Study of the Transamidative Ring Expansion of *N*-ω-Halogenoalkyl-β-lactams of Alkyl Chain Lengths 2–12 in Liquid Ammonia and Other Liquid Amines: Syntheses of 7-, 8- and 9-Membered 1,5-Diaza Cyclic Ketones, including Routes to (±)-Dihydroperiphylline and (±)-Celabenzine

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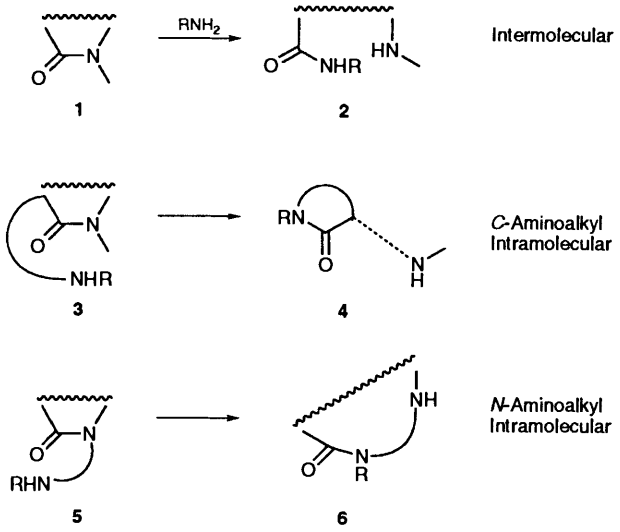
N-(3-Halogenopropyl)-4-phenylazetidin-2-ones undergo amination in liquid ammonia followed by transamidative ring expansion to give the eight-membered 4-phenyl-1,5-diazacyclooctan-2-one in excellent yield. Ring expansion of the amines in liquid ammonia is found to be much more effective than in hydrocarbon solvents. Formation of 7-, 8-, and 9-membered azalactams from the requisite ω-halogenoalkyl-β-lactams is an excellent synthetic process, though it is not applicable to 10-membered rings. In the cases of rings of 13-, 15- and 17-members, although amination and apparent expansion takes place, the large rings appear not to be stable to ammonia and the final products are acyclic amides. *N*-[4-Halogenobut-2(Z)-enyl]-4-phenylazetidin-2-one satisfactorily forms a 9-membered (*Z*)-olefinic azalactam, but the (*E*)-isomer gives an acyclic amino amide. By using alkyl-substituted β-lactam side-chains, *C*-substituted medium rings can be obtained; the relative instability of *N*-acyl β-lactams to ammonia, however, leads to acylamino amides rather than expanded rings.

Employing ethylamine in place of ammonia, it is shown that *N*-ethylated azalactams are formed satisfactorily, and using allylamine, *N*-allyl medium rings capable of further elaboration are obtained. The chemistry of these systems is discussed. Using transamidation in liquid ammonia, a short synthesis of the 9-membered spermidine alkaloid (±)-dihydroperiphylline is reported. Synthesis of key intermediates, whose transformation into the 13-membered alkaloids of the celabenzine group has already been effected, has been carried out.

X-Ray single-crystal structure determinations for 4-phenyl-1,5-diazacyclononan-2-one, *trans*-4-phenyl-8-methyl-1,5-diazacyclooctan-2-one and (*Z*)-4-phenyl-1,5-diazacyclonon-7-en-2-one are reported, and comment is made on certain conformational features.

A host of useful transformations involve nucleophilic attack at a carbonyl group bearing α-anion stabilisation, and transamidation falls into this class. Three types may be distinguished (Scheme 1): intermolecular, **1** ⟶ **2**; *C*-aminoalkyl intramolecular attack **3** ⟶ **4**; and *N*-aminoalkyl intramolecular attack **5** ⟶ **6**. The last area has been developed with examples by, amongst others, Rappoport[1] and Hassall,[2] and with particular elegance for the synthesis of large ring structures, by the Zürich school of Hesse and Schmid,[3–5] and Wasserman[6] at Yale. It provides a general method for the isomerisation of suitable *N*,*N*-disubstituted cyclic amides, where one substituent is aminoalkyl, to *N*-monosubstituted ring-expanded cyclic amides. Transamidation proceeds to completion under strongly basic conditions [potassium 3-aminopropylamide (KAPA)[7–9] in 1,3-diaminopropane (1,3-DAP)], driven forward by the resonance stabilisation of the final monosubstituted amide anion **6a** derived from **6**; R = H.

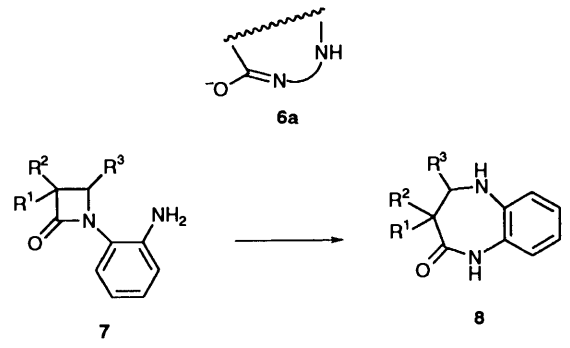
At the outset of our work[10] very little had been done on the transamidative ring expansion of *N*-substituted azetidinones, although the conversion of the azetidinone **7** into the benzodiazepine **8** had been reported,[11,12] and it was known that expansion to piperazinones could occur.[13,14] We thought that the release of ring strain might provide driving force for ring expansion and that the β-lactam system would be an appropriate synthon for making eight-membered spermine alkaloids of the homaline group, in which we were particularly interested. β-Lactams had not been included in the earlier Zürich studies and we initially envisaged the use of the KAPA base system for ring expansion. In the event, however, a simple and much milder method was discovered, suitable for the synthesis of seven-, eight- and nine-membered azalactams by the transamidation of azetidin-2-ones.



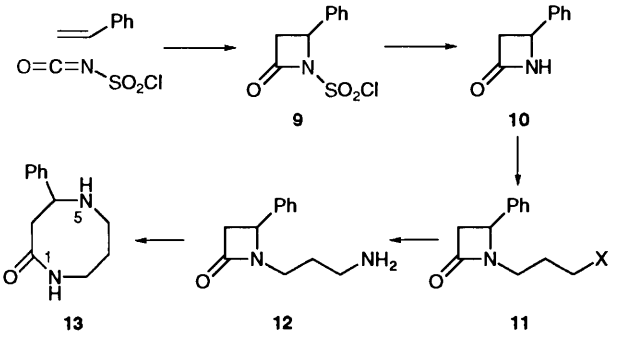
Scheme 1 Types of transamidation

Results and Discussion

Transamidation in Liquid Ammonia using N-ω-*Halogenoalkyl- and* N-ω-*Aminoalkyl-4-phenylazetidin-2-one.*—Initial studies were carried out using 4-phenylazetidin-2-one **10**,



readily available *via* sulfamoyl chloride **9** from styrene and chlorosulfonyl isocyanate.[15] The work of Hesse and his colleagues suggested that the insertion of an *N*-(3-aminopropyl) side-chain is preferred,[4] presumably because of the favourable nature of the six-membered intermediate involved in this process, so the preparation of eight-membered lactam **13** was examined. Cyanoethylation of compound **10** to give nitrile **14**, followed by catalytic hydrogenation, sometimes presented difficulties in the separation of amine **12** from polyacrylonitrile residues. Alkylation under solid–liquid phase-transfer conditions was unpromising when *N*-(3-bromopropyl)phthalimide was employed, but 1-bromo-3-iodopropane gave compound **11** (X = Br) in 55% yield together with 1,3-bis-(2-oxo-4-phenylazetidin-1-yl)propane **15** (30%) and unchanged material (10%). When 3 mole equivalents of the bromo iodo compound were employed the yield of compound **11** (X = Br) was raised to 75%, along with an 18% yield of compound **15**, but the formation of the latter was completely avoided by using 1-bromo-3-chloropropane when **11** (X = Cl) was obtained in 80–97% yield. The azetidinone **11** (X = Cl) could also be conveniently prepared on a large scale by the alkylation method of Johnstone and Rose,[16] using potassium hydroxide in dimethyl sulfoxide (DMSO). The lactam was obtained in 84% yield, with traces of the *N*-allyl elimination product arising only when the reaction time was > 8 h or the temperature > 20 °C.



Scheme 2 Synthesis of 4-phenyl-1,5-diazacyclooctan-2-one **13** from *N*-(3′-halogenopropyl)-4-phenylazetidin-2-one **11**

As a mild procedure for conversion of compound **11** (X = Br) into the corresponding amine, the procedure of Tettenbaum[17] was selected. *N*-(3-Bromopropyl)-4-phenylazetidin-2-one was dissolved in liquid ammonia in a sealed tube and kept for 8 days at room temperature, conditions under which the four-membered ring of a test *N*-alkylated 4-phenylazetidin-2-one was itself quite stable (see later). Unexpectedly, the product from substrate **11** (X = Br) (75% after chromatography) was not amine **12**, but the eight-membered 4-phenyl-1,5-diazacyclooctan-2-one **13** formed by transamidation of the former (Scheme 2). The carbonyl frequency of the β-lactam near 1760 cm^{-1} was replaced by an absorption at 1650 cm^{-1} in the crystalline diazacyclooctan-2-one, and two exchangeable

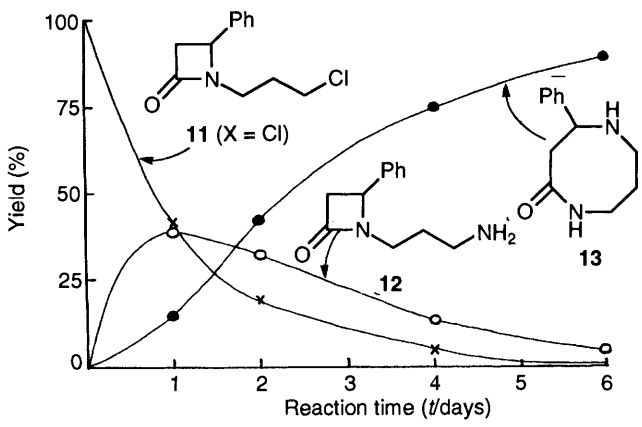


Fig. 1 Yields of products *versus* time for the reaction of halogeno β-lactam **11** (X = Cl) with liquid ammonia

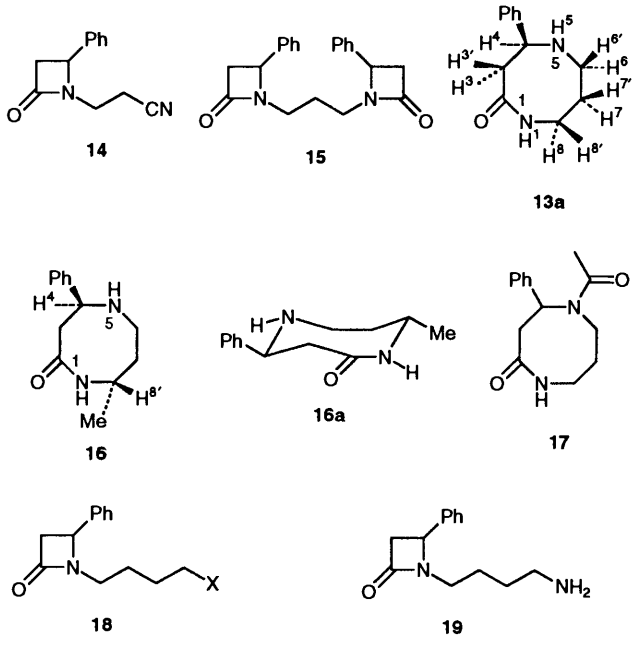
Table 1 Reaction of halides **11** with liquid ammonia at 20 °C

Starting material	Time (*t*/h)	Yield (%) Unchanged **11**	**12**	**13**	Total
11 (X = Cl)	48	18	34	42	94
11 (X = Br)	48	0	17	80	97

hydrogens were present (δ 1.85 and 5.68): the compound had a negative Fluram[18] spray test. The expected primary amine intermediate **12** (positive Fluram test) could, in fact, be isolated if the reaction was allowed to proceed for a shorter time and this intermediate compound was fully characterised spectrally after chromatographic isolation by employing an elution solvent containing isopropylamine. The amine **12** slowly isomerised to the diazacyclooctane **13** on storage, either as a neat gum (> 90% conversion after 40 days) or more rapidly in $CDCl_3$

Fig. 1 shows the progress of the reaction between the chloride **11** (X = Cl) and liquid ammonia at 20 ± 2 °C. Consumption of the chloride is complete after approximately 5 days, but as Table 1 shows, the corresponding bromide undergoes substitution appreciably faster, and this more rapid formation of amine from the bromide becomes important when intermolecular transamidation is competitive *e.g.*, when more nucleophilic alkylamines are used in place of ammonia (see later). Using the chloride, the maximum amount of the intermediate amine **12** is present after about a day, when it represents ~ 40 mol % of the total reaction mixture.

The NMR spectrum (250 MHz) of the diazacyclooctanone **13a** showed a marked non-equivalence of geminal methylene protons caused by their diastereotopic nature and possible conformational rigidity in the eight-membered ring. Restriction of free rotation around the C–Ph bond was suggested by the complex appearance of the aromatic signals (these appear as a pseudo-singlet in 4-phenyl-β-lactam **10**). The H^3,$H^{3'}$,H^4 system was identified by decoupling, and assignments for the remaining protons are given in the Experimental section from results of deuteriation and the spectra of the crystalline *N*-acetyl derivative **17** as well as the *trans*-compound **16** (preparation described below) as NMR models. We have determined the X-ray single-crystal structure of the latter compound, and this is shown in Fig. 2. The ring adopts a 'chair-boat' conformation **16a** with the phenyl and methyl *trans*-diequatorial, and with the amide linkage *cis* as expected for an eight-membered ring[19] [torsion angle about the N(1)–C(2) bond −11.8°]. A pseudo-mirror-plane lies through C(4) and C(8). A similar chair-boat conformation for the eight-membered ring is found in the alkaloid homaline,[20] a synthesis of which is described in the



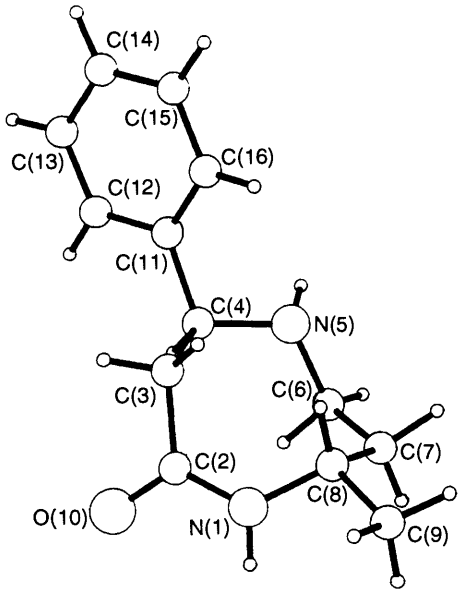


Fig. 2 X-Ray molecular structure of 8-methyl-4-phenyl-1,5-diazacyclooctan-2-one **16**

following paper,[21] but here the pseudo-mirror-plane is formed between C(3) and C(7).

Dependence of Transamidation Products on Substituent Chain Length: Synthesis of 7-, 8- *and* 9-*Membered Azalactams in Liquid Ammonia.*—With the novel β-lactam amination-transamidation reaction established, its scope and limitations were now investigated in terms of the ring size formed, substituent effects, and any competing side reactions. Treatment of 4-

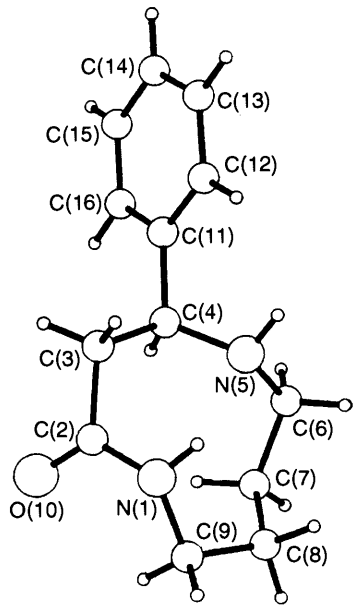


Fig. 3 X-Ray molecular structure of 4-phenyl-1,5-diazacyclononan-2-one **20**

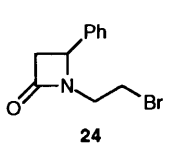
phenylazetidin-2-one with 1-bromo-4-iodobutane (3 mol equiv.) gave the bromide **18** (X = Br) in 81% yield with very little formation of bis-(β-lactam)butane. Reaction of compound **18** (X = Br) with liquid ammonia at room temperature (sealed tube, 5 days) gave *N*-(4-aminobutyl)-4-phenylazetidin-2-one **19** as the main product (78%), identified by spectral data and by its positive reaction with Fluram reagent. A faster running component was identified as the crystalline nine-membered azalactam **20**, identical with the compound prepared by Wasserman by different routes.[22] Moreover, the latter ring-enlarged product could be obtained in up to 67% yield by raising the reaction temperature to 55–65 °C (sealed tube, 5–8 days) by using either the bromide **18** (X = Br) or the chloride (X = Cl) as starting materials. None of the primary amine **19** was observed under these conditions, nor were any other compounds isolated, though it is possible that some of the unrecovered material is the highly polar acyclic diamino amide **21**.

A sample of 1-(4-aminobutyl)-β-lactam **19** was also made by alkylation of lactam **10** with 4-iodobutyronitrile (62%) followed by hydrogenation (72%) over a platinum catalyst. Heating of the β-lactam **19** in refluxing toluene under nitrogen for 6 days led to a mixture (~1:1) of unchanged β-lactam **19** and azalactam **20**. Replacement of the toluene by mixed xylenes or addition of pyridine (2 mol equiv.) did not significantly alter the proportions of β-lactam and azalactam (44 and 47% respectively), suggesting that under these conditions an equilibrium exists, in contrast to the situation in liquid ammonia.

The nine-membered azalactam formed both an *N*-acetyl **22** and an *N*,*N'*-diacetyl **23** derivative when treated with acetic anhydride. On crystallisation from chloroform–hexane or diethyl ether–hexane the azalactam **20** formed crystals suitable for single-crystal X-ray structure work and Fig. 3 shows the molecule and its conformation. The amide is *trans* [N(1)–C(2) torsion angle ~150°] as has been shown for the parent azacyclononan-2-one.[23] There is an intramolecular hydrogen bond of length 2.77 Å between the nitrogen atoms across the ring. Although the solution conformation was not investigated in detail, it was noted that there were small anomalous signals in the NMR spectrum (250 MHz) of an otherwise analytically pure sample, suggesting that an equilibrium might be present in $CDCl_3$ solution. The solution conformation of different ring-size lactams has been studied spectroscopically by Roberts[19]

and by Wilson[24] and it is known that whilst lactams of eight or fewer members adopt the *cis*-amide conformation, the nine-membered lactams exist as mixtures of *cis*- and *trans*-forms in a variety of solvents. Ten-membered and larger lactams behave like acyclic amides in adopting exclusively the *trans* geometry.

The higher temperature required to effect the transformation of amine **19** into the nine-membered ring **20** as compared with the formation of the eight-membered **13**, is presumably a reflection of the requirement for an energetically less favourable seven-membered intermediate to be involved in the trans-amidation. Hesse and his colleagues have investigated base (KAPA)-induced transamidation reactions of a large number of *N*-(ω-aminoalkyl) lactams and have pointed out the preference for five- or six-membered transition states in these processes.[4] To demonstrate the facility of ring expansion by an *N*-(2-aminoethyl) residue in our system, the bromide **24** was prepared by phase-transfer alkylation of 4-phenylazetidin-2-one **10** with 1,2-dibromoethane (98% yield, 41% conversion). Reaction of bromide **24** with liquid ammonia (sealed tube; 40 °C; 14 days) gave the seven-membered diazepinone **25** (74%), demonstrating the ready formation of five-centred transition states. The



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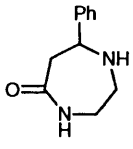

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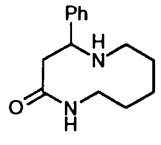

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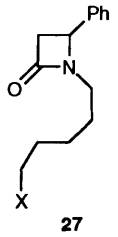

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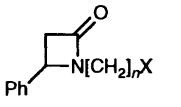
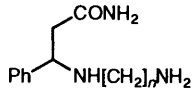
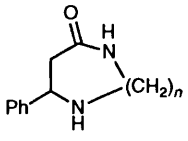


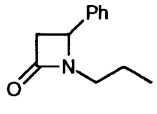
28 $n = 8$
29 $n = 10$
30 $n = 12**



31 $n = 8$
32 $n = 10$
33 $n = 12**



34 $n = 8$
35 $n = 10$
36 $n = 12**



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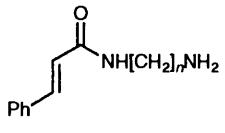

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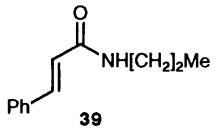

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diazepinone **25** showed similar spectral characteristics to the eight- and nine-membered homologues **13** and **20**, though the coupling between the C*H*Ph and one of the protons α- to the carbonyl was unresolved at 250 MHz in the ^{1}H NMR spectrum, indicating a dihedral angle close to 90°. In the larger ring systems **13** and **20**, this coupling constant is small, but measurable (*J* 2.2) and 2.7 Hz, respectively), and in the nine-membered ring the X-ray data show the dihedral angle to be 65°. In the IR spectra, the three compounds **25**, **13** and **20** showed carbonyl stretching frequencies decreasing with ring size increase 1665, 1650, 1630 cm^{-1}, respectively).

