Synthesis of Some 9-Benzyl-8-azabicyclo[4.3.0]nonan-7-ones

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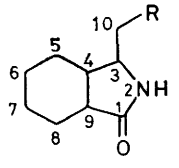
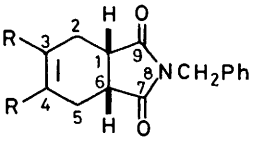
A route to *cis,cis*-9-benzyl-8-azabicyclo[4.3.0]nonan-7-one, based on the reaction of benzylmagnesium chloride with *N*-benzyl-*cis*-hexahydrophthalimide and in which *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]nonan-7-one is a key intermediate, is described, and the introduction of carbon and oxygen substituents at C-6 of 8,9-dibenzyl-8-azabicyclo[4.3.0]nonan-7-one is reported. The preparation and some reactions of the *cis,cis,cis*- and *trans,cis,trans*-forms of *N*-benzyl-5-hydroxymethyl-2-methyl-8-azabicyclo[4.3.0]non-3-ene-7,9-dione are also described.

THE cytochalasans [1] are a group of over 20 cytologically active mould metabolites which have been investigated extensively during the last ten years. A common structural feature is the bicyclic amide system (1; R = Ph



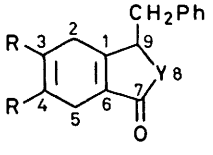
(1)

(cytochalasan numbering [2])



(2)

(bicyclo[4.3.0]nonane numbering)



(3)

or indol-3-yl) corresponding to atoms 1—10 (cytochalasan numbering [2]) in the natural products. We report here experiments on the synthesis of 9-benzyl-8-azabicyclo[4.3.0]nonan-7-one (1; R = Ph; bicyclononane numbering) and related structures which were exploratory experiments in connection with possible synthetic approaches [3] to the cytochalasans and simpler synthetic analogues.

We initially investigated a Grignard route [4] for the introduction of the benzyl group at C-9 (bicyclononane numbering), and chose to generate the lactam function protected by an *N*-benzyl group, which would also permit subsequent steps employing strongly basic reagents. Reaction of the readily available bicyclic imide (2; R = H) [5,†] with benzylmagnesium chloride, followed by an acidic work-up, gave 8,9-dibenzyl-8-azabicyclo[4.3.0]-nona-1(6),3-dien-7-one (3; R = H, Y = NCH_2Ph) in 51% yield. The dimethyl-substituted lactam (3; R = Me, Y = CH_2Ph) could only be obtained in 7% yield by applying the same procedure to the imide (2; R = Me) prepared from the corresponding anhydride,[6] and with the saturated imide (4), also prepared from the anhydride, a mixture of the two double bond isomers, 8,9-dibenzyl-8-azabicyclo[4.3.0]non-2(6)-en-7-one (5; Y = NCH_2Ph) and *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]nonan-7-one (6) was formed.

The two isomers could be separated from each other, and from (4), with considerable difficulty, by column chromatography. Only one geometrical isomer of (6)

† All work was carried out with racemic materials; only one enantiomer is shown in displayed formulae.

[1] M. Binder and Ch. Tamm, *Angew. Chem. Internat. Edn.*, 1973, **12**, 370.

[2] M. Binder, Ch. Tamm, W. B. Turner, and H. Minato, *J.C.S. Perkin I*, 1973, 1146.

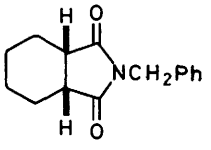
[3] *Cf.* J. Auerbach and S. M. Weinreb, *J. Org. Chem.*, 1975, 3311.

[4] *Cf.* Y. Gourion, C. Fayat, and A. Fancard, *Bull. Soc. chim. France*, 1970, 2293.

[5] R. Newman, B. J. Magerlein, and W. B. Wheatley, *J. Amer. Chem. Soc.*, 1946, **68**, 2112.

