The Reduction of Tertiary *N*-Styrylenamides

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Magnesium and methanol reduction of *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (**6**) gave all four racemates of *N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**1**)—(**4**), with a 13:6 ratio of *cis*-fused to *trans*-fused products. Selective reduction of *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-1(6),3-dien-7-one (**5**) gave almost exclusively the two *cis*-fused racemates of *N*,9-dibenzyl-8-azabicyclo-[4.3.0]non-3-en-7-one (**9**) and (**10**). Magnesium and methanol did not reduce (*E*)-*N*-benzyl-9-benzylidene-*cis*-bicyclo[4.3.0]nonan-7-one (**7**) and (*E*)-*N*-benzyl-*N*-(1-methyl-2-phenylvinyl) acetamide (**16a**), but did reduce (*E*)-*N*-benzyl-*N*-styrylacetamide (**16b**) and (*E*)- and (*Z*)-*N*-styrylpyrrolidin-2-one (**13**) and (**14**); incomplete reduction of (*Z*)-*N*-benzyl-*N*-(1-methyl-2-phenylvinyl)-acetamide (**15a**) and (*Z*)-*N*-benzyl-*N*-styrylacetamide (**15b**) was observed. Reduction does not occur when the styryl phenyl group is twisted out of conjugation.

Sodium and liquid ammonia reduction of (*E*)-*N*-benzyl-9-benzylidene-*cis*-8-azabicyclo-[4.3.0]nonan-7-one (**7**) gave (1*RS*,6*SR*,9*RS*)-9-benzyl-8-azabicyclo[4.3.0]nonan-7-one and *N*-benzyl-2-(2-phenylethyl)cyclohexane-1-carboxamide (**20**). A similar cleavage of the β-styryl–nitrogen bond was observed in the reduction of (*Z*)-*N*-benzyl-*N*-(1-methyl-2-phenylvinyl)acetamide (**15a**), but not with (*E*)-*N*-styrylpyrrolidin-2-one (**13**).

Several tertiary *N*-styrylenamides were not reduced by sodium cyanoborohydride in acetic acid but *N*-benzyl-9-benzylidene-*cis*-8-azabicyclo[4.3.0]non-3-en-7-one (**8**) and *N*-benzyl-9-benzylidene *cis*-8-azabicyclo[4.3.0]nonan-7-one (**7**) gave (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]non-3-en-7-one (**9**) and (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**) respectively.

We have recently reported[1] the preparation, by an intramolecular Diels–Alder approach, of all four racemates (**1**)—(**4**)† of *N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one, as models for the reduced isoindolone unit present in the largest group of cytochalasans. We had earlier reported[2] the preparation, by an intermolecular Diels–Alder approach, of the unsaturated analogues (**5**)—(**8**) and had shown that catalytic hydrogenation of compound (**7**) gave exclusively the product (**2**).‡ At that time the configuration of the olefinic bond in compound (**7**) was not known. Recently the observation of a significant nuclear Overhauser enhancement for the vinylic proton on irradiation of the *N*-benzylic protons[3] and for the *N*-benzylic protons (with a larger enhancement for H_A than for H_B) on irradiation of the vinylic proton has established that the olefinic bond has the *E*-configuration. We assume that the exocyclic bond in compound (**8**) also has the *E*-configuration.

We now report our experiments on the chemical reduction of compounds (**5**)—(**8**).

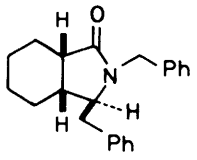
We have recently reported[4] that magnesium and methanol is a very good general reducing system for αβ-olefinic amides and lactams. Application of this method to compound (**6**) gave a mixture containing all the four possible saturated bicyclic lactams (**1**)—(**4**). High-performance liquid chromatography (h.p.l.c.) on a milligram scale using the previously reported[1] conditions permitted the separate isolation of the two *cis*-fused lactams (**1**) and (**2**) and a mixture of the two *trans*-fused lactams (**3**) and (**4**), together with some unreduced starting material (**6**). The proportions (**1**):(**2**):[(**3** + **4**)]:(**6**) as judged by peak areas based on refractive index absorbance in the h.p.l.c. separation were 7:6:6:1. All the racemates were identified by ^{1}H n.m.r. spectroscopy at 400 MHz, by direct comparison with the previously recorded[1] spectra of compounds (**1**)—(**4**). In addition compound (**2**) was shown to be identical on h.p.l.c. with the hydrogenation product of compound (**7**) prepared earlier.[2] The reduction of the isomer (**6**) by magnesium and methanol thus leads to a predominance of the two racemates (**1**) and (**2**) with a *cis*-ring fusion.

When the magnesium and methanol reduction was applied to compound (**5**) the isolated double bond, as expected,[4] was not affected, but reduction of the αβ-olefinic lactam system occurred. However, the stereochemical outcome differed somewhat from that seen in the reduction of compound (**6**). The products of the reaction could be separated from some starting material (**5**) and partially from each other by h.p.l.c. The lactam (**9**) could be isolated in a pure state and was identified as a product by catalytic hydrogenation to give saturated lactam (**2**), characterised by its ^{1}H n.m.r. spectrum at 400 MHz. Hydrogenation of a second product fraction gave a mixture which consisted mostly of saturated lactam (**1**), identified by its ^{1}H n.m.r. spectrum at 400 MHz, but the ^{1}H n.m.r. spectrum showed that it was accompanied by a smaller amount of the *trans*-isomer (**4**); signals due to the racemate (**3**) were not observed. It follows that the magnesium and methanol reduction of compound (**5**) also gave lactam (**10**) together with a smaller quantity of the *trans*-isomer (**11**). Another material isolated by h.p.l.c. from the reaction products was identified from the spectroscopic and microanalytical data as the phthalimidine (**12**), an oxidation product of the starting material. The ready oxidation of dihydroaromatic systems has previously been noted in the literature.[5] The proportions (**12**):(**9**):(**10**):(**11**):(**5**) in the product mixture can be shown to be 2:10:15:5:8 on the basis of the peak areas on the h.p.l.c. trace and the integration of the ^{1}H n.m.r. spectrum of the mixture of lactams (**1**) and (**3**). The proportion of *cis*-fused reduction products is thus much greater in the case of compound (**5**) than in the case of compound (**6**).