It was not possible to prepare the ten-membered homologue **26** *via* the amination/transamidation procedure, the eight-membered transition state being unfavourable for the reaction. Hence, when treated with liquid ammonia for 7 days at 65 °C, the bromide **27** (X = Br), made by the usual phase-transfer procedure, gave only the substitution product **27** (X = NH_2). This finding is consistent with Corey's studies on translactonisation.[25]

Since an increase in the ring size of the intermediate should reduce unfavourable transannular interactions, an investigation of the possibility of making larger ring sizes was undertaken. Using the powdered KOH–Bu_4NHSO_4–tetrahydrofuran (THF) alkylation method of Reuschling and colleagues,[26] the *N*-(ω-bromoalkyl) derivatives **28**, **29**, and **30** (X = Br) were prepared from compound **10** and 1,8-dibromooctane, 1,10-dibromodecane and 1,12-dibromododecane in 50, 65 and 74% yield, respectively. Treatment of the bromide **30** (X = Br) with liquid ammonia in a sealed tube at 20 °C for 7 days gave only the amination product, the *N*-(ω-aminoalkyl)azetidinone **30** (X = NH_2) in almost theoretical yield, whereas treatment of all three homologues **28**, **29** and **30** (X = Br) under similar conditions, but at 70 °C for a more prolonged period of 28 days, gave instead the acyclic amides **31**, **32** and **33**. Intermediate reaction conditions afforded various mixtures of the amines and amides, but none of the hoped for ring-expanded azalactams **34**, **35** or **36** was encountered.

At first sight these results might indicate that the ring-opened products arise from intermolecular transamidation of the aminoalkyl β-lactams by ammonia, but a test of the stability of such lactams suggests that this is not so. Thus, 4-phenyl-*N*-propylazetin-2-one **37**, readily made by alkylation in 91% yield, could be recovered unchanged from liquid ammonia at 70 °C after periods of at least 28 days and the high stability of β-lactams to aminolysis has previously been noted.[27] This suggests that the expected large rings **34**–**36** are, in fact, formed, but are then destroyed by the intermolecular attack of ammonia to give amides **31**–**33**. Apparently, the conformationally mobile large-ring lactams behave as expected of an acyclic amide and undergo transamidation. Unlike large rings, those with 7- and 8-members have *cis*-amide groups and approach of the nucleophile to the carbonyl is hindered by the ring. Thus, the 8-membered azalactam **13** is recovered quantitatively after treatment with liquid ammonia at 70 °C for 7 days.

Another possible fate of the lactams is β-elimination and indeed traces of cinnamamides **38** were observed by ^{1}H NMR spectroscopy in the above crude reactions products. Under basic conditions (sodamide) and using 4-phenyl-*N*-propylazetidin-2-one as a test sample, *N*-propylcinnamamide **39** was obtained in 50% yield.

Transamidation of (Z)- *and* (E)-N-(*Halogenobut-2-enyl*)-4-*phenylazetidin-2-ones in Liquid Ammonia.*—In order to examine the effect of geometric constraint in the halogeno-alkyl chain, we have made the *N*-4-(halogenobut-2-enyl)azetidinones in (*Z*)-**40** (61%) and (*E*)-**42** (76%) forms from the corresponding 1,4-dihalogenobut-2-enes by using the KOH–Bu_4NHSO_4–THF method. Treatment of the (*Z*)-halide **40** with liquid ammonia at room temperature gave the amine **41** (72%) together with the azalactam **43** (27%). Heating of the (*Z*)-isomer in liquid ammonia at 70 °C for 10 days, however, gave the nine-membered unsaturated azalactam **43** in much higher yield (57%). Its structure was verified by an X-ray single-crystal structure determination (Figs 4 and 5). The amide structure is *trans* [N(1)–C(2) torsion angle ~150°] and there is no cross-ring hydrogen bond since the conformation does not allow the N–N lone pairs to point in a suitable direction. The N–N separation is 2.91 Å. On the other hand, the (*E*)-isomer under the same conditions gave only the acyclic amino amide **44**. Taking into account the stability of azetidinones to ammonolysis, this result suggests that ring expansion to the nine-membered ring does occur, but that the (*E*)-double bond introduces sufficient strain to induce ring opening by ammonia.

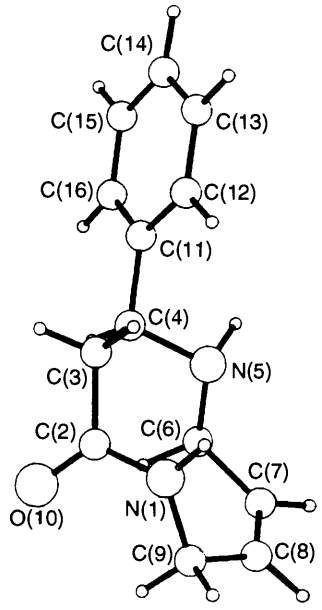


Fig. 4 X-Ray molecular structure of (*Z*)-4-phenyl-1,5-diazacyclonon-7-en-2-one **43** (view 1)

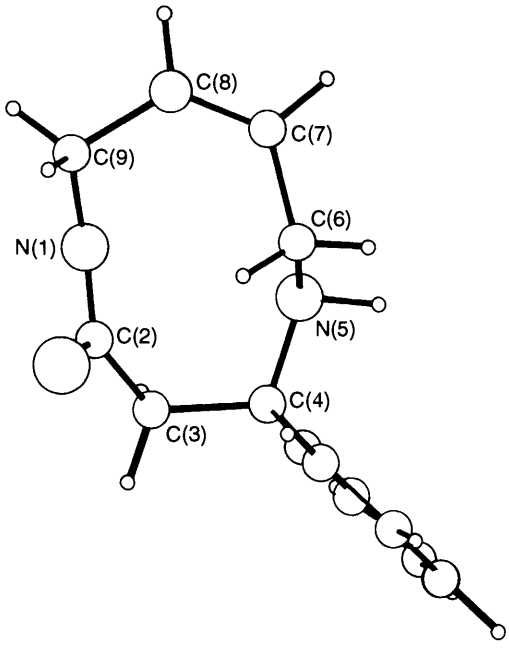
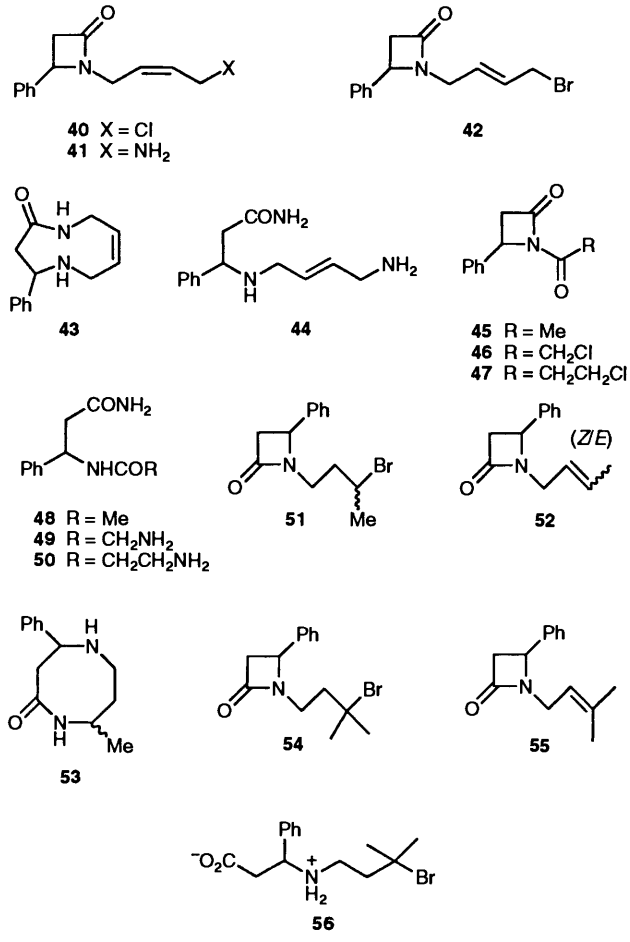


Fig. 5 X-Ray molecular structure of (*Z*)-4-phenyl-1,5-diazacyclonon-7-en-2-one **43** (view 2)

Treatment of N-*Acyl*-4-*phenylazetidin*-2-*ones with Liquid Ammonia*.—The stability of the azetidinone ring towards ammonolysis can be overcome by the introduction of an electron-withdrawing substituent at nitrogen.[1,27–29] Thus, 4-phenylazetidin-2-one **10** could be acetylated (50%) with butyllithium in THF and acetyl chloride and the resulting *N*-acetyl-β-lactam **45** was easily converted (liquid ammonia, 20 °C) into the amide **48** in 87% yield. The *N*-(2-chloroacetyl) and *N*-(3-chloropropanoyl) azetidinones **46** and **47** were similarly converted into the diamides **49** and **50**.

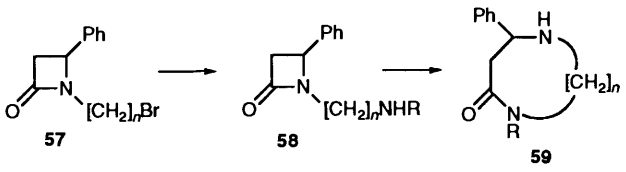
Influences of 4-*Substitution and* ω-*Halogenoalkyl Chain-branching on Transamidation in Liquid Ammonia*.—Having established the ring-size limitations for the transamidation of β-lactams, we examined the effect of certain substitutions. The 4-substitution has little influence on the efficiency of the reaction,



inasmuch as ring expansion of various 4-alkylazetidin-2-ones proceeds in yields comparable to the 4-phenyl cases.[30] Branching in the *N*-side-chain was introduced by treatment of 4-phenylazetidin-2-one **10** with 1,3-dibromobutane, when the secondary bromide **51** (a mixture of diastereoisomers as shown by the C*H*Ph ^{1}H NMR resonance which appeared as a five-line multiplet due to overlapping) was obtained. The reaction of compound **51** with liquid ammonia yielded products from both elimination (**52**) [as a mixture of (*Z*) and (*E*) isomers], and substitution with transamidation (**53**). The relative amounts of the two types of product varied with temperature, elimination being favoured by lower temperatures. By using medium-pressure chromatography, or crystallisation, the diastereoisomers of compound **53** (62–71% yield) could be separated and the less polar racemic diastereoisomer **16** was examined by X-ray crystallography and shown to be the *trans* compound having the expected *cis*-conformation for the amide group (see above).

Synthesis of the tertiary bromide **54** by treatment of compound **10** with 1,3-dibromo-3-methylbutane[31] was attempted but even under mild phase-transfer conditions gave only elimination product, 4-phenyl-*N*-prenylazetidine-2-one **55**, identical with an authentic sample made in 90% yield from prenyl bromide. Treatment of the *N*-lithio derivative of the azetidinone **10**[32] with the 1,3-dibromide at −30 °C was also unsuccessful, and treatment of the *N*-prenyl compound **55** with HBr in acetic acid apparently caused ring cleavage, producing on work-up the zwitterionic species **56**.

Transamidations in Ethylamine.—In the next phase of the investigation we took up the question of making, by transamidation, enlarged azalactam ring systems having an unsubstituted amino but an alkylated amide function **59**, by



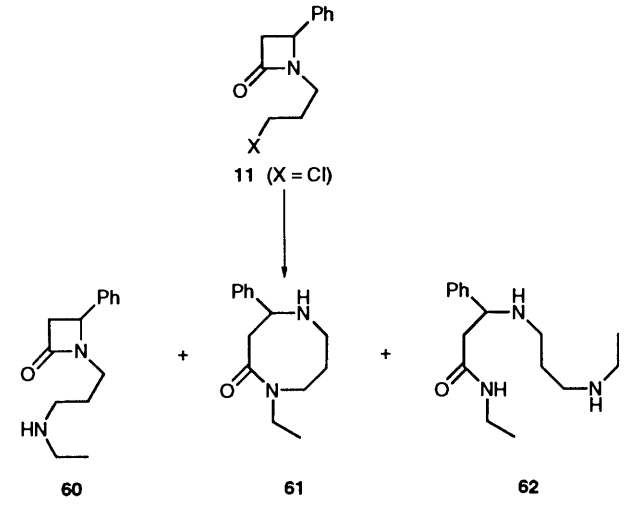
Scheme 3 Azetidin-2-one ring expansion using primary amines

Table 2 Products and yields from treatment of chloro β-lactam **11** (X = Cl) with ethylamine.

Conditions	Yield (%) Unchanged halide **11** (X = Cl)	Amino β-lactam **60**	Diazacyclo-octanone **61**	Acyclic amide **62**
20 °C; 1.5 days	0	58	13	n.p.[a]
40 °C; 7 days	0	21	31	33
60 °C; 7 days	0	0	46	40

[a] n.p. = not produced.

replacing liquid ammonia by an alkylated amine (Scheme 3). There are various factors to be considered. Since the amine also constitutes the solvent, a low boiling point facilitates removal: the large excess minimises unwanted side reactions between the halide **57** and its substitution product **58**. The extra nucleophilicity of alkylamines relative to ammonia might promote side reactions and the extra steric bulk of the alkyl group might bring about congested transition states, retarding ring expansion. Our first choice was anhydrous ethylamine (b.p. 18 °C), used in sealed-tube reactions. Upon employment of the chloride **11** (X = Cl) the initial substitution proceeded smoothly, no starting material being detected after 1.5 days, and Table 2 and Scheme 4 show that there are three main products,



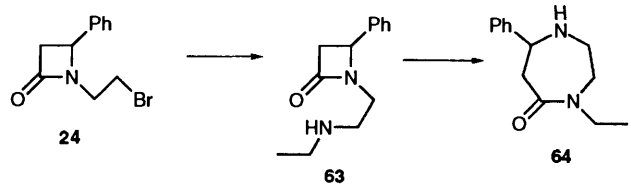
Scheme 4. Transamidation with ethylamine: eight-membered azalactam

the eight-membered azalactam **61**, an aminolysis product **62** and the amino β-lactam **60**. Attention was focussed on the maximization of the ring-expansion product **61**, and it is clear that β-lactam **60** is only slowly transamidated to this compound, probably because of increased steric hindrance. Raising of the reaction temperature did increase the yield of compound **61** to 46% but a change of halogen to the more reactive bromide **11** (X = Br) allowed an improvement of yield to 60% and this would doubtless be responsive to further fine-tuning.

In other experiments the amino β-lactam **60** could be obtained (89%) by treatment of 1-(3-chloropropyl)-4-phenylazetidin-2-one **11** (X = Cl) with ethylamine at 20 °C, with only traces of starting material and azalactam **61** being detected. Heating of the amino β-lactam in toluene under reflux for 9 days gave the azalactam **61** (44%), along with recovered starting material (35%). However, when the reaction was repeated in liquid ammonia at 70 °C for 7 days, the azalactam was obtained in 79% yield. When using sodium-dried iron-free redistilled liquid ammonia the yield was 76%, so there is no evidence of iron catalysis. Other amines were less effective in this solvent role. Thus, the β-lactam **60** was recovered unchanged after several days refluxing in triethylamine (b.p. 89 °C) or diisopropylamine (b.p. 84 °C). The sealed tube/liquid ammonia conditions appear particularly favourable to these transamidations and, among other factors, the dielectric properties may be significant (ammonia: ε = 16.9; toluene: ε = 2.37; triethylamine: ε = 2.42; diisopropylamine: ε = 2.9, all at 25 °C).[33]

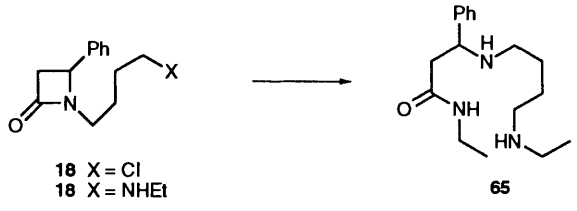
The eight-membered azalactam **61** was a distillable oil having ν_{max} 1640 cm^{-1} (disubstituted amide). In the ^1H NMR (250 MHz) spectrum the exocyclic methylene protons showed marked non-equivalence, being separated by ~0.8 ppm in chemical shift and appearing as overlapping double quartets. Irradiation of the methyl signal at δ 1.2 caused both methylene signals to collapse to doublets J 13.4 Hz.

As was expected, the seven-membered *N*-ethylazalactam **64** was formed in 88% yield when *N*-(2-bromoethyl)-4-phenylazetidin-2-one **24** was heated for 7 days with anhydrous ethylamine in a sealed tube (Scheme 5). The reactive bromide



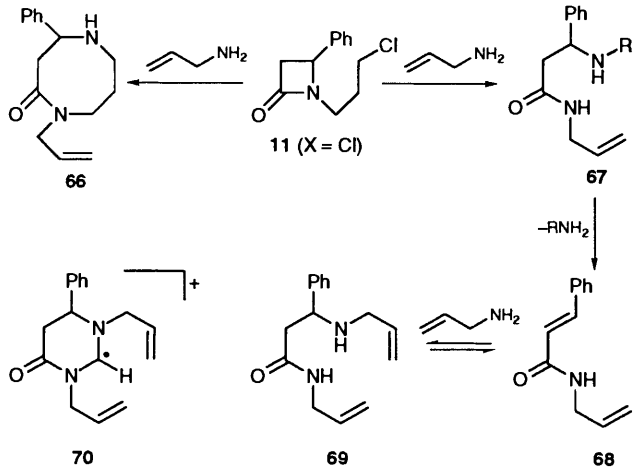
Scheme 5 Transamidations with ethylamine: seven-membered azalactam

allows rapid formation of the amine **63** which undergoes transamidation *via* a favoured five-membered transition state and the relative freedom from by-products may be ascribed to this. On the other hand, *N*-(4-chlorobutyl)-4-phenylazetidinone **18** (X = Cl) with a less reactive chlorine substituent and a seven-membered transition state for transamidation gave only the open-chain diamine **65** when treated with ethylamine at



60 °C for 7 days. It is clear that the choice of halogen is of importance, but whether the acyclic product arises in this case by cleavage of the azalactam or the β-lactam is uncertain. However, the lower homologue **11** (X = NHEt) (≡**60**) is stable to refluxing iso-propylamine for 7 days and this tends to favour the former view. The ethylaminobutyl β-lactam **18** (X = NHEt) could be isolated (56%) by reaction of the chloro compound **18** (X = Cl) with ethylamine (24 h; 20 °C), but on heating with liquid ammonia transamidation did not occur. The example presents two unfavourable factors—steric hindrance and a seven-membered transition state.

Transamidation in Allylamine.—The case of allylamine (b.p.



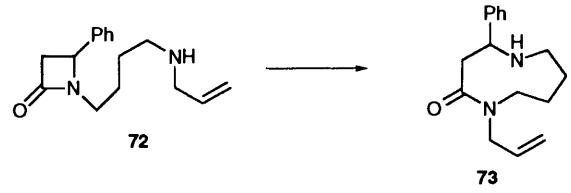
Scheme 6 Transamidation using allylamine: formation of azalactam and other products

53 °C) was now investigated since *N*-allylazalactams would be suitable candidates for further side-chain elaboration. Indeed, *N*-(3-chloropropyl)-4-phenylazetidin-2-one **11** (X = Cl), when heated with allylamine in a sealed tube at 85 °C for 7 days, gave the eight-membered allyl compound **66** in 55% yield. Also isolated (Scheme 6) was the acyclic bis-allyl compound **69** (7%).* The origins of the latter are of interest. It is probably not formed by simple dehydrohalogenation. The reaction is envisaged as involving formation of open-chain compound **67** in which the nature of R is indefinite at this stage, as it could originate from the chloride **11** (X = Cl) or its amine. Base-mediated elimination of an amine molecule RNH_2 now gives the cinnamamide **68** and conjugate addition of allylamine gives final product **69**: allylamine is acting as a base, a nucleophile and a solvent.

Our reasons for viewing the reaction in this way come from a study of a similar reaction between allylamine and *N*-(4-chlorobutyl)-4-phenylazetidin-2-one **18** (X = Cl) (Scheme 7).

Scheme 7 Products from reaction with allylamine at 90 °C (6 days)

When these substrates were heated together at 90 °C in a sealed tube for 6 days no expected product **71** was observed and the only identifiable products were the cinnamamide **68** and the bisallyl **69**: in this case the latter can only be formed by Michael addition to compound **68**. Under milder conditions (reflux; 3.5 days), the chloride **18** (X = Cl) reacted to yield the substituted β-lactam **72** (58%) and in a second experiment (18 h reflux) the yield of only slightly impure compound **72** was almost quantitative. The latter underwent ring expansion to the desired *N*-allylazalactam **73** when heated in refluxing toluene (Scheme 8). The yield was 60% at a conversion of 58% of the β-lactam **72**.