[6] E. H. Farmer and F. L. Warren, *J. Chem. Soc.*, 1929, 897.

was detected (t.l.c.); the configuration was not established. Compound (5; Y = NCH_2Ph) could also be obtained by catalytic hydrogenation of (3; R = H, Y = NCH_2Ph) over palladium at room temperature, under which conditions the tetrasubstituted double bond was



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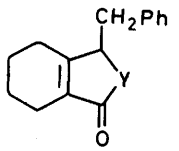

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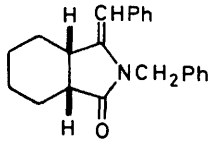
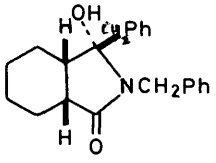


(6)

not reduced. The proportions in which (5; Y = NCH_2-Ph) and (6) were formed were dependent on the time taken over the acidic work-up of the Grignard reaction, and it was established that the benzylidene isomer (6) is completely converted into the isomer (5; Y = NCH_2Ph) by treatment with aqueous acid for 2 h. By using a modified procedure it was then possible to ensure complete isomerisation to (5; Y = NCH_2Ph) which could thus be obtained from (4) in 52% yield. To improve the yield of (6), we repeated the reaction of (4) with benzylmagnesium chloride, but used a neutral work-up procedure, and in this way isolated the two epimeric



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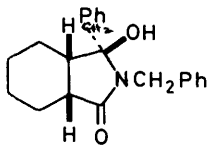

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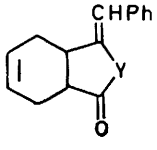

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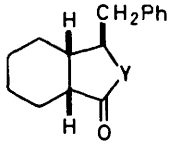


(10)

tertiary alcohols (7) and (8), together with (6). Both the alcohols were dehydrated in benzene at 80 °C to a common, geometrical isomer of compound (6), the one isolated in the earlier experiments, one alcohol reacting twelve times more rapidly. The Grignard reaction with (4), using a neutral work-up procedure, followed by thermal dehydration gave the benzylidene isomer (6) in 25% yield. Similarly (2; R = H) gave a single geometrical isomer of *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]-non-3-en-7-one (9; Y = NCH_2Ph) in 11% yield, but some (3; R = H, Y = NCH_2Ph) was also formed, in 8% yield, together with other unidentified products, and (9; Y = NCH_2Ph) could only be separated after extensive chromatography.

Catalytic hydrogenation of (6) over palladium under ambient conditions gave *cis,cis*-8,9-dibenzyl-8-azabicyclo-[4.3.0]nonan-7-one (10; Y = NCH_2Ph). We were unable to find conditions under which the tetrasubstituted double bond in the isomer (5; Y = NCH_2Ph) could be reduced without simultaneous partial reduction of the phenyl rings; conditions used in a closely analogous monocyclic system [7] were not successful in the bicyclic series. Assignment of the *cis*-ring junction in (10; Y = NCH_2Ph) follows from the stereochemistry of the starting material (4) and the value of the coupling constant $J_{1,9}$ (5 Hz) is in keeping with a *trans*-relation between H-1 and -9 so that the C-9 benzyl group and the bridgehead protons are *cis*-related. A coupling constant of 3.5 Hz has been reported [8] for the analogous protons in a cytochalasan degradation product in which the *trans*-relation between the protons has been firmly established by an *X*-ray crystal structure determination, but in other cytochalasan degradation products [9] a value of 9 Hz has been reported for this *trans*-coupling constant. A *trans*-relation between H-1 and -9 in (10; Y = NCH_2Ph) corresponds to delivery of hydrogen to the α-face of (6) during the catalytic hydrogenation.

