The Synthesis of 9-Substituted *N*-Benzyl-8-azabicyclo[4.3.0]non-4-en-7-ones by the Intramolecular Diels–Alder Reaction

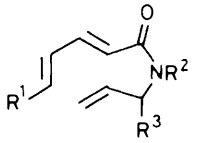
Roger Brettle * and Iftikhar A. Jafri
Department of Chemistry, The University, Sheffield S3 7HF

The intramolecular thermal cyclisation of *N*-allyl-*N*-benzylpenta-2(*E*),4-dienamide in refluxing *NN*-dimethylformamide gives *N*-benzyl-*cis*- and *trans*-8-azabicyclo[4.3.0]non-4-en-7-one; *N*-allyl-*N*-benzylhexa-2(*E*),4(*E*)-dienamide gives (1*RS*, 3*RS*, 6*SR*)-3-methyl- and (1*RS*, 3*RS*, 6*RS*)-3-methyl-*N*-benzyl-8-azabicyclo[4.3.0]non-4-en-7-one. 9-Benzyl- and 9-isobutyl-*N*-benzyl-8-azabicyclo[4.3.0]-non-4-en-7-one are prepared by the analogous intramolecular thermal cyclisation of the appropriate α-substituted *N*-allylpenta-2(*E*),4-dienamides. The major products all have *cis*-fused rings, but all the possible configurations are formed in each case, including the products with *trans*-fused rings. The relative stereochemistries of the bicyclic products are assigned on the basis of their high-resolution ^{1}H n.m.r. spectra.

In continuation of our studies [1] on the synthesis of 9-substituted 8-azabicyclo[4.3.0]nonan-7-ones as models for the reduced isoindolone units present in cytochalasans we have investigated a route to such structures based on the intramolecular Diels–Alder reaction. A preliminary account of the intramolecular cyclisations of two *N*-allylalka-2,4-dienamides to give 8-azabicyclo[4.3.0]non-4-en-7-ones has appeared [2] and we were attracted to this route, rather than the alternative route from *N*-alka-2,4-dienylacrylamides,[3] by the accessibility of the starting materials.

An attempted cyclisation of *N*-allylsorbamide (1; R^1 = Me, R^2 = R^3 = H) failed; the material was recovered unchanged after it had been heated in refluxing *NN*-dimethylformamide (DMF) under nitrogen for 72 h. We attribute this lack of reaction to the fact that the preferred conformation of the amide part of the molecule is unfavourable for cyclisation. This phenomenon has been observed previously in the attempted intramolecular Diels–Alder reaction with amides of the type (1; R^2 = H).[3] Successful cyclisation of an amide of the type (1; R^2 = H) has been observed [4] but in that case the diene component was a 5,6-bismethylenecyclohexa-1,3-diene, generated *in situ*, so that closure generated an aromatic system. The reported [2] cyclisation of compound (1; R^1 = Me, R^2 = $CH_2CH{=}CH_2$, R^3 = H), where one of the *N*-allyl groups must necessarily be favourably placed for cyclisation, and the expected effect on the amide conformation of replacing the hydrogen on the amide nitrogen by a bulkier group [3] led us to use amides of the type (1; R^2 = CH_2Ph) in our work.

Cyclisation of *N*-allyl-*N*-benzylpenta-2(*E*),4-dienamide (1; R^1 = R^3 = H, R^2 = CH_2Ph) was complete after 1.5 h in refluxing DMF. The two products,† formed in the ratio 7 : 3, could be separated by column chromatography and were shown to be the *cis*- (2) and *trans*- (3) forms of *N*-benzyl-8-azabicyclo[4.3.0]non-4-en-7-one by analysis of their ^{1}H n.m.r. spectra. The stereochemical assignments were confirmed by the separate hydrogenation of the two products which gave the known [5] saturated lactams, identified by direct comparison (i.r., ^{1}H n.m.r., h.p.l.c.) with authentic samples. The *trans*-form (3) can only adopt a single, rigid conformation. In the ^{1}H n.m.r. spectrum the protons at C-9 in (3) occur as the



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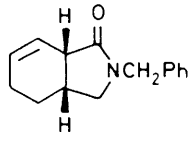

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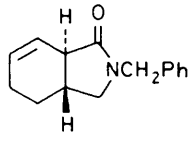

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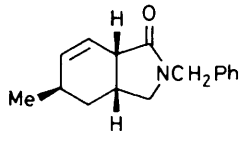
AB part of an ABX system, with J_{AB} 10 Hz, a value observed previously for the vicinal coupling constant of the 9-protons in *N*-benzyl-8-azabicyclo[4.3.0]nonan-7-ones,[5] with further couplings of 6 and 10 Hz corresponding to $J_{1,9\beta}$ and $J_{1,9\alpha}$, respectively. The signal for 6-H occurs as a broadened doublet at δ 2.65 with a *J* value of 14 Hz. Inspection of a model of compound (3) shows that the dihedral angle between 5-H and 6-H is *ca.* 90°, in accord with the small coupling between 5-H and 6-H. The coupling of 14 Hz was confirmed as $J_{1,6}$ by decoupling of the signal due to 1-H at δ 2.05, which caused the signal at δ 2.65 to collapse to a broad singlet. The large value for $J_{1,6}$ is in agreement with the dihedral angle of *ca.* 180°: values in the range 10—13 Hz have been reported for $J_{1,6}$ in related *trans*-fused 8-azabicyclo[4.3.0]non-4-en-7-ones.[2,4] The vinylic protons 4- and 5-H in compound (3) have markedly different chemical shifts, δ 5.65 and 6.15, respectively, whereas in the *cis*-fused compound (2) the vinyl protons have the same chemical shift, δ 5.9. A similar coincidence in the chemical shifts of the vinyl protons 4- and 5-H has been noted in the analogous *cis*-fused lactone 9α-butyl-8-oxabicyclo[4.3.0]non-4-en-7-one [6,‡] where, in the *cis*-fused system, 5-H is free from the shielding effect of the carbonyl group; this is not the case in the *trans*-fused system.

The *cis*-fused lactam (2) can exist as two interconvertible half-boat forms. Analysis of the ^{1}H n.m.r. spectrum of compound (2) yielded the values of $J_{1,9\alpha}$, $J_{1,9\beta}$, $J_{1,6}$, and $J_{5,6}$ as 4, 7, 9, and *ca.* 0 Hz, respectively, consistent with the half-boat conformation in which the corresponding dihedral angles are *ca.* 140, 20, 40, and 90°, respectively. Values for $J_{1,6}$ of 7—8 Hz have been reported for similar *cis*-8-azabicyclo[4.3.0]non-4-en-7-ones.[4]

Cyclisation of the amide (1; R^1 = Me, R^2 = CH_2Ph, R^3 = H) was complete (t.l.c.) in 12 h in refluxing DMF. The reac-

† All work was carried out with racemic materials. Only one enantiomer is shown in displayed formulae; the designations α and β refer to the enantiomer depicted. Specified stereochemistry *R* and *S* refers to the stereochemistry only in that enantiomer depicted in the formula.

‡ 9*R*-stereochemistry.