Scheme 8 Synthesis of nine-membered *N*-allylazalactam from an azetidinone by transamidation

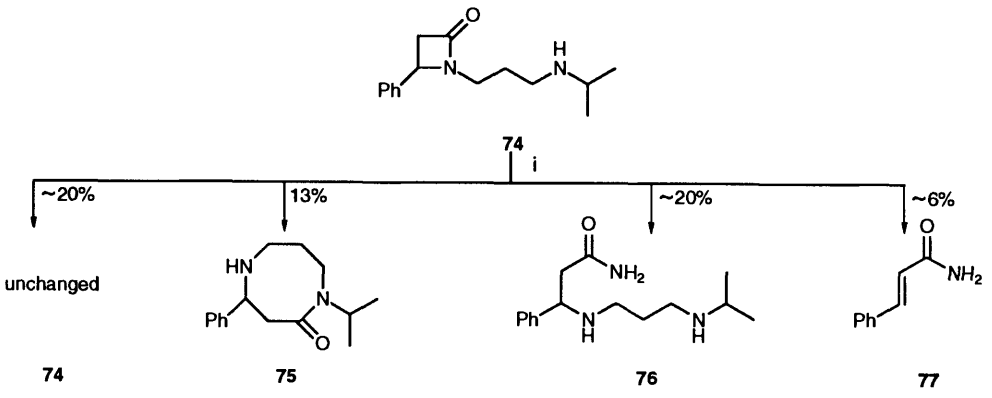
The use of refluxing mixed xylenes as solvent, however, caused decomposition with a much decreased yield of compound **73**.

Transamidation in Isopropylamine.—Treatment of the chloro β-lactam **11** (X = Cl) with isopropylamine (b.p. 33 °C) (7 days; 20 °C; sealed tube) gave 1-[3-(isopropylamino)propyl]-4-phenylazetidin-2-one **74** (75%). The latter, when treated with liquid ammonia at 70 °C for 14 days, gave a number of products as summarized in Scheme 9. The intrusion of the acylic diamino amide **76** may reflect strain introduced into the amide bond by the bulky isopropyl group in compound **75**, rendering it more susceptible to ammonolysis. Cinnamamide **77** seems more likely to originate from the azalactam *via* open-chain amide **76**, than more directly from the β-lactam. For comparison purposes, the azalactam **75** was made in low yield (20%) by alkylation of azalactam **13** with 2-iodopropane in the presence of $KN(SiMe_3)_2$–THF.

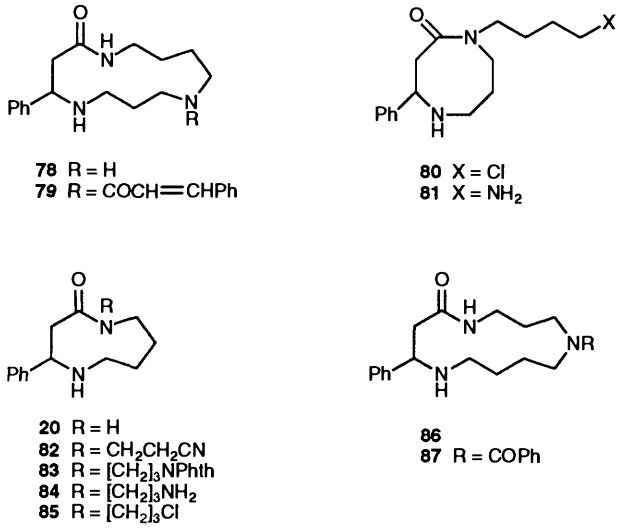
Synthesis of (±)-Dihydroperiphylline **79** *and (±)-Celabenzine* **87** *by Transamidation.*—Dihydroperiphylline **79** is one of a group of alkaloids isolated by Hocquemiller and his colleagues[35] from the leaves of *Peripterygia marginata* (Baill.) Loes. (Celastraceae) and has been synthesized by Wasserman[36] using an imino ether approach, and in (*S*)-(+)-form by Kaseda and his colleagues.[37] 4-Phenyl-1,5-diazacyclooctan-2-one **13** is readily prepared in 75% yield by our β-lactam transamidation approach, and forms a very suitable synthetic intermediate (see earlier). Alkylation of this compound using 1-bromo-4-chlorobutane and potassium bis(trimethylsilyl)amide in THF gave compound **80** (88%). Treatment of the latter with liquid ammonia (room temperature; 7 days) then gave the amine **81** (89%) and intramolecular transamidation of the latter using potassium bis(trimethylsilyl)amide as the base at room temperature gave the desired thirteen-membered ring system **78** in 21% yield. By using the acylation technique of Yamamoto[38] this could be selectively acylated with cinnamoyl chloride, thus completing a synthesis of (±)-dihydroperiphylline **79**.

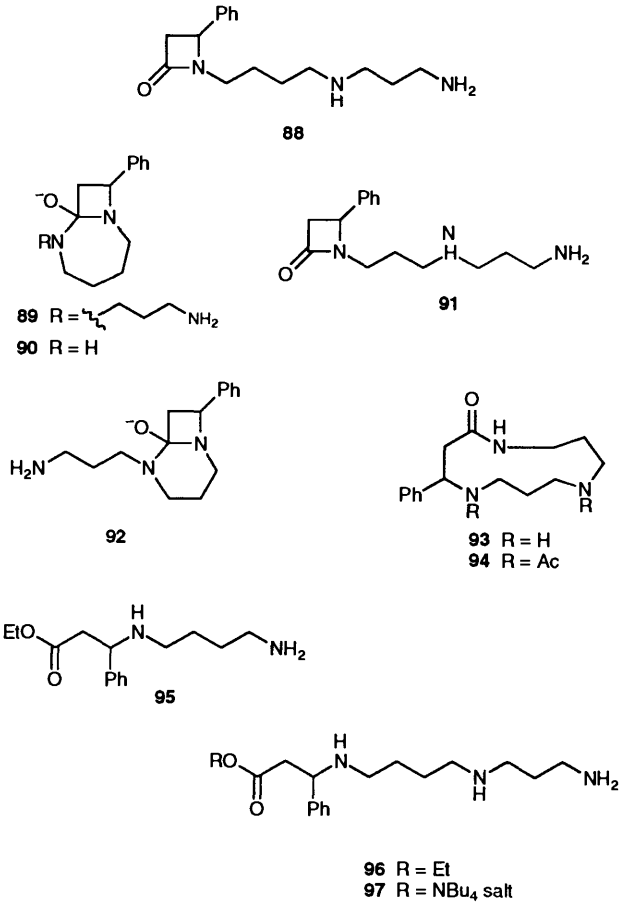
Celabenzine **87** is one of a group of spermidine alkaloids, having a common alkaloid core which is isomeric with that found in dihydroperiphylline; the group includes celacinnine **86** (R = cinnamoyl), and celafurine **86** (R = β-furoyl). They were isolated from the twigs and roots of *Maytenus serrata* and *Tripterygium wilfordii* (thunder-god vine) (both members of the Celastraceae).[39] Several syntheses have been reported,[38,40-42] and the present one is formal. Transamidation of compound **18** (X = Cl) by our liquid ammonia method allows formation of the nine-membered ring compound **20** in 67% yield. The latter could be cyanoethylated to form compound **82** (82%) and hence gave the amine **84** (81%) by reduction. Alternatively, the halide **85** could be made from free amine **20** by alkylation (76%) with 1-bromo-3-chloropropane, and ammonolysed (20 °C; 10 days) to give amine **84** (81%). The nine-membered ring compound **20** could also be alkylated by ω-bromopropylphthalimide using the $KN(SiMe_3)_2$–THF base system giving compound **83**, a key intermediate in Wasserman's

* The diallyl compound showed a weak molecular ion (M^+, 244) in the mass spectrum and a larger ion at *m/z* 255 with accurate mass consistent with the species **70**. The presence of these $(M + 11)^+$ peaks in the mass spectra of 1,2- and 1,3-diamines is a widespread phenomenon and has been discussed by Hesse.[34] Such peaks are due to fragment ions derived from the condensation of the diamines with aldehydes, especially formaldehyde impurities in methanol used in chromatography or synthesis. Loss of a hydrogen atom (or methyl from the acetaldehyde product) and an electron leads to species **70**.



Scheme 9 Transamidation of isopropylated amino β-lactam **74** in liquid ammonia. *Reagents and conditions:* i, liq. ammonia, sealed tube, 14 days.





synthesis,[22] in 53% yield. He was able to convert this phthalimide **83**, *via* amine **84** and transamidation into compound **86** (R = H), and hence by benzoylation into celabenzine **87**.

In connection with the 13-membered tris-aza ring system of celabenzine, some experiments were carried out to see if it might be attained using 'zip' reaction conditions on the amine **88**. This is not a favourable case because of the seven-membered intermediate that must be realised,[4] but it was hoped that strain energy from cleavage of the four-membered ring might assist the process. To this end the primary amine **88** was made from compound **19** by cyanoethylation (71%) followed by catalytic reduction over a 5% rhodium on alumina catalyst (94% yield) (superior to the employment of platinum oxide in acid medium). However, treatment of compound **88** with KAPA at 20 or 55 °C gave only recovered material, and an attempt to induce ring-expansion of the simpler amine **19** under similar conditions did not succeed. As some verification that the formation of intermediates **89** and **90** having seven-membered rings, and leading ultimately to 13- and 9-membered rings, respectively, were unfavourable factors, the primary amine **91** in which a six-membered intermediate **92** would be involved, was made by a double cyanoethylation–reduction sequence. Treatment of compound **91** at 20 °C for 7 h with KAPA in 1,3-diaminopropane allowed ring expansion to take place, though in poor yield, giving the 12-membered lactam **93** having the expected spectral data, and a negative fluorescamine test. It was characterised by the preparation of a diacetyl derivative **94**.

In view of this outcome, the β-lactam **88** was ethanolysed by ethanolic hydrogen chloride to form the ester **96** which can be converted into the tetrabutylammonium salt **97**. Ganem[40] has shown that the latter compound, prepared by a different route, can be cyclised to compound **86** by his catechol–borane procedure, and the product can be acylated to give celabenzine **87** or celacinnine. Alternatively, the cyclisation can be performed on compound **96** using tris(dimethylamino)borane.[38] This provides a second formal synthesis of the 13-membered lactam ring. The ethanolysis procedure was also applied to β-lactam **19** to afford the amino ester **95**.

Syntheses of the compounds of the Homaline alkaloid group are reported in two papers which follow.

Experimental

^{1}H NMR Spectra were run in $CDCl_3$ unless specified otherwise, using a Perkin-Elmer R32 (90 MHz), a JEOL MH 100, a Bruker WM 250, or a Bruker AM400 spectrometer. Acidic protons were identified by exchange with D_2O. Coupling constants J are in Hz. In ^{13}C NMR spectra, peaks cancelled or inverted by a

DEPT (Distortionless Enhancement by Polarization Transfer) pulse sequence are designated by italicisation. IR spectra were recorded on a Pye-Unicam SP3-100 IR Spectrometer with polystyrene as standard. Mass spectra were recorded either on an AEI MS902 or a VG7070F instrument. Usually electron impact (EI) methods were used, though occasionally chemical ionisation (Cl) (methane) or fast-atom bombardment (FAB) methods were employed using thioglycerol. All spectra were recorded in the positive-ion mode.

Analytical TLC was carried out using 5 × 2 cm glass plates coated with silica gel HF 254 (0.25 mm) or pre-coated Polygram sheets. For preparative TLC (PLC) glass plates were 20 × 20 cm, coated with silica gel containing HF 254 fluorescer. Fluorescamine (Fluram) in acetone spray was used for detection of the presence or absence of primary amino groups. Some 500 picomoles of primary amine is detectable as a highly fluorescent spot under UV light (λ 366 nm). Pretreatment of the plate with a sprayed solution of 10% triethylamine in dichloromethane increases the stability and sensitivity of the fluorescence.[43,44] All new compounds were checked for purity by TLC, running as one spot on several solvent systems. Drying normally implies the use of anhydrous sodium sulfate. Evaporation was carried out under reduced pressure.

4-Phenylazetidin-2-one **10**.—Freshly distilled styrene (20.8 g, 0.2 mol) was added dropwise during 1 h to stirred *N*-chlorosulfonyl isocyanate (17.4 cm^3, 28.3 g, 0.2 mol) in dry diethyl ether (70 cm^3). The solution was seeded with a few crystals of the product, stirred for 1 h at room temperature, and stored at −5 °C overnight. The solid was filtered off, washed with cold diethyl ether, and dried *in vacuo* to give *N*-chlorosulfonyl-4-phenylazetidin-2-one **9** (39.2 g, 80%), m.p. 92–93 °C (lit.,[15] 89–90 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 970, 1360, 1410, 1455, 1815 and 3050; δ_H 7.28 (5 H, m, Ph), 5.16 (1 H, dd, *J* 5 and 7, C*H*Ph), 3.66 (1 H, dd, *J* 7 and 18, CH_aHCO) and 3.22 (1 H, dd, *J* 5 and 18, CHH_bCO). Compound **9** (12.0 g, 49 mmol) as a solution, in diethyl ether–chloroform (1 : 1; 140 cm^3) was added during 30 min, to rapidly stirred, aq. sodium sulfite (25% w/v; 200 cm^3) and chloroform (75 cm^3). The aqueous phase was kept basic by addition of aliquots (2 cm^3) of aq. potassium hydroxide (10%). After being stirred (1 h), the phases were separated, the aqueous phase being extracted by further chloroform (150 cm^3). Drying, evaporation, and crystallisation from methanol–water (3 : 5; 25 cm^3) gave 4-phenylazetidin-2-one **10** (6.34 g, 88%), m.p. 105–106 °C (lit.,[15] 108–109 °C) (Found: C, 73.2; H, 6.25%; M$^+$, 147.068. Calc. for C_9H_9NO: C, 73.45; H, 6.15%; *M*, 147.067); $\nu_{max}(CHCl_3)/cm^{-1}$ 965, 1160, 1355, 1445, 1750 and 3250; $\delta_H(CDCl_3)$ 7.24 (5 H, m, Ph), 6.48 (1 H, br s, NH), 4.54 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.28 (1 H, dd, *J* 5 and 15, CH_aHCO) and 2.72 (1 H, dd, *J* 2 and 15, CHH_bCO); δ_C *47.8* (C-3), 50.3 (C-4), 125.6, 128.1, 128.8, *140.4* and *168.4* (C = O).

Alkylation of β-Lactams.—Method A.[26] Tetrabutylammonium hydrogen sulfate (1–4 mmol 0.1 mol equiv.) powdered potassium hydroxide (1.4 mol equiv.) and the appropriate alkyl halide (1–10 mol equiv.) (normally 1.1 mol equiv. except for certain dibromoalkanes or iodobromoalkanes where 3–10 mol equiv. were used) were added to stirred 4-phenylazetidin-2-one **10** (1 mol equiv.) in dry THF (25 cm^3) under nitrogen. The suspension was stirred at room temperature for 2–8 h until TLC indicated complete consumption of the 4-phenylazetidin-2-one. After evaporation of the solvent, the residue was partitioned between chloroform (25 cm^3) and water (25 cm^3). The aqueous phase was extracted with chloroform (25 cm^3) and the combined organic phases were dried and evaporated. The remaining oil was chromatographed on silica gel to give the *N*-alkylazetidin-2-one.

Method B.[16] Powdered potassium hydroxide (5–20 mmol, 4 mol equiv.) was added to DMSO (30–40 cm^3) and the suspension was stirred (15 min). 4-Phenylazetidin-2-one **10** (1 mol equiv.) and the alkyl halide (2 mol equiv.) were added, and the mixture was stirred (6–24 h) and then poured into water (100–200 cm^3). The resulting suspension was extracted with chloroform (3 × 150 cm^3) and the combined extracts were reduced by evaporation to ~ 100 cm^3 before being washed with water (3 × 150 cm^3). Drying and evaporation gave the *N*-alkylazetidin-4-one (usually as an oil), which was purified by chromatography on silica gel.

N-(3-*Bromopropyl*)-4-*phenylazetidin*-2-*one* **11** (X = Br). 4-Phenylazetidin-2-one **10** (0.37 g, 2.5 mmol) was treated with 1-bromo-3-iodopropane (1.89 g, 7.5 mmol) for 5 h under the conditions of Method A above. Chromatography on silica gel, elution with chloroform, then with chloroform–methanol (19 : 1), gave N-(3-*bromopropyl*)-4-*phenylazetidin*-2-*one* **11** (X = Br) (0.50 g, 75%), an oil (Found: M$^+$, 267.023. $C_{12}H_{14}BrNO$ requires *M*, 267.026); ν_{max}(film)/cm^{-1} 700, 985, 1395, 1490 and 1760; δ_H 7.54 (5 H, m, Ph), 4.68 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.68–2.92 (5 H, m, CH_2Br, CH_2N, CH_aHCO), 2.88 (1 H, dd, *J* 2 and 15, CHH_bCO) and 2.20–1.88 (2 H, m, CH_2CHBr). Further elution gave 1,3-*bis*-(2-*oxo*-4-*phenylazetidin*-1-*yl*)*propane* **15** (75 mg, 18%) (Found: M$^+$, 334.168. $C_{21}H_{22}N_2O_2$ requires *M*, 334.168); ν_{max}(film)/cm^{-1} 700, 990, 1205, 1455, 1495 and 1780; δ_H 7.60 (10 H, m, Ph), 4.64 (2 H, dd, *J* 2 and 5, CHPh), 3.70–3.20 (4 H, m, 2 × CH_aHN, 2 × CH_aHCO), 3.12–2.76 (4 H, m, 2 × CHH_bN, 2 × CHH_bCO) and 1.92–1.52 (2 H, m, CH_2CH_2N).

N-(3-*Chloropropyl*)-4-*phenylazetidin*-2-*one* **11** (X = Cl). 4-Phenylazetidin-2-one **10** (0.50 g, 3.4 mmol) was allowed to react with 1-bromo-3-chloropropane (0.80 g, 5.1 mmol) for 5 h, using Method A. Chromatography and elution with chloroform–hexane (19 : 1), then with chloroform, gave *N*-(3-chloropropyl)-4-phenylazetidin-2-one (0.74 g, 97%).

In a larger-scale experiment 4-phenylazetidin-2-one **10** (2.0 g, 13.6 mmol) was alkylated with 1-bromo-3-chloropropane (4.28 g, 27.2 mmol) in DMSO (20 cm^3) using Method B and a reaction time of 24 h. Work-up gave compound **11** (X = Cl) as an oil (2.55 g, 84%), b.p. 168 °C at 2 mmHg (Found: C, 64.3; H, 6.3%; M$^+$, 223.076. $C_{12}H_{14}ClNO$ requires C, 64.4; H, 6.3%; *M*, 223.076); ν_{max}(film)/cm^{-1} 700, 930, 1110, 1400, 1455, 1760 and 2910; δ_H 7.32 (5 H, m, Ph), 4.48 (1 H, dd, *J* 2.5 and 5, CHPh), 3.60–3.20 (4 H, m, CH_2Cl, CH_aHN, CH_aHCO), 3.14–2.82 (1 H, m, CHH_bN), 2.80 (1 H, dd, *J* 2.5 and 15, CHH_bCO) and 2.12–1.72 (2 H, m, CH_2CH_2Cl).

General Directions for Experiments with Liquid Ammonia Under Pressure.—Experiments were carried out in flame-sealed Carius tubes or a series of thick-walled (3–4 mm) glass Carius tubes equipped with side-arms sealed with 'Rotaflo' compression sealing taps. The dimensions of the Carius tubes were as follows:

	External diameter (mm)	Length (mm)	Capacity (approx.) (cm^3)
Type A	25	130	75
Type B	32	150	125
Type C	40	200	175

Liquid ammonia was used in an efficient fume-cupboard with the experimenter wearing gloves and a full face shield. Effective screening should be used at all times during a reaction. **Filling:** Mobile oils were introduced directly into the Carius tube using a micropipette. More viscous compounds were introduced in solution in chloroform, the chloroform then being evaporated off under reduced pressure. The desired volume of liquid ammonia was then introduced *cautiously*, direct from the

ammonia cylinder, and the tube was immediately sealed and placed behind the safety screen.

Emptying: At the end of the reaction the tube was cooled in liquid nitrogen to relieve pressure. [*It is best not to freeze the ammonia as this can cause explosive evaporation when the tube is opened.*] The tap is then opened and removed, and the contents poured into a large conical flask and the ammonia allowed to evaporate off completely before continuing with the work-up. Care is needed if material is precipitated during the cooling stage and the best procedure then is to place the tube in a large beaker, to open the tap somewhat, and to allow the ammonia to evaporate undisturbed.

N-(3-*Aminopropyl*)-4-*phenylazetidin*-2-*one* **12**.—*N*-(3-Chloropropyl)-4-phenylazetidin-2-one (1.06 g, 4.8 mmol) was dissolved in liquid ammonia (20 cm^3), sealed in a Carius tube, and kept at room temperature for 24 h. The residue was dissolved in chloroform (25 cm^3), filtered, and chromatographed directly on silica, and eluted first with chloroform–methanol (49:1), then with chloroform–isopropylamine (49:1). Unchanged chloride (460 mg, 43%) was eluted first, followed by 4-phenyl-1,5-diazacyclooctan-2-one **13** (151 mg, 15.5%) (see below). Further elution gave N-(3-*aminopropyl*)-4-*phenylazetidin*-2-*one* **12** (364 g, 38.5%) (Found: M^+, 204.125. $C_{12}H_{16}N_2O$ requires *M*, 204.126); ν_{max}(film)/cm^{-1} 1080, 1205, 1400, 1750, 3320sh and 3370; δ_H 7.43 (5 H, m, Ph), 4.60 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.70–3.26 (2 H, m, CH_aHN, CH_aHCO), 3.10–2.60 (4 H, m, CHH_bN, CHH_bCO, CH_2N), 1.73–1.43 (2 H, q, CH_2CH_2N) and 1.22 (2 H, s, NH_2). The compound gave a positive Fluram spray test.