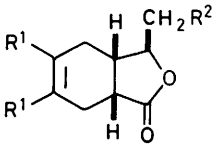
The low resolution mass spectra of compounds (3; R = H or Me, Y = NCH_2Ph) and (5; Y = NCH_2Ph) all showed a base peak at $M - 91$ (loss of C_7H_7) but those of the benzylidene isomers (6) and (9; Y = NCH_2Ph) only showed a minor peak at $M - 91$, the base peak being the molecular ion; this suggests that in the first three compounds the major fragmentation involves the loss of the *C*-benzyl group. In the ^1H n.m.r. spectra of (3; R = H or Me, Y = NCH_2Ph), (5; Y = NCH_2Ph), (6), and (9; Y = NCH_2Ph) the CH_2 protons of the *N*-benzyl group give rise to AB systems, with J_{AB} 15 Hz. The α-protons of the *C*-benzyl groups in (3; R = H or Me, Y = NCH_2Ph) and (5; Y = NCH_2Ph) are equivalent and give rise to a doublet, with *J* 6 Hz, due to coupling with H-9, establishing that the tetrasubstituted double bond is at the 1(6)- and not the 1(9)-position in these compounds. The benzylidene protons in (6) and (9; Y = NCH_2Ph) occur as sharp singlets at δ 5.70 and 5.67, respectively, confirming that only a single geometrical isomer is present in each case.

An attempt to debenzylate (10; Y = NCH_2Ph) with acetic acid in 10M-hydrochloric acid [10] was unsuccessful, but the deprotected lactam (10; Y = NH) was obtained, in 35% yield, by treatment of (10; Y = NCH_3Ph) with

[7] H. Plieninger and U. Lerch, *Annalen*, 1966, **698**, 196.
[8] W. Rothweiler and Ch. Tamm, *Helv. Chim. Acta*, 1970, **53**, 696.
[9] J. C. Vaderas, W. Graf, L. David, and Ch. Tamm, *Helv. Chim. Acta*, 1975, **58**, 1886.
[10] *Cf.* W. Goldberg and L. H. Sternbach, U.S.P., 2,489,232/1949; 2,489,238/1949 (*Chem. Abs.*, 1951, **45**, 184b and 186a).

methanesulphonic acid [11] at 110 °C for 48 h. *N*-Debenzylation of (5; Y = NCH_2Ph) was achieved similarly, by the methanesulphonic acid method.

An alternative route to (10; Y = NH or NCH_2Ph) through the lactone (10; Y = O) was also explored. The only product we could isolate from a Grignard reaction between 1,2,3,6-tetrahydrophthalic anhydride and benzylmagnesium chloride was 9,9-dibenzyl-8-oxabicyclo[4.3.0]non-3-en-7-one; no product corresponding to (3; R = H, Y = O) or (9; Y = O) was detected.



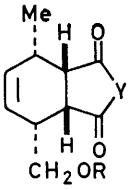
(11)

However cycloaddition of buta-1,3-diene to δ-phenyl-Δ^1-angelica lactone [12] [5-benzylfuran-2(5*H*)-one] gave the lactone (11; R^1 = H, R^2 = Ph) in 34% yield. 2,3-Dimethylbuta-1,3-diene similarly gave the lactone (11; R^1 = Me; R^2 = Ph). The *cis,cis*-stereochemistry of (11; R^1 = H, R^2 = Ph) follows from known cycloaddition stereospecificity and from the value for $J_{1,9}$ of 4.5 Hz; a value of 2 Hz has been reported [13] for $J_{1,9}$ in the analogous Diels–Alder product (11; R^1 = R^2 = H). The isolated double bond in (11; R^1 = H; R^2 = Ph) was readily hydrogenated to give (10; Y = O) but attempts to replace the ring oxygen atom by a nitrogen atom, based on analogous reported transformations, were unsuccessful. The lactone (10; Y = O) was unchanged after treatment with ammonia for 3 h in a sealed tube at 230 °C [14] and after heating for 3 h at 110 °C and then for 5 h at 280 °C with benzylamine.[15]