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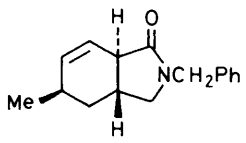
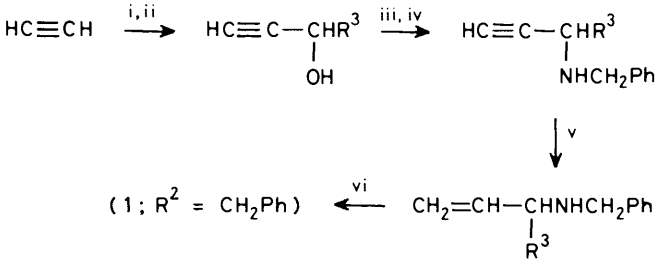


(5)

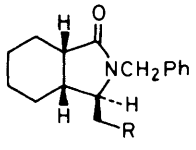
tion gave two products, with R_F values of 0.47 and 0.61, in the ratio of 4 : 1, which were separated by column chromatography and identified spectroscopically as compounds (4) and (5). The *trans*-fused racemate (5) can only adopt a single, rigid conformation. The ^{1}H n.m.r. spectrum of compound (5) was very similar to that of the demethyl compound (3); the *trans*-fused ring geometry was demonstrated by the values for $J_{1,9\alpha}$, $J_{1,9\beta}$, and $J_{1,6}$ of 10, 5.5, and 12 Hz, respectively, and by the large chemical-shift difference between the two vinyl protons which gave signals at δ 5.55 and 6.15. The signals for the 2-protons occurred at δ 1.6 and 1.8. The higher-field signal appeared as a doublet with a J value of 12 Hz, and only small additional coupling, whereas the lower-field signal appeared as a double triplet due to two large couplings, each of 12 Hz, and a further coupling of 7 Hz. This pattern demonstrates that the methyl group in compound (5) has the β-orientation (*R*-stereochemistry), the signal at δ 1.6 being due to 2-H$_\beta$ since, in addition to the large geminal coupling there is another large coupling to 1-H (dihedral angle *ca.* 180 °), and a medium-sized coupling to 3-H$_\alpha$ (dihedral angle *ca.* 0°); the signal at δ 1.8 due to 2-H$_\alpha$ shows only small coupling to 1-H (dihedral angle *ca.* 60°) and 3-H$_\alpha$ (dihedral angle *ca.* 120°). These assignments were supported by the appropriate double-irradiation experiments.

The *cis*-fused racemate (4) can adopt either of two interconvertible half-boat conformations. The ^{1}H n.m.r. spectrum of compound (4) was clearly not like that expected of the other possible *trans*-fused racemate, and indeed showed many similarities to that of the corresponding *cis*-fused demethyl compound (2). The observed coupling constants $J_{1,9}$ and $J'_{1,9}$ of 7 and 0 Hz are compatible with the conformation of compound (4) for which the dihedral angles between 1-H and 9-H$_\beta$ and 1-H and 9-H$_\alpha$ are *ca.* 15 and 95°, respectively. The signal for only one of the protons at C-2 is clearly visible, the other being largely obscured by the signal due to the methyl group. The signal appears as a double triplet with J values of 13, 4.5, and 4.5 Hz; irradiation at the position of the 1-H or 3-H signal causes the signal to collapse to a double doublet by removal of one or other of the 4.5-Hz couplings. These results are insufficient to establish the stereochemistry at C-3, being compatible with the signal for 2-H$_\beta$ regardless of whether the methyl group has the α- or the β-orientation in the conformation adopted. However, the signals for the vinyl protons do not have the same chemical shifts in this *cis*-fused compound, but occur as a doublet at δ 5.73 4-H and a multiplet at δ 5.96 (5-H). Double-irradiation experiments confirm that 5-H is coupled to 6-H, but that 4-H is not coupled to 3-H. This shows that the methyl group in the conformation adopted has the β-orientation (*R*-stereochemistry), and occupies a pseudo-equatorial position, since the dihedral angle between 3-H$_\alpha$ and 4-H is *ca.* 90° only for that particular orientation of the methyl group.

We then extended our investigation to amides substituted in the allylamine moiety *i.e.* (1; R^3 ≠ H), so that cyclisation would lead to 9-substituted 8-azabicyclo[4.3.0]non-4-en-7-ones. The required amides were prepared from ethyne by the route shown in Scheme 1. There are adequate precedents [7] for each of the steps outlined in Scheme 1 although most of the intermediates and none of the amides have previously been reported.



Scheme 1. *Reagents and conditions:* i, EtMgBr; ii, R^{3}CHO; iii, $MeC_6H_4SO_2Cl$, NaOH; iv, $PhCH_2NH_2$; v, H_2, Lindlar catalyst; vi, R^{1}CH=CHCH=CHCOCl, −78 °C, diethyl ether



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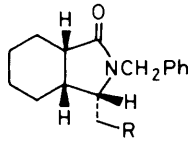

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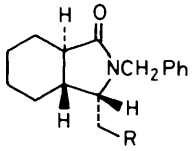

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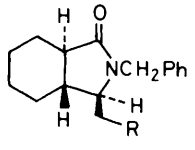


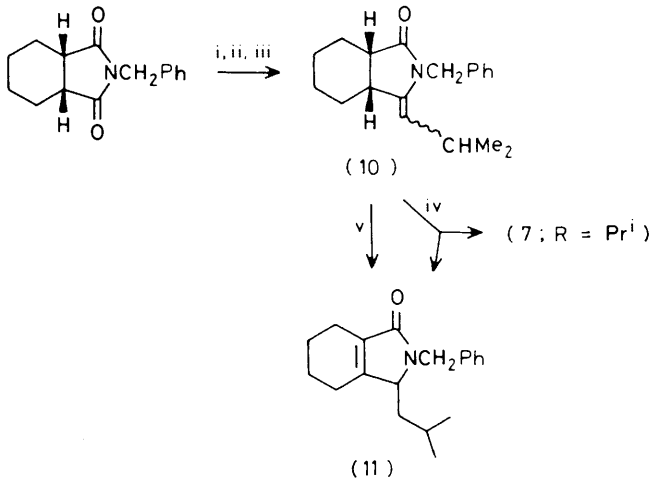
(9)

