied according to the nature of the heteroatom X in **5** (Table 1). Thus, when X was oxygen (**5a**) and nitrogen (**5c**), the six-membered compounds **10a** and **10c** predominated over the seven-membered compounds **11a** and **11c**, respectively. Conversely, when X was CH_2 (**5d**) the seven-membered compound **11d** predominated over the six-membered compound **10d**. The tetrahydro-4*H*-1,4-thiazine derivative **5b** (X = S) formed nearly equal amounts of **10b** and **11b**. In summary, the ratio of the seven-membered compound **11** to the six-membered compound **10** increased in the order NMe (**5c**) < O (**5a**) < S (**5b**) < CH_2 (**5d**).

Table 2 LUMO frontier electron densities [*fr*(n)] for **5a–d** and **9a–d**



5a-d



9a-d

	X = O		X = S		X = NMe		X = CH_2	
	5a	**9a**	**5b**	**9b**	**5c**	**9c**	**5d**	**9d**
fr(1)	0.0038	0.3195	0.0036	0.2738	0.0034	0.3316	0.0043	0.2175
fr(2)	0.0062	0.2690	0.0064	0.3008	0.0058	0.2518	0.0022	0.3509

Table 3 Frontier electron densities [*fr*(n)] for the aziridinium intermediates **9a–d** and the formation ratios (**10**:**11**)

Compound[a]	X	*fr*(1)	*fr*(2)	**10**:**11**
9c	NMe	0.3316	0.2518	85:15
9a	O	0.3195	0.2690	68:32
9b	S	0.2738	0.3008	44:56
9d	CH_2	0.2175	0.3509	38:62

[a] Arranged by the ascending order of the seven-membered ring product **11**.

Further interest in the mode of reactions of **5** with NaN_3 led us to carry out a computational study of the starting compounds **5a–d** and the postulated intermediates **9a–d**. Semiempirical molecular orbital calculations were performed by the AM1 method[10] with the MOPAC package of programs with molecular geometry optimization. As the measure of reactivity against a nucleophile, we adopted values of LUMO frontier electron densities *fr*(1) and *fr*(2) for the methylene carbon (1) and the methine carbon (2), respectively, of **5a–d** and **9a–d** (Table 2). A comparison of the *fr* values between each pair of compounds clearly shows that all the aziridinium intermediates **9a–d** have much higher electron densities and, accordingly, are much more reactive than the corresponding chloromethyl compounds **5a–d** towards nucleophiles. Thus, it is reasonably concluded that the reaction proceeds *via* the aziridinium intermediates **9a–d**.

To make a comparison between reactivities of the aziridinium intermediates **9a–d** and product ratio of **10** *vs.* **11** easier, the values of *fr*(n) of **9a–d** and the formation ratio (**10**:**11**) are shown again in Table 3. In **9a** (X = O) and **9c** (X = NMe), their *fr*(1) values are higher than their *fr*(2) values, thus showing that the methylene carbon(1) is more reactive than the methine carbon(2) and hence an attack of the azide anion proceeds at the methylene carbon(1) rather than at the methine carbon(2), leading to the predominant formation of **10a**, **c** over **11a**, **c** in accordance with the experimental observation. In the case of **9b** (X = S), the *fr*(1) and *fr*(2) values are similar, so accounting for the formation of nearly equal amounts of **10b** and **11b**. As for **9d** (X = CH_2), its *fr*(2) is greater than *fr*(1), a situation which reflects the fact that **11d** is the major product.

In summary, the nucleophilic reaction of 4-benzyl-3-chloromethylmorpholine **5a** and its analogues **5b–d** with NaN_3 proceeded *via* the aziridinium intermediates **9a–d** to give the novel ring-expanded products **11a–d** as well as the normally substituted six-membered products **10a–d** in a ratio dependent on the electronic nature of the hetero atom X. Predominance of either product **10** or **11** is reasonably explained by the frontier electron densities (*fr*) for the methylene carbon(1) and the bridge-head methine carbon(2) of the aziridinium intermediates **9a–d**.