The natural cytochalasans all have a substituent at the bridgehead position adjacent to the lactam carbonyl group, which forms part of a macrocyclic system; the atom attached to C-6 (bicyclononane numbering) may be carbon or oxygen.[1] We have therefore investigated the functionalisation of (10; Y = NCH_2Ph) at this position. Treatment of (10; Y = NCH_2Ph) with lithium diisopropylamide at −70 °C generated the anion, which reacted with iodomethane at −30 °C to give 8,9-dibenzyl-6-methyl-8-azabicyclo[4.3.0]nonan-7-one in 57% yield. We believe that the carbon substituent at C-6 is *cis*-related to H-1 and the benzyl group at C-9, as is the case in the natural cytochalasans,[1] since protonation of the anion from (10; Y = NCH_2Ph) gave back the starting *cis*-fused bicyclic system, with none of the *trans*-fused system being detected, and we expect protonation and methylation to occur from the same side of the molecule. When the anion from (10; Y = NCH_2Ph) was treated with molecular oxygen at 0 °C,[16] the corresponding tertiary alcohol, 8,9-dibenzyl-6-hydroxy-8-azabicyclo[4.3.0]-nonan-7-one, was formed in 27% yield; the stereochemistry at C-6 is not known. An attempt to prepare the corresponding tertiary benzoate by reaction of the anion from (10; Y = NCH_2Ph) with dibenzoyl peroxide [17] was unsuccessful.

Finally we report an attempt to extend our Grignard approach to the 9-benzyl-8-azabicyclo[4.3.0]nonan-7-one system in which substituents (corresponding to atoms 11 and 13 in the cytochalasans [1]) are introduced at C-5 and C-8. The natural cytochalasans possess a methyl group at C-5 (position 2, bicyclononane numbering) and a carbon atom forming part of a C=C double bond at C-8 (position 5, bicyclononane numbering) which is modified to a hydroxymethyl group in several degradation products.[1]

Reaction of hexa-2,4-dienyl acetate with maleic anhydride at 50 °C gave a product which on the basis of known cycloaddition stereospecificity is the *trans,cis,-trans*-bicyclic anhydride (12; R = Ac, Y = O). The use of hexa-2,4-dien-1-ol in this cycloaddition led not to



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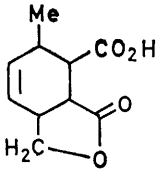

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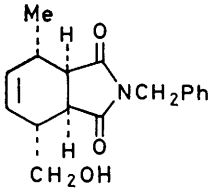

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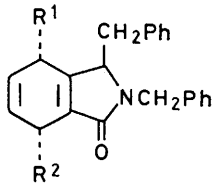

(15)

the anhydride (12; R = H, Y = O), but to the isomeric lactone-acid (13); a similar intramolecular reorganisation occurs in the reaction between maleic anhydride and hexa-2,4-diene-1,6-diol.[18] Treatment of the acetoxy-anhydride (12; R = Ac, Y = O) with 2 equiv. of benzylamine at 180—200 °C gave the *cis,cis,cis*-hydroxy-*N*-benzyl-lactam (14). Condensation of hexa-2,4-dien-1-ol and *N*-benzylmaleimide at 80 °C gave an isomeric (t.l.c., i.r., and n.m.r.) hydroxy-*N*-benzyl-lactam, which on the basis of known cycloaddition stereospecificity has the *trans,cis,trans*-structure (R = H, Y = NCH_2Ph). This

[11] B. Loev, M. A. Hass, and F. Douralo, *Chem. and Ind.*, 1968, 973.
[12] J. Thiele and W. Wedemann, *Annalen*, 1906, **347**, 132.
[13] D. Taub, Z. S. Zelawski, and N. L. Wender, *Tetrahedron Letters*, 1975, 3667.
[14] *Cf.* E. Spath and J. Lintner, *Ber.*, 1936, **69**, 2727.
[15] *Cf.* F. B. Zienty and G. W. Steahly, *J. Amer. Chem. Soc.*, 1947, **69**, 715.
[16] *Cf.* H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Letters*, 1975, **21**, 1731; E. J. Corey and H. E. Ensley, *J. Amer. Chem. Soc.*, 1975, **97**, 6908.
[17] *Cf.* A. E. Greene, J. C. Muller, and G. Ourisson, *Tetrahedron Letters*, 1972, 3375.
[18] E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1954, 1854.