Cyclisation of the amide (1; R^1 = H, R^2 = R^3 = CH_2Ph) was complete (t.l.c.) after 6 h in refluxing DMF. The results and their interpretation presented below show that the major products were the *N*,9(α and β)-dibenzyl-*cis*-8-azabicyclo-[4.3.0]non-4-en-7-ones, the only other products being lesser amounts of the two corresponding *trans*-isomers. Analytical t.l.c. showed the presence of two components, having R_F values of 0.42 and 0.65, which were readily separated by column chromatography and shown to be present in the ratio *ca.* 4 : 1. Inspection of the ^{1}H n.m.r. spectra of the two separated materials showed that each was a mixture of two of the possible racemates of *N*,9-dibenzyl-8-azabicyclo[4.3.0]non-4-en-7-one. In particular the signals due to all the *N*-benzylic methylene groups could clearly be seen, in the region δ 3.1—5.2, showing that the material having R_F 0.42 was a mixture of two racemates in the ratio of 5 : 4, whereas the material having R_F 0.65 contained a mixture of the other two racemates in the ratio of 4 : 1. The pure racemates could not be separated by h.p.l.c. It was noted that the mixture having R_F 0.42 gave only one region of absorption for the vinyl protons, at δ 5.8—6.1, whereas the mixture having R_F 0.65 gave two absorptions of equal integrated area in the vinyl region at δ 5.55—5.70 and 6.08—6.22. By analogy with the vinyl region of the spectra of compounds (2) and (3) we tentatively assumed that the two racemates having R_F 0.42 both had a *cis*-ring junction, and that the two racemates having R_F 0.65 both had a *trans*-ring junction. A large R_F difference between the *cis*- and *trans*-forms of a highly substituted 9-benzyl-8-azabicyclo[4.3.0]-nonan-7-one has been observed previously,[8] the *cis*-form having the smaller R_F value, as is the case for the *cis*–*trans* pair (4) and (5). Separate hydrogenations of the mixtures having R_F values of 0.42 and 0.65 over palladium–charcoal gave mixtures of the corresponding saturated compounds. At this stage it was possible to separate (h.p.l.c.) the two racemates considered to have a *cis*-ring junction. One of these, compound (7; R = Ph), was shown to be identical (m.p., ^{1}H n.m.r., h.p.l.c.) with a sample prepared earlier [1] by a totally different route, the hydrogenation of *N*-benzyl-9-benzylidene-*cis*-8-

azabicyclo[4.3.0]nonan-7-one, which had firmly established the *cis*-ring-junction stereochemistry. This result conclusively confirmed our tentative assignment of the ring-junction stereochemistry of the precursor which was based on consideration of the vinyl absorptions in the ^{1}H n.m.r. spectrum of the two racemates having R_F 0.42, and strengthened the case for assigning a *cis*-ring junction to the second separated hydrogenation product (6; R = Ph). The relative stereochemistries at C-9 in compounds (6; R = Ph) and (7; R = Ph) were assigned on the basis of the $J_{1,9}$ values of 0 and 4.5 Hz, respectively, which were obtained from 400-MHz ^{1}H n.m.r. spectra as J_{MX} by first-order analysis of the ABMX system formed by the *C*-benzyl methylene protons, 9-H, and 1-H. The zero coupling constant is only compatible with one of the two possible chair conformations of compound (6; R = Ph) in which the 9-benzyl group occupies the β-position (9*S*-stereochemistry), and the dihedral angle between 1-H and 9-H is *ca.* 90°. It follows that the other *cis*-fused racemate (7; R = Ph) has the α-orientation (9*R*-stereochemistry) of the benzyl substituent at C-9 although, on the basis of the dihedral angles between 1-H and 9-H for the possible chair or boat conformations of 0—30°, a somewhat larger value than 4.5 Hz for $J_{1,9}$ might have been expected. These conclusions reverse our previous assignment [1] of stereochemistry to the sole product (h.p.l.c.) of the hydrogenation of *N*-benzyl-9-benzylidene-*cis*-8-azabicyclo[4.3.0]nonan-7-one, made without the advantage of available ^{1}H n.m.r. spectra of both compounds (6; R = Ph) and (7; R = Ph); it follows that in the hydrogenation the hydrogen adds exclusively from the top (convex) side of the molecule. Coupling constants $J_{1,9}$ of 9 Hz have been recorded [9] for two *cis*-fused 9β-benzyl-8-azabicyclo[4.3.0]-nonan-7-ones (9*S*-stereochemistry) obtained by the degradation of natural cytochalasans; these are compatible with the alternative chair conformation in which the dihedral angle between 1-H and 9-H is 160°.

We could not separate the two *trans*-fused hydrogenation products (8; R = Ph) and (9; R = Ph) by h.p.l.c., but sufficient line separation was obtained in a ^{1}H n.m.r. spectrum of the mixture at 400 MHz for us to measure $J_{1,9}$ for both the major and minor components. In the major component (8; R = Ph) the value for $J_{1,9}$ was 6.8 Hz which, in the *trans*-fused series where only a single chair conformation is possible, is only compatible with the α-orientation (*R*-stereochemistry) of the *C*-benzyl group, such that the dihedral angle between 1-H and 9-H$_\beta$ is *ca.* 30°. In the minor component (9; R = Ph) the value of $J_{1,9}$ was 9 Hz, in good agreement with the expected value for the case where the benzyl group is β-orientated (*S*-stereochemistry), and the dihedral angle between 1-H and 9-H$_\alpha$ is *ca.* 160°.

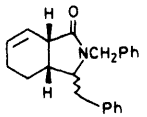
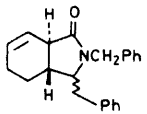
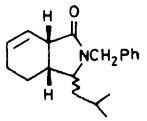
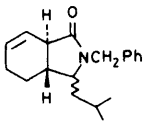
Compounds [(6)—(9); R = Ph] possess the basic non-macrocyclic structure of the biggest group of natural cytochalasans, with a benzyl group at C-9 in the azabicyclo-[4.3.0]nonan-7-one ring system. Recently, aspochalasins A, B, C, and D have been isolated and shown [10] to have an isobutyl group attached to C-9 of the azabicyclo[4.3.0]nonan-7-one ring. As models for the aspochalasins we have therefore also prepared a mixture of compounds [(6)—(9); R = Pr^i] by hydrogenation of the products of the thermal cyclisation of the amide (1; R^1 = H, R^2 = CH_2Ph, R$_3$ = CH_2CHMe_2), prepared by the route shown in Scheme 1. The cyclisation was complete (t.l.c.) after 8 h in refluxing DMF. The results and their interpretation presented below show that the major products were the *N*-benzyl-9(α and β)-isobutyl-*cis*-8-azabicyclo[4.3.0]non-4-en-7-ones, the only other products being lesser amounts of the two corresponding *trans*-isomers. Analytical t.l.c. showed the presence of two components having R_F values of 0.44 and 0.60 which were readily separated by column chromatography and were shown to be present in



Scheme 2. *Reagents and conditions:* i, Me_2CHCH_2MgBr; ii, NH_4Cl-H_2O; iii, Reflux in C_6H_6; iv, H_2, Pd–C; v, H^+