We have thus far discussed the reactivity of the reactant **5** and the intermediate **9** without taking account of the nature of the azide anion as a nucleophile. In order to generalize the explanation of the reactions of **5** with other nucleophiles, such as the cyanide anion examined by Brown *et al.*, it is necessary to calculate the transition state including the nucleophile. This will be studied later.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer. MS spectra were taken by the electron-impact method on a JEOL JMS D-300 spectrometer. ^1H NMR spectra were recorded on a Varian GEMINI-200 (200 MHz) or Varian XL-300 (300 MHz) spectrometer. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane as an internal standard and coupling constants (J) are given in Hz. Analytical HPLC was carried out on Shimadzu LC-6A system. Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck Kieselgel 60 and Yamazen YFLC gel were used for column chromatography.

Molecular Modelling and Molecular Orbital Calculation.—The structures of the aziridinium cations **9a–d** and the chloromethyl compounds **5a–d** were built up using molecular modelling package MOL-GRAPH (Ver. 2.8 available from Daikin Industries Ltd., Shinjuku-ku Tokyo). Semiempirical MO calculations using program MOPAC (Ver. 6.0. QCPE program No. 455) with AM1 hamiltonian were run on a μ-VAX 3600 computer. The value of frontier electron density (*fr*) was calculated according to the following equation

$$fr(n) = \sum^{LUMO} 2 \cdot {}^{n}Cr^2$$

where ^nCr is the LCAO coefficient of 2s, 2px, 2py and 2pz atomic orbitals of carbon atom (n) in the molecule on the LUMO.

4-Benzyl-3-chloromethylmorpholine **5a**,[11] 4-benzyl-3-chloromethyl-1-methylpiperazine **5c**[12] and 1-benzyl-2-chloromethylpiperidine **5d**[13] were prepared according to the cited literature methods.

*4-Benzyl-3-chloromethyltetrahydro-*4H*-1,4-thiazine* **5b**.—A mixture of 3-hydroxymethyltetrahydro-4*H*-1,4-thiazine[14] (10.0 g, 75 mmol), K_2CO_3 (20.7 g, 150 mmol), benzyl bromide (12.8 g, 75 mmol) and butan-2-one (100 cm^3) was heated to reflux for 6 h. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$ to give 4-benzyl-3-hydroxymethyltetrahydro-4*H*-1,4-thiazine (13.9 g, 83%), as a pale brown oil; ν_{max}(neat)/cm^{-1} 3400, 2910 and 1450; δ_H(200 MHz; $CDCl_3$) 2.35

(1 H, m), 2.50 (1 H, m), 2.74 (2 H, m), 2.95 (2 H, m), 3.18 (1 H, m), 3.75 (1 H, d, *J* 13, C*H*$_2$Ph), 3.79 (1 H, dd, *J* 10 and 6, C*H*$_2$OH), 3.91 (1 H, d, *J* 13, C*H*$_2$Ph), 3.99 (1 H, dd, *J* 10 and 7, C*H*$_2$OH) and 7.30 (5 H, m, CH$_2$*Ph*); *m/z* 223 (M^+), 192 (M^+ − HOCH$_2$) and 91. A mixture of this oil (13.9 g, 62 mmol), thionyl chloride (14.0 g, 120 mmol) and $CHCl_3$ (139 cm^3) was heated to reflux for 1 h. The solvent was evaporated and the residue was basified with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was concentrated to give a crude product, which was chromatographed on silica gel with $CHCl_3$ to afford **5b** (14.6 g, 85%) as a pale brown oil; ν_{max}(neat)/cm^{-1} 2910, 2810 and 1440; δ_H(200 MHz; $CDCl_3$) 2.39 (1 H, m), 2.64–2.90 (4 H, m), 3.05 (1 H, m), 3.17 (1 H, m), 3.75 (3 H, m, C*H*$_2$Ph and CH$_2$Cl), 4.22 (1 H, dd, *J* 11 and 10, CH$_2$Cl) and 7.31 (5 H, m, CH$_2$*Ph*); *m/z* 241 (M^+), 192 (M^+ − ClCH$_2$) and 91.