As the reductions of compounds (**5**) and (**6**) gave mixtures of bicyclic lactams with both *cis*- and *trans*-geometry at the ring junctions we turned to the reduction of the isomeric bicyclic *N*-

† All work was carried out on racemic materials. Only one enantiomer is shown in displayed formulae.

‡ In the original report[2] the stereochemistry of the hydrogenation product was given as (**1**) but this was corrected to (**2**) in our second paper.[1]



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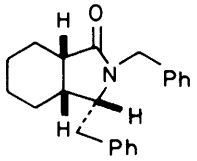

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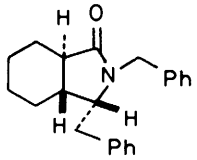

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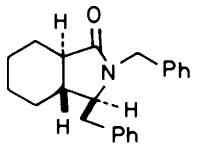

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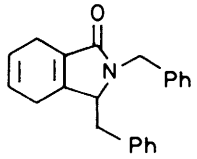

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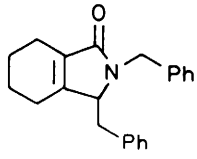

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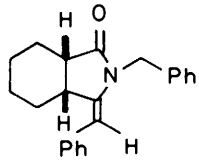

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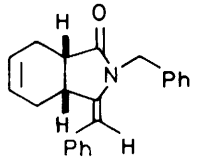

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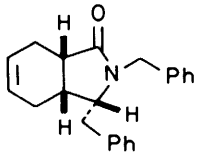

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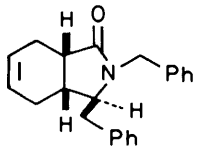

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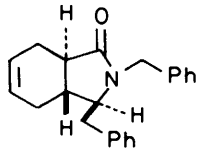

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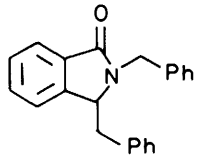

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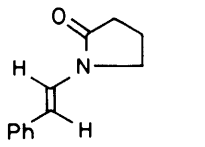
styrylenamides (**7**) and (**8**) in which *cis*-geometry at the ring junction had already been established. Enamides have been reduced to saturated amides by catalytic hydrogenation,[6] by sodium cyanoborohydride in formic or acetic acids,[5] and by formic acid in the presence of *N*-methylformamide or sodium formate.[7] Sodium borohydride has also sometimes been successful, but has been ineffective in other cases.[8] It occurred to us that tertiary *N*-styrylenamides like (**7**) and (**8**) might be reducible by magnesium and methanol, since parallel studies had shown that an analogous enesulphonamide, *N*-phenyl-*N*-styryltoluene-*p*-sulphonamide was reduced at the styryl double bond with, in addition, reductive cleavage of the nitrogen–sulphur bond.[9] Reduction of the styryl double bond of the two model enamides (**13**)[10] and (**14**)[11] with magnesium and methanol proceeded in high yield to give *N*-(2-phenylethyl)-pyrrolidin-2-one.[12] We could not obtain the *E*-product (**13**) satisfactorily by the reported[10] thermal dehydrochlorination of *N*-(2-chloro-2-phenylethyl)pyrrolidin-2-one, but the use of refluxing ethanolic potassium hydroxide led to a 45% yield of compound (**13**); acid-catalysed thermal dehydration of the corresponding hydroxy compound gave only a 17% yield.



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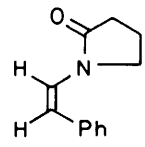

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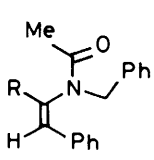

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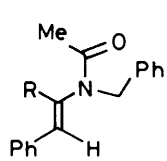

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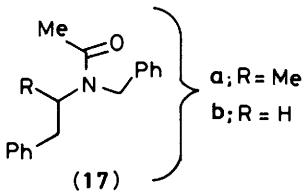
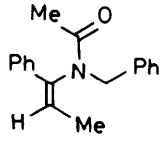


(17)

a; R = Me
b; R = H

Unfortunately, when the reduction of compound (**7**) with magnesium and methanol was attempted no reduction occurred and the starting material was recovered. The main difference between compound (**7**) and the model compounds (**13**) and (**14**) is the presence of a carbon substituent at the β-styryl position in (**7**). With this in mind we investigated the action of magnesium and methanol on two enamides (**15a**) and (**16a**)[13] which include this structural feature. One of these enamides, (**16a**), with the same *E*-configuration as (**7**) was not reduced at all. Analytical t.l.c. and ^{1}H n.m.r. spectroscopy showed that reduction of the *Z*-isomer (**15a**) had occurred, to the extent of 10%; the reduction product was isolated by h.p.l.c. and shown to be identical with the product of the catalytic hydrogenation of compound (**15a**), the saturated amide (**17a**). It would thus appear that the rotation of the phenyl groups in compound (**7**), (**15a**), and (**16a**) out of the plane of the carbon–carbon double bond either by the methyl, or methylene, carbon atom attached to the β-styryl position, or by the nitrogen atom and its substituents, reduces the degree of conjugation and increases the reduction potential of the system to such an extent that reduction by magnesium and methanol is no longer possible or only takes place to a small extent. To investigate this phenomenon further we also studied the magnesium and methanol reduction of the demethyl *N*-styrylenamides (**15b**) and (**16b**).[13] As expected the *E*-compound (**16b**) was completely reduced to give a compound identical with the material (**17b**) obtained by the catalytic hydrogenation of (**16b**), whereas the *Z*-isomer (**15b**) was only partly reduced to (**17b**); analytical t.l.c. and ^{1}H n.m.r. spectroscopy of the second reaction mixture showed the presence of *ca.* 30% of starting material (**15b**). The enamide (**18**),[13] in which the phenyl group is cross-conjugated with the enamide function, was reduced to the extent of *ca.* 60% to give material identical with the product of the catalytic hydrogenation of (**18**). As expected the enamide (**19**), prepared by the *N*-benzylation of the corresponding NH compound,[9] and lacking any degree of phenyl conjugation, was recovered unchanged after treatment with magnesium and methanol.