the ratio 4 : 1. From an inspection of the ^{1}H n.m.r. spectra of the two separate components it was clear that the cyclisation had taken place, but also that each component was a mixture of two racemates. The material of lower R_F value showed only a single absorption in the vinyl region at δ 5.85—6.10, but showed signals assignable to two different *N*-benzylic methylene groups in the region δ 3.8—5.1 in the ratio 4.5 : 1. By analogy with the earlier results we assign a *cis*-ring fusion to each member of this pair of racemates. The material of higher R_F value showed two separate areas of absorption in the vinyl region, at δ 5.5—5.6 and δ 6.1—6.2, and from the magnitude of the absorptions in the *N*-benzylic methylene region, δ 3.8—5.2, was assumed to contain the two *trans*-fused racemates in a ratio *ca.* 1 : 1. Attempts to separate individual racemates by h.p.l.c. at this stage were unsuccessful and so the components of R_F 0.44 and 0.60 were separately hydrogenated using a palladium catalyst. From the mixture of the *cis*-fused racemates (6; R = Pr^i) and (7; R = Pr^i) thus formed it was then possible to isolate one pure racemate by h.p.l.c. and to establish its stereochemistry as (7; R = Pr^i) (the 1*RS*, 6*SR*, 9*RS*-isomer pair) by ^{1}H n.m.r. spectroscopy at 400 MHz. The signals for 1-, 6-, and 9-H could be identified as groups of signals centred at δ 2.25, 2.50, and 3.42, respectively and, after double-irradiation experiments, the values of $J_{1,9}$, $J_{1,6}$, $J_{5,6}$, and $J'_{5,6}$ were found to be 5, 6, 6, and *ca.* 1 Hz, respectively. These are only consistent with a *cis*-fused ring system; the value of $J_{1,6}$ in *N*-benzyl-*cis*-8-azabicyclo[4.3.0]-nonan-7-one is 5 Hz.[5] The other coupling constants for 6-H are only consistent with a chair conformation in which 6-H is equatorial, and in that case the value of 5 Hz for $J_{1,9}$ indicates the α-orientation for the isobutyl group at C-9 (9*R* in isomer shown), the dihedral angle between 1-H and 9-Hβ being *ca.* 30°. [The value of $J_{1,9\beta}$ in compound (7; R = Ph) is 4.5 Hz.] In the isobutyl series, using h.p.l.c., we were able to obtain a sample of one of the *trans*-fused racemates of *ca.* 80% purity. The major constituent was identified as compound (8; R = Pr^i) by a partial analysis of the 400-MHz ^{1}H n.m.r. spectrum of the mixture, which established the value of $J_{1,9}$ as 6.0 Hz. In view of the rigid conformations of the *trans*-fused racemates this is only consistent with the α-orientation (*R*-stereochemistry) of the isobutyl group at C-9. [The value of $J_{1,9\beta}$ in compound (8; R = Ph) is 6.8 Hz.] Signals at δ 4.0 and 5.0, both doublets, J_{AB} 15 Hz, and δ 3.1 could be attributed to the *N*-benzylic methylene protons and 9-H, respectively, in the minor constituent (9; R = Pr^i); the corresponding signals

Table 1. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) for *N*-benzyl-8-azabicyclo[4.3.0]non-4-en-7-ones in $CDCl_3$ solution at 220 MHz *

Compound	1-H	2-H_2	3-H_2	4-H	5-H	6-H	9-H_α	9-H_β	$J_{1,6}$	$J_{5,6}$	$J_{1,9\alpha}$	$J_{1,9\beta}$	$J_{9\alpha,9\beta}$	NCH_A [a]	NCH_B [a]	Other data
(2)	2.49	1.3—1.7	1.95	5.90	5.90	3.00	2.85	3.30	9	*ca.* 0	4	7	9	4.35	4.41	*d*
(3)	2.05	1.5—1.9	2.2	5.65	6.15	2.65	2.95	3.15	14	*ca.* 0	10	6	10	4.38	4.51	*d*
(4)	2.43	0.85—1.65	2.13 [b]	5.73	5.96	3.00	2.87	3.42	—	—	—	7	10	4.38	4.47	*d*, *e*, *f*
(5)	2.10	1.6, 1.8	2.50 [b]	5.55	6.15	2.59	2.95	3.15	12	*ca.* 0	10	5.5	10	4.38	4.51	*d*, *g*, *h*
		—	—	5.81—6.10		—	—	—	—	—	—	—	—	3.85, 4.19,	5.14, 4.91	—
	—	—	—	5.55—5.70	6.08—6.22	—	—	—	—	—	—	—	—	3.14,[c] 4.12	5.00,[c] 5.07	—
	—	—	—	5.85—6.10		—	—	—	—	—	—	—	—	3.82,[c] 4.08	5.05,[c] 4.86	—
	—	—	—	5.50—5.60	6.10—6.22	—	—	—	—	—	—	—	—	3.80, 4.05	5.13, 5.00	—

[a] J_{AB} 15 Hz. [b] 3-H_α. [c] Major isomer [d] 7.1—7.4 (Ph) [e] 0.75, *J* 7 Hz (3-Me_β). [f] $J_{1,2\beta}$ 4.5, $J_{3,2\beta}$ 4.5, $J_{2\alpha,2\beta}$ 13, $J_{3\alpha,4}$ 0 Hz. [g] 1.01, *J* 7 Hz (3-Me-). [h] $J_{1,2\alpha}$ 12, $J_{3,2\alpha}$ 7, $J_{2\alpha,2\beta}$ 12 Hz.
* Configurations α and β refer to the enantiomers shown in the structures (2)—(5).

Table 2. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) for *N*-benzyl-8-azabicyclo[4.3.0]nonan-7-ones in $CDCl_3$ at 400 MHz *

Compound	1-H	6-H	9-H$_\alpha$	9-H$_\beta$	$J_{1,9}$	NCH$_A$ [a]	NCH$_B$ [a]	CCH$_A$H$_B$Ph	CCH$_A$H$_B$Ph	$J_{AB'}$	J_{AM}	J_{BM}	Other data
(6; R = Ph)	2.05	2.45	3.05	—	*ca.* 0	4.20	5.10	2.65	2.90	13.5	8.5	5.0	*b*, *d*
(7; R = Ph)	2.05	2.45	—	3.75	4.5	4.15	5.00	2.60	3.05	14.0	11.0	4.5	*b*, *d*
(8; R = Ph)	1.80	1.60	—	3.56	6.8	3.08	4.95	2.7—2.8		14.0	8.2	5.0	*b*, *d*
(9; R = Ph)	—	—	3.35	—	9.0	4.08	5.09	2.59	3.19	14.0	8.5	5.0	*b*, *d*
(7; R = Pr^i)	2.25	2.50	—	3.42	5.0	4.10	4.90	—	—	—	—	—	*c*, *d*, *e*
(8; R = Pr^i)	1.70	—	—	3.15	6.0	3.80	5.10	—	—	—	—	—	*d*, *f*

* Configurations α and β refer to the enantiomers shown in structures (6)—(9).

[a] J_{AB} 15 Hz. [b] 7.1—7.4 (2 × Ph). [c] 7.2—7.4 (Ph). [d] 1.0—1.7 (other CH and CH$_2$ groups). [e] 0.7 and 0.9 (2 × Me), $J_{H,Me}$ 6 Hz. [f] 0.8 and 0.9 (2 × Me), $J_{H,Me}$ 6 Hz.

for the major constituent (8; R = Pr^i), occurred at δ 3.8, 5.1, and 3.15, respectively.