on heating at 180—200 °C with benzylamine is quantitatively isomerised to the all-*cis*-isomer (14). The benzylamine is necessary for this isomerisation, which is thus not caused by cycloreversion–readdition under conditions of thermodynamic control. That this is a double, base-catalysed epimerisation is supported by the fact that the dihydro-derivative of (12; R = H, Y = NCH_2Ph) is also slowly isomerised to the dihydro-derivative of (14) under the same conditions. Analogous amine-catalysed isomerisations have been reported for the Diels–Alder adduct of penta-1,3-diene and maleic anhydride (12; Y = O, H instead of CH_2OR) and for its dihydro-derivative.[19] In that series the anhydrides with *trans*-ring junctions were prepared and shown to isomerise, with amine catalysis, to the more stable isomers having a *cis*-ring junction. We detected no sign of any compund having a *trans*-ring junction in our series, although the double epimerisation must involve a compound of that type as an intermediate. The bicyclic imide (2; R = H) was not isomerised to the *trans*-fused isomer by treatment with benzylamine at 180—200 °C. Thus *cis*-ring fusion is evidently preferred in bicyclo[4.3.0]nonane-7,9-dione systems.[20]

The all-*cis*-*N*-benzyl-lactam (14) was protected by conversion into its tetrahydropyranyl ether, formed as a mixture (t.l.c.) of both possible stereoisomers, and treated with benzylmagnesium chloride as for (2; R = H). Acidic work-up then gave a product which ran as one spot on t.l.c. but which is presumably a mixture of both possible stereoisomers at the acetal centre, and which is analogous to (3; R = H, Y = NCH_2Ph), with a tetrasubstituted double bond in conjugation with the lactam carbonyl group. On the evidence available a distinction between the structures (15; R^1 = Me, R^2 = CH_2OThp) and (15; R^1 = CH_2OThp, R^2 = Me) is not possible. Preferential attack of benzylmagnesium chloride at the less hindered of the carbonyl groups in certain unsymmetrical *N*-substituted succinimides has been reported.[4] An attempt to isolate a compound analogous to (9; Y = NCH_2Ph) by using a neutral work-up procedure was unsuccessful owing to the complexity of the product mixture. The tetrahydropyranyl group could be removed from (15; R^1 or R^2 = Me or CH_2OThp) by methanol–0.1M-hydrochloric acid at room temperature. Catalytic hydrogenation of (15; R^1 and R^2 = Me and CH_2OThp) under high pressure over Raney nickel caused reduction of the non-conjugated olefinic bond without partial reduction of the phenyl groups, but did not cause reduction of the tetrasubstituted olefinic bond.

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded with Perkin-Elmer R12 or Varian HA 100 instruments for solutions in $CDCl_3$, unless otherwise stated, with Me_4Si as internal standard. I.r. spectra were measured with a Perkin-Elmer 157G or 457 instrument for thin films, Nujol mulls, or solutions in the stated solvents. Low resolution mass spectra were obtained with an A.E.I. MS-12 instrument and high resolution spectra with an A.E.I. MS-9 instrument. Analytical t.l.c. was performed on silica gel chromatoplates (4 × 20 cm); for preparative separations larger (20 × 28 cm) chromatoplates were used. Column chromatography was performed on silica gel columns, which were wet-packed. Light petroleum refers to the fractions having b.p. 60—80 °C. Solutions in organic solvents were dried over anhydrous magnesium sulphate.