In the hope that a more powerful reducing agent would be successful in reducing the styryl double bond in tertiary *N*-styrylenamides we submitted the model compound (**13**) to reduction with sodium in liquid ammonia. Quenching with ammonium chloride gave, as the sole product, the desired saturated amide *N*-(2-phenylethyl)pyrrolidin-2-one. However,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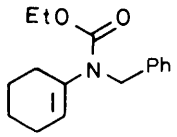
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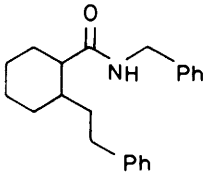
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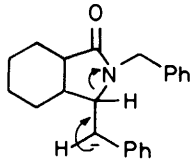
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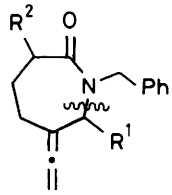
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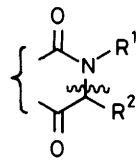
(23)

when compound (**7**) was reduced using the same procedure two major products were obtained. They were separated by column chromatography. One of them was identified as (1*RS*,6*SR*,9*RS*)-9-benzyl-8-azabicyclo[4.3.0]nonan-7-one by comparison with material obtained earlier,[2] in low yield, by the debenzylation of (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**) with methanesulphonic acid. None of the lactam (**2**) could be detected (t.l.c.) in the mixture from the reduction. The second product was shown to be *N*-benzyl-2-(2-phenylethyl)cyclohexane-1-carboxamide (**20**). High-resolution mass spectroscopy showed the molecular formula to be $C_{22}H_{27}NO$, corresponding to the addition of four hydrogen atoms during the reduction. There was no signal in the vinylic region in the ^1H n.m.r. spectrum. The two-proton signal at δ 4.38 assigned to the methylene protons of the *N*-benzyl group appeared as a doublet and there was a broad, single-proton triplet at δ 5.88; deuterium exchange removed the latter signal, assigned to the NH proton, and caused the methylene signal at δ 4.38 to collapse to a singlet. The ^{13}C n.m.r. spectrum showed a signal at δ_C 174.5 p.p.m., characteristic of an amide carbonyl group, and the i.r. spectrum showed absorptions at 1 630 and 3 260 cm^{-1}, assigned to the CO and NH group respectively of the amide. The relative stereochemistry of the two side-chains in compound (**20**) has not been established. Integration of a ^1H n.m.r. spectrum of the crude reduction products showed that the two products are formed in approximately equal amounts. Presumably, in the reduction of compound (**7**), at an intermediate stage in the reduction of the styryl system, cleavage of the carbon–nitrogen bond in the sense shown in (**21**), leading to (**20**), occurs in competition with the reduction to give (**2**). Further reductive debenzylation of lactam (**2**) to give the second observed product is unexceptionable[14] and, indeed, when compound (**2**) was separately reduced with sodium in liquid ammonia it was cleanly debenzylated. The availability of this product by this route permitted better purification[2] of the material to be achieved.

With a view to establishing the generality of this novel cleavage reaction we then investigated the reduction of compound (**15a**) with sodium and liquid ammonia, under the same conditions. The reaction gave a mixture of two products (*ca.* 3:1) contaminated by a trace of a third. The two main products were separated by preparative t.l.c. (p.l.c.) and identified as *N*-benzylacetamide and the reduced compound (**17a**) respectively. The production of *N*-benzylacetamide involves a βC–N cleavage exactly analogous to that observed in the formation of compound (**20**) from enone (**7**); the other product, the hydrocarbon 1-phenylpropane, would have been lost during the work-up and purification procedures. Treatment of the amide (**17a**) with sodium and liquid ammonia caused smooth debenzylation and gave *N*-(1-methyl-2-phenylethyl)-acetamide which was identical with a sample prepared by the catalytic hydrogenation of (*Z*)-*N*-(1-methyl-2-phenylvinyl)-acetamide[13] and was also identified (^1H n.m.r.) as the trace product from the sodium in liquid ammonia reduction of compound (**15a**).