Further confirmation of the *cis*-ring fusion in compound (7; R = Pr^i) was provided by its synthesis from *N*-benzyl-*cis*-hexahydrophthalimide by a route analogous to that reported earlier [1] for the 9-benzyl-substituted compound (7; R = Ph). This synthesis is shown in Scheme 2. The samples of compound (7; R = Pr^i) prepared by the two routes were identical (h.p.l.c., ^{1}H n.m.r.). The intermediate ene–lactam (10) appeared (^{1}H n.m.r.) to be a single isomer. As in the benzylidene series (*vide supra*) hydrogenation of compound (10) gave a single saturated product (7; R = Pr^i) by addition of hydrogen from the top (convex) side of the molecule. During the hydrogenation with palladium–charcoal as catalyst a small amount of *N*-benzyl-9-isobutyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (11) was also formed. Such double-bond migrations have been observed previously during hydrogenations using palladium–charcoal as catalyst.[11] The conjugated, tetrasubstituted olefinic bond in compound (11) is not reduced under the conditions used. The conjugated olefinic lactam (11) was also formed by the acid-catalysed rearrangement of compound (10), in analogy to the rearrangement in the corresponding 9-benzylidene series,[1] and it could be debenzylated by refluxing with methanesulphonic acid for 48 h to give 9-isobutyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one in very much better yield, 94%, than was the case with the corresponding 9-benzyl compound.

It has become evident as a result of the current intensive study of the intramolecular mode of the Diels–Alder reaction [12] that at elevated temperatures secondary orbital interactions are not dominant in determining the transition states for such reactions and the requirement to form an *endo*-transition state does not apply. Moreover the atoms in the chain connecting the diene and the dienophile parts of the molecule, and particularly the groups attached to them, influence the stereochemical outcome in ways which cannot at present be predicted. In the work reported here on the cyclisation of the amides (1; R^1 = H, R^2 = CH$_2$Ph, R$_3$ = CH$_2$Ph or CH$_2$CHMe$_2$), all possible stereochemistries were formed in each case, but with a preponderance of products having a *cis*-fused ring junction.

Experimental

^{1}H N.m.r. spectra were recorded on Bruker WH 400 (400 MHz) or Perkin-Elmer R34 (220 MHz) instruments for solutions in $CDCl_3$ with Me_4Si as internal standard; data for the lactams are given in Tables 1 and 2; i.r. spectra on a Perkin-Elmer 157G spectrophotometer, for thin films, Nujol mulls, or as KBr discs; and mass spectra on Kratos MS 25 or MS 80 instruments. H.p.l.c. was performed on an apparatus consisting of a Waters R401 differential refractometer and a Cecil CE 212 u.v. spectrophotometer. Analytical h.p.l.c. was conducted on columns (25 cm × 4 mm i.d.) containing 5μ Hypersil or 5μ silica, and preparative h.p.l.c. was conducted on columns (25 cm × 12 mm i.d.) containing 14μ Spherisorb; the developing solvents were mixtures of redistilled ethyl acetate and light petroleum (b.p. 60—80 °C) in the proportions stated. G.l.c. was performed either on a Perkin-Elmer F11 chromatograph using a 6ft glass column containing 5% Carbowax 1540 on 80—100 mesh AWDMCS Chromosorb G at 60—150 °C (programmed at 10 °C min^{-1}) (condition A) or on a Carlo Erba 4200 chromatograph, using a 6-ft glass column containing 3% OV 1 on 80—100 mesh Diatomite CLQ, at 100—250 °C (programmed at 10 °C min^{-1}) (condition B). Column chromatography was performed using the short-path technique with a column slurry-packed with Whatman SOTLC or Merck 7736 silica gel, and with the application of pressure from an external source. Analytical t.l.c. was performed on glass plates, 20 × 3 cm, coated with *ca.* 1 mm of Merck Kieselgel G, using mixtures of freshly distilled diethyl ether and light petroleum (b.p. 60—80 °C) as the developing solvent. Light petroleum for crystallisations refers to the fraction having b.p. 40—60 °C unless otherwise stated. Solutions in organic solvents were dried with anhydrous magnesium sulphate, and the solvents were evaporated on a Büchi Rotavapor rotary evaporator. M.p.s were determined on a Kofler hot-stage apparatus.

Starting Materials.—Penta-2(*E*),4-dienoic acid [13] and its acid chloride,[14] hexa-2(*E*),4(*E*)-dienoyl chloride,[15] 1-phenylbut-3-yn-2-ol [7b] and its toluene-*p*-sulphonate,[7b] *N*-allylbenzylamine,[16] and *N*-benzylhexahydrophthalimide [1] were prepared by methods described in the literature.

5-Methylhex-1-yn-3-ol.—A 1.43M solution of ethylmagnesium bromide in dry tetrahydrofuran (THF) (300 ml, 0.4 mol) was added dropwise during 1 h under nitrogen to THF (300 ml) saturated with ethyne and through which a stream of ethyne was being passed. Freshly distilled 3-methylbutanal (17.2 g, 0.2 mol) was then added dropwise during 1 h at room temperature with continued ethyne bubbling. The gas stream was then discontinued and the mixture was stirred for 24 h at room temperature under nitrogen. The mixture was then decomposed by the addition of saturated aqueous ammonium chloride (100 ml), the organic layer was separated, and the aqueous layer was extracted (3 ×) with diethyl ether. The combined organic layer and extracts were dried, the solvents were evaporated off, and the residue was distilled to give 5-methylhex-1-yn-3-ol (14.6 g, 65%), b.p. 60—62 °C at 18 mmHg (lit.,[17] 65—66 °C at 20 mmHg); δ 0.95 (6 H, d, *J* 5 Hz, 2 × Me), 1.55—1.72 (2 H, m, CH$_2$), 1.88 (1 H, m, C*H*Me$_2$), 2.48 (1 H, d, *J* 2 Hz, HC≡C), 3.25br (1 H, s, OH), and 4.42 (1 H, m, C*H*OH); *toluene*-p-*sulphonate*, m.p. 34 °C (from ethanol–light petroleum); $\nu_{max.}$ (KBr) 3 290 and 2 120 cm^{-1} (HC≡C);

δ 0.90 (6 H, d, *J* 5 Hz, 2 × Me), 1.6—1.9 (total 3 H, complex m, CH_2CHMe_2), 2.32 (1 H, d, *J* 2 Hz, HC≡C), 2.42 (3 H, s, MeC_6H_4), 5.1 (1 H, m, CHO), and 7.32 and 7.82 (total 4 H, AA'XX', *J* 9 Hz, C_6H_4); *m/z* 266 (Found: C, 63.4; H, 6.8; S, 12.0. $C_{14}H_{18}O_3S$ requires C, 63.4; H, 6.8; S, 12.0%).

Prop-2-ynylamines.—A solution of 1-benzylprop-2-ynyl toluene-*p*-sulphonate * (9.0 g, 29 mmol) in sodium-dried benzene (200 ml) was added dropwise to a stirred solution of benzylamine (9.6 g, 91 mmol) in sodium-dried benzene (200 ml) and the mixture was then refluxed for 2 h. The solution was then shaken with 5M aqueous sodium hydroxide (50 ml) and the benzene layer was separated. The aqueous layer was extracted with benzene and the combined benzene phases were dried and distilled to give N-(1-*benzylprop-2-ynyl*)*benzylamine* * (4.1 g, 58%) as a pale-yellow liquid, b.p. 129 °C at 0.01 mmHg; $\nu_{max.}$ (neat) 3 350 (NH) and 3 290 and 2 115 cm^{-1} (HC≡C); δ 1.5br (1 H, s, NH) 2.3 (1 H, d, *J* 2 Hz, HC≡C), 2.91 (2 H, d, *J* 7 Hz, CCH_2Ph), 3.58 (1 H, m, $CHCH_2$), 3.79 and 3.91 (each 1 H, d, J_{AB} 14 Hz, together NCH_2), and 7.25 (10 H, m, 2 × Ph); *m/z* 235 (Found: C, 86.8; H, 7.2; N, 5.7. $C_{17}H_{17}N$ requires C, 86.8; H, 7.2; N, 5.9%).