4-*Phenyl*-1,5-*diazacyclooctan*-2-*one* **13**.—*N*-(3-Bromopropyl)-4-phenylazetidin-2-one **11** (X = Br) (721 mg, 2.69 mmol) was treated with liquid ammonia in a sealed tube at room temperature for 48 h. Work-up, and chromatography on silica, and elution first with chloroform, then with chloroform containing 2–5% methanol, then with chloroform containing 5% of isopropylamine, gave 4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **13** (447 mg, 81%) as a crystalline solid, m.p. 128–130 °C (from chloroform–hexane) (Found: C, 70.8; H, 7.9; N, 13.4%; M^+, 204.125. $C_{12}H_{16}N_2O$ requires C, 70.6; H, 7.9; N, 13.7%; *M*, 204.126); ν_{max}(KBr)/cm^{-1} 700, 795, 955, 1130, 1320, 1465, 1610, 1650 and 3290; δ_H (see **13a**) 7.43–7.24 (5 H, m, Ph), 5.68 (1 H, br d, NHCO), 4.04 (1 H, dd, *J* 2.2 and 10.7, C*H*Ph), 3.99–3.81 (1 H, m, CH_aHNCO), 3.30–3.18 (2 H, m, CH_2N), 2.93 (1 H, dd, *J* 10.7 and 10.7, CH_aHCO), 2.63–2.51 (1 H, m, CHH_bNCO), 2.47 (1 H, dd, *J* 2.2 and 10.7, CHH_bCO) and 1.84–1.52 (3 H, m, inner CH_2 and NH). On shaking of the sample with D_2O the peak at δ 5.68 disappeared, whilst that centred at δ 1.70 was reduced to two protons. Irradiation of the dd at δ 2.93 causes the dds at δ 4.04 and δ 2.47 to collapse to doublets with *J* 2.2. The compound gave a negative Fluram test.

Continued elution gave primary amine **12** (above) (98 mg, 18%).

N-(3-Chloropropyl)-4-phenylazetidin-2-one (3.0 g, 13.4 mmol) in liquid ammonia for 4 days at 60 °C similarly gave the 1,5-diaza compound **13** (1.56 g, 57%), m.p. 128–130 °C.

5-*Acetyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **17**.—A solution of the azalactam **13** (100 mg, 0.49 mmol) in dry pyridine (15 cm^3) was added to acetic anhydride (5 cm^3), stirred (2 days), and poured into iced 1 mol dm^{-3} HCl (120 cm^3). Extraction with chloroform, washing of the extract with 2 mol dm^{-3} HCl, drying and PLC gave the *title acetate* **17** (87 mg, 73%), m.p. 183–185 °C (Found: M^+, 246.136. $C_{14}H_{18}N_2O_2$ requires *M*, 246.137); ν_{max}(KBr)/cm^{-1} 705, 1040, 1220, 1430, 1610, 1655 and 3300; δ_H 7.47–7.19 (5 H, m, Ph), 6.12 (1 H, br s, NHCO), 5.49 (1 H, dd, *J* 4.6 and 11.8, C*H*Ph), 4.11 (1 H, m, CH_aHN), 3.54–3.25 (2 H, m, CH_2N), 3.18 (1 H, dd, *J* 11.8 and 11.8, CH_aHCO), 2.98 (1 H, dd, *J* 4.6 and 11.8, CHH_bCO), 2.77–2.65 (1 H, m, CHH_bN), 2.36–2.15 (1 H, m, C*H*CH_2N), 2.21 (3 H, s, Me) and 1.62–1.54 (1 H, m, C*H*CH_2N). The resonance at δ 6.12 is removed on shaking with D_2O. Irradiation of the signal at δ 5.49 causes the resonances at δ 3.18 dd and δ 2.98 dd to collapse to doublets, *J* 10.8. Irradiation of the multiplet at δ 4.11 causes change in the shape of the signal at δ 2.70, but has no effect on the two-proton signal centred at δ 3.40, showing that the last pair of protons are part of the same methylene.

N-(4-*Bromobutyl*)-4-*phenylazetidin*-2-*one* **18** (X = Br).—4-Phenylazetidin-2-one **10** (0.37 g, 2.5 mmol) was allowed to react with 1-bromo-4-iodobutane for 6 h using Method A. Chromatography on silica gel, and elution with chloroform–hexane (19:1), then with chloroform, gave N-(4-*bromobutyl*)-4-*phenylazetidin*-2-*one* **18** (0.57 g, 81%) as a pale oil (Found: M^+, 281.043. $C_{13}H_{16}BrNO$ requires *M*, 281.042); ν_{max}(film)/cm^{-1} 700, 1080, 1205, 1400, 1460 and 1750; δ_H 7.42 (5 H, m, Ph), 4.60 (1 H, dd, *J* 2.5 and 5, C*H*Ph), 3.60–2.76 (6 H, m, CH_2Br, CH_2N and CH_2CO) and 2.04–1.40 (4 H, $CH_2CH_2CH_2Br$). Continued elution gave, as shown by ^1H NMR spectroscopy, a mixture of unchanged 4-phenylazetidin-2-one **10** and 1,4-bis-(2-oxo-4-phenylazetidin-1-yl)butane (66 mg) which were not separated.

N-(4-*Chlorobutyl*)-4-*phenylazetidin*-2-*one* **18** (X = Cl).—4-Phenylazetidin-2-one **10** (2.00 g, 13.6 mmol) was treated with 1-bromo-4-chlorobutane (4.66 g, 27.2 mol) in DMSO (20 cm^3) for 23 h according to Method B. Chromatagraphy on silica gel, and elution with chloroform–hexane (19:1), then with chloroform, gave N-(4-*chlorobutyl*)-4-*phenylazetidin*-2-*one* **18** (X = Cl) (2.22 g, 69%), b.p. 163 °C at 0.7 mmHg (Found: C, 65.3; H, 7.1; N, 5.7%; M^+, 237.091. $C_{13}H_{16}ClNO$ requires C, 65.7; H, 6.8; N, 5.9%; *M*, 237.092); ν_{max}(film)/cm^{-1} 700, 1080, 1205, 1400, 1460 and 1750; δ_H 7.40 (5 H, m, Ph), 4.59 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.62–3.25 (4 H, m, CH_2Cl, CH_aHN and CH_aHCO), 3.08–2.70 (2 H, m, CHH_bN, CHH_bCO) and 1.96–1.46 (4 H, m, $CH_2CH_2CH_2N$).

N-(4-*Aminobutyl*)-4-*phenylazetidin*-2-*one* **19**.—*N*-(4-Bromobutyl)-4-phenylazetidin-2-one **18** (X = Br) (547 mg, 1.94 mmol) was dissolved in liquid ammonia (20 cm^3) in a sealed Carius tube and set aside at room temperature for 5 days. Work-up by partition between water and chloroform, followed by extraction (chloroform) and evaporation gave an oil. This was chromatographed on silica gel with chloroform–methanol (49:1 rising to 3:1) as eluent and gave 4-phenyl-1,5-diazacyclononan-2-one **20** (26 mg, 6%) (see below) and then the *title aminobutyl compound* **19** (331 mg, 78%) as an oil. It gave a positive Fluram test (Found: M^+, 218.141. $C_{13}H_{18}N_2O$ requires *M*, 218.142); ν_{max}(film)/cm^{-1} 710, 760, 1205, 1405, 1460, 1500, 1735 and 3430; δ_H 7.36 (5 H, m, Ph), 4.56 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.60–3.24 (2 H, m, CH_aHCO and CH_aHN), 3.04–2.44 (4 H, m, CHH_bCO, CHH_bN and CH_2NH_2), 2.06 (2 H, br s, NH_2) and 1.72–1.20 (4 H, m, $CH_2CH_2CH_2N$). The resonance at δ 2.06 disappeared on shaking with D_2O.

The title compound was also made from the chlorobutyl lactam (84%) by storage in liquid ammonia for 6 days at 20 °C.

4-*Phenyl*-1-5-*diazacyclononan*-2-*one* **20**.—*N*-(4-Chlorobutyl)-4-phenylazetidin-2-one **18** (X = Cl) (1.12 g, 4.7 mmol) was kept in a sealed Carius tube containing liquid ammonia (30 cm^3) at 55 °C for 5 days. Work-up followed by chromatography on silica gel and elution with chloroform–methanol (99:1, then 49:1) gave 4-phenyl-1,5- diazacyclononan-2-one **20** (0.69 g, 67%), m.p. 88–89 °C (lit.,[22] 87–88 °C) (Found: C, 71.2; H, 8.45; N, 12.7%; M^+, 218.141. Calc. for $C_{13}H_{18}N_2O$: C, 71.5, H, 8.3, N, 12.85%; *M*, 218.142); ν_{max}(KBr)/cm^{-1} 700,

1125, 1315, 1440, 1550, 1630, 3280 and 3350; δ_H 7.40–7.23 (5 H, m, Ph), 6.98 (1 H, br d, *J*, 9.2, NHCO), 3.86–3.66 (1 H, m, CHNCO), 3.57 (1 H, dd, *J* 2.7 and 11.6, C*H*Ph), 2.90–2.68 (3 H, m, CHNCO and CH_2N), 2.52 (1 H, dd, *J*, 11.6 and 11.6, CH_aHCO), 2.37 (1 H, dd, *J* 2.7 and 11.6 CHH_bCO), 1.75 (1 H, s, NH) and 2.00–1.35 (4 H, m, inner CH_2 s). The resonances at δ 1.75 and 6.98 disappeared on shaking with D_2O; δ_C *25.8*, *29.2*, *40.3*, *46.3*, *51.3*, 61.4 (C-4), 125.8, 127.5, 129.0, *144.6*, *176.1*. The compound gave a negative Fluram spray test.

In a second experiment the β-lactam was heated at 70 °C for 5 days in liquid ammonia and gave the diaza compound in 66% yield.

Thermolysis of N-(4-*Aminobutyl*)-4-*phenylazetidin*-2-*one* **18** (X = NH_2) *in Refluxing Toluene*.—The β-lactam (0.51 g, 2.4 mmol) was heated under reflux in toluene (69 cm^3) under nitrogen for 6 days, by which time TLC indicated steady-state conditions. Work-up gave a product which ^1H NMR spectroscopy indicated to be an ~ 1:1 mixture of unchanged β-lactam and azalactam **20**. Chromatography on silica gel, and elution with methanol–chloroform (1:49), gave the nine-membered azalactam **20** (0.25 g, 48%). Continued elution with isopropylamine–chloroform (1:19) gave recovered β-lactam **19** (0.14 g, 26% recovery).

Acetylation of 4-*Phenyl*-1,5-*diazacyclononan*-2-*one* **20**.—A solution of lactam **20** (288 mg, 1.32 mmol) in dry pyridine (6 cm^3) was stirred with acetic anhydride at room temperature for 29 h. Customary work-up, and chromatography on silica gel, and elution with chloroform–methanol (49:1), gave 1,5-diacetyl-4-phenyl-1,5-diazacyclononan-2-one **23** (62 mg, 16%), *m*/*z* 302 (M^+, 26%), 259 (56), 104 (59), 86 (100) and 84 (100); $\nu_{max}(CHCl_3)/cm^{-1}$ 990, 1370, 1640 and 1690; δ_H 7.50–7.12 (5 H, m, Ph), 5.56 (1 H, dd, *J* 5 and 11, C*H*Ph), 4.46–4.10 (1 H, m, CHN), 4.10–3.25 (3 H, m, 2 × CHN, CH_aHCO), 3.20–2.55 (2 H, m, CHN, CHH_bCO), 2.50 (3 H, s, imide MeCO), 2.14 (3 H, s, amide MeCO) and 2.10–1.45 (4 H, m, $CH_2CH_2CH_2$).

Continued elution gave 5-acetyl-4-phenyl-1,5-diazacyclononan-2-one **22** (226 mg, 66%), *m*/*z* 260 (M^+, 86%), 217 (100), 146 (44), 104 (100) and 70 (64); δ_H 7.55–7.10 (6 H, m, Ph, NHCO), 5.56 (1 H, dd, *J* 5 and 11, C*H*Ph), 4.10–3.10 (4 H, m, 3 × CHN, CH_aHCO), 2.90–2.44 (2 H, m, CHN, CHH_bCO), 2.16 (3 H, s, MeCO) and 2.10–1.45 (4 H, m, 2 × CH_2CH_2N).

N-(2-*Bromoethyl*)-4-*phenylazetidin*-2-*one* **24**.—4-Phenylazetidin-2-one **10** (0.5 g, 3.4 mmol) was allowed to react with 1,2-dibromoethane (6.54 g, 35 mmol) for 8 h, under the conditions of Method A. Purification by chromatography on silica gel, and elution with chloroform–hexane (19:1), then with chloroform, then with chloroform–methanol (49:1), gave the bromoethyl product **24** (0.35 g, 41%), δ_H 7.40 (5 H, m, Ph), 4.75 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.96–3.60 (1 H, m, CH_aHN), 3.60–3.10 (4 H, m, CHH_bN, CH_2Br and CH_aHCO) and 2.83 (1 H, dd, *J* 2 and 15, CHH_bCO).

Further elution gave unchanged 4-phenylazetidin-2-one **10** (0.29 g, 58%). Allowing for recovered starting material, the yield of bromide **24** was 98%.

4-*Phenyl*-1,5-*diazacycloheptan*-2-*one* **25**.—*N*-(2-Bromoethyl)-4-phenylazetidin-2-one **24** (345 mg, 1.36 mmol) was kept for 14 days at 40 °C in liquid ammonia (15 cm^3) contained in a sealed Carius tube. Work-up by extraction (chloroform) gave an oil, which was chromatographed on silica gel, and elution with chloroform–methanol (49:1) gave 4-*phenyl*-1,5-*diazacycloheptan*-2-*one* **25** (191 mg, 74%), m.p. 102–103 °C (from diethyl ether) (Found: C, 69.65; H, 7.6; N, 14.7%; M^+, 190.111. $C_{11}H_{14}N_2O$ requires C, 69.45; N, 7.4; N, 14.7%; *M*, 190.111); ν_{max}(KBr)/cm^{-1} 770, 1000, 1180, 1350, 1665 and 3230; δ_H 7.42–7.23 (5 H, m, Ph), 6.74 (1 H, br s, NHCO), 3.93 (1 H, d, *J* 0 and 10.4, C*H*Ph), 3.59–3.46 (1 H, m, CHN), 3.28–3.17 (2 H, m, 2 × CHN), 3.07–2.90 (2 H, m, CHN, CH_aHCO), 2.61 (1 H, d, *J* 0 and 14.2, CHH_bCO) and 2.03 (1 H, s, NH). The signals at δ 6.74 and 2.03 disappeared on shaking with D_2O. The compound gave a negative Fluram test.

N-(5-*Bromopentyl*)-4-*phenylazetidin*-2-*one* **27** (X = Br).—4-Phenylazetidin-2-one **10** (0.50 g, 3.4 mmol) and 1,5-dibromopentane (3.91 g, 17.0 mmol) were allowed to react for 16 h under the conditions of Method A. Chromatography on silica gel and elution with chloroform–hexane (9:1; then 19:1; then chloroform) gave N-(5-*bromopentyl*)-4-*phenylazetidin*-2-*one* **27** (X = Br) (612 mg, 61%) (Found: M^+, 295.059. $C_{14}H_{18}BrNO$ requires *M*, 295.057); ν_{max}(film)/cm^{-1} 750, 1090, 1210, 1400, 1460, 1650 and 2950; δ_H 7.40 (5 H, m, Ph), 4.60 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.55–3.25 (4 H, m, CH_2Br, CH_aHN, CH_aHCO), 3.10–2.70 (2 H, m, CHH_bN, CHH_bCO) and 2.00–1.40 (6 H, m, inner CH_2s).

N-(5-*Aminopentyl*)-4-*phenylazetidin*-2-*one* **27** (X = NH_2).—A mixture of the bromo compound **27** (X = Br) (563 mg, 1.9 mmol) in liquid ammonia was kept sealed for 7 days at 65 °C. After the usual work-up the product was chromatographed on silica gel, and eluted with chloroform–isopropylamine (99:1; then 49:1; then 19:1), to afford the *title amine* **27** (X = NH_2) (274 mg, 62%) (Found: [$M^+ - CH_2NH_2$], 202.1232. $C_{13}H_{16}NO$ requires *m*/*z* 202.1232); ν_{max}(film)/cm^{-1} 1200, 1395, 1570, 1640, 2940 and 3360; δ_H 7.40 (5 H, m, Ph), 4.60 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.66–3.28 (2 H, m, CH_aHN, CH_aHCO), 3.10–2.50 (4 H, m, CHH_bN, CHH_bCOCH_2N) and 1.94 (2 H, s, NH_2). The resonance at δ 1.94 disappeared on shaking with D_2O.

N-(12-*Bromododecyl*)-4-*phenylazetidin*-2-*one* **30** (X = Br).—This was prepared by alkylation Method A (above) from 4-phenylazetidin-2-one **10** (0.74 g, 5 mmol), 1,12-dibromododecane (4.10 g, 12.5 mmol), potassium hydroxide (0.45 g, 8 mmol) and tetrabutylammonium hydrogen sulfate (0.17 g, 0.5 mmol) in THF (25 cm^3). The product was chromatographed on silica gel and eluted with hexane–chloroform (1:4) and gave the N-(12-*bromododecyl*) *compound* **30** (X = Br) (1.46 g, 74%) (Found: M^+, 393.169. $C_{21}H_{32}BrNO$ requires *M*, 393.167); ν_{max}(film)/cm^{-1} 1748; δ_H 7.30 (5 H, s, Ph), 4.50 (1 H, dd, *J* 2 and 5, 4-H), 3.35 (2 H, t, *J* 7, CH_2Br), 3.50–3.15 (2 H, m, 3-H′ and NCH*H*), 2.95–2.60 (2 H, m, 3-H and NC*H*H) and 1.90–1.10 (20 H, m, 10 × CH_2).

N-(10-*Bromodecyl*)-4-*phenylazetidin*-2-*one* **29** (X = Br).—This *compound* was obtained by a procedure analogous to that above (65%) (Found: C, 62.6; H, 7.9; N, 3.6%; M^+, 365.135. $C_{19}H_{28}BrNO$ requires C, 62.3; H, 7.7; N, 3.8%; *M*, 365.135); ν_{max}(film)/cm^{-1} 1740; δ_H 7.33 (5 H, s, Ph), 4.50 (1 H, dd, *J* 2 and 5, 4-H), 3.40 (2 H, t, *J* 7, CH_2Br), 3.30 (2 H, m, 3-H′ and NCH*H*), 2.75 (2 H, m, 3-H and NC*H*H) and 2.00–1.10 (16 H, m, 8 × CH_2).

N-(8-*Bromooctyl*)-4-*phenylazetidin*-2-*one* **28** (X = Br).—The *compound* (50%) was obtained by the above method (Found: M^+, 337.103. $C_{17}H_{24}BrNO$ requires *M*, 337.104); ν_{max}(film)/cm^{-1} 1740; δ_H 7.30 (5 H, m, Ph), 4.50 (1 H, dd, *J* 2,5, 4-H), 3.50–3.20 (4 H, m, CH_2Br, 3-H′ and NCH*H*), 3.00–2.80 (2-H, m, 3-H and NCH*H*H) and 1.90–1.10 (12 H, m, 6 × CH_2).

N-(12-*Aminododecyl*)-4-*phenylazetidin*-2-*one* **30** (X = NH_2).—The bromododecyl β-lactam **30** (X = Br) (0.277 mg, 0.7 mmol) was sealed up with liquid ammonia (20 cm^3) for 7 days at room temperature. Work-up gave the *title amino compound* (0.228 g, 99%) (Found: M^+, 330.268. $C_{21}H_{34}N_2O$ requires *M*, 330.267); ν_{max}(film)/cm^{-1} 1740 and 3300; δ_H 7.30

(5 H, m, Ph), 4.50 (1 H, dd, *J* 2 and 5, 4-H), 3.40–2.50 (8 H, m, 3-H_2, CH_2NH_2, NCH_2) and 1.70–0.95 (20 H, m, 10 × CH_2).

Treatment of N-(ω-*Bromoalkyl*)-4-*phenylazetidin*-2-*ones with Liquid Ammonia at Elevated Temperatures*.—(i) N-(10-*Bromodecyl*)-4-*phenylazetidin*-2-*one* **29** (X = Br). The bromide (0.55 g, 1.5 mmol) was sealed with liquid ammonia (20 cm^3) at 70 °C for 38 days. The product was 3-[(10-aminodecyl)amino]-3-phenylpropanamide **32** (0.464 g, 97%) (*m/z* 319); ν_{max}(film)/cm^{-1} 1665 and 2900–3500 br; δ_H 7.30 (5 H, m, Ph), 7.70–7.00 (2 H, br, $CONH_2$), 3.95 (1 H, dd, *J* 6,8, PhC*H*), 2.90–2.25 (9 H, m, CH_2CO, CH_2NH_2, CH_2NH) and 1.75–1.00 (16 H, m, 8 × CH_2).

(ii) N-(8-*Bromooctyl*)-4-*phenylazetidin*-2-*one* **28** (X = Br). The bromide was heated in a similar way in liquid ammonia at 70 °C for 36 days and gave 3-[(8-aminooctyl)amino]-3-phenylpropanamide **31** in 99% yield, δ_H 7.70–7.00 (7 H, m, Ph and $CONH_2$), 4.20 (1 H, m, PhC*H*), 3.00–2.40 (6 H, m, CH_2CO, CH_2NH_2 and CH_2NH) and 1.70–0.90 (15 H, m, 6 × CH_2, NH_2, NH).