The novel cleavage of the β-styryl–nitrogen bond on reduction with sodium in liquid ammonia is observed with two enamides (**15a**) and (**7**) which are reduced with difficulty, or not at all, by magnesium and methanol, but not with the enamide (**13**) which is easily reduced by magnesium and methanol. Speckamp has very recently reported[15] cleavage of the non-benzylic C–N bond in lactams of the type (**22**) on reduction with sodium in liquid ammonia, which may also cause C–N bond cleavage in amides having the partial structure (**23**).[16]

We finally turned to the reduction of enamides by sodium cyanoborohydride in acidic media.[6] Treatment of compound (**7**) with sodium cyanoborohydride in acetic acid gave a single product, in 57% yield, which was easily identified as lactam (**2**) by its ^1H n.m.r. spectrum at 400 MHz.[1] When the reaction was conducted in formic acid rather than acetic acid the only reduced product was again lactam (**2**), isolated in 45% yield, but it was accompanied by a similar amount (^1H n.m.r. spectroscopy) of the rearranged product (**6**). The rearrangement of compound (**7**) to the conjugated isomer (**6**) catalysed by mineral acid has been noted previously;[2] blank experiments showed that compound (**7**) also rearranged to (**6**) under the conditions (acid; temperature; duration) of the cyanoborohydride reactions and that compound (**6**) is unaffected by sodium cyanoborohydride in acetic acid. The reduction of enamide (**7**) by sodium cyanoborohydride is stereospecific; the product formed, lactam (**2**), is the same as the only product from the catalytic hydrogenation of compound (**7**).[1,2] Successful reduction of enamide (**8**) was also accomplished using sodium cyanoborohydride in acetic acid; the reduction was selective and again stereospecific, the only product being compound (**9**), identified by comparison with the material isolated earlier from the magnesium and methanol reduction of compound (**5**).

It is not our experience that all enamides can be reduced to amides by sodium cyanoborohydride. The enamides (**15a**), (**16b**), and (**18**) were not reduced in either acetic or formic acid. The enamide (**13**) was not reduced in acetic acid, but 50% reduction was achieved in formic acid; with the diastereoisomeric enamide (**14**) 30% reduction was achieved in acetic acid, and complete reduction in formic acid.

Experimental

For general directions see ref. 13. Relative proportions of products were estimated from the peak areas of assigned signals in the ^1H n.m.r. spectra of crude product mixtures. Comparisons of samples of the same compound from different reactions to establish identity were made by ^1H n.m.r. and i.r. spectroscopy and by behaviour on t.l.c.

Starting Materials.—The preparations of compounds (**2**), (**5**)—(**8**), (**14**, (**15a** and **b**), (**16a** and **b**), and (**18**) have been reported previously.[2,11,13] Crystallisation of compound (**6**) from ether–light petroleum raised the m.p. to 93—94 °C; it has δ_C 20.2, 21.7, 22.1, and 23.8 (ring CH_2s), 36.2 ($CHCH_2Ph$), 43.8 ($CHCH_2Ph$), 61.6 (NCH_2Ph), 126.6, 127.1, 127.9, 128.2, 128.4, and 128.9 (aromatic CH), 131.7 (=*C*CH), 136.1 and 137.7 (*ipso* aromatic carbons), 153.5 (=*C*–CO), and 171.6 p.p.m. (C=O) (Found: C, 83.5; H, 7.5; N, 4.6. Calc. for $C_{22}H_{23}NO$: C, 83.2; H, 7.3; N, 4.4%).

(E)-N-*Styrylpyrrolidin-2-one* (**13**).—(i) *N*-(2-Hydroxy-2-phenylethyl)pyrrolidin-2-one,[10] m.p. 116 °C (lit.,[10] 117—118 °C) (25.0 g) was heated under reflux in toluene (250 ml) containing toluene-*p*-sulphonic acid (1.5 g) for 25 h. The reaction mixture was then cooled, washed with water (50 ml), and dried. Column chromatography on silica, using dichloromethane as eluant, of the material remaining after evaporation of the solvent gave a solid (4.5 g) which on recrystallisation from light petroleum gave (*E*)-*N*-styrylpyrrolidin-2-one (4.0 g, 17%), m.p. 127—128 °C (lit.,[10] 128—129 °C); δ_H 2.13 (2 H, m, *J* 7 Hz, $CH_2CH_2CH_2$), 2.5 (2 H, t, *J* 7 Hz, CH_2CO), 3.61 (2 H, t, *J* 7 Hz, NCH_2), 5.86 (1 H, d, J_{AB} 14.6 Hz, $PhCH_B{=}CH_AN$), 7.1—7.4 (5 H, m, Ph), and 7.64 (1 H, d, $PhCH_B{=}CH_AN$).

(ii) A mixture of *N*-(2-hydroxy-2-phenylethyl)pyrrolidin-2-one[10] (47.0 g, 0.23 mol) and thionyl chloride (95.3 g, 0.8 mol) was heated at 50 °C for 2 h, and then kept at room temperature overnight. Excess of thionyl chloride was then evaporated off and the resultant crude chloro compound (48.0 g, 0.2 mol) was heated under reflux for 24 h in 10% ethanolic potassium hydroxide (250 ml). The cooled reaction mixture was shaken vigorously with trichloromethane (150 ml) and undissolved potassium chloride was removed by filtration. The trichloromethane extract was washed with water and dried. Column chromatography on silica of the material obtained by evaporation of the solvent, using 3:2 dichloromethane–ethyl acetate as eluant, gave (*E*)-*N*-styrylpyrrolidin-2-one (18 g, 45%), m.p. 127—128 °C.