N-(1-*Ethynyl*-3-*methylbutyl*)*benzylamine*,* b.p. 78 °C at 0.01 mmHg; $\nu_{max.}$ (neat) 3 360 (NH) and 3 295 and 2 100 cm^{-1} (HC≡C); δ 0.9 (6 H, d, 2 × Me), 1.3br (1 H, s, NH), 1.5 (2 H, m, CH_2CH), 1.95 (1 H, m, $CHMe_2$), 2.40 (1 H, d, *J* 2 Hz, HC≡C), 3.42 (1 H, m, CHNH), 3.25 and 3.42 (each 1 H, d, J_{AB} 14 Hz, together NCH_2), and 7.35 (5 H, m, Ph); *m/z* 201 (Found: C, 83.8; H, 9.2; N, 6.9. $C_{13}H_{19}N$ requires C, 83.6; H, 9.5; N, 6.9%) was similarly prepared from 1-ethynyl-3-methylbutyl toluene-*p*-sulphonate.

Allylamines.—*N*-(1-Benzylprop-2-ynyl)benzylamine (3.4 g), Lindlar catalyst (340 mg), quinoline (81 mg), and hexane (300 ml) were stirred together under hydrogen until the amount of hydrogen required for semi-hydrogenation (1 mol equiv.) had been taken up. The catalyst was then filtered off and was washed with hexane, and the combined filtrate and washings were distilled to give N-(1-*benzylprop-2-enyl*)*benzylamine* * (3.2 g, 94%) as a pale-yellow oil, b.p. 116—118 °C at 0.2 mmHg, which was pure by g.l.c. (condition B); $\nu_{max.}$ (neat) 3 320 cm^{-1} (NH); δ 1.41br (1 H, s, NH), 2.72 (2 H, m, CCH_2Ph), 3.25 (1 H, m, CHNH), 3.55 and 3.70 (each 1 H, d, J_{AB} 15 Hz, together NCH_2), 5.0 (2 H, m, CH_2=C), 5.7 (1 H, m, CH_2=CH), and 7.2 (10 H, complex m, 2 × Ph) (Found: M^+, 237.1500. $C_{14}H_{21}N$ requires *M*, 237.1517).

N-(3-*Methyl*-1-*vinylbutyl*)*benzylamine*,* an oily liquid, b.p. 100 °C at 0.2mmHg, pure by g.l.c. (condition A); $\nu_{max.}$ (neat) 3 300 cm^{-1} (NH); δ 0.89 (6 H, d, Me_2C), 1.35 (2 H, m, $CHCH_2$), 1.55br (1 H, s, NH), 1.65 (1 H, m, $CHMe_2$), 3.1 (1 H, m, CHNH), 3.65 and 3.75 (each 1 H, d, J_{AB} 15 Hz, together NCH_2), 5.15 (2 H, m, CH_2=C), 5.75 (1 H, m, CH_2=CH), and 7.30 (5 H, m, Ph) (Found: M^+, 203.1657. $C_{14}H_{21}N$ requires *M*, 203.1674) was similarly prepared from *N*-(1-ethynyl-3-methylbutyl)benzylamine.

Amides.—A solution of penta-2(*E*),4-dienoyl chloride (1.16 g, 0.01 mol) in diethyl ether (150 ml) was added dropwise during 45 min to a stirred solution of *N*-allylbenzylamine (2.90 g, 0.02 mol) in diethyl ether (300 ml) cooled to −78 °C. When the addition was complete the mixture was stirred for a further 4 h at −78 °C and then for 24 h at room temperature. The precipitated amine salt was filtered off and the filtrate was washed in turn with water (2 × 75 ml), 2M hydrochloric acid (2 × 75 ml), and water (75 ml). The ethereal phase was dried and evaporated to dryness, and the residue was purified by short-column chromatography. Elution with diethyl ether–light petroleum (1 : 9 v/v) gave the *amide* (2*E*)-(1; R^1 = R^3 = H, R^2 = CH_2Ph) (1.14 g, 50%); $\nu_{max.}$ 1 655 cm^{-1} (CO); δ 3.8—4.1 (2 H, m, NCH_2CH=CH_2), 4.5—4.7 (2 H, m, NCH_2Ph), 5.12 (2 H, m, CH_2=$CHCH_2$), 5.3—5.6 (2 H, m, CH_2=$CHCH$=CH), 5.75 (1 H, m, CH_2=$CHCH_2$) 6.28 (1 H, d, *J* 15 Hz, CH=CH-CO), 6.45 (1 H, m, CH_2=$CHCH$=CH), 7.23 (5 H, m, Ph), and 7.37 (1 H, dd, *J* 15, *J'* 10 Hz, CH=CHCO); *m/z* 227 (Found: C, 79.5; H, 7.9; N, 6.3. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.6; N, 6.2%).

The following amides were prepared in 47—50% yield by analogous procedures, and after short-column chromatography with diethyl ether–light petroleum as eluant were obtained as viscous oils. *Amide* (2*E*,4*E*)-(1; R^1 = Me, R^2 = CH_2Ph, R^3 = H); $\nu_{max.}$ 1 675 cm^{-1} (CO); δ 1.78 (1 H, m, Me), 3.8—4.1 (2 H, m, NCH_2CH=CH_2), 4.5—4.7 (2 H, m, NCH_2Ph), 5.12 (2 H, m, CH_2=$CHCH_2$), 5.75 (1 H, m, CH_2=$CHCH_2$), 5.9—6.3 (total 2 H, m, $MeCH$=CH), 6.18 (1 H, d, *J* 15 Hz, CH=CHCO), 7.20 (5 H, m, Ph), and 7.37 (1 H, dd, *J* 15, *J'* 10 Hz, CH=CHCO); *m/z* 241 (Found: C, 79.4; H, 8.0; N, 5.8. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.9; N, 5.8%).

Amide (2*E*,4*E*)-(1; R^1 = Me, R^2 = R^3 = H); $\nu_{max.}$ 1 670 cm^{-1} (CO); δ 1.80 (3 H, d, *J* 7 Hz, Me), 3.90 (2 H, m, NCH_2), 5.0—5.2 (2 H, m, CH_2=$CHCH_2$), 5.85 (1 H, m, CH_2=$CHCH_2$), 5.9 (1 H, d, *J* 15 Hz, CH=CHCO), 6.0—6.25 (total 2 H, m, $MeCH$=CH), 7.18 (1 H, dd, *J* 15, *J'* 10 Hz, CH=CHCO), and 7.2 (1 H, m, NH); *m/z* 151 (Found: C, 71.4; H, 8.5; N, 9.0. $C_9H_{13}NO$ requires C, 71.5; H, 8.6; N, 9.2%).