3-(*Acetylamino*)*methyl*-4-*benzylmorpholine* **12a** *and* 6-*Acetylamino*-4-*benzylhexahydro*-1,4-*oxazepine* **13a**.—A mixture of **5a** (5.1 g, 23 mmol), NaN_3 (3.0 g, 46 mmol) and MeCN (100 cm^3) was heated to reflux for 2 h. The reaction mixture was concentrated to dryness and the residue was extracted with ethyl acetate (AcOEt). The extract was washed with water, dried and concentrated to give a pale brown oil consisting of **10a** and **11a** (4.6 g, 87%); ν_{max}(neat)/cm^{-1} 2090 (N_3); *m/z* 232 (M^+). The oil was analysed by HPLC (see footnote *a* in Table 1); the retention time and the ratio of **10a** and **11a** were 6.6 min (68%) and 7.9 min (32%), respectively. Sodium bis(2-methoxyethoxy)-aluminium hydride (70% solution in toluene; 11.5 g, 40 mmol) was added dropwise to a stirred solution of the oily mixture of **10a** and **11a** (4.6 g) in toluene (50 cm^3) over a period of 30 min at 5 °C. The reaction mixture was stirred at the same temperature for an additional 3 h. The excess of reagent was decomposed with water at 5 °C. To the solution was added 48% aq. NaOH, and the resulting organic layer was separated, dried and filtered. To the filtrate was added Ac_2O (4.0 g, 49 mmol). The mixture was stirred at room temperature for 1 h and washed successively with 48% aq. NaOH and water. The organic layer was dried and concentrated to give crude products, which were purified by medium pressure column chromatography on silica gel with hexane–AcOEt (5:1) to give **12a** (2.8 g, 57%) and **13a** (1.2 g, 24%).

Compound **12a**: m.p. 78–80 °C (from diethyl ether) (Found: C, 67.5; H, 8.2; N, 11.3. $C_{14}H_{20}N_2O_2$ requires C, 67.72; H, 8.12; N, 11.28%); ν_{max}(KBr)/cm^{-1} 1640 (CONH); δ_H(300 MHz; $CDCl_3$) 2.00 (3 H, s, COMe), 2.33 (1 H, ddd, *J* 11, 10 and 3, 5-H$_{ax}$), 2.65 (1 H, m, 3-H), 2.74 (1 H, ddd, *J* 11, 3 and 3, 5-H$_{eq}$), 3.31 (1 H, d, *J* 13, C*H*$_2$Ph), 3.46 (3 H, m, C*H*$_2$NHAc and 2-H$_{ax}$), 3.56 (1 H, ddd, *J* 11, 10 and 3, 6-H$_{ax}$), 3.74 (1 H, dddd, *J* 11, 3, 3 and 1, 6-H$_{eq}$), 3.79 (1 H, ddd, *J* 11, 3 and 1, 2-H$_{eq}$), 4.03 (1 H, d, *J* 13, C*H*$_2$Ph), 6.30 (1 H, m, CONH) and 7.27–7.42 (5 H, m, CH$_2$*Ph*); *m/z* 248 (M^+), 176 (M^+ − 72) and 91.

Compound **13a**: pale brown oil (Found: C, 66.7; H, 8.1; N, 11.3. $C_{14}H_{20}N_2O_2$·1/4 H_2O requires C, 66.51; H, 8.17; N, 11.08%); ν_{max}(neat)/cm^{-1} 1645 (CONH); δ_H(300 MHz; $CDCl_3$) 1.79 (3 H, s, COMe), 2.64 (1 H, ddd, *J* 13, 12 and 6, 3-H), 2.72 (1 H, dd, *J* 13 and 4, 5-H), 2.85 (1 H, dd, *J* 13 and 3, 5-H′), 2.90 (1 H, ddd, *J* 13, 8 and 5, 3-H′), 3.58 (1 H, d, *J* 13, C*H*$_2$Ph), 3.66–3.78 (2 H, m, 2-H), 3.67 (1 H, ddd, *J* 13, 3 and 1, 7-H), 3.72 (1 H, d, *J* 13, C*H*$_2$Ph), 3.89 (1 H, dd, *J* 13 and 4, 7-H′), 4.08 (1 H, m, 6-H), 6.30 (1 H, m, CONH) and 7.25–7.42 (5 H, m, CH$_2$*Ph*); *m/z* 248 (M^+), 189 (M^+ − 59) and 91.