Ethyl N-*Benzyl*-N-*cyclohex*-1-*enylcarbamate* (**19**).—Ethyl *N*-cyclohex-1-enylcarbamate, δ_C 14.6 (CH_3), 22.3, 22.8, 24.1, and 27.5 (ring CH_2), 60.5 (CH_2Me), 110.1 and 132.5 (C=C), and 154.1 p.p.m. (CO); b.p. 136—140 °C at 14 mmHg, was prepared by the method of Hoch[17] and had i.r. and ^1H n.m.r. spectra in agreement with published data.[18] This material (10.0 g, 0.059 mol) in *NN*-dimethylformamide (300 ml) was treated under nitrogen with sodium hydride (50% dispersion in oil; 1.4 g, 0.059 mol) and then, at 0 °C, with redistilled benzyl chloride (7.8 g, 0.062 mol). The reaction mixture was heated for 24 h under reflux and then poured into water (150 ml). The product was extracted with dichloromethane (3 × 150 ml) and the extracts were washed with water (150 ml) and dried. Distillation then gave *ethyl* N-*benzyl*-N-*cyclohex*-1-*enylcarbamate* (**19**) as an oil (8.0 g, 53%), b.p. 146—150 °C at 0.3 mmHg; δ_H 1.17 (3 H, t, *J* 7 Hz, Me), 1.36—1.63 and 1.9—2.04 (each 4 H, m, together 4 × ring CH_2), 4.14 (2 H, q, *J* 7 Hz, CO_2CH_2), 4.55 (2 H, s, NCH_2Ph), 5.42 (1 H, s, C=C*H*), and 7.1—7.3 (5 H, m, Ph); *m/z* 259 ($M^{+\cdot}$) and 186 ($M^{+\cdot} - CO_2Et$) (Found: C, 73.9; H, 7.9; N, 5.5. $C_{16}H_{21}NO$ requires C, 74.1; H, 8.1; N, 5.4%).

Catalytic Hydrogenations.—(*Z*)-*N*-Benzyl-*N*-(1-methyl-2-phenylvinyl)acetamide (**15a**) (1.0 g) in methanol (15 ml) was hydrogenated at room temperature and pressure in the presence of 10% palladium–charcoal (0.1 g). Bulb-tube distillation of the product gave N-*benzyl*-N-(1-*methyl*-2-*phenylethyl*)*acetamide* (**17a**) (0.9 g, 90%) as an oil, δ_H 1.11 [d, J_{MX} 7 Hz, $PhCH_AH_BCH_MC(H_X)_3$, major rotamer], 1.13 (d, J_{MX} 7 Hz, H_X, minor rotamer), 1.94 (s, COMe, minor rotamer), 1.98 (s, COMe, major rotamer), 2.62—2.72 [complex J_{AM} (both rotamers) 7 Hz, overlapping signals for H_A, both rotamers], 2.85 (dd, J_{AB} 14, J_{BM} 7 Hz, H_B, minor rotamer), 2.95 (dd, J_{AB} 14, J_{BM} 7 Hz, H_B, major rotamer), 4.14 (m, J_{AM} 7 Hz, H_M, minor rotamer), 4.29 (d, J_{AB} 17 Hz, NCH_AH_BPh, major rotamer), 4.38 (d, J_{AB} 15 Hz, NCH_AH_BPh, minor rotamer), 4.41 (d, NCH_AH_BPh, major rotamer), 4.75 (m, H_M, major rotamer), 4.86 (d, NCH_AH_BPh, minor rotamer), and 7.0—7.35 (complex 2 Ph, both rotamers); *m/z* 268 ($M^{+\cdot}$ + H) and 176 ($M^{+\cdot}$ + H − CH_2Ph) (Found: C, 80.6; H, 7.8; N, 5.4. $C_{18}H_{21}NO$ requires C, 80.8; H, 7.9; N, 5.2%).

Similarly, hydrogenation of (**16b**) gave N-*benzyl*-N-(2-*phenylethyl*)*acetamide*, (**17b**) as an oil (75%), δ_H 2.02 (s, COMe, major rotamer), 2.12 (s, COMe, minor rotamer), 2.78 (t, *J* 7 Hz, $PhCH_2CH_2N$, major rotamer), 2.85 (t, *J* 7 Hz, $PhCH_2CH_2B$, minor rotamer), 3.44 (t, *J* 7 Hz, $PhCH_2CH_2N$, major rotamer), 3.59 (t, *J* 7 Hz, $PhCH_2CH_2N$, minor rotamer), 4.35 (s, NCH_2Ph, minor rotamer), 4.63 (s, NCH_2Ph, major rotamer), and 7.0—7.4 (complex 2 Ph, both rotamers); *m/z* 253 ($M^{+\cdot}$ − $PhCH_2$ (Found: C, 80.4; H, 7.5; N, 5.2. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.5; N, 5.5%.

Hydrogenation of (**18**) gave N-*benzyl*-N-(1-*phenylpropyl*)-*acetamide* (79%) as an oil, δ_H 0.92 (t, $MeCH_2CHPhN$, both rotamers), 1.92 (m, $MeCH_2CHPhN$, both rotamers), 2.04 (s, COMe, major rotamer), 2.36 (s, COMe, minor rotamer), 3.99 (d, J_{AB} 15 Hz, NCH_AH_BPh, minor rotamer), 4.29 (d, J_{AB} 15 Hz, NCH_AH_BPh, major rotamer), 4.44 (d, H_B, major rotamer), 4.81 (d, H_B, minor rotamer), 4.89 (t, $MeCH_2CHPhN$, minor rotamer), 5.90 (t, $MeCH_2CHPhN$, major rotamer), and 6.9—7.4 (complex, 2 Ph, both rotamers); *m/z* 267 ($M^{+\cdot}$) (Found: C, 81.0; H, 8.2; N, 5.0. $C_{18}H_{21}NO$ requires C, 80.8; H, 7.9; N, 5.2%). Hydrogenation of (*Z*)-*N*-(1-methyl-2-phenylvinyl)acetamide gave *N*-(1-methyl-2-phenylethyl)acetamide (97%), m.p. 91—92 °C (lit.,[19] 93 °C); δ_H 1.1 (3 H, d, *J* 6 Hz, CH*Me*), 1.93 (3 H, s, COMe), 2.7 (1 H, q, J_{AB} 14, J_{AX} 7 Hz, $PhCH_AH_B$), 2.85 (1 H, q, J_{BX} 6 Hz, $PhCH_AH_B$), 4.28 (1 H, c, C*H*MeN), 5.65—5.70 (1 H, br s, NH), and 7.15—7.4 (5 H, m, Ph).