Amide (2*E*)-(1; R^1 = H, R^2 = R^3 = CH_2Ph); $\nu_{max.}$ 1 670 cm^{-1} (CO); δ 2.8—3.2 (2 H, m, CCH_2Ph), 4.35 and 4.55 (each 1 H, d, J_{AB} 14 Hz, together NCH_2), 5.0—5.5 (total 5 H, complex m, CH_2=$CHCH$N and $CHCO$), 6.0—6.4 (total 3 H, complex m, CH_2=$CHCH$=CH), and 7.0—7.4 (total 11 H, complex m, 2 × Ph and CH=CHCO); *m/z* 317 (Found: C, 83.2; H, 7.3; N, 4.5. $C_{22}H_{33}NO$ requires C, 83.3; H, 7.3; N, 4.5%).

Amide (2*E*)-(1; R^1 = H, R^2 = CH_2Ph, R^3 = CH_2CHMe_2); $\nu_{max.}$ 1 675 cm^{-1} (CO); δ 0.85 (6 H, d, 2 × Me), 1.5 (total 3 H, complex m, CH_2CHMe_2), 4.45 and 4.55 (each 1 H, d, J_{AB} 14 Hz, together NCH_2), 4.8 (1 H, m, CHN), 5.08—5.20 (2 H, m, CH_2=CHCHN), 5.3—5.6 (2 H, m, CH_2=$CHCH$=CH), 5.75 (1 H, m, CH_2=$CHCHN$), 6.15 (1 H, d, *J* 15 Hz, CHCO), 6.45 (1 H, m, CH_2=$CHCH$=CH), and 7.1—7.4 (total 6 H, complex m, Ph and CH=CHCO); *m/z* 283 (Found: C, 80.5; H, 8.6; N, 4.9. $C_{19}H_{25}NO$ requires C, 80.5; H, 8.8; N, 4.9%).

Amide Cyclisations.—(i) The amide (2*E*)-(1; R^1 = R^3 = H, R^2 = CH_2Ph) (1.5 g) was heated under reflux in DMF (30 ml) under nitrogen for 1.5 h. Evaporation of the solvent left an oil which, on analytical t.l.c. (diethyl ether–light petroleum, 1 : 1 v/v), showed two spots with R_F values 0.40 and 0.60. Short-column chromatography with diethyl ether–light petroleum (1 : 9 v/v) as eluant gave N-*benzyl*-trans-8-*azabicyclo*[4.3.0]-*non*-4-*en*-7-*one* (3) (0.44 g, 30%) as an oil, $\nu_{max.}$ 1 690 cm^{-1} (CO); *m/z* 227 (Found: C, 79.5; H, 7.7; N, 6.2. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2%) and N-*benzyl*-cis-8-*azabicyclo*[4.3.0]*non*-4-*en*-7-*one* (2) (1.03 g, 70%) as an oil, $\nu_{max.}$ 1 680 cm^{-1} (CO); *m/z* 227 (Found: C, 79.1; H, 7.7; N, 6.0%). For ^1H n.m.r. data see Table 1. Hydrogenation of compound (3) (300 mg) in methanol (20 ml) in the presence of 10% palladium–charcoal (30 mg) at 1 atm for 1 h gave *N*-benzyl-*trans*-8-azabicyclo[4.3.0]nonan-7-one (275 mg, 90%) as an oil, identical [i.r., ^1H n.m.r., analytical h.p.l.c. (silica; ethyl acetate–light petroleum, 1 : 3 v/v)] with an authentic sample.[5] Similarly, hydrogenation of compound (2) gave *N*-benzyl-*cis*-8-azabicyclo[4.3.0]nonan-7-one (94%) as an oil, identical (conditions as above) with an authentic sample.[5]

(ii) The amide (2*E*,4*E*)-(1; R^1 = Me, R^2 = CH_2Ph, R^3 =

* Non-systematic name.

H) (2.5 g) was heated under reflux in DMF (75 ml) under nitrogen for 12 h. Evaporation of the solvent left an oil which, on analytical t.l.c. (diethyl ether–light petroleum, 3 : 7 v/v), showed two spots with R_F values of 0.47 and 0.61. Short-column chromatography with diethyl ether–light petroleum (1 : 9 v/v) as eluant gave (1RS, 3RS, 6RS)-N-*benzyl*-3-*methyl*-8-*azabicyclo*[4.3.0]*non*-4-*en*-7-*one* (5) (0.46 g, 18%) as an oil, $\nu_{max.}$ 1 680 cm^{-1} (CO); *m/z* 241 (Found: C, 79.4; H, 7.9; N, 6.0. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.8; N, 5.9%) and (1RS, 3RS, 6SR)-N-*benzyl*-3-*methyl*-8-*azabicyclo*[4.3.0]*non*-4-*en*-7-*one* (4) (1.86 g, 75%) as an oil, $\nu_{max.}$ 1 670 cm^{-1} (CO); *m/z* 241 (Found: C, 79.5; H, 7.9; N, 6.0%). For ^1H n.m.r. data see Table 1.

(iii) The amide (2*E*)-(1; R^1 = H, R^2 = R^3 = CH_2Ph) (2.0 g) was heated under reflux in DMF under nitrogen for 6 h. Evaporation of the solvent gave an oil which, on analytical t.l.c. (diethyl ether–light petroleum, 1 : 1 v/v) gave two spots with R_F values 0.42 and 0.65. Short-column chromatography with diethyl ether–light petroleum (1 : 1 v/v) as eluant gave two oils, one of which (1.56 g, 78%) had R_F 0.42 and from its ^1H n.m.r. spectrum (Table 1) was shown to be a mixture of the two *N*,9-dibenzyl-*cis*-8-azabicyclo[4.3.0]non-4-en-7-ones, and the other of which (0.39 g, 19%) had R_F 0.65 and its ^1H n.m.r. spectrum (Table 1) indicated that it was a mixture of the two *N*,9-dibenzyl-*trans*-8-azabicyclo[4.3.0]-non-4-en-7-ones. Hydrogenation of the material with R_F 0.42 under the conditions used for compound (2) gave a product which was shown to contain two components by analytical h.p.l.c. (Hypersil; ethyl acetate–light petroleum, 1 : 9 v/v). Preparative h.p.l.c. (ethyl acetate–light petroleum, 1 : 9 v/v) gave samples of (1RS, 6SR, 9SR)-N,9-*dibenzyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (6; R = Ph) as an oil, $\nu_{max.}$ 1 680 cm^{-1} (CO); *m/z* 319 (Found: C, 82.9; H, 7.6; N, 4.4. $C_{22}H_{25}NO$ requires C, 82.7; H, 7.8; N, 4.4%) and (1*RS*, 6*SR*, 9*RS*)-*N*,9-dibenzyl-*cis*-8-azabicyclo-[4.3.0]nonan-7-one (7; R = Ph), m.p. 90—91 °C (lit.,[1] 89 °C), identical [i.r., ^1H n.m.r., analytical h.p.l.c. (above conditions)] with the previously described [1] material (Found: C, 82.9; H, 7.6; N, 4.4. Calc. for $C_{22}H_{25}NO$: C, 82.7; H, 7.8; N, 4.4%).