(iii) N-(12-*Bromododecyl*)-4-*phenylazetidin*-2-*one* **30** (X = Br). The bromide was heated with liquid ammonia at 70 °C for 28 days and gave 3-[(12-aminododecyl)amino]-3-phenylpropanamide **33** (95%) $C_{19}H_{33}N_2$, M − C_2H_4NO, requires *m/z* 289.264) (Found: *m/z* 289.261. δ_H 7.25 (5 H, m, Ph), 5.70 (2 H, s, $CONH_2$), 3.93 (1 H, dd, *J* 6 and 8, PhC*H*), 2.00–2.80 (9 H, m, CH_2CO, CH_2NH, CH_2NH_2) and 1.60–0.85 (20 H, m, 10 × CH_2).

4-*Phenyl*-1-*propylazetidin*-2-*one* **37**.—Prepared by alkylation method B (above) from 4-phenylazetidin-2-one (4.00 g, 27 mmol), 1-bromopropane (5 cm^3, 54 mmol) and potassium hydroxide (4.6 g, 82 mmol) in DMSO (190 cm^3), the N-*propyl compound* **37** (4.68 g, 91%) had b.p. 128–131 °C at 2.5 mmHg (Found: C, 75.75; H, 8.3; N, 7.25%; M^+, 189.114. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7.4%; *M*, 189.115); ν_{max}(film)/cm^{-1} 1745; δ_H 7.30 (5 H, s, Ph), 4.50 (1 H, dd, *J* 2 and 5, 4-H), 3.50–3.15 (2 H, m, 3-H′ and NCH*H*), 2.95–2.60 (2 H, m, 3-H and NC*H*H), 1.40 (2 H, m, CH_2Me) and 0.85 (3 H, t, *J* 7, Me).

Treatment of 4-*Phenyl*-1-*propylazetidin*-2-*one* **37** *with Sodamide*.—The β-lactam (0.344 g, 1.8 mmol) was heated in toluene (27 cm^3) at reflux with sodamide (0.08 g, 2 mmol) for 20 h. Water was added and the product was worked up and purified by chromatography on silica gel, and eluted with hexane–chloroform (1:9), to give *N*-propylcinnamamide **39** (0.153 g, 50%), m.p. 79–81 °C (lit.,[45] 80–81 °C) (Found: M^+,189.115. Calc. for $C_{12}H_{15}NO$: *M*, 189.115); ν_{max}(Nujol mull)/cm^{-1} 1610, 1650 and 3260; δ_H 7.60 (1 H, d, *J* 18, 3-H), 7.50–7.00 (5 H, m, Ph), 6.50 (1 H, d, *J* 18, 2-H), 6.57 (1 H, br s, NH), 3.30 (2 H, q, *J* 7. NCH_2), 1.56 (2 H, sextuplet, *J* 7, CH_2) and 0.90 (3 H, t, *J* 7, Me).

(Z)-N-(4-*Chlorobut*-2-*enyl*)-4-*phenylazetidin*-2-*one* **40**.—By use of the phase-transfer procedure, this *compound* (0.97 g, 61%) was prepared from 4-phenylazetidin-2-one **10** (1.00 g, 6.8 mmol), potassium hydroxide (0.57 g, 10 mmol), tetrabutylammonium hydrogen sulfate (0.23 g, 0.68 mmol), and freshly distilled (*Z*)-1,4-dichlorobut-2-ene (1.5 cm^3, 14 mmol) and THF (30 cm^3). It was chromatographed on silica gel, and eluted with hexane–chloroform (1:4) (Found: M^+, 235.076. $C_{13}H_{14}ClNO$ requires *M*, 235.076); ν_{max}(film)/cm^{-1} 1740; δ_H 7.30 (5 H, m, Ph), 5.80–5.40 (2 H, m, CH=CH), 4.53 (1 H, dd, *J* 2 and 5, 4-H), 4.05 (1 H, dd, *J* 6 and 15, NCH*H*), 3.80 (2 H, d, *J* 7, CH_2Cl), 3.50 (1 H, dd, *J* 7 and 15, NC*H*H), 3.32 (1 H, dd, *J* 5 and 14, 3-H′) and 2.77 (1 H, dd, *J* 2 and 14, 3-H).

Treatment of (Z)-N-(4-*Chlorobut*-2-*enyl*)-4-*phenylazetidin*-2-*one* **40** *with Liquid Ammonia*.—(i) *At room temperature*. The chloro olefin (0.40 g, 1.7 mmol) was dissolved in liquid ammonia (20 cm^3) and the tube was sealed and kept at room temperature for 9 days. Work-up and chromatography on silica gel, and elution with methanol–chloroform (1:49), gave (*Z*)-4-phenyl-1,5-diazacyclonon-7-en-2-one **43** (see below) (0.099 g, 27%). Continued elution with isopropylamine–chloroform (1:9) gave (Z)-N-(4-*aminobut*-2-*enyl*)-4-*phenylazetidin*-2-*one* **41** (0.266 g, 72%) [Found: M^+ − 17, 199.100. $C_{13}H_{13}NO$ ($C_{13}H_{16}N_2O$ − NH_3) requires *m/z*, 199.100]; ν_{max}(film)/cm^{-1} 1665, 1740 and 3300 br; δ_H 7.34 (5 H, m, Ph), 5.90–5.30 (2 H, m, CH=CH), 4.55 (1 H, dd, *J* 2 and 5, 4-H), 4.15 (1 H, m, NCH*H*), 3.63 (2 H, m, CH_2NH_2), 3.01 (1 H, m, NC*H*H), 3.30 (1 H, dd, *J* 5 and 15, 3-H), 2.75 (1 H, dd, *J* 2 and 15, 3-H) and 1.90 (2 H, br s, NH_2).

(ii) *At* 70 °C. The chloro olefin (0.374 g, 1.6 mmol) was heated in liquid ammonia (20 cm^3) at 70 °C for 10 days. Chromatography on silica gel, and elution with methanol–chloroform (1:49), gave (Z)-4-*phenyl*-1,5-*diazacyclonon*-7-*en*-2-*one* **43** (0.195 g, 57%), which was crystallised slowly from ethyl acetate–hexane, m.p. 122.5–123.5 °C (Found: C, 72.5; H, 7.8; N, 13.1%; M^+, 216.125. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.5; N, 13.0%; *M*, 216.126); ν_{max}(film)/cm^{-1} 1640, 3100 and 3275; δ_H 7.30 (5 H, m, Ph), 6.60 (1 H, apparent d, 1-H), 5.85 (2 H, m, CH=CH), 4.72 (1 H, m, 9-H_a), 4.15 (1 H, dd, *J* 3.9 and 10.4, 4-H), 3.60–3.25 (2 H, m, 6-H_a, 9-H_b), 2.85 (1 H, dd, *J* 10.4 and 15, 3-H_a), 2.20–2.55 (2 H, m, 3-H_b, 6-H_b) and 1.85 (1 H, s, 5-H).

(E)-N-(4-*Bromobut*-2-*enyl*)-4-*phenylazetidin*-2-*one* **42**.—The *bromide* (1.44 g, 76%) was obtained by the method above using (*E*)-1,4-dibromobut-2-ene (2.91 g, 14 mmol) (Found: M^+, 200.107. $C_{13}H_{14}NO$ requires *M*, 200.113); ν_{max}(film)/cm^{-1} 1740; δ_H 7.45–7.20 (5 H, m, Ph), 5.80–5.60 (2 H, m, CH=CH), 4.55 (1 H, dd, *J* 2.3 and 5.2, 4-H), 4.11 (1 H, dd, *J* 4.2 and 15, NCH*H*), 3.86 (2 H, d, *J* 6.8, CH_2Br), 3.42 (1 H, m, NC*H*H), 3.37 (1 H, dd, *J* 5.2 and 14.7, 3-H′) and 2.87 (1 H, dd, *J* 2.3 and 14.7, 3-H).

When heated in liquid ammonia in a sealed tube at 70 °C for 10 days, the (*E*)-bromide **42** gave the (*E*)-amino amide **44** in ~20% yield.

N-(3-*Bromobutyl*)-4-*phenylazetidin*-2-*one* **51**. – 4-Phenylazetidin-2-one **10** (0.50 g, 3.4 mmol) was alkylated with 1,3-dibromobutane (1.10 g, 5.10 mmol) for 4 h using Method A. Work-up, and chromatography on silica gel, and elution with chloroform–hexane (19:1), then with chloroform, gave N-(3-*bromobutyl*)-4-*phenylazetidin*-2-*one* **51**, (0.82 g, 85%) (Found: M^+, 281.042. $C_{13}H_{16}BrNO$ requires *M*, 281.042); ν_{max}(film)/cm^{-1} 700, 1090, 1210, 1400, 1500 and 1755; δ_H 7.39 (5 H, m, Ph), 4.65–4.48 (1 H, m, C*H*Ph), 4.30–3.85 (1 H, m, CHBr), 3.70–2.85 (3 H, m, CH_2N, CH_aHCO), 2.82 (1 H, dd, *J* 2.5 and 14, CH_bCO), 2.15–1.80 (2 H, m, CH_2CH_2N) and 1.66 (3 H, d, *J* 7, Me).

N-(*But*-2-*enyl*)-4-*phenylazetidin*-2-*one* **52** *and* 8-*Methyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **53**.—The 3-bromobutyl compound **51** (353 mg, 1.25 mmol) was kept in a sealed Carius tube containing liquid ammonia (15 cm^3) for 7 days at 25 °C. Work-up and chromatography on silica gel, and elution first with chloroform, then with chloroform–methanol (99:1; then 49:1) gave (Z)/(E)-N-(*but*-2-*enyl*)-4-*phenylazetidin*-2-*one* **52** (64 mg, 25%) (Found: M^+, 201.114. $C_{13}H_{15}NO$ requires *M*, 201.115); ν_{max}(film)/cm^{-1} 700, 970, 1200, 1395, 1460, 1760 and 3040; δ_H 7.43 (5 H, m, Ph), 5.80–5.30 (2 H, m, CH=CH), 4.61 (1 H, dd, *J* 2 and 5, C*H*Ph), 4.28–3.98 (1 H, m, CH_aHN), 3.70–3.20 (2 H, m, CH_bN, CH_aHCO), 2.84 (1 H, dd, *J* 2 and 15, CH_bCO), 1.68–1.38 (3 H, m, Me of *Z* and *E* isomers).

Further elution gave 8-*methyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* (169 mg, 62%) as a solid showing two spots on TLC (diastereoisomers), m.p. 144–146 °C (from chloroform–hexane) (Found: M^+, 218.140. $C_{13}H_{18}N_2O$ requires M, 218.142);

ν_{max}(KBr)/cm^{-1} 760, 1185, 1410, 1650, 2930, 3050 and 3100. The diasteroisomeric mixture was again chromatographed using medium-pressure methods and Merck Kieselgel 60, with ethyl acetate–ethanol (49 : 1) as eluent, to give pure trans-8-*methyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **16** (used for X-ray single-crystal analysis), m.p. 151–152 °C (from acetone–hexane) (Found: C, 71.7; H, 8.35; N, 12.7. $C_{13}H_{18}N_2O$ requires C, 71.55; H, 8.3; N, 12.85%); δ_H 7.41–7.22 (5 H, m, Ph), 5.64 (1 H, d, *J* 9.9, NHCO), 4.21–4.05 (1 H, m, C*H*Me), 4.03 (1 H, dd, *J* 1.7 and 11.1, C*H*Ph), 3.23–3.14 (1 H, m, CH_aHN), 2.91 (1 H, dd, *J* 11.1 and 11.4, CH_aHCO), 2.58–2.47 (1 H, m, CHH_bN), 2.44 (1 H, dd, *J* 1.7 and 11.7, CHH_bCO), 1.96 (1 H, br s, NH), 1.93–1.79 (1 H, m, inner C*H*H), 1.39–1.26 (1 H, m, inner CH*H*) and 1.28 (3 H, d, *J* 6.6, Me).

The reaction was repeated by employing a reaction temperature of 60 °C for 5 days, when compound **52** was obtained (18%) together with the diastereoisomeric azalactam mixture **53** (71%).

N-(3-*Methylbut*-2-*enyl*)-4-*phenylazetidine*-2-*one* **55**.—4-Phenylazetidin-2-one **10** (0.50 g, 3.4 mmol) was allowed to react with 3-methylbut-2-enyl (prenyl) bromide for 3 h using Method A. Chromatography on silica gel, and elution with chloroform–hexane (9 : 1), then with chloroform, gave the *title compound* **55** (0.64 g, 88%) (Found: M$^+$, 215.130. $C_{14}H_{17}NO$ requires *M*, 215.131); ν_{max}(film)/cm^{-1} 700, 940, 1200, 1390, 1455 and 1755; δ_H 7.40 (5 H, m, Ph), 5.30–5.04 (1 H, m, CH=), 4.55 (1 H, dd, *J* 2 and 5, C*H*Ph), 4.08 (1 H, dd, *J* 6.5 and 15, CH_aHN), 3.60–3.20 (2 H, m, CHH_bN, CH_aHCO), 2.82 (1 H, dd, *J* 2 and 15, CHH_bCO), 1.66 (3 H, s, Me) and 1.42 (3 H, s, Me).

4-Phenylazetidin-2-one **10** (0.50 g, 3.4 mmol) reacted with 1,3-dibromo-3-methylbutane (1.17 g, 5.1 mmol) under similar conditions to yield compound **55** (0.36 g, 50%) and not the desired bromide **54**.

N-(3-*Bromo*-3-*methylbutyl*)-β-*phenyl*-β-*alanine* **56**.—The prenyl derivative **55** (360 mg, 1.67 mmol) was treated overnight with HBr in acetic acid (45% w/w; 5 cm^3) at room temperature. Work-up, and chromatography on silica gel, and elution with chloroform–methanol (99 : 1), gave the *title zwitterion* **56** (364 mg, 69%), m.p. 110–114 °C (Found: [M$^+$ − HBr], 233.140. $C_{14}H_{19}NO_2$ requires *m*/*z* 233.142); ν_{max}(KBr)/cm^{-1} 700, 760, 1130, 1250, 1400, 1565, 2300–2600 br; δ_H (CF_3CO_2D) 11.68 (2 H, s, exchangeable protons as CF_3CO_2H), 7.64 (5 H, m, Ph), 4.90 (1 H, dd, *J* 5.5 and 9, C*H*Ph), 3.62–3.32 (4 H, m, CH_2N^+, $CH_2CO_2^-$), 2.39–2.20 (2 H, m, $CH_2CH_2N^+$), 1.78 (3 H, s, Me) and 1.75 (3 H, s, Me).

Treatment of N-(3-*Chloropropyl*)-4-*phenylazetidin*-2-*one* **11** (X = Cl) *with Anhydrous Ethylamine*.—The title azetidinone (379 mg, 1.70 mmol) was sealed in a Carius tube with ethylamine (15 cm^3) and kept at 40 °C for 7 days. After work-up the product was chromatographed on silica gel, and eluted with chloroform–methanol (99 : 1), then with chloroform–methanol–isopropylamine (94 : 5 : 1), to yield three products. First eluted was 1-*ethyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **61** (120 mg, 31%), an oil, which was distilled in a bulb tube at 148–150 °C (oven temp.)/0.05 mmHg (Found: M$^+$, 232.157. $C_{14}H_{20}N_2O$ requires M, 232.158); ν_{max}(film)/cm^{-1} 710, 775, 1080, 1180, 1320, 1640, 2950 and 3340; δ_H 7.41–7.22 (5 H, m, Ph), 4.18–4.05 (1 H, m, ring C*H*NCO), 4.02 (1 H, dd, *J* 1.7 and 10.5, C*H*Ph), 3.82 (1 H, J_{gem} 13.4, MeC*H*H), 3.31–3.14 (2 H, m, ring C*H*NCO, C*H*HN), 3.14–2.94 (2 H, m, MeCH*H*, C*H*HCO), 2.51 (1 H, dd, *J* 1.7 and 12.8, CH*H*CO), 2.48–2.34 (1 H, m, CH*H*N), 1.80 (1 H, s, NH), 1.87–1.58 (2 H, m, CH_2CH_2N) and 1.18 (3 H, t, *J* 7.2). The resonance at δ 1.80 disappeared on shaking with D_2O. The J_{gem} coupling at δ 3.82 was determined after irradiation of the methyl group; δ_C 13.1 (Me), *31.6*, *40.3*, *44.2*, *44.7*, *45.4*, 64.6 (C-4), 126.4, 127.4, 128.5, *144.9* and *172.6* (C=O).

In elution order there followed N-(3-*ethylaminopropyl*)-4-*phenylazetidin*-2-*one* **60**, (83 mg, 21%) (Found: M$^+$, 232.157. $C_{14}H_{20}N_2O$ requires *M*, 232.158); ν_{max}(film)/cm^{-1} 930, 1365, 1520, 1740, 3320 and 3460; δ_H 7.40 (5 H, m, Ph), 4.60 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.68–3.26 (2 H, m, C*H*HCO, C*H*NCO), 3.12–2.50 (6 H, m, CH*H*CO, C*H*NCO, 2 × CH_2N), 1.84–1.46 (3 H, m, CH_2CH_2N, NH) and 1.08 (3 H, t, *J* 7, Me).

Finally, N-*ethyl*-3-*phenyl*-4,8-*diazadecanamide* **62** (154 mg, 33%) was eluted. (Found: M$^+$ + 11], 288.206 and M$^+$, 277.214. $C_{17}H_{26}N_3O$ [M + 11] requires *m*/*z*, 288.207 and $C_{16}H_{27}N_3O$ requires M, 277.215); ν_{max}($CHCl_3$)/cm^{-1} 925, 1025, 1520, 1655, 3250 and 3450; δ_H 7.50–7.20 (6 H, m, Ph, NHCO), 3.98 (1 H, dd, *J* 6 and 8, C*H*Ph), 3.42–3.10 (2 H, m, CH_2NCO), 2.80–2.42 (8 H, m, CH_2CO and 3 × CH_2N), 1.84 (2 H, s, 2 × NH), 1.82–1.42 (2 H, q, CH_2CH_2N) and 1.10 (6 H, t, *J* 7.5, 2 × Me). See also Table 2.

In an experiment in which the chloropropyl compound was treated with ethylamine at 20 °C for 48 h, the ethylamino-azetidin-2-one **60** (89% yield) was obtained after chromatography on silica gel, and elution with isopropylamine–chloroform (1 : 9).

Ring Expansion of N-[3-(*Ethylamino*)*propyl*]-4-*phenylazetidin*-2-*one* **60**.—(i) *In refluxing toluene*. The β-lactam (500 mg, 2.2 mmol) was refluxed in dry toluene (60 cm^3) under nitrogen for 9 days. Work-up, and chromatography on silica gel, and elution with methanol–chloroform (1.5 : 98.5), gave 1-ethyl-4-phenyl-1,5-diazacyclooctan-2-one **61** (see above) (219 mg, 44%). On continued elution with isopropylamine–chloroform (1 : 9) the starting β-lactam (177 mg, 35%) was recovered.

(ii) *In liquid ammonia*. The β-lactam **60** (319 mg, 1.4 mmol) in liquid ammonia (20 cm^3) was kept at 70 °C in a Carius tube for 7 days. Work-up, and chromatography gave 1-ethyl-4-phenyl-1,5-diazacyclooctan-2-one **61** (258 mg, 79%), b.p. 240 °C at 0.5 mmHg.

1-*Ethyl*-4-*phenyl*-1,5-*diazacycloheptan*-2-*one* **64**.—*N*-(2-Bromoethyl)-4-phenylazetidin-2-one **24** (246 mg, 0.97 mmol) was sealed with ethylamine (25 cm^3) at 45 °C for 7 days. Chromatography on silica, after work-up, and elution with chloroform, then with chloroform–methanol (49 : 1), gave 1-*ethyl*-4-*phenyl*-1,5-*diazacycloheptan*-2-*one* **64** (187 mg, 88%) which was distilled in a bulb tube at 119–120 °C (oven temp.)/0.01 mmHg (Found: C, 71.55; H, 8.65; N, 12.4%; M$^+$, 218.140. $C_{13}H_{18}N_2O$ requires C, 71.5; H, 8.3; N, 12.8%; *M*, 218.142); ν_{max}(film)/cm^{-1} 1215, 1310, 1480, 1640 and 3310; δ_H 7.46–7.21 (5 H, m, Ph), 3.88 (1 H, d, *J* 10, C*H*Ph), 3.81–3.69 (1 H, m, ring CHN), 3.60–3.37 (2 H, m, MeCH_2), 3.33–3.22 (2 H, m, 2 × ring CHN), 3.06–2.87 (2 H, m, ring CHN and C*H*HCO), 2.69 (1 H, dd, *J* 0.8 and 14.1, CH*H*CO), 2.02 (1 H, s, NH) and 1.15 (3 H, t, *J* 7, Me). The resonance at δ 2.02 disappeared on shaking with D_2O. The exocyclic methylene was located by irradiation of the Me triplet at δ 1.15 when only the signal centred on δ 3.50 was affected. Irradiation of the signal at δ 2.69 (CH*H*CO) indicated the position of the geminal resonance (C*H*HCO) to be within the multiplet centred on δ 3.0.