Magnesium and Methanol Reductions.—Reductions with magnesium and methanol were carried out using the general procedures described previously[4] using either hydrochloric acid (method A) or aqueous acetic acid (method B) for the work-up.

Reduction (method A) of *N*, 9-dibenzyl-8-azabicyclo-[4.3.0]non-1(6)-en-7-one (**6**) (3.0 g) gave an oil (2.6 g) which was shown by analytical t.l.c. to contain three components, one of which had the R_F value of reactant (**6**). Preparative h.p.l.c. on a part of the material, on a milligram scale, using the conditions described previously[1] led to the isolation of compound (**6**), (1*RS*,6*SR*,9*SR*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**1**), (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**), and a mixture of (1*RS*,6*RS*,9*RS*)- and (1*RS*,6*RS*,9*SR*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one [(**3**) and (**4**) respectively] which were identified by their ^1H n.m.r. spectra at 400 MHz which showed no differences from those reported earlier.[1]

Reduction (method A) of *N*,9-dibenzyl-8-azabicyclo-[4.3.0]nona-1(6),3-dien-7-one (**5**) (3.0 g) gave an oil (3.0 g), preparative h.p.l.c. on a small portion of which afforded samples of the starting material (**5**), (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]non-3-en-7-one (**9**) (Found: *m/z* 317.1767. $C_{22}H_{23}NO$ requires *M*, 317.1780), a mixture of (1*RS*,6*SR*,9*SR*)- and (1*RS*,6*RS*,9*SR*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]non-3-en-7-one [(**10**) and (**11**) respectively], and a solid which on recrystallisation from light petroleum–benzene gave N,9-*dibenzyl*-8-*azabicyclo*[4.3.0]*nona*-1(6),2,4-*trien*-7-*one* (**12**), m.p. 80—81 °C, δ_H 2.8 (1 H, dd, J_{AB} 14, J_{AX} 8 Hz, $CH_XCH_AH_BPh$), 3.35 (1 H, dd, J_{BX} 5 Hz, $CH_XCH_AH_BPh$), 4.23 (1 H, d, J_{AB} 14 Hz, NCH_AN_BPh), 4.55 (1 H, dd, $CH_XCH_AH_BPh$), 5.48 (1 H, d, NCH_AH_BPh), and 6.8—7.9 (14 H, complex, ArH); *m/z* 313 ($M^{+\cdot}$) (Found: C, 84.1; H, 6.2; N, 4.4. $C_{22}H_{19}NO$ requires C, 84.3; H, 6.1; N, 4.5%). The ^1H n.m.r. data for compound (**9**)—(**11**) are given in the Table. The identities of the three reduced products were established by their catalytic hydrogenation, using the procedure described above, when compound (**9**) gave (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**) and the mixture of compounds (**10**) and (**11**) gave a mixture of (1*RS*,6*SR*,9*SR*)- and (1*RS*,6*RS*,9*SR*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one [(**1**) and (**4**) respectively], all of which were identified by their ^1H n.m.r. spectra at 400 MHz.[1]

Reduction (method B) of (*E*)-*N*-styrylpyrrolidin-2-one (**13**)

Table. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) for *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-3-en-7-ones in $CDCl_3$ at 400 MHz

Compound	1-H	6-H	9-H_α*	9-H_α*	$J_{1,9}$	NCH_A[a]	NCH_B[a]	$CCH'_ACH'_BPh$	$CC'_ACH'_BPh$	$J_{A'B'}$	$J_{A'M}$	$J_{B'M}$	Other data
(9)	2.2	2.62		3.82	5.0	4.14	4.98	2.62	3.06	14.0	10.5	5.0	*b,c,d*
(10)	2.2	2.70	3.12		1.5	3.82	5.12	2.68	2.96	14.0	9.0	4.5	*d,e,f*
(11)			3.4		10.0	4.12	5.16	2.5	3.3	14.0	10.0	5.0	*c,d,g*

* The configurations α and β refer to the enantiomers shown in structures (**9**), (**10**), and (**11**). [a] J_{AB} 15 Hz. [b] δ 5.7 (2 H, m, vinylic protons). [c] δ 1.9—2.68 (other CH and CH_2 groups). [d] δ 7.0—7.36 (2 Ph). [e] δ 1.3—2.58 (other CH and CH_2 groups). [f] δ 5.58 and 5.74 (each 1 H, m, vinylic proton). [g] δ 5.47 and 5.68 (each 1 H, m, vinylic proton).

and, separately, of (*Z*)-*N*-styrylpyrrolidin-2-one (**14**) gave, after recrystallisation from light petroleum, *N*-(2-phenylethyl)pyrrolidin-2-one (33 and 60% respectively), m.p. 49—51 °C (lit.,[12] b.p. 129—132 °C at 1.0 mmHg); δ_H 1.92 (2 H, m, *J* 7 Hz, $NCH_2CH_2CH_2CO$), 2.33 (2 H, t, *J* 7 Hz, $NCH_2CH_2CH_2CO$), 2.83 (2 H, t, *J* 7 Hz, $PhCH_2CH_2N$), 3.23 (2 H, t, *J* 7 Hz, $NCH_2CH_2CH_2CO$), 3.52 (2 H, t, *J* 7 Hz, $PhCH_2CH_2N$), and 7.14—7.36 (5 H, m, Ph).

Reduction (method **B**) of (*Z*)-*N*-benzyl-*N*-(1-methyl-2-phenylvinyl)acetamide (**15a**) (1.3 g) gave an oil (1.2 g) which on p.l.c., using 7:3 light petroleum–ethyl acetate as developing solvent, gave starting material (**15a**) (0.8 g recovery) and an oil, which after purification by h.p.l.c. gave *N*-benzyl-*N*-(1-methyl-2-phenylethyl)acetamide (**17a**) (0.04 g, 2%), identical with an authentic sample.