Compounds **12b–d** and **13b–d** were prepared by the same procedure. The retention times of **10b–d** and **11b–d** and their ratios were determined by HPLC and are summarized in Table 1.

3-(*Acetylamino*)*methyl*-4-*benzyltetrahydro*-4H-1,4-*thiazine* **12b**: 41%; m.p. 89–91 °C (from diethyl ether) (Found: C, 63.6; H, 7.9; N, 10.7; S, 11.9. $C_{14}H_{20}N_2OS$ requires C, 63.60; H, 7.63; N, 10.60; S, 12.13%); ν_{max}(KBr)/cm^{-1} 1635 (CONH); δ_H(300 MHz; $CDCl_3$) 1.95 (3 H, s, COMe), 2.41 (1 H, ddd, *J* 14, 6 and 3, 6-H), 2.46 (1 H, dd, *J* 14 and 6, 2-H), 2.67 (1 H, ddd, *J* 14, 9 and 3, 6-H′), 2.78 (1 H, ddd, *J* 12, 6 and 3, 5-H), 2.87 (1 H, dd, *J* 14 and 3, 2-H′), 2.98 (1 H, m, 3-H), 3.16 (1 H, ddd, *J* 12, 9 and 3, 5-H′), 3.62 (2 H, m, C*H*$_2$NHAc), 3.71 (1 H, d, *J* 14, C*H*$_2$Ph), 3.85 (1 H, d, *J* 14, C*H*$_2$Ph), 5.78 (1 H, m, CONH) and 7.20–7.38 (5 H, m, CH$_2$*Ph*); *m/z* 264 (M^+), 192 (M^+ − 72) and 91.

6-*Acetylamino*-4-*benzylhexahydro*-1,4-*thiazepine* **13b**: 48%; m.p. 95–97 °C (from diethyl ether) (Found: C, 63.5; H, 7.9; N, 10.6; S, 12.0. $C_{14}H_{20}N_2OS$ requires C, 63.60; H, 7.63; N, 10.60; S, 12.13%); ν_{max}(KBr)/cm^{-1} 1645 (CONH); δ_H(300 MHz; $CDCl_3$) 1.70 (3 H, s, COMe), 2.60–2.71 (2 H, m), 2.77 (1 H, dd, *J* 14 and 5), 2.81–2.85 (2 H, m), 2.87 (1 H, dd, *J* 5 and 2), 2.99 (1 H, dd, *J* 14 and 3), 3.08 (1 H, dt, *J* 14 and 5), 3.56 (1 H, d, *J* 13, C*H*$_2$Ph), 3.78 (1 H, d, *J* 13, C*H*$_2$Ph), 4.12 (1 H, m, 6-H), 5.88 (1 H, m, CONH) and 7.22–7.38 (5 H, m, CH$_2$*Ph*); *m/z* 264 (M^+), 205 (M^+ − 59) and 91.

3-(*Acetylamino*)*methyl*-4-*benzyl*-1-*methylpiperazine* **12c**: 68%; pale brown oil (Found: C, 69.1; H, 9.0; N, 15.8. $C_{15}H_{23}N_3O$ requires C, 68.93; H, 8.87; N, 16.08%); ν_{max}(neat)/cm^{-1} 1640 (CONH); δ_H(200 MHz; $CDCl_3$) 1.97 (3 H, s, COMe), 2.08–2.23 (2 H, m), 2.25 (3 H, s, NMe), 2.34 (1 H, dt, *J* 10 and 3), 2.54 (1 H, m), 2.59–2.66 (2 H, m), 2.81 (1 H, ddd, *J* 12, 4 and 3), 3.28 (1 H, d, *J* 14, C*H*$_2$Ph), 3.46 (2 H, m), 3.98 (1 H, d, *J* 14, C*H*$_2$Ph), 6.19 (1 H, m, CONH) and 7.20–7.38 (5 H, m, CH$_2$*Ph*); *m/z* 261 (M^+), 189 (M^+ − 72) and 91.