N-*Ethyl*-3-*phenyl*-4,9-*diazaundecanamide* **65**.—*N*-(4-Chlorobutyl)-4-phenylazetidin-2-one **18** (X = Cl) (360 mg, 1.52 mmol) and ethylamine (15 cm^3) were heated in a sealed Carius tube for 7 days at 60 °C. Work-up, and chromatography on silica gel, with chloroform–isopropylamine (49 : 1) as eluent, gave the *title amide* **65** (195 mg, 44%) (Found: M$^+$, 291.231. $C_{17}H_{29}N_3O$ requires *M*, 291.231); ν_{max}(film)/cm^{-1} 1120, 1455, 1560, 1645 and 3300; δ_H 7.70–7.15 (6 H, m, Ph, NHCO), 3.90 (1 H, dd, *J* 6 and 8, C*H*Ph), 3.46–2.08 (2 H, m, CH_2N), 2.70–2.20 (8 H, m, 3 × CH_2,

CH_2CO), 1.68 (2 H, s, 2 × NH), 1.60–1.28 (4 H, m, inner CH_2s) and 1.00 (6 H, t, *J* 7, 2 × Me).

1-[4-(*Ethylamino*)*butyl*]-4-*phenylazetidin*-2-*one* **18** (X = NHEt).—1-(4-Chlorobutyl)-4-phenylazetidin-2-one **18** (X = Cl) (2.05 g, 8.6 mmol) was kept in ethylamine (40 cm^3) for 24 h at room temperature in a Carius tube. The ethylamine was evaporated off and the residue was dissolved in chloroform (100 cm^3) and the solution was again evaporated. The oil was chromatographed on silica gel, and eluted first with methanol–chloroform (1:49) to remove unchanged starting chloride (0.90 g, 44%), and then with isopropylamine–chloroform (1:9) to give the title amine **18** (X = NHEt) (1.20 g, 56%): δ_H 1.05 (3 H, t, *J* 7, NCH_2Me), 1.50 (4 H, m, $CH_2CH_2CH_2NEt$), 2.40 (1 H, br s, exchanges with D_2O, NH), 3.50–2.45 (8 H, m, 3-H_2 and 3 × CH_2N), 4.55 (1 H, dd, *J* 5 and 2, 4-H) and 7.30 (5 H, s, Ph).

1-*Allyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **66**.—*N*-(3-Chloropropyl)-4-phenylazetidin-2-one **11** (X = Cl) (742 mg, 3.32 mmol) was dissolved in freshly distilled allylamine (15 cm^3) and the solution was kept in a sealed tube at 85 °C for 7 days. Partition between water and chloroform, followed by extraction (chloroform), gave, on evaporation, an oil, which was chromatographed on silica gel [eluent chloroform, then chloroform–methanol (49:1)]. First eluted was the *title cyclooctanone* **66** (447 mg, 55%) (Found: M^+, 244.156. $C_{15}H_{20}N_2O$ requires *M*, 244.158); ν_{max}(film)/cm^{-1} 700, 760, 930, 1170, 1460, 1630 and 3310; δ_H 7.56–7.24 (5 H, m, Ph), 6.10–5.68 (1 H, m, CH=), 5.32–5.08 (2 H, m, H_2C=), 4.52 (1 H, dd, *J* 5 and 15, C*H*CH=), 4.35–3.90 (1 H, m, C*H*HN), 4.06 (1 H, dd, *J* 2 and 10, C*H*Ph), 3.60 (1 H, dd, *J* 7 and 15, C*H*CH=), 3.42–2.88 (3 H, m, CH_2N, C*H*HCO), 2.58–2.20 (1 H, m, CH*H*N), 2.54 (1 H, dd, *J* 2 and 13, CH*H*CO), 1.98–1.50 (2 H, m, CH_2CHN) and 1.88 (1 H, s, NH). The signal at δ 1.88 disappeared on shakng with D_2O.

There followed N-*allyl*-3-*phenyl*-4-*azahept*-6-*enamide* **69** (56 mg 7%) (Found: [M^+ + 11], 255.148; M^+, 244.156. $C_{16}H_{19}N_2O$ [M + 11] requires *m/z*, 255.150; $C_{15}H_{20}N_2O$ requires *M*, 244.158); ν_{max}(film)/cm^{-1} 760, 920, 1540, 1650, 2900, 3070 and 3280; δ_H 7.55–7.24 (6 H, m, Ph, NHCO), 6.10–5.62 (2 H, m, 2 × CH=), 5.30–5.00 (4 H, m, 2 × H_2C=), 4.06 (1 H, dd, *J* 5.5 and 9, C*H*Ph), 3.96–3.76 (2 H, m, CH_2NCO), 3.18–3.02 (2 H, m, CH_2N), 2.64–2.48 (2 H, m, CH_2CO) and 2.16 (1 H, s, NH). The peak at δ 2.16 disappeared on shaking with D_2O.

Reaction of N-(4-*Chlorobutyl*)-4-*phenylazetidin*-2-*one* **18** (X=Cl) *with Allylamine*.—(i) *At* 90 °C. The azetidinone **18** (X=Cl) (1.13 g, 4.75 mmol) was kept in allylamine (40 cm^3) in a sealed tube at 90 °C for 6 days. Work-up gave a gum (1.54 g), which on chromatography on silica gel, and elution with chloroform, then with chloroform–methanol (49:1), gave N-*allylcinnamamide* **68** (121 mg, 14%) (Found: M^+, 187.101. $C_{12}H_{13}NO$ requires *M*, 187.100); δ_H 7.70 [1 H, d, *J* 16, (*E*)-OCHC=], 7.60–7.26 (5 H, m, Ph), 6.90 (1 H, br s, NHCO), 6.65 [1 H, d, *J* 16, (*E*)-PhC*H*=], 6.20–5.74 (1 H, m, C*H*=CH_2), 5.40–5.08 (2 H, m, CH=CH_2) and 4.12–3.90 (2 H, m, CH_2N). Continued elution gave *N*-allyl-3-phenyl-4-azahept-6-enamide **69** (see above).

(ii) *At* 53 °C. A mixture of the azetidin-2-one (624 mg, 2.63 mmol) in allylamine (30 cm^3) was heated under reflux for 3.5 days and then worked up by chromatography on silica gel, with chloroform, then with chloroform–methanol (19:1) as eluent. N-(4-*Allylaminobutyl*)-4-*phenylazetidin*-2-*one* **72** (375 mg, 58%) was isolated as an oil (Found: M^+, 258.171. $C_{16}H_{22}N_2O$ requires *M*, 258.173); ν_{max}(film)/cm^{-1} 750, 920, 1400, 1750 and 3320. δ_H 7.40 (5 H, s, Ph), 6.14–5.66 [1 H, m, (*E*)-CH=], 5.30–4.96 (2 H, m, H_2C=), 4.60 (1 H, dd, *J* 2 and 5, C*H*Ph), 3.60–3.10 (4 H, m, C*H*HCO, 3 × CHN), 3.05–2.46 (4 H, m, CH*H*CO, 3 × CHN), 1.65–1.30 (4 H, m, inner CH_2s) and 1.34 (1 H, s, NH). The signal at δ 1.34 disappeared on shaking with D_2O.

1-*Allyl*-4-*phenyl*-1,5-*diazacyclononan*-2-*one* **73**.—N-(4-Allylaminobutyl)-4-phenylazetidin-2-one **72** (349 mg, 1.35 mmol) was heated under reflux in toluene (50 cm^3) for 4 days. Work-up, and chromatography on silica gel, and elution with chloroform–methanol (49:1), gave the *title cyclononanone* **73** (123 mg, 35%) (Found: M^+, 258.174. $C_{16}H_{22}N_2O$ requires *M*, 258.173); ν_{max}(film)/cm^{-1} 925, 1135, 1460, 1625, 2940 and 3360; δ_H 7.35 (5 H, s, Ph), 6.14–5.68 (1 H, m, CH=), 5.40–5.08 (2 H, m, H_2C=), 5.00–4.50 (2 H, m, =CHCH_2N), 3.84 (1 H, d, *J* 10, C*H*Ph), 3.62–2.60 (5 H, m, C*H*HCO, 2 × CH_2N), 2.65 (1 H, d, *J* 13, CH*H*CO) and 2.20–1.20 (5 H, m, inner CH_2s and NH). The last signal lost a singlet at δ 1.7 on shaking with D_2O. Further elution led to recovery of starting azetidinone (147 mg, 42%). Allowing for recovered material the yield was 60% (at 58% conversion).

N-(3-*Isopropylaminopropyl*)-4-*phenylazetidin*-2-*one hydrochloride*, cf. **74**.—*N*-(3-Chloropropyl)-4-phenylazetidin-2-one **11** (X=Cl) (600 mg, 2.53 mmol) was kept in isopropylamine (25 cm^3) at 45 °C, sealed in a Carius tube for 4 days. Work-up, and chromatography on silica gel, and elution with chloroform, then with chloroform–methanol (19:1), gave N-(3-*isopropylaminopropyl*)-4-*phenylazetidin*-2-*one hydrochloride*, *i.e.* compound **74** as its hydrochloride (561 mg, 74%), m.p. 135–136 °C (from acetone) (Found: C, 63.25; H, 8.3; N, 9.55%; M^+, 246.173. $C_{15}H_{23}ClN_2O$ requires C, 63.7; H, 8.2; N, 9.9%. $C_{15}H_{22}N_2O$ requires *M*, 246.173); ν_{max}(KBr)/cm^{-1} 1160, 1200, 1360, 1400, 1600, 1760, 2500 and 2750 br; δ_H 7.50 (2 H, s, $^+NH_2$), 7.40 (5 H, m, Ph), 4.78 (1 H, dd, *J* 2.5 and 5, C*H*Ph), 3.70–3.16 (3 H, m, C*H*HCO, 2 × CHN), 3.14–2.68 (4 H, m, CH*H*CO, 3 × CHN), 2.26–1.86 (2 H, m, CH_2CH_2N) and 1.36 (6 H, d, *J* 7, 2 × Me).

In a second experiment the β-lactam chloride was treated with isopropylamine for 7days at room temperature and the free base **74** was isolated as an oil (75%) (Found: M^+, 246.172. $C_{15}H_{22}N_2O$ requires *M*, 246.173); ν_{max}(film)/cm^{-1} 1740 and 3420 br.

1-*Isopropyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **75**.—The azalactam **13** (408 mg, 2 mmol) was alkylated (22.5 h) with 2-iodopropane (0.4 cm^3, 4 mmol) in THF (20 cm^3) in the presence of potassium bis(trimethylsilyl)amide (2.1 mmol). Work-up, and chromatography on silica gel, and elution with methanol–chloroform (1:99), gave the *isopropyl derivative* **75** (98 mg, 20%) as a golden oil which slowly crystallised to a white solid, m.p. 77–80 °C (Found: M^+, 246.174. $C_{15}H_{22}N_2O$ requires *M*, 246.173); ν_{max}(Nujol mull)/cm^{-1} 1615 and 3280; δ_H 7.40–7.20 (5 H, m, Ph), 4.73 (1 H, septet, *J* 6.8, C*H*Me_2), 4.05 (1 H, dd, *J* 10.9 and 1.8, 4-H), 3.90 (1 H, m, 8-H_a), 3.40 (1 H, m, 8-H_b), 3.17 (1 H, dt, *J* 15.0 and 3.7, 6-H_a), 3.00 (1 H, dd, *J* 12.6 and 10.9, 3-H_a), 2.53 (1 H, dd, *J* 12.8 and 1.8, 3-H_b), 2.50 (1 H, m, 6-H_b), 1.82 (1 H, br s, NH), 1.72 (2 H, m, 7-H_2) and 1.20 (6 H, app. dd, CH*Me*$_2$).

Continued elution with methanol–chloroform (1:19) allowed recovery of unchanged starting material (323 mg, 79%) so the yield at low conversion was near theoretical.

Treatment of N-[3-(*Isopropylamino*)*propyl*]-4-*phenylazetidin*-2-*one* **74** *with Liquid Ammonia*.—The β-lactam (510 mg, 2.1 mmol) was dissolved in liquid ammonia (20 cm^3) and the tube was sealed for 7 days at 70 °C. Work-up gave a gum, which was examined by ^1H NMR spectroscopy: this showed that only ~30% of the β-lactam had reacted. The gum was redissolved in liquid ammonia and the tube was again sealed up for 7 days at 70 °C. Work-up gave a new gum which contained ~20% of starting β-lactam. It was chromatographed on silica gel, and eluted with methanol–chloroform (1:49). First eluted was

N-isopropyl-4-phenyl-1,5-diazacyclooctan-2-one **75** (68.5 mg, 13%), spectroscopically identical with the specimen above, followed by cinnamamide **77** (18.9 mg, 6%). The latter had δ_H($CDCl_3$ containing 3 drops of CF_3CO_2D) 7.80 (1 H, d, *J* 15.5, PhC*H*=CHCO), 7.60–7.20 (5 H, m, Ph), 6.45 (d, *J* 15.5, CH=C*H*CO).

Continued elution with isopropylamine–chloroform (1:9) gave an approximately equimolar mixture (191 mg, ~20% of each) of unchanged starting lactam **74** and the straight-chain diamino amide **76**. The latter had δ_H 7.50–7.20 (7 H, m, Ph, $CONH_2$), 4.00 (1 H, dd, *J* 6 and 8, PhC*H*N), 3.70–2.30 (7 H, m, 3 × CH_2, NC*H*Me_2), 2.00–1.80 (2 H, br, 2 × NH), 1.60 (2 H, m, CH_2) and 1.00 (6 H, m, CH*Me*$_2$). [During work-up of this experiment a white precipitate was produced, which ^{1}H NMR spectroscopy indicated was largely cinnamamide **77**: this presumably makes up the mass balance.]

N-*Acetyl*-4-*phenylazetidin*-2-*one* **45**.—Butyllithium (15 mmol) was added at −30 °C to a solution of 4-phenylazetidin-2-one **10** (2.00 g, 14 mmol) in dry THF (40 cm^3) and the mixture was stirred at this temperature for 30 min after which acetyl chloride (1.1 cm^3, 16 mmol) was added. The mixture was allowed to warm to room temperature over a period of 4 h and then worked up. Chromatography on silica gel, and elution with hexane–chloroform (1:4), gave the *acetyl compound* **45** (1.26 g, 50%) (Found: M^+, 189.079. $C_{11}H_{11}NO_2$ requires *M*, 189.079); ν_{max}(film)/cm^{-1} 1695 and 1775; δ_H 7.31 (5 H, m, Ph), 5.00 (1 H, dd, *J* 3 and 6, 4-H), 3.42 (1 H, dd, *J* 6 and 16, 3-H′), 2.87 (1 H, dd, *J* 3 and 16, 3-H) and 2.37 (3 H, s, Me).

Treatment of N-*Acetyl*-4-*phenylazetidin*-2-*one* **45** *with Liquid Ammonia*.—The acetyl β-lactam (0.51 g, 2.7 mmol) was sealed with liquid ammonia (20 cm^3) at room temperature for 6 days. Work-up (**CARE**, as the mixture set solid) gave 3-*acetamido*-3-*phenylpropanamide* **48** (0.485 g, 87%), m.p. 225–227 °C (Found: M^+, 206.104. $C_{11}H_{14}N_2O_2$ requires *M*, 206.106); ν_{max}(Nujol mull)/cm^{-1} 1650, 3185, 3320 and 3385; δ_H(CF_3CO_2D) 7.00 (5 H, m, Ph), 5.15 (1 H, t, *J* 7, PhC*H*), 2.80 (2 H, d, *J* 7, CH_2) and 2.05 (3 H, s, Me).

N-(*Chloroacetyl*)-4-*phenylazetidin*-2-*one* **46**.—4-Phenylazetidin-2-one **10** (1.00 g, 6.8 mmol) was treated with butyllithium (7.6 mmol) in dry THF (25 cm^3) at −25 °C and, after the mixture had been stirred (15 min), chloroacetyl chloride (0.6 cm^3, 7.5 mmol) was added and the mixture was allowed to attain room temperature. Work-up, and chromatography on silica gel, with hexane–chloroform (1:4) as eluent, gave the *chloro compound* **46** (0.87 g, 58%) (Found: M^+, 223.039. $C_{11}H_{10}ClNO_2$ requires *M*, 223.040); ν_{max}(film)/cm^{-1} 1700 and 1780; δ_H 7.30 (5 H, m, Ph), 5.00 (1 H, dd, *J* 3 and 6, 4-H), 4.37 (2 H, s, CH_2Cl), 3.45 (1 H, dd, *J* 6 and 18, 3-H′) and 2.90 (1 H, dd, *J* 3 and 18, 3-H).

Treatment of N-(*Chloroacetyl*)-4-*phenylazetidin*-2-*one* **46** *with Liquid Ammonia*.—The chloroacetyl compound **46** (0.60 g, 2.7 mmol was heated in liquid ammonia (20 cm^3) at 70 °C for 7 days. Work-up gave 3-(2-*aminoacetamido*)-3-*phenylpropanamide* **49** [Found: M^+ − 58, 163.087. $C_9H_{11}N_2O$ ($C_{11}H_{15}N_3O_2$ − CH_3CONH) requires *m/z* 163.087]; ν_{max}(film)/cm^{-1} 1650 and 3000–3500 br; δ_H 7.25 (5 H, m, Ph), 6.40–7.10 (3 H, br, $CONH_2$, CONH), 4.31 (1 H, t, *J* 7, CH), 3.20 (2 H, s, CH_2NH_2) and 2.43 (2 H, d, *J* 7, CH_2CONH_2).

N-(3-*Chloropropanoyl*)-4-*phenylazetidin*-2-*one* **47**.—4-Phenylazetidin-2-one **10** (500 mg, 3.4 mmol) in dry THF (25 cm^3) at −40 °C and under nitrogen was treated with butyllithium (1.34 mol dm^{-3} in hexane; 2.80 cm^3, 3.7 mmol) and stirred (15 min). 3-Chloropropanoyl chloride (475 mg, 3.7 mmol) was added with agitation and, after 1 h, solvents were evaporated off and the residue was chromatographed on silica gel with chloroform–hexane (9:1, then 19:1) as eluent to give N- (3-*chloropropanoyl*)-4-*phenylazetidin*-2-*one* **47** (594 mg, 74%), crystallised from acetone–hexane, m.p. 75–77 °C (Found: C, 60.75; H, 5.1; N, 5.95%; M^+, 237.053. $C_{12}H_{12}ClNO_2$ requires C, 60.65; H, 5.1; N, 5.9%; *M*, 237.056; ν_{max}(KBr)/cm^{-1} 770, 1050, 1290, 1385, 1700 and 1780; δ_H 7.42 (5 H, m, Ph), 5.10 (1 H, dd, *J* 4.5 and 7, C*H*Ph), 3.82 (2 H, t, *J* 6, CH_2Cl), 3.52 (1 H, dd, *J* 7 and 17, C*H*HCO), 3.26 (2 H, t, *J* 6, CH_2CO) and 2.96 (1 H, dd, *J* 4.5 and 17, CH*H*CO).

Reaction between N-3-(*Chloropropanoyl*)-4-*phenylazetidin*-2-*one* **47** *and Liquid Ammonia*.—*N*-(3-Chloropropanoyl)-4-phenylazetidin-2-one **47** (315 mg, 1.33 mmol) was treated at 60 °C for 7 days with liquid ammonia in a sealed Carius tube. Work-up gave a gum (350 mg) and TLC on silica [eluent methanol–aq. ammonia (6:1)] indicated one predominant component. Spectral analysis of the crude material indicated that it was 3-(3-*aminopropanamido*)-3-*phenylpropanamide* **50** (Found: M^+, 235.131. $C_{12}H_{17}N_3O_2$ requires *M*, 235.132); δ_H(CD_3OD) 7.60–7.10 (5 H, m, Ph), 5.50–5.20 (1 H, m, C*H*Ph), 3.30–3.00 (2 H, m, CH_2N) and 2.90–2.50 (4 H, m, 2 × CH_2CO).

1-(2-*Cyanoethyl*)-4-*phenyl*-1,5-*diazacyclononan*-2-*one* [3-(2-*Oxo*-4-*phenyl*-1,5-*diazacyclononyl*)*propanonitrile*]**82**.—Sodium (250 mg, 11 mg-atom) was dissolved in absolute ethanol (10 cm^3). Part of the solution (1 cm^3 containing 1.1 mmol of NaOEt) was evaporated to dryness and dry toluene (7 cm^3) and 4-phenyl-1,5-diazacyclononan-2-one **20** (218 mg, 1 mmol) was added. The suspension was heated under nitrogen until a pale yellow solution was obtained, and was then cooled to 20 °C. A solution of freshly distilled acrylonitrile (0.73 cm^3, 0.56 g, 11 mmol) in toluene (5 cm^3) was added during 3 h to the vigorously stirred mixture, which was then stirred for a further 3 h. The product was poured into ethyl acetate (50 cm^3) and the solution was filtered and then evaporated. The resulting oil was chromatographed on silica gel with chloroform as eluent, then with chloroform–methanol (49:1), to give 1-(2-*cyanoethyl*)-4-*phenyl*-1,5-*diazacyclononan*-2-*one* **82** as an oil (222 mg, 82%), after distillation in a bulb tube (oven temperature 166–170 °C, 0.1 mmHg) (Found: M^+, 271.167. $C_{16}H_{21}N_3O$ requires *M*, 271.169); ν_{max}(film)/cm^{-1} 915, 1130, 1375, 1460, 1620, 2250 and 3340; δ_H 7.35 (5 H, m, Ph), 5.12–4.76 (1 H, m, CNH), 4.18–2.40 (10 H, m, C*H*Ph, CH_2CO, 5 × CHN, CH_2CN) and 2.20–1.20 (5 H, m, 2 × CH_2 β to N, NH). The latter group of signals was reduced to 4 H on shaking with D_2O.