Starting Materials.—2,3-Dimethylbuta-1,3-diene,[21] b.p. 68—70° (lit.,[21] 69—70.5 °C); *N*-benzyl-*cis*-1,2,3,6-tetrahydrophthalimide,[5] m.p. 87° (lit.,[5] b.p. 175—178° at 0.5 mmHg), $\nu_{max.}$ ($CHCl_3$) 1 775 and 1 700 cm^{-1}, δ 2.1—2.8 (4 H, m, 2 × CH_2), 3.02—3.15 (2 H, m, 2 × bridgehead CH), 4.63 (2 H, s, CH_2Ph), 5.9 (2 H, t, *J* 4 Hz, CH=CH), and 7.26 (5 H, s, Ph), *m/e* 241 (M^+); 4,5-dimethyl-*cis*-1,2,3,6-tetrahydrophthalic anhydride,[6] m.p. 78° (lit.,[6] 78°), $\nu_{max.}$ ($CHCl_3$) 1 840 and 1 775 cm^{-1}, δ (6 H, s, 2 × Me), 2.1—2.5 (4 H, m, 2 × CH_2), and 3.24—3.36 (2 H, m, 2 × CH); *N*-benzylmaleimide,[22] m.p. 92° (lit.,[22] 93°), δ 4.7 (2 H, s, NCH_2Ph), 6.7 (2 H, s, CH=CH), and 7.35 (5 H, s, Ph); hexa-2,4-dien-1-ol,[23] m.p. 30° (lit.,[23] 30.5—31.5°); and hexa-2,4-dienyl acetate,[24] b.p. 84° at 20 mmHg (lit.,[24] 94—95° at 31 mmHg), were prepared by methods described in the literature. δ-Phenyl-Δ^1-angelica lactone [12] [5-benzylfuran-2(5*H*)-one], $\nu_{max.}$ (film) 1 750 cm^{-1}, δ 2.8—3.3 (2 H, m, $CH_X{\cdot}CH_AH_BPh$), 5.1—5.3 (1 H, *m*, $CH_X{\cdot}CH_AH_BPh$), 6.04 (1 H, dd, *J* 6 and 2 Hz, CH:$CH{\cdot}CH{\cdot}CH_2Ph$), 7.2—7.3 (5 H, m, Ph), and 7.37 (1 H, dd, *J* 6 and 1.5 Hz, $CO{\cdot}CH{:}CH$), *m/e* 174 (M^+) and 91 ($M^+ - C_4H_3O_2$), was prepared from cinnamaldehyde *via* 5-phenylpenta-2,4-dienoic acid, m.p. 164—165° (lit.,[25] 165°), 5-phenylpent-3-enoic acid, b.p. 138° at 0.4 mmHg (lit.,[26] 178—181° at 10 mmHg), and 3,4-dibromo-5-phenylpentanoic acid, m.p. 107° (lit.,[27] 109—110°).

Preparation of N-*Benzylimides.*—(i) *cis*-Hexahydrophthalic anhydride (50 g) was melted in a flask fitted for distillation and stirred at 190—200 °C while benzylamine (39 g) was added dropwise; water and the excess of benzylamine distilled out. After 2 h at 200—210 °C the melt was poured out and the material, which solidified on cooling, was crystallised from aqueous ethanol to give N-*benzyl*-cis-*hexahydrophthalimide* (50.5 g, 62%), m.p. 70—71°, $\nu_{max.}$ ($CHCl_3$) 1 775 and 1 700 cm^{-1}, δ 1.25—1.9 (8 H, complex, 4 × ring CH_2), 2.7—2.9 (2 H, m, 2 × bridgehead CH), 4.62 (2 H, s, CH_2Ph), and 7.2—7.4 (5 H, m, Ph), *m/e* 243 (M^+) (Found: C, 74.3; H, 7.1; N, 5.9. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.0; N, 5.8%).

(ii) N-*Benzyl*-4,5-*dimethyl*-cis-1,2,3,6-*tetrahydrophthalimide*, m.p. 104° (from H_2O–EtOH; charcoal), $\nu_{max.}$ ($CHCl_3$) 1 770 and 1 690 cm^{-1}, δ 1.5 (6 H, s, 2 × Me), 2.0—2.5 (4 H, m, 2 × ring CH_2), 2.96—3.0 (2 H, m, 2 × bridgehead CH), 4.56 (2 H, s, CH_2Ph), and 7.2 (5 H, m, Ph), *m/e* 269 (M^+) (Found: C, 75.9; H, 7.2; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%), was prepared similarly in 70% yield from 4,5-dimethyl-*cis*-1,2,3,6-tetrahydrophthalic anhydride.