6-*Acetylamino*-4-*benzyl*-1-*methylhexahydro*-1H-1,4-*diazepine* **13c**: 15%; pale brown oil (Found: C, 68.7; H, 8.6; N, 16.3. $C_{15}H_{23}N_3O$ requires C, 68.93; H, 8.87; N, 16.08%); ν_{max}(neat)/cm^{-1} 1640 (CONH); δ_H(200 MHz; $CDCl_3$) 1.85 (3 H, s, COMe), 2.37 (3 H, s, NMe), 2.40–3.01 (8 H, m, 2-H, 3-H, 5-H and 7-H), 3.50 (1 H, d, *J* 15, C*H*$_2$Ph), 3.70 (1 H, d, *J* 15, C*H*$_2$Ph), 4.01 (1 H, m, 6-H), 6.48 (1 H, m, CONH) and 7.25–7.37 (5 H, m, CH$_2$*Ph*); *m/z* 261 (M^+), 202 (M^+ − 59) and 91.

2-(*Acetylamino*)*methyl*-1-*benzylpiperidine* **12d**: 32%; pale brown oil (Found: C, 72.9; H, 8.9; N, 11.2. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00; N, 11.37%); ν_{max}(neat)/cm^{-1} 1640 (CONH); δ_H(200 MHz; $CDCl_3$) 1.20–1.80 (6 H, m, 3-H, 4-H and 5-H), 1.98 (3 H, s, COMe), 2.15 (1 H, dt, *J* 12 and 3, 6-H), 2.52 (1 H, m, 2-H), 2.90 (1 H, dt, *J* 12 and 4, 6-H′), 3.30 (1 H, d, *J* 15, C*H*$_2$Ph), 3.45 (2 H, m, C*H*$_2$NHAc), 3.98 (1 H, d, *J* 15, C*H*$_2$Ph), 6.18 (1 H, m, CONH) and 7.22–7.42 (5 H, m, CH$_2$*Ph*); *m/z* 246 (M^+), 174 (M^+ − 72) and 91.

3-*Acetylamino*-1-*benzylhexahydro*-1H-*azepine* **13d**: 54%; m.p. 68–70 °C (from toluene) (Found: C, 72.3; H, 9.1; N, 11.3. $C_{15}H_{22}N_2O$·1/5 H_2O requires C, 72.08; H, 9.03; N, 11.21%); ν_{max}(KBr)/cm^{-1} 1630 (CONH); δ_H(200 MHz; $CDCl_3$) 1.40–1.91 (6 H, m, 4-H, 5-H and 6-H), 1.74 (3 H, s, COMe), 2.52–3.10 (4 H, m, 2-H and 7-H), 3.46 (1 H, d, *J* 14, C*H*$_2$Ph), 3.73 (1 H, d, *J* 14, C*H*$_2$Ph), 3.94 (1 H, m, 3-H), 6.18 (1 H, m, CONH) and 7.22–7.41 (5 H, m, CH$_2$*Ph*); *m/z* 246 (M^+), 187 (M^+ − 59) and 91.

N-*Benzyl*-2-(*benzyloxycarbonyl*)*amino*-3-*hydroxypropionamide* **15**.—A mixture of *N*-benzyloxycarbonyl-DL-serine (5.0 g, 21 mmol), benzylamine (2.23 g, 21 mmol), 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride (4.02 g, 21 mmol) and DMF (25 cm^3) was stirred at room temperature for 6 h and then poured into ice–water. The precipitate was filtered off and recrystallized from EtOH to give **15** (4.2 g, 59%), m.p. 142 °C (Found: C, 65.6; H, 6.0; N, 8.7. $C_{18}H_{20}N_2O_4$ requires C, 65.84; H, 6.14; N, 8.53%); δ_H[200 MHz; $(CD_3)_2SO$] 3.52–3.72 (2 H, m, C*H*$_2$OH), 4.10 (1 H, m, 2-H), 4.30 (2 H, d, *J* 6, NC*H*$_2$Ph), 4.89 (1 H, t, *J* 4, CH$_2$O*H*), 5.05 (2 H, s, CO$_2$C*H*$_2$Ph), 7.15–7.44 (10 H, m, CH$_2$*Ph*) and 8.41 (1 H, t, *J* 6, N*H*CO$_2$CH$_2$Ph).