1-(3-*Aminopropyl*)-4-*phenyl*-1,5-*diazacyclononan*-2-*one* **84** *by Hydrogenation*.—The above cyanoethyl compound (0.63 g, 2.3 mmol) and conc. HCl (0.6 cm^3, 7 mmol) in ethanol (80 cm^3) were shaken in hydrogen (1 atm; 20 °C) over a platinum oxide catalyst (100 mg). After 7 h, TLC indicated incomplete reaction so further catalyst (100 mg) was added and hydrogenation was continued for 18 h more. Filtration through Kieselguhr and evaporation left a solid, which was treated with saturated ammoniacal chloroform (50 cm^3) and was again filtered and evaporated. Chromatography on silica gel, with chloroform–isopropylamine (99:1; then 19:1) as eluent, gave 1-(3-*aminopropyl*)-4-*phenyl*-1,5-*diazacyclononan*-2-*one* **84** as an oil (0.52 g, 81%) (Found: M^+, 275.200. $C_{16}H_{25}N_3O$ requires *M*, 275.200); ν_{max}(film)/cm^{-1} 750, 1135, 1470, 1620 and 3360; δ_H 7.36 (5 H, m, Ph), 4.98–4.58 (1 H, m, CHN), 4.18–3.74 (2 H, m, C*H*Ph, CHN), 3.42–2.52 (8 H, m, CH_2CO, 6 × CHN), 2.14 (3 H, br s, NH, NH_2) and 2.00–1.24 (6 H, m, 3 × CH_2 β to N). The resonance at δ 2.14 was removed on shaking with D_2O.

4-*Phenyl*-N-(3-*phthalimidopropyl*)-1,5-*diazacyclononan*-2-*one*

83.—A solution of 4-phenyl-1,5-diazacyclononan-2-one **20** (566 mg, 2.6 mmol) in THF (10 cm^3) was treated with potassium bis(trimethylsilyl)amide (2.9 mmol) and a solution of *N*-(3-bromopropyl)phthalimide (780 mg, 2.9 mmol) in THF (13 cm^3), and the mixture was stirred for 24 h. Work-up gave the *title compound* **83** (553 mg, 53%) (Found: M^+, 405.204. $C_{24}H_{27}N_3O_3$ requires *M*, 405.205); ν_{max}(film)/cm^{-1} 1615, 1700, 1770 and 3150; δ_H 7.90–7.55 (4 H, m, phthalimide), 7.50–7.10 (5 H, m, Ph), 4.75 (1 H, m, NCH*H*[CH_2]$_2$NPht), 4.05–2.30 (10 H, m, 3-, 6-and 9-H_2, CH_2NPht NC*H*H[CH_2]$_2$NPh and 4-H) and 2.11–1.20 (7 H, m, 3 × CH_2 and NH).

1-(3-*Chloropropyl*)-4-*phenyl*-1,5-*diazacyclononan*-2-*one* **85**.—The azalactam **20** (1.358 g, 6.3 mmol) was alkylated (20 h) with 1-bromo-3-chloropropane (1.6 cm^3, 16 mmol) in THF (50 cm^3) in the presence of potassium bis(trimethylsilyl)amide (7 mmol). Work-up, and chromatography on silica gel, with pentane–chloroform (3:17) as eluent, gave the chloropropyldiazacyclononan-2-*one* **85** (0.727 g, 39%), ν_{max}/cm^{-1} (film) 1640 and 3300; δ_H 7.27 (5 H, s, Ph), 4.75 (1 H, m, NCH*H*[CH_2]$_2$Cl), 3.55 (2 H, t, *J* 7, CH_2Cl), 4.00–2.40 (8 H, m, 3-, 6- and 8-H_2, 4-H and NCH*H*[CH_2]$_2$Cl) and 1.20–2.20 (7 H, m, CH_2 and NH).

Continued elution gave recovered starting azalactam (0.667 g, 49%), giving a yield of 76% at 51% conversion.

1-(3-*Aminopropyl*)-4-*phenyl*-1,5-*diazacyclononan*-2-*one* **84** *by Amination*.—The above chloropropyl compound (727 mg, 2.5 mmol) was dissolved in liquid ammonia (40 cm^3), and the container was sealed, and kept at room temperature for 10 days. Work-up, and chromatography on silica gel, and elution with methanol–chloroform (3:97), gave 1-allyl-4-phenyl-1,5-diazacyclononan-2-one **73** (133 mg, 21%) (see above).

Continued elution with isopropylamine–chloroform (1:9) gave the title aminopropyl compound **84** (above) (354 g, 52%) (Found: M^+, 275.202. Calc. for $C_{16}H_{25}N_3O$: *M*, 275.200).

1-(4-*Chlorobutyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **80**—4-Phenyl-1,5-diazacyclooctan-2-one **13** (300 mg, 1.5 mmol) and 1-bromo-4-chloropropane (504 mg, 3.0 mmol) were added to a mixture of powdered potassium hydroxide (327 mg, 5.8 mmol) and DMSO (2 cm^3) which had been pre-stirred (15 min). The product was stirred at 20 °C for 70 h, then was poured into water and extracted with dichloromethane. After evaporation the product was chromatographed on silica gel and eluted with chloroform, and then with chloroform–methanol (49:1), to give the *title compound* **80** (317 mg, 73%) (Found: M^+, 294.150. $C_{16}H_{23}ClN_2O$ requires *M*, 294.150); ν_{max}(film)/cm^{-1} 705, 760, 1170, 1320, 1465, 1635 and 3320; δ_H 7.50–7.20 (5 H, m, Ph), 4.35–3.50 (2 H, m, 2 × CHN), 4.05 (1 H, dd, *J* 2 and 10, C*H*Ph), 3.65–3.50 (2 H, m, CH_2Cl), 3.35–2.80 (4 H, m, C*H*HCO, 3 × CHN), 2.50–2.15 (1 H, m, CHN), 2.50 (1 H, dd, *J* 2 and 12, CH*H*CO) and 2.00 (1 H, s, NH) 1.60–1.90 (6 H, m, 3 × CH_2); δ_C *25.2*, *30.0*, *31.5*, *44.2*, *44.5*, *44.7*, *45.0*, *45.4*, 64.7 (C-4), 126.4, 127.5, 128.6, *144.9* and *173*.

The alkylation was also performed using potassium bis(trimethylsily)amide (8.4 mmol), azalactam **13** (1.5 g, 7.4 mmol) and 1-bromo-4-chlorobutane (2.2 cm^3, 19 mmol) in THF (60 cm^3) with a reaction time of 24 h. The yield of chlorobutyl derivative **80** was 1.91 g (88%).

1-(4-*Aminobutyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **81**.—The chlorobutyl compound **80** (1.30 g, 4.4 mmol) was dissolved in liquid ammonia (20 cm^3) and the mixture was kept at room temperature for 7 days in a sealed tube. After unsealing, and evaporation of the ammonia, the residue was treated with chloroform (30 cm^3) and filtered from precipitated ammonium chloride. Evaporation gave an oil, which was chromatographed on silica gel, and eluted with chloroform, and then with chloroform–isopropylamine (49:1; then 19:1) to afford the *title aminobutyl compound* **81** (1.08 g, 89%) which gave a positive Fluram spray test (Found: M^+, 275.198. $C_{16}H_{25}N_3O$ requires *M*, 275.200); ν_{max}(film)/cm^{-1} 970, 1175, 1320, 1470, 1620 and 3330; δ_H 7.56–7.26 (5 H, m, Ph), 4.32–3.66 (2 H, m, 2 × CHN), 4.08 (1 H, dd, *J* 2 and 11, C*H*Ph), 3.40–2.20 (8 H, m, 6 × CHN, CH_2CO), 1.90–1.30 (6 H, m, 3 × CH_2 β to N) and 1.46 (3 H, s, NH, NH_2). The last signal disappeared on shaking with D_2O; δ_C *25.3*, *30.7*, *31.6*, *41.7*, *44.3*, *45.2*, *45.3*, *45.5*, 64.7 (C-4), 126.4, 127.5, 128.6, *145.0* and *173.0* (C=O).

1-(3-*Chloropropyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one*.—A solution of 4-phenyl-1,5-diazacyclooctan-2-one **13** (204 mg, 1 mmol) in dry THF was treated with tetrabutylammonium hydrogen sulfate (34 mg, 0.1 mmol), 1-bromo-3-chloropropane (173 mg, 1.1 mmol) and powdered potassium hydroxide (67 mg, 1.2 mmol). The suspension was stirred under nitrogen for 4 h at 20 °C and then worked up. Chromatography on silica gel, and elution with chloroform, then with chloroform–methanol (49:1), gave 1-(3-*chloropropyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* (147 mg, 52%) (Found: M^+, 280.135. $C_{15}H_{21}ClN_2O$ requires *M*, 280.134); ν_{max}(film)/cm^{-1} 750, 1170, 1460, 1630 and 3320; δ_H 7.54–7.24 (5 H, m, Ph), 4.40–3.60 (2 H, m, 2 × CHN), 4.03 (1 H, dd, *J* 2 and 11, C*H*Ph), 3.60 (2 H, t, *J* 7, CH_2Cl), 3.44–2.86 (4 H, m, 3 × CHN, C*H*HCO), 2.60–2.30 (1 H, m, CHN), 2.49 (1 H, dd, *J* 2 and 13, CH*H*CO), 2.34–1.90 (3 H, m, CH_2CH_2Cl, NH) and 1.90–1.54 (2 H, m, CH_2CH_2N). The signal centred on δ 2.2 was reduced to two protons on shaking with D_2O.

Further elution led to recovery of the starting lactam **13** (90 mg, 44%), giving a yield of 93% at 56% conversion.

1-(3-*Aminopropyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one*.—The above chloropropyl compound (191 mg, 0.68 mmol) was sealed with liquid ammonia (10 cm^3) at 20 °C for 1 day, then for 4 days at 50 °C). Work-up by evaporation, dissolution in chloroform, filtration, and evaporation gave an oil, which was chromatographed on silica gel, and eluted with chloroform–methanol (49:1), then with chloroform–isopropylamine (19:1; then 9:1). First eluted was 1-allyl-4-phenyl-1,5-diazacyclooctan-2-one **66** (42 mg, 25% (Found: M^+, 244.158. Calc. for $C_{15}H_{20}N_2O$: *M*, 244.158); ν_{max}($CHCl_3$)/cm^{-1} 1330, 1460, 1625 and 3360; δ_H 7.54–7.22 (5 H, m, Ph), 6.14–5.64 (1 H, m, CH=), 5.48–5.08 (2 H, m, CH_2=), 4.50 (1 H, dd, *J* 5 and 15, =CHC*H*H), 4.44–3.94 (1 H, m, CHN), 4.06 (1 H, dd, *J* 2 and 11, C*H*Ph), 3.58 (1 H, dd, *J* 5 and 15, =CH*H*), 3.40–2.88 (3 H, m, C*H*HCO, 2 × CHN), 2.60–2.20 (1 H, m, CHN), 2.54 (1 H, dd, *J* 2 and 13, CH*H*CO), 1.94 (1 H, s, NH) and 1.90–1.50 (2 H, m, CH_2CH_2N). The resonance at δ 1.94 disappears on shaking with D_2O.

Continued elution gave 1-(3-*aminopropyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* (115 mg, 65%) which showed a positive Fluram test (Found: M^+, 261.183. $C_{15}H_{23}N_3O$ requires *M*, 261.184); ν_{max}(film)/cm^{-1} 1040, 1180, 1470, 1630 and 3350 br; δ_H 7.56–7.18 (5 H, m, Ph), 4.36–3.74 (2 H, m, 2 × CHN), 4.04 (1 H, dd, *J* 2 and 11, C*H*Ph), 3.42–2.10 (8 H, m, CH_2CO, 6 × CHN) and 2.10–1.56 (7 H, m, 2 × CH_2CH_2N, NH, NH_2). The last signal is reduced to 4 H, on shaking with D_2O. No ring-expansion product was observed under these conditions.

4-*Phenyl*-1,5,9-*triazacyclotridecan*-2-*one* **78**—Potassium bis(trimethylsilyl)amide (0.34 mol dm^{-3} in toluene; 4.6 cm^3, 1.6 mmol) was added to an ice-cold solution of the amine **81** (275 mg, 1 mmol) in dry THF (10 cm^3). The mixture was stirred under nitrogen for 1 h at 0 °C and then at room temperature for 23 h, before being poured into water and extracted with chloroform. Work-up, and chromatography on silica gel. with methanol–chloroform (1:49) as eluent, gave the title compound **78** (38 mg, 14%), ν_{max}(film)/cm^{-1} 1623, 3320 and 3440; δ_H 7.70–

6.90 [6 H, m, Ph and N(1)H], 4.01 (1 H, dd, *J* 2 and 11, 4-H), 4.30–2.15 (10 H, m, 3-H_2 and 4 × CH_2N) and 2.10–1.15 [8 H, m, 7-, 11- and 12-H_2, N(5)-H, N(9)-H].

Continued elution with isopropylamine–chloroform (1:20) permitted recovery of starting material (88 mg, 32%). Allowing for recovery material, the yield was 21%.

9-Cinnamoyl-4-phenyl-1,5,9-triazacyclotridecan-2-one, (±)-Dihydroperiphylline **79**.—A solution of (*E*)-cinnamoyl chloride (37 mg, 0.19 mmol) in dry dichloromethane (2 cm^3) was added to a mixture of the azalactam **78** (35 mg, 0.13 mmol) and 4-dimethylaminopyridine (43 mg, 0.35 mmol) in dry dichloromethane (10 cm^3) at −78 °C. The mixture was stirred at this temperature for 16 h and then at −20 °C for 6 h before being poured into aq. ammonium hydroxide (10 mol dm^{-3}; 10 cm^3) and extracted with chloroform (3 × 20 cm^3). After washing with brine, drying ($MgSO_4$), and evaporation, the product was chromatographed on silica gel and eluted with pentane–chloroform (3:17) to give (±)-dihydroperiphylline **79** (36 mg, 69%) [Found (FAB): $(M^+ + 1)$, 406. Calc. for $C_{25}H_{31}N_3O_2$: $(M + 1)$, 406]; ν_{max}(film)/cm^{-1} 1600, 1640 and 3400; δ_H 7.65 (1 H, d, *J* 15.5, PhC*H*=CH), 7.75–7.10 (10 H, m, Ph), 6.93 (1 H, d, *J* 15.5, PhCH=C*H*), 5.70 [1 H, m, N(1)H] and 4.30–1.40 [18 H, m, N(5), H, 8 × CH_2 and CHN].

N-(2-*Cyanoethyl*)-4-*phenylazetidin*-2-*one* [3-(2-*Oxo*-4-*phenylazetidin*-1-*yl*)*propanonitrile*] **14**.—4-Phenylazetidin-2-one **10** (0.37 g, 2.5 mmol), freshly distilled acrylonitrile (3 cm^3, 45.6 mmol) and saturated aq. sodium hydroxide (0.2 cm^3) were stirred together in THF (4 cm^3) for 20 h. The solvent was removed and the residue was distilled under reduced pressure to give the *title compound* (0.46 g, 92%), b.p. 175 °C/0.1 mmHg (Found: M^+, 200.097. $C_{12}H_{12}N_2O$ requires *M*, 200.095); ν_{max}(film)/cm^{-1} 1750 and 2300; δ_H 7.45 (5 H, s, Ph), 4.76 (1 H, dd, *J* 2 and 6, C*H*Ph), 3.80–3.00 (3 H, m, CH*H*CO, NCH_2), 2.86 (1 H, dd, *J* 2 and 16, C*H*HCO) and 2.55 (2 H, t, *J* 7, CH_2CN).

N-(3-*Cyanopropyl*)-4-*phenylazetidin*-2-*one* [4-(2-*Oxo*-4-*phenylazetidin*-1-*yl*)*butanonitrile*] **11** (X=CN).—4-Phenylazetidin-2-one **10** (1.1 g, 7.5 mmol), sodamide (0.3 g, 7.8 mmol) and liquid ammonia (20 cm^3) were stirred at −36 °C for 20 min and 4-iodobutyronitrile (0.84 cm^3, 7.5 mmol) was then added. The mixture was stirred (3 h), the ammonia was allowed to evaporate off, and water (20 cm^3) and chloroform (25 cm^3) were added. Work-up of the organic layer, followed by bulb-to-bulb distillation, gave the *title nitrile* (1.26 g, 82%), b.p. (bath) 120 °C/0.01 mmHg; n_D^{20} 1.5234 (Found: M^+, 214.110. $C_{13}H_{14}N_2O$ requires *M*, 214.111); ν_{max}(film)/cm^{-1} 1735, 1745, 2300, 2930 and 3020; δ_H 7.44 (5 H, s, Ph), 4.71 (1 H, dd, *J* 2 and 7, C*H*Ph), 3.56 (1 H, t, *J* 7, NCH*H*), 3.44 (1 H, dd, *J* 7 and 15, CH*H*CO), 3.12 (1 H, t, *J* 7, NC*H*H), 2.82 (1 H, dd, *J* 2 and 15, C*H*HCO), 2.40 (2 H, t, *J* 7, CH_2CN) and 1.84 (2 H, m, CH_2C).

N-(4-*Aminobutyl*)-4-*phenylazetidin*-2-*one* **19** (*Second Method*).—*N*-(3-Cyanopropyl)-4-phenylazetidin-2-one (0.18 g, 0.84 mmol) in methanol (30 cm^3) and conc. hydrochloric acid (0.1 cm^3) was hydrogenated over Adams catalyst (40 mg) until the calculated volume of hydrogen had been absorbed. Filtration and work-up gave the crude hydrochloride (0.19 g), which was dissolved in water (10 cm^3), treated with aq. sodium hydrogen carbonate (5%), and extracted with chloroform. Work-up of the latter gave the amine **19** (0.13 g, 72%), b.p. 112 °C/0.1 mmHg (Found: M^+, 218.141. $C_{13}H_{18}N_2O$ requires *M*, 218.142). It gave a positive Fluram spray reaction; ν_{max}(film)/cm^{-1} 1740, 3260 and 3350; δ_H 7.38 (5 H, s, Ph), 4.58 (1 H, dd, PhC*H*), 3.50–3.30 (2 H, m, CONCH*H*, COCH*H*), 2.90–2.60 (4 H, m, CH_2NH_2, CONC*H*H, COC*H*H), 1.60 (2 H, s, NH_2) and 1.48 (4 H, m, 2 × CH_2C).

N-[4-(2-*Cyanoethylamino*)*butyl*]-4-*phenylazetidin*-2-*one* {3-[4-(2-*Oxo*-4-*phenylazetidin*-1-*yl*)*butylamino*]*propanonitrile*}.—Amine **19**, as its hydrochloride (10 g, 37 mmol), was stirred in triethylamine (6 cm^3)–acrylonitrile (40 cm^3) at 20 °C for 6 days. After evaporation under reduced pressure, water (50 cm^3) was added and the product was isolated by extraction with diethyl ether. It was purified by PLC on silica gel (diethyl ether), and the band at R_f 0.2 was collected to give the *title nitrile* (7.3 g, 71%), b.p. 140 °C/0.1 mmHg; n_D^{20} 1.5368 (Found: C, 70.4; H, 7.95; N, 15.7%; M^+, 271.168. $C_{16}H_{21}N_3O$ requires C, 70.8; H, 7.8; N, 15.5%; *M*, 271.168); ν_{max}(film)/cm^{-1} 1740, 2270 and 3300; δ_H 7.22 (5 H, s, Ph), 4.26 (1 H, dd, PhC*H*), 3.40–3.10 (2 H, m, CH_2), 2.76 (4 H, m, CH_2N), 2.42 (4 H, m, CH_2CN, CH_2N), 2.00 (1 H, br, NH) and 1.45 (4 H, m, 2 × CH_2C).

1-(8-*Amino*-5-*azaoctyl*)-4-*phenylazetidin*-2-*one* **88**.—*N*-[4-(2-Cyanoethylamino)butyl]-4-phenylazetidin-2-one (2.7 g., 10 mmol) in methanol (70 cm^3)–aq. ammonia (*d* 0.88; 7 cm^3) was hydrogenated over 5% rhodium on alumina (400 mg) at 20 °C and room temperature. Filtration and work-up gave the *amine* **88** (2.6 g, 94%), pure by TLC and giving a positive Fluram spray test. On distillation, b.p. 160 °C/0.05 mmHg, there was considerable loss of material through decomposition. The amine had n_D^{20} 1.4300 (Found: $M^+ - C_2H_6N$, 231.149. $C_{14}H_{19}N_2O$ $(M - C_2H_6N)$ requires *m/z*, 231.150); ν_{max}(film)/cm^{-1} 1740, 3270, 3320 and 3420; δ_H 7.48 (5 H, s, Ph), 4.60 (1 H, dd, PhC*H*), 3.60–3.30 (3 H, br), 3.00–2.40 (7 H, br) and 1.70–1.40 (9 H, br, 3 × CH_2C, NH, NH_2). On shaking with D_2O the latter signal was reduced to 6 H.