Reduction (method **B**) of (*E*)-*N*-benzyl-*N*-styrylacetamide (**16b**) (0.8 g) gave *N*-benzyl-*N*-(2-phenylethyl)acetamide (**17b**) (0.6 g, 75%), identical with an authentic sample. Reduction (method **B**) of (*Z*)-*N*-benzyl-*N*-styrylacetamide (**15b**) (0.15 g) gave an oil (0.11 g) which was shown by analytical t.l.c., using 7:3 light petroleum–ethyl acetate as developing solvent, and by ^{1}H n.m.r. spectroscopy, to be a 7:3 mixture of *N*-benzyl-*N*-(2-phenyethyl)acetamide and starting material (**15b**).

Reduction (method **B**) of (*Z*)-*N*-benzyl-*N*-(1-phenylprop-1-enyl)acetamide (**18**) (1.0 g) gave an oil which, by comparison (^{1}H n.m.r. spectroscopy) with authentic samples, was shown to be a 2:3 mixture of starting material (**18**) and *N*-benzyl-*N*-(1-phenylpropyl)acetamide.

Sodium in Liquid Ammonia Reductions.—A solution of (*E*)-*N*-styrylpyrrolidin-2-one (**13**) (1.0 g, 0.0053 mol) in dry tetrahydrofuran (10 ml) was rapidly added to a stirred solution of sodium metal (0.5 g, 0.0212 g-atom) in anhydrous ammonia under argon. After 0.5 h the solution was quenched by the slow addition of ammonium chloride (4.2 g, 0.784 mol). Ether (75 ml) was added and the ammonia was evaporated off. The mixture was then acidified with 6M-hydrochloric acid, water (50 ml) was added (to dissolve inorganic salts), and the solution was extracted with ether (2 × 50 ml). The combined ethereal extracts were washed with brine (3 × 40 ml) and dried, and the solvents were evaporated off to leave an oil (0.7 g), which solidified at 0 °C. Recrystallisation from light petroleum gave *N*-(2-phenylethyl)pyrrolidin-2-one (0.4 g, 40%), m.p. 49—51 °C, identical with the material described above.

Using the same procedure, *N*-benzyl-9-benzylidene-*cis*-8-azabicyclo[4.3.0]nonan-7-one (**7**) (1.7 g, 0.0053 mol) was reduced by sodium (0.8 g, 0.034 g-atom) in liquid ammonia to give an oil (1.45 g) which solidified with time. Analytical t.l.c. using 7:3 light petroleum–ethyl acetate as developing solvent showed the presence of two major components (R_F 0.59 and 0.14) and the absence of both starting material (R_F 0.70) and compound (**2**) (R_F 0.51). The mixture (2.8 g) was chromatographed on a silica column, using 7:3 light petroleum–ethyl acetate as eluant, and gave N-*benzyl*-2-(2-*phenylethyl*)-*cyclohexane*-1-*carboxamide* (**20**) (1.5 g), m.p. 94—95 °C, as white needles, $\nu_{max.}$(Nujol) 1 630 (CO) and 3 260 cm^{-1} (NH); δ_H 1.2—1.9 (11 H, complex, ring CH_2s, $CHCH_2$, and CH_2CH_2Ph), 2.25—2.7 (3 H, complex CHCO, and CH_2CH_2Ph), 4.38 (2 H, d, $NHCH_2Ph$), 5.88 (1 H, br t, NH), and 7.05—7.34 (10 H, m, 2 Ph); δ_C 21.96, 24.33, 25.21, 28.18, 30.88, 33.88, and 37.04 (saturated ring carbons + CH_2CH_2Ph), 43.23 (CH_2CH_2Ph), 46.99 (NCH_2Ph), 125.62, 127.29, 127.74, 128.19, 128.32, and 128.56 (*o*, *m*, and *p*-aromatic carbons), 138.63 and 142.39 (*ipso* aromatic carbons), and 174.52 (CO) (Found: M^+, 321.2097. $C_{22}H_{27}NO$ requires *M*, 321.2093); R_F (on analytical t.l.c.) 0.59 with ethyl acetate as eluant, a yellow solid (0.9 g) was eluted, R_F (analytical t.l.c.) 0.14. Recrystallisation of the second product from light petroleum–benzene gave (1*RS*,6*SR*,9*RS*)-9-benzyl-8-azabicyclo[4.3.0]nonan-7-one (0.6 g), m.p. 128—130 °C, identical with the material reported earlier[2] and below. Integration of the ^{1}H n.m.r. spectrum of the reduction mixture showed that the two products were formed in approximately equal amounts.

Using the same procedure, (*Z*)-*N*-benzyl-*N*-(1-methyl-2-phenylvinyl)acetamide (**15a**), (0.35 g) was reduced by sodium (0.35 g) in liquid ammonia to give a mixture shown by analytical t.l.c., using 1:1 light petroleum–ethyl acetate as developing solvent, to contain starting material, R_F 0.63, and two other components, R_F 0.13 and 0.48, which were separated by p.l.c. using 3:7 light petroleum–ethyl acetate as developing solvent. The product with R_F 0.13 solidified and showed minor, characteristic signals in its ^{1}H n.m.r. spectrum in the regions δ_H 2.6—2.9 and 4.2–4.4, attributable to *N*-(1-methyl-2-phenylethyl)acetamide on the basis of a direct comparison with the spectrum of an authentic sample. Crystallisation of the solid from light petroleum removed this trace impurity (^{1}H n.m.r.), and gave *N*-benzylacetamide (0.05 g, 26%), m.p. 57—59 °C (lit.,[20] 61 °C); δ_H 2.00 (3 H, s, COMe), 4.41 (2 H, d, *J* 5 Hz, $NHCH_2Ph$), 6.35 (1 H, br s, NH), and 7.2—7.4 (5 H, m, Ph), identical with an authentic sample.[20] The oil with R_F 0.48 (0.024 g, 7%) was identified as *N*-benzyl-*N*-(1-methyl-2-phenylethyl)-acetamide (**17a**) by direct comparison with the sample described above.