Similarly, hydrogenation of the material with R_F 0.65 gave a mixture of (1*RS*, 6*RS*, 9*RS*)-(8; R = Ph) and (1*RS*, 6*RS*, 9*SR*)-*N*,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (9; R = Ph) which could not be separated by preparative h.p.l.c. (above condtions). For the ^1H n.m.r. spectra of the reduced compounds see Table 2.

(iv) The amide (2*E*)-(1; R^1 = H, R^2 = CH_2Ph, R^3 = CH_2CHMe_2) (1.9 g) was heated under reflux in DMF (50 ml) under nitrogen for 8 h. Short-column chromatography of the products with diethyl ether–light petroleum (1 : 9 v/v) as the eluant gave two fractions having R_F values on analytical t.l.c. (diethyl ether–light petroleum, 1 : 1 v/v) of 0.44 (1.29 g, 72%) and 0.60 (0.33 g, 18%) which, from their ^1H n.m.r. spectra (Table 1), were mixtures of the *N*-benzyl-9-isobutyl-*cis*-8-azabicyclo[4.3.0]non-4-en-7-ones and the *N*-benzyl-9-isobutyl-*trans*-8-azabicyclo[4.3.0]non-4-en-7-ones, respectively. The two fractions were separately hydrogenated under the conditions used for compound (2). Preparative h.p.l.c. (ethyl acetate–light petroleum, 1 : 9 v/v) on the material from the hydrogenation of the fraction having R_F 0.44 gave a sample of (1RS, 6SR, 9RS)-N-*benzyl*-9-*isobutyl*-8-*azabicyclo*[4.3.0]-*nonan*-7-*one* (7; R = Pr^i) as an oil which was pure by analytical h.p.l.c. [Hypersil; ethyl acetate–light petroleum (1 : 19 v/v)]; $\nu_{max.}$ 1 670 cm^{-1} (CO) (Found: M^+, 285. 2127. $C_{19}H_{27}NO$ requires *M*, 285.2106). For ^1H n.m.r. data see Table 2.

Similarly, preparative h.p.l.c. (ethyl acetate–light petroleum, 7 : 93 v/v) of the material from the hydrogenation of the fraction having R_F 0.65 gave an impure sample of (1*RS*, 6*RS*, 9*RS*)-*N*-benzyl-9-isobutyl-8-azabicyclo[4.3.0]nonan-7-one (8; R = Pr^i) identified from its ^1H n.m.r. spectrum (Table 2).

Preparation of N-*Benzyl*-9-*isobutylidene*-cis-8-*azabicyclo*-[4.3.0]*nonan*-7-*one* (10) *and* N-*Benzyl*-9-*isobutyl*-8-*azabicyclo*-[4.3.0]*non*-1(6)-*en*-7-*one* (11).—A solution of isobutylmagnesium bromide (0.1 mol) in dry diethyl ether (300 ml) was added dropwise during 1 h under nitrogen to a well stirred solution of *N*-benzyl-*cis*-hexahydrophthalimide (12.1 g, 0.05 mol) in dry diethyl ether–benzene (1 : 1 v/v; 200 ml). The mixture was then stirred and heated under reflux for 24 h, and then cooled. Saturated aqueous ammonium chloride (100 ml) was then added cautiously and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 50 ml). The combined organic phases were dried and evaporated and the residual oil was heated under reflux in benzene (350 ml) under nitrogen for 24 h and the benzene was then evaporated off. Short-column chromatography of the residue with diethyl ether–light petroleum (3 : 7 v/v) as eluant then gave N-*benzyl*-9-*isobutylidene*-cis-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (10) (7.85 g, 55%) as an oil, $\nu_{max.}$ (neat) 1 710 and 1 650 cm^{-1}; δ 0.87 and 0.92 (each 3 H, d, *J* 7 Hz, Me), 1.15—2.49 (total 9 H, complex m, 4 × CH_2 and C*H*Me_2), 2.45 (1 H, d, *J* 9 Hz, C=CH), 2.69 (1 H, m, 1-H), 2.95 (1 H, m, 6-H), 4.55 and 4.74 (each 1 H, d, J_{AB} 15 Hz, together NCH_2), and 7.1—7.3 (5 H, m, Ph); *m/z* 283 (Found: C, 80.5; H, 8.8; N, 5.0. $C_{19}H_{25}NO$ requires C, 80.5; H, 8.8; N, 4.9%). When an identical Grignard reaction was worked up by treatment with 2M hydrochloric acid rather than aqueous ammonium chloride, short-column chromatography of the crude product with diethyl ether–light petroleum (3 : 7 v/v) as eluant gave N-*benzyl*-9-*isobutyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one* (11) (85%), m.p. 85 °C; $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1}; δ 0.79 and 0.85 (each 3 H, d, *J* 7 Hz, Me), 1.5—2.3 (total 11 H, complex m, 5 × CH_2 and C*H*Me_2), 3.72br (1 H, s, CHN), 4.0 and 5.25 (each 1 H, d, J_{AB} 15 Hz, together NCH_2), and 7.2—7.35 (5 H, m, Ph) (Found: C, 80.5; H, 8.8; N, 5.0%).

Hydrogenation of N-*Benzyl*-9-*isobutylidene*-cis-8-*azabicyclo*-[4.3.0]*nonan*-7-*one* (10).—Hydrogenation of compound (10) (1.5 g) in ethanol (250 ml) containing 10% palladium–charcoal (150 mg) at room temperature and 1 atm pressure gave after work-up, an oil which, on short-column chromatography with diethyl ether–light petroleum (3 : 7 v/v) as eluant, gave the previously prepared isomer (11) (200 mg, 13%), m.p. 85 °C, and (1*RS*, 6*SR*, 9*RS*)-*N*-benzyl-9-isobutyl-8-azabicyclo[4.3.0]-nonan-7-one (7; R = Pr^i) (1.3 g, 85%); both products were shown in separate experiments to be identical [i.r., ^1H n.m.r., analytical h.p.l.c. (Hypersil; ethyl acetate–light petroleum, 1 : 19 v/v)] with the materials described above.

9-*Isobutyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one*.—*N*-Benzyl-9-isobutyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (11) (0.5 g) and methanesulphonic acid (5 ml) were heated at 110 °C for 48 h. The mixture was cooled and poured into ice–water (500 ml) and the product was isolated with diethyl ether (3 × 25 ml). Work-up and crystallisation of the residue from light petroleum–benzene gave 9-*isobutyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one* (320 mg, 94%), m.p. 159—161 °C; $\nu_{max.}$ (Nujol) 3 200 (NH) and 1 665 cm^{-1} (CO); δ 0.93 and 0.95 (each 3 H, d, *J* 7 Hz, Me), 1.1—2.3 (total 11 H, complex m, 5 × CH_2 and C*H*Me_2), 3.95 (1 H, d, *J* 8 Hz, CHN), and 6.7br (1 H, s, NH); *m/z* 193 (Found: C, 74.6; H, 9.9; N, 7.1. $C_{12}H_{19}NO$ requires C, 74.6; H, 9.8; N, 7.2%).

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