N-(3-*Aminopropyl*)-4-*phenylazetidin*-2-*one* **12** (*Second Method*).—*N*-(2-Cyanoethyl)-4-phenylazetidin-2-one **14** (0.73 g, 3.7 mmol) in methanol (30 cm^3)–aq. ammonia (*d* 0.88; 1 cm^3) was hydrogenated over platinum oxide (100 mg). Work-up gave the amine **12** (0.69 g, 93%), b.p. 140 °C/0.1 mmHg, pure by TLC [ethyl acetate–methanol (9:1)]. The Fluram test was positive (Found: M^+, 204.125. Calc. for $C_{12}H_{16}N_2O$: *M*, 204.126); ν_{max}(film)/cm^{-1} 1740, 3370 and 3460.

N-[3-(2-*Cyanoethylamino*)*propyl*]-4-*phenylazetidin*-2-*one* {3-[3-(2-*Oxo*-4-*phenylazetidin*-1-*yl*)*propylamino*]*propanonitrile*}.—The 3-aminopropyl compound **12** (0.54 g, 2.6 mmol) and triethylamine (1 cm^3) were stirred in acrylonitrile (20 cm^3) for 6 days at room temperature. Work-up and PLC on silica gel (diethyl ether) gave the *title nitrile* (0.56 g, 81%) (Found: M^+, 257.154. $C_{15}H_{19}N_3O$ requires *M*, 257.153); ν_{max}(film)/cm^{-1} 1740, 2290 and 3420; δ_H 7.30 (5 H, s, Ph), 4.52 (1 H, dd, *J* 2 and 6, PhC*H*), 3.40–3.20 (2 H, m, NCH_2), 3.00–2.26 (8 H, m, CH_2N, CH_2CO, CH_2CN), 1.85 (1 H, s, NH) and 1.60 (2 H, m, CH_2C). The signal at δ 1.85 was removed on shaking with D_2O.

1-(7-*Amino*-4-*azaheptyl*)-4-*phenylazetidin*-2-*one* **91**.—N-[3-(2-Cyanoethylamino)propyl]-4-phenylazetidin-2-one (0.2 g, 0.8 mmol) in methanol (20 cm^3) containing aq. ammonia (*d* 0.88; 1 cm^3) was hydrogenated at room temperature and atmospheric pressure over 5% rhodium on alumina catalyst (50 mg). Work-up gave the *amine* **91** (0.18 g, 90%), one spot on TLC [ethyl acetate–methanol (9:1)], giving a positive Fluram test (Found: M^+, 261.183. $C_{15}H_{23}N_3O$ requires *M*, 261.184); ν_{max}(film)/cm^{-1} 1730, 3360 and 3400; δ_H 7.30 (5 H, s, Ph), 4.52 (1 H, dd, PhC*H*), 3.40–3.20 (2 H, m, CH_2N), 3.34 (2 H, s, NH_2), 3.00–2.24 (8 H, m, 2 × NCH_2, 2 × CH_2CO) and 1.56 (5 H, m, 2 × CH_2C, NH). The resonance at δ 3.34 disappeared, and that at δ 1.56 was reduced to 4 H, on shaking with D_2O.

4-*Phenyl*-1,5,9-*triazacyclododecan*-2-*one* **93**.—1-(7-Amino-4-azaheptyl)-4-phenylazetidin-2-one **91** (0.46 g, 1.76 mmol) was added to potassium hydride (40% dispersion in mineral oil; 180

mg, 1.8 mmol KH) in dry 1,3-diaminopropane (30 cm^3) at room temperature under nitrogen, and the mixture was stirred for 3 days. The reaction mixture was quenched with water (30 cm^3), concentrated under reduced pressure, and the residue was taken up in aq. potassium hydroxide (5 mol dm^{-3}; 20 cm^3) and extracted with dichloromethane. Evaporation of the latter extracts gave an oil, which was dissolved in methanol–water (19:1; 100 cm^3) and washed with pentane. The aqueous methanolic extract was evaporated and the product was separated by PLC on silica [chloroform–methanol (9:1)] to give recovered azetidinone **91** (80 mg) and 4-*phenyl*-1,5,9-*triazacyclododecan*-2-*one* **93** (18 mg) as the faster running band [Found: $M^+ - C_3H_7N$, 204 (85%). $C_{12}H_{16}N_2O$ ($C_{15}H_{23}N_3O - C_3H_5N$) requires *m/z*, 204]. The molecular ion was not observed; ν_{max}(film)/cm^{-1} 1640, 1660, 3100, 3250 and 3340; δ_H 7.42 (5 H, m, Ph), 6.20 (1 H, br, NHCO), 4.10 (1 H, PhC*H*), 3.60–2.40 (12 *H*, m, 4 × CH_2N, CH_2CO, 2 × NH) and 1.80 (4 H, m, 2 × CH_2C). The compound gave no colour with Fluram and was characterised as its N-*diacetyl derivative* **94**. The triaza compound **93** (18 mg) was stirred with pyridine–acetic anhydride (1:1, 6 cm^3) overnight at 20 °C. Work-up gave 5,9-*diacetyl*-4-*phenyl*-1,5,9-*triazacyclododecan*-2-*one* **94** (20 mg), forming a single spot on TLC [ethyl acetyl–methanol (9:1)] (Found: $[M + 1]^+$, 346. For $C_{19}H_{27}N_3O_3$, M + 1 requires *m/z*, 346) (Found: $[M - C_3H_7N - C_2H_2O]^+$, 246. $C_{14}H_{18}N_2O_2$ requires *m/z*, 246); δ_H 7.24 (5 H, m, Ph), 4.50 (1 H, m), 3.60–3.00 (10 H, m), 2.40–1.80 (7 H, m) and 1.50 (4 H, m, 2 × CH_2C).

Ethyl 3-(4-*Aminobutylamino*)-3-*phenylpropionate* **95**.—*N*-(4-aminobutyl)-4-phenylazetidin-2-one **19** (1 g, 4 mmol) was heated under reflux with saturated ethanolic hydrogen chloride (20 cm^3) overnight. Evaporation under reduced pressure gave a solid (1.06 g), which was crystallised from ethanol to give the *title ester* as its *hydrochloride*. (Found: $[M - Cl]^+$, 265; $[M - HCl]^+$, 264. For $C_{14}H_{24}N_2O_2$·HCl [*M* − Cl] requires *m/z*, 265 and [*M* − HCl] requires *m/z*, 264); ν_{max}(KBr)/cm^{-1} 1725 (ester C=O) and 3000 br (NH_3^+). The crude hydrochloride was taken up in 2 mol dm^{-3} ammonia (20 cm^3) and extracted with chloroform. Evaporation and purification by PLC on silica gel, [chloroform–methanol (9:1)], gave the *title ester* **95** (0.27 g, 25%) (Found: M^+, 264.184. $C_{14}H_{24}N_2O_2$ requires *M*, 264.184); ν_{max}(film)/cm^{-1} 1720 (ester) and 3300 br (NH); δ_H 7.36 (5 H, s, Ph), 4.10 (3 H, m, OCH_2, PhC*H*), 2.46–2.30 (6 H, m, CH_2CO, 2 × CH_2N), 1.76 (3 H, br, NH_2, NH), 1.44 (4 H, m, CH_2C) and 1.18 (3 H, t, C-Me). On shaking with D_2O the resonance at δ 1.76 disappeared.

Ethyl-3-[4-(3-*Aminopropylamino*)*butylamino*]-3-*phenylpropionate Hydrochloride* (**96**, *as Hydrochloride*).—1-(8-Amino-5-azaoctyl)-4-phenylazetidin-2-one **88** (100 mg, 0.36 mmol) was refluxed as above in saturated ethanolic hydrogen chloride (10 cm^3) overnight. Work-up, and PLC on silica gel, with chloroform–methanol (1:1), gave the title hydrochloride (69 mg, 44%), ν_{max}(KBr)/cm^{-1} 1715 (ester), 2500 and 3000 br (NH_3^+); δ_H 7.20 (5 H, m, Ph), 4.28 (1 H, m, PhC*H*), 3.72 (2 H, q, *J* 7, OCH_2), 3.04–2.40 (10 H, m, 4 × CH_2N, CH_2CO), 1.40 (6 H, m, 3 × CH_2C) and 0.72 (3 H, t, *J* 7 Me). The azetidinone can be hydrolysed direct by being refluxed with 6 mol dm^{-3} hydrochloric acid at 80 °C (3 h), and converted into sodium and tetrabutylammonium salts.

Crystallographic Data.—Crystal data for compound **16**: $C_{13}H_{18}N_2O$, M = 218.29, Monoclinic, *a* = 11.696(1), *b* = 8.158(1), *c* = 13.677(1) Å, *β* = 108.94(1)°, *V* = 1234.35 $Å^3$, *Z* = 4, D_C = 1.17 g cm^{-3}, *F*(000) = 472, space group $P2_1/n$, Cu-K*α* radiation, *λ* = 1.54178 Å, *μ*(Cu-K*α*) = 6.03 cm^{-1}.

Crystal data for compound **20**: $C_{13}H_{18}N_2O$, M = 218.29, Monoclinic, *a* = 10.198(1), *b* = 6.790(1), *c* = 17.139(2) Å, *β* = 104.45(1)°, *V* = 1228.13 $Å^3$, *Z* = 4, D_c = 1.18 g cm^{-3}, *F*(000) = 472, space group $P2_1/c$, Cu-K*α* radiation, *λ* = 1.541 78 Å, *μ*(Cu-K*α*) = 6.06 cm^{-1}.

Crystal data for compound **43**: $C_{13}H_{16}N_2O$, M = 216.27, Orthorhombic, *a* = 18.079(1), *b* = 40.455(2), *c* = 6.469(1) Å, *V* = 4731.24 $Å^3$, *Z* = 16, D_c = 1.21 g cm^3, *F*(000) = 1856, space group *Fdd* 2, Cu-K*α* radiation, *λ* = 1.541 78 Å, *μ*(Cu-K*α*) = 6.92 cm^{-1}.

Crystals of each compound were mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections were used to determine accurate lattice parameters. Intensity data were collected for 1° < *θ* < 76° (**20**), 1° < *θ* < 66° (**43**) and 1° < *θ* < 75° (**16**). Totals of 2565 (**20**), 1134 (**43**) and 2532 (**16**) independent reflections were measured of which 1808, 659 and 1590, respectively, had $I > 3\sigma(I)$ and were considered observed and used in the subsequent refinement. Periodic measurement of standard reflections throughout the data collection demonstrated their stability. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed using the CRYSTALS system of programs.[46] The structures were solved by direct method using the MULTAN program.[47] Least-squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis [for **20** and **16**, but not **43** in which the hydrogen atoms were included in calculated positions, except for the two hydrogens on nitrogen which were located in a difference map without refinement] terminated at *R*

Table 3 Fractional atomic coordinates for compound **16**, with standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	0.4479(2)	0.1981(2)	0.4317(1)
C(2)	0.4289(2)	0.2242(3)	0.5216(1)
C(3)	0.3713(2)	0.3818(3)	0.5391(2)
C(4)	0.2323(2)	0.3805(3)	0.5042(1)
N(5)	0.1787(2)	0.3844(2)	0.3915(1)
C(6)	0.1858(2)	0.2306(3)	0.3371(2)
C(7)	0.2720(2)	0.2409(3)	0.2752(2)
C(8)	0.3996(2)	0.2940(2)	0.3373(1)
C(9)	0.4849(2)	0.2791(3)	0.2742(2)
O(10)	0.4601(2)	0.1222(2)	0.5929(1)
C(11)	0.1913(2)	0.5294(2)	0.5502(1)
C(12)	0.1895(2)	0.6832(3)	0.5083(2)
C(13)	0.1575(2)	0.8193(3)	0.5544(2)
C(14)	0.1284(2)	0.8032(4)	0.6433(2)
C(15)	0.1313(2)	0.6510(3)	0.6867(2)
C(16)	0.1609(2)	0.5150(3)	0.6396(2)

Table 4 Fractional atomic coordinates for compound **20**, with standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	0.061 5(1)	0.307 0(3)	0.346 7(1)
C(2)	0.126 9(2)	0.409 1(3)	0.303 7(1)
C(3)	0.160 8(2)	0.293 8(3)	0.236 9(1)
C(4)	0.267 7(2)	0.145 8(2)	0.275 8(1)
N(5)	0.222 0(1)	0.005 7(2)	0.326 98(8)
C(6)	0.301 5(2)	−0.011 7(3)	0.409 4(1)
C(7)	0.287 3(2)	0.157 3(3)	0.464 8(1)
C(8)	0.157 0(2)	0.182 8(4)	0.482 2(1)
C(9)	0.076 3(2)	0.342 5(4)	0.432 4(1)
O(10)	0.163 3(2)	0.578 0(2)	0.320 3(1)
C(11)	0.321 3(2)	0.051 3(2)	0.211 0(1)
C(12)	0.262 6(2)	−0.108 9(3)	0.167 3(1)
C(13)	0.310 6(2)	−0.189 8(4)	0.106 6(1)
C(14)	0.418 0(2)	−0.112 5(4)	0.089 7(1)
C(15)	0.477 5(2)	0.043 5(3)	0.133 2(1)
C(16)	0.429 9(2)	0.126 2(3)	0.193 7(1)

0.0428 (R_w 0.0518) for **20**, R 0.0408 (R_w 0.0503) for **43** and at R 0.0390 (R_w 0.0466) for **16**.

The refined fractional atomic coordinates are shown in Tables 3, 4 and 5 respectively and the resulting molecular structures are illustrated in Figs. 2, 3 and 4 and 5. The bond lengths and angles for all three structures are collected in Tables 6 and 7 and show remarkably good agreement between structures. The torsion angles within the rings are listed in Table 8 to illustrate the ring shapes. The eight-membered ring in compound **16** adopts the chair-boat conformation with the pseudo-mirror-plane through C(4) and C(8). This is different from the alkaloid homaline in which the chair-boat shows pseudo-mirror symmetry through C(3) and C(7). The torsion angle about the N(1)–C(2) bond of −11.8° shows a *cis*-amide linkage.

In both nine-membered rings **20** and **43** this torsion angle is approximately −150° showing a *trans*-linkage. Away from this feature all three structures show similar conformations in the C(2)–C(4)–C(6) region of the ring. The nine-membered rings show very similar torsion angles away from the immediate vicinity of the C(7)–C(8) double bond in compound **43**. The hydrogen bonds are listed in Table 9. Only structure **20** shows an intramolecular hydrogen bond between the nitrogen atoms across the ring, of length 2.766 Å. In structures **43** and **16** the N–N separation is increased to 2.911 and 3.377 Å, respectively, but the conformations do not allow the lone pairs to point in an appropriate direction to form a hydrogen bond. The remaining N–H groups form intermolecular hydrogen bonds, in most cases to the amide oxygen, but in compound **16** the electron donation to N(5) is from the aromatic π-bonds of the phenyl

Table 5 Fractional atomic coordinates for compound **43**, with standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	0.505 7(2)	0.103 8(1)	0.154 0
C(2)	0.555 7(2)	0.125 4(1)	0.221(1)
C(3)	0.525 3(3)	0.158 6(1)	0.274(1)
C(4)	0.497 6(2)	0.158 6(1)	0.502(1)
N(5)	0.445 9(2)	0.130 62(9)	0.536 5(9)
C(6)	0.485 1(3)	0.100 2(1)	0.602 5(9)
C(7)	0.449 6(3)	0.068 9(1)	0.519(1)
C(8)	0.464 8(3)	0.054 8(1)	0.338(1)
C(9)	0.514 5(3)	0.068 3(1)	0.174(1)
O(10)	0.621 2(2)	0.117 8(1)	0.250 7(9)
C(11)	0.458 2(2)	0.190 8(1)	0.553(1)
C(12)	0.400 9(3)	0.202 6(1)	0.432(1)
C(13)	0.364 6(3)	0.231 6(1)	0.484(1)
C(14)	0.384 4(3)	0.248 7(2)	0.659(1)
C(15)	0.440 7(4)	0.237 0(1)	0.781(1)
C(16)	0.475 9(3)	0.208 4(1)	0.729(1)

Table 6 Bond lengths (Å) with standard deviations in parentheses

	16	**20**	**43**
N(1)–C(2)	1.335(2)	1.339(3)	1.329(6)
N(1)–C(9) [C(8)]	1.458(2)	1.458(3)	1.447(6)
C(2)–C(3)	1.507(3)	1.507(3)	1.494(7)
C(2)–O(10)	1.243(3)	1.223(2)	1.238(5)
C(3)–C(4)	1.538(3)	1.557(2)	1.558(7)
C(4)–N(5)	1.464(2)	1.463(2)	1.485(6)
C(4)–C(11)	1.515(3)	1.519(3)	1.519(6)
N(5)–C(6)	1.474(3)	1.465(2)	1.483(6)
C(6)–C(7)	1.515(3)	1.522(3)	1.520(7)
C(7)–C(8)	1.521(3)	1.531(3)	1.330(8)
C(8)–C(9)	1.521(3)	1.517(4)	1.498(8)
C(11)–C(12)	1.377(3)	1.384(3)	1.386(7)
C(11)–C(16)	1.384(3)	1.386(2)	1.378(7)
C(12)–C(13)	1.387(3)	1.389(3)	1.384(8)
C(13)–C(14)	1.372(4)	1.378(3)	1.375(9)
C(14)–C(15)	1.372(4)	1.363(3)	1.373(9)
C(15)–C(16)	1.382(3)	1.388(3)	1.365(7)

Table 7 Bond angles (°) with standard deviations in parentheses

	16	**20**	**43**
C(2)–N(1)–C(9) [C(8)]	126.7(2)	121.9(2)	123.2(4)
N(1)–C(2)–C(3)	120.0(2)	114.4(2)	114.6(4)
N(1)–C(2)–O(10)	121.5(2)	123.0(2)	122.6(5)
C(3)–C(2)–O(10)	118.6(2)	122.4(2)	122.5(5)
C(2)–C(3)–C(4)	115.3(2)	108.0(2)	109.8(4)
C(3)–C(4)–N(5)	112.0(2)	110.2(1)	110.1(4)
C(3)–C(4)–C(11)	108.1(2)	110.1(1)	111.0(4)
N(5)–C(4)–C(11)	109.6(2)	114.5(1)	109.0(4)
C(4)–N(5)–C(6)	116.0(2)	115.0(2)	112.0(3)
N(5)–C(6)–C(7)	113.0(2)	114.4(2)	112.8(4)
C(6)–C(7)–C(8)	114.4(2)	116.8(2)	125.5(5)
C(7)–C(8)–C(9)	111.4(2)	114.1(2)	126.4(5)
N(1)–C(8)–C(7)	111.7(2)		
N(1)–C(8)–C(9)	108.8(2)		
N(1)–C(9)–C(8)		110.5(2)	111.1(4)
C(4)–C(11)–C(12)	121.4(2)	121.2(2)	121.6(4)
C(4)–C(11)–C(16)	120.4(2)	120.4(2)	120.9(4)
C(12)–C(11)–C(16)	118.1(2)	118.4(2)	117.5(4)
C(11)–C(12)–C(13)	120.7(2)	120.5(2)	120.7(5)
C(12)–C(13)–C(14)	120.5(3)	120.3(2)	120.2(6)
C(13)–C(14)–C(15)	119.5(2)	119.6(2)	119.5(6)
C(14)–C(15)–C(16)	120.0(2)	120.5(2)	119.8(6)
C(11)–C(16)–C(15)	121.2(2)	120.6(2)	122.2(5)

Table 8 Ring torsion angles (°)

	16	**20**	**43**
C(9)–N(1)–C(2)–C(3)	−11.8*	−146.8	−153.9
N(1)–C(2)–C(3)–C(4)	88.2	72.9	86.4
C(2)–C(3)–C(4)–N(5)	−72.7	−62.6	−52.6
C(3)–C(4)–N(5)–C(6)	74.0	127.5	89.3
C(4)–N(5)–C(6)–C(7)	−110.0	−76.9	−145.5
N(5)–C(6)–C(7)–C(8)	55.1	−63.6	88.1
C(6)–C(7)–C(8)–C(9)		99.8	−5.8
C(7)–C(8)–C(9)–N(1)	50.2*	−55.6	−39.1
C(8)–C(9)–N(1)–C(2)	−83.3*	103.1	106.5

* C(9) is replaced by C(8) *etc.* in this 8-membered ring.

Table 9 Hydrogen bonds (Å) and angles (°)

	N–X	N–H	H–X	N–H–X
16				
N(1)–H(1)···O10 (1 − *x*, −*y*, 1 − *z*)	2.887	0.88	2.00	176
N(5)–H(5)···C15 (−*x*, 1 − *y*, 1 − *z*)	3.443	0.91	2.60	154
20				
N(1)–H(1)···N(5) (*x*, *y*, *z*)	2.766	0.87	2.20	123
N(5)–H(5)···O(10) (*x*, *y* − 1, *z*)	2.970	0.88	2.21	145
43				
N(1)–H(1)···O10 (*x*–0.25, 0.25 − *y*, *z* − 0.25)	2.868	1.01	1.87	172
N(5)–H(5)···O10 (*x* − 0.25, 0.25 − *y*, *z* + 0.75)	3.294	1.11	2.29	150

ring. Observed and calculated structure factors, thermal parameters, and fractional atomic coordinates of hydrogen atoms are all listed in Supplementary Publication No. . . ..*

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* *Supplementary publications scheme.* See Instructions for Authors, in the January issue.

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