3-*Benzylamino*-2-(*benzyloxycarbonyl*)*aminopropan*-1-*ol* **16**.—To a stirred solution of compound **15** (4.0 g, 12.2 mmol)

in THF (80 cm^3) was added BH_3·THF (1 mol dm^{-3}; 43 cm^3, 43 mmol) at 5 °C. The mixture was stirred at room temperature for 16 h after which the excess of reagent was decomposed with 10% HCl (26 cm^3). The reaction mixture was heated to reflux for 1 h and then concentrated to dryness. The residue was basified with 48% aq. NaOH and extracted with diethyl ether. The organic layer was dried and concentrated to give **16** (2.8 g, 75%), m.p. 92–93 °C (from diethyl ether) (Found: C, 68.7; H, 7.3; N, 8.7. $C_{18}H_{22}N_2O_3$ requires C, 68.77; H, 7.05; N, 8.91%); δ_H(200 MHz; $CDCl_3$) 2.81 (1 H, dd, *J* 12 and 4, CH_2NH), 3.04 (1 H, dd, *J* 12 and 4, CH_2NH), 3.65–3.90 (3 H, m, $CHCH_2OH$), 3.77 (2 H, s, CH_2Ph), 5.12 (2 H, s, CO_2CH_2Ph), 5.78 (1 H, m, $NHCO_2$) and 7.25–7.41 (10 H, m, CH_2Ph).

4-Benzyl-6-(benzyloxycarbonyl)aminohexahydro-1,4-oxazepin-3-one **18**.—To a mixture of compound **16** (2.0 g, 6.4 mmol), triethylamine (770 mg, 7.7 mmol) and CH_2Cl_2 (20 cm^3) was added chloroacetyl chloride (713 mg, 6.4 mmol) at −5 °C. The reaction mixture was stirred for 1 h and then washed with water. The organic layer was dried and concentrated to give a crude product, which was chromatographed on silica gel to give 3-(*N*-benzyl-*N*-chloroacetyl)amino-2-(benzyloxycarbonyl)aminopropan-1-ol **17** as a pale brown oil (1.5 g, 60%). To a solution of **17** (1.5 g, 3.8 mmol) in THF (30 cm^3) was added Bu^{t}OK (650 mg, 5.8 mmol). After being stirred at room temperature for 12 h, the reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel with $CHCl_3$ to give **18** (0.6 g, 44%) as a pale brown oil; ν_{max}(neat)/cm^{-1} 1700 (CO_2CH_2Ph) and 1630 (CON); δ_H(200 MHz; $CDCl_3$) 3.52–3.98 (5 H, m, 5-H, 6-H and 7-H), 4.17 (1 H, d, *J* 14, 2-H), 4.25 (1 H, d, *J* 15, CH_2Ph), 4.45 (1 H, d, *J* 14, 2-H'), 4.73 (1 H, d, *J* 15, CH_2Ph), 5.04 (2 H, s, CO_2CH_2Ph), 5.08 (1 H, m, $NHCO_2$) and 7.15–7.40 (10 H, m, CH_2Ph and CO_2CH_2Ph).

4-Benzyl-6-(benzyloxycarbonyl)aminohexahydro-1,4-oxazepine **19**.—To a solution of compound **18** (0.4 g, 1.13 mmol) in anhydrous THF (12 cm^3) was added BH_3·THF (1 mol dm^{-3}; 3.4 cm^3, 3.4 mmol) at 5 °C. The reaction mixture was stirred at room temperature for 16 h after which the excess of reagent was decomposed with 5% aq. HCl (12 cm^3). The mixture was heated to reflux for 1 h and then concentrated to dryness. The residue was basified with 48% NaOH and extracted with diethyl ether. The extract was dried and concentrated to give **19** as a pale brown oil (0.31 g, 74%); ν_{max}(neat)/cm^{-1} 1710 (CO_2CH_2Ph); δ_H(200 MHz; $CDCl_3$) 2.45–2.95 (4 H, m, 3-H and 5-H), 3.50–3.82 (6 H, m, 2-H, 7-H and CH_2Ph), 3.91 (1 H, m, 6-H), 5.06 (2 H, s, CO_2CH_2Ph), 5.68 (1 H, m, CONH) and 7.20–7.42 (10 H, m, CH_2Ph); *m/z* 340 (M^+), 189 (M^+ − 151) and 91.