Similarly, sodium in liquid ammonia reduction of (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**) (0.1 g) gave, after recrystallisation from light petroleum–benzene, (1*RS*,6*SR*,9*RS*)-9-benzyl-8-azabicyclo[4.3.0]nonan-7-one, m.p. 129—130 °C (lit.,[2] 101—103 °C for unrecrystallised material); δ_H 1.1—1.9 (10 H, complex, protons on six-membered ring), 2.7 (1 H, dd, J_{AB} 10 Hz, $CH_XCH_AH_BPh$), 2.8 (1 H, dd, J_{BB} 5 Hz, $CH_XCH_AH_BPh$), 3.86 (1 H, m, $CH_XCH_AH_BPh$), 5.38 (1 H, b, NH), and 7.18—7.38 (5 H, m, Ph); *m/z* 138 ($M^{+\bullet} - CH_2Ph$) (Found: M^+, 229.1475. $C_{15}H_{19}NO$ requires *M*, 229.1466), having a ^{1}H n.m.r. spectrum identical with the previously reported[2] spectrum.

Similarly, sodium in liquid ammonia reduction of *N*-benzyl-*N*-(1-methyl-2-phenylethyl)acetamide (**17a**) (1.0 g) gave a solid which, on crystallisation from light petroleum–benzene, gave *N*-

(1-methyl-2-phenylethyl)acetamide, m.p. 93 °C (lit.,[19] 93 °C) (0.51 g, 76%), identical with the sample described above.

Reductions with Sodium Cyanoborohydride.—Sodium cyanoborohydride (0.66 g, 0.01 mol) was added in portions during a few minutes to a stirred solution of *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]non-3-en-7-one (**8**) (0.2 g, 0.0031 mol) in acetic acid (10 ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 3 h, then heated at 50 °C for 2 h, stirred overnight at room temperature, and then cooled in ice–water. Water (25 ml) and 50% aqueous sodium hydroxide were then added, until the mixture was strongly basic. The mixture was extracted with ether (3 × 50 ml) and the extracts were washed with brine (50 ml) and dried. Evaporation of the solvent gave an oil which was purified by bulb-tube distillation. The solid distillate, on crystallisation from light petroleum, gave (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]non-3-en-7-one (**9**) as white crystals (0.1 g, 50%), m.p. 77—78 °C (Found: C, 83.2; H, 7.3; N, 4.4. Calc. for $C_{22}H_{23}NO$: C, 83.0; H, 7.2; N, 4.4%), having a ^{1}H n.m.r. spectrum (Table) identical with that of the sample described above.

Similarly, reduction of *N*-benzyl-9-benzylidene-*cis*-8-azabicyclo[4.3.0]nonan-7-one (**7**) (0.35 g) by sodium cyanoborohydride in acetic acid gave (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**) (0.2 g, 57%), m.p. 92—93 °C (lit.,[2] 89 °C), identical with an authentic sample. When this reduction was repeated using the same procedure but with formic acid in place of acetic acid the product was an oil shown, by analytical t.l.c. using 1:4 light petroleum–ethyl acetate as developing solvent, to contain two components, which were separated by p.l.c. using the same solvent system as developer. The component with the higher R_F value (45%) was identified as (1*RS*,6*SR*,9*RS*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (**2**) and the other component (46%) was identified as *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (**6**) by comparison with authentic samples.

Reduction of (*E*)-*N*-styrylpyrrolidin-2-one (**13**) with sodium cyanoborohydride in formic acid gave a material (80%) shown by ^{1}H n.m.r. spectroscopy to be a 2:3 mixture of starting material and *N*-(2-phenylethyl)pyrrolidin-2-one. A similar reduction of (*Z*)-*N*-styrylpyrrolidin-2-one (**14**) gave *N*-(2-phenylethyl)pyrrolidin-2-one (90%) identical with the sample described above. Reduction of (*Z*)-*N*-styrylpyrrolidin-2-one (**14**), but using acetic acid as the solvent, gave a material (95%) shown by ^{1}H spectroscopy to be a 7:3 mixture of starting material and *N*-(2-phenylethyl)pyrrolidin-2-one.

Isomerisation of N-*Benzyl*-9-*benzylidene*-cis-8-*azabicyclo*-[4.3.0]*nonan*-7-*one* (**7**).—Acetic acid (10 ml) containing *N*-benzyl-9-benzylidene-*cis*-8-azabicyclo[4.3.0]nonan-7-one (**7**) (0.1 g) was stirred at room temperature for 3 h, then heated at 50 °C for 2 h, and then stirred for a further 24 h at room temperature. The solution was then poured into water (25 ml) and the resultant solution was made strongly basic with 50% aqueous sodium hydroxide and extracted with ether (3 × 25 ml). The ethereal extracts were washed with water (25 ml) and dried, and the solvent was evaporated off. The resultant oil (0.095 g, 95%) was shown by ^{1}H n.m.r. spectroscopy and analytical t.l.c., using 7:3 light petroleum–ethyl acetate as developing solvent, to be essentially *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (**6**) with a trace of starting material. Repetition of the procedure but with formic acid as the solvent gave only *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (**6**), identical with an authentic sample.

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