Alternative Synthesis of **13a**.—A mixture of compound **19** (0.8 g, 2.4 mmol) and 47% HBr (4 cm^3) was heated at 60 °C for 3 h. After cooling to room temperature, the reaction mixture was washed with ether. The aqueous layer was basified with 48% aq. NaOH, extracted with $CHCl_3$ and dried. Ac_2O (0.48 g, 4.8 mmol) was added to the extract and the mixture was stirred at room temperature for 16 h. The mixture was washed successively with aqueous NaOH and brine and then dried and evaporated to leave **13a** as a pale brown oil (0.49 g, 82%).

Methyl 2-Acetylamino-3-[2(benzylamino)ethylsulfanyl]propionate **24**.—A mixture of methyl 2-acetylaminoacrylate **21**[6] (1.2 g, 8.4 mmol) and 2-benzylaminoethanethiol **22**[7] (1.5 g, 8.4 mmol) was stirred at room temperature for 16 h. The reaction mixture was chromatographed on silica gel with $CHCl_3$ to give **24** as a pale brown oil (1.67 g, 62%); ν_{max}(neat)/cm^{-1} 1740 (CO_2Me) and 1650 (CONH); δ_H(200 MHz; $CDCl_3$) 2.01 (3 H, s, COMe), 2.65–2.95 (4 H, m, SCH_2CH_2N), 2.99 (2 H, d, *J* 5, CH_2S), 3.75 (3 H, s, CO_2Me), 3.81 (2 H, s, CH_2Ph), 4.85 (1 H, m, AcNHC*H*), 6.64 (1 H, m, CONH) and 7.22–7.40 (5 H, m, CH_2Ph).

Methyl 2-Acetylamino-3-[N-(2-benzylaminoethyl)-N-methylamino]propionate **25**.—According to the procedure described above, the reaction of **21** (5.0 g, 35 mmol) with N^1-benzyl-N^2-methylethylenediamine **23**[8] (14.4 g, 87.5 mmol) gave **25** (9.2 g, 86%) as a pale brown oil; ν_{max}(neat)/cm^{-1} 1740 (CO_2Me) and 1650 (CONH); δ_H(200 MHz; $CDCl_3$) 2.24 (3 H, s, COMe), 2.35 (3 H, s, NMe), 2.49–2.88 (7 H, m), 3.71 (3 H, s, CO_2Me), 3.78 (2 H, s, CH_2Ph), 4.51 (1 H, dd, *J* 13 and 6) and 7.05–7.28 (5 H, m, CH_2Ph).

Alternative Synthesis of **13b**.—To a stirred solution of compound **24** (1.67 g, 5.2 mmol) in toluene (32 cm^3) was added a solution of diisobutylaluminium hydride in THF (1 mol dm^{-3}; 15.5 cm^3, 15.5 mmol) at −70 °C. The mixture was stirred at the same temperature for 1 h after which the excess of reagent was decomposed with MeOH (32 cm^3) at −70 °C. $NaBH_4$ (196 mg, 5.2 mmol) was added to the reaction mixture at −20 °C which was then stirred at room temperature for 16 h and finally concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$ to give **13b** (0.9 g, 66%) as a pale brown oil.

Alternative Synthesis of **13c**.—According to the procedure described above, compound **25** (4.5 g, 14.7 mmol) was cyclized to **13c** as a pale brown oil (3.0 g, 78%).

Alternative Synthesis of **13d**.—A mixture of 3-amino-1-benzylhexahydro-1*H*-azepine[9] (1.0 g, 4.9 mmol), Ac_2O (0.6 g, 5.9 mmol) and $CHCl_3$ (10 cm^3) was stirred at room temperature for 16 h. The mixture was then washed successively with aqueous NaOH and brine, dried and evaporated to leave a crude product. This was chromatographed on silica gel with $CHCl_3$ to afford **13d** (1.1 g, 91%) as a pale brown oil.

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