8,9-*Dibenzyl*-8-*azabicyclo*[4.3.0]*nona*-1(6),3-*dien*-7-*one* (3; R = H, Y = NCH_2Ph).—Ethereal M-benzylmagnesium

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chloride (150 ml, 0.15 mol) was refluxed for 24 h with a solution of *N*-benzyl-*cis*-1,2,3,6-tetrahydrophthalimide (12.0 g, 0.05 mol) in dry ether–benzene (1 : 1; 200 ml). When cold, the Grignard complex was carefully decomposed with 2M-hydrochloric acid, and the organic layer was separated. The aqueous layer was extracted with ether, and the combined organic layers were dried and evaporated. Purification of the resultant oil by column chromatography, using ether–light petroleum (1 : 1) as eluant, gave the *azabicyclononadienone* (8.0 g, 51%), m.p. 96—97°, $\nu_{max.}$ (Nujol) 1 665 cm^{-1}, δ 2.5—3.0 (6 H, complex, 2 × ring CH_2 + $CHCH_2Ph$), 3.94 (1 H, m, J_{AB} 15 Hz, NCH_AH_BPh), 4.0 (1 H, t, *J* 6 Hz, $CHCH_2Ph$), 5.25 (1 H, m, NCH_AH_BPh), 5.55—5.85 (2 H, m, CH=CH), and 6.91—7.31 (10 H, complex, 2 × Ph), *m/e* 315 (M^+) and 224 ($M^+ - C_7H_7$) [Found: C, 83.5; H, 6.8; N, 4.4(5). $C_{22}H_{21}NO$ requires C, 83.8; H, 6.7; N, 4.4%].

8,9-*Dibenzyl*-3,4-*dimethyl*-8-*azabicyclo*[4.3.0]*nona*-1(6),3-*dien*-7-*one* (3; R = Me, Y = NCH_2Ph).—A Grignard reaction similar to that described above but using *N*-benzyl-3,4-dimethyl-*cis*-1,2,3,6-tetrahydrophthalimide (13.45 g, 0.05 mol) and benzylmagnesium chloride (0.05 mol) and a 5 h reaction time gave, after an identical acidic work-up, an oil which on column chromatography using dichloromethane–ether (49 : 1) as the eluant, yielded this *azabicyclononadienone* (1.2 g, 7%), m.p. 87—89°, $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1}, δ 1.62 and 1.70 (each 3 H, s, Me), 2.5—2.9 (4 H, m, 2 × ring CH_2), 2.92 (2 H, d, *J* 6 Hz, $CH{\cdot}CH_2Ph$), 3.90 (1 H, m, J_{AB} 15 Hz, NCH_AH_BPh), 3.98 (1 H, t, *J* 6 Hz, $CHCH_2Ph$), 5.22 (1 H, m, NCH_AH_BPh), and 7.0—7.4 (10 H, complex, 2 × Ph), *m/e* 343 (M^+) and 252 ($M^+ - C_7C_7$) [Found: C, 83.7; H, 7.4; N, 4.2(5). $C_{24}H_{25}NO$ requires C, 84.0; H, 7.3; N, 4.1%].

8,9-*Dibenzyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one* (5; Y = NCH_2Ph).—(i) A Grignard reaction similar to those described above but using *N*-benzyl-*cis*-hexahydrophthalimide (12.1 g, 0.05 mol) and benzylmagnesium chloride (0.1 mol) and a 24 h reaction time gave, after an identical acidic work-up, an oil which on column chromatography, using ether–light petroleum (1 : 1) as the eluant, yielded this *azabicyclononenone* (8.2 g, 52%) as an oil which ran as a single material on t.l.c. and which eventually crystallised; m.p. 56—57°, $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1}, δ 1.5—2.3 (8 H, complex, 4 × ring CH_2), 2.92 (2 H, d, *J* 6 Hz, $CH{\cdot}CH_2Ph$), 3.94 (1 H, m, J_{AB} 15 Hz, NCH_AH_BPh), 3.96 (1 H, t, *J* 6 Hz, $CH{\cdot}CH_2Ph$), 5.24 (1 H, m, NCH_AH_BPh), and 6.95—7.4 (10 H, complex, 2 × Ph), *m/e* 317 (M^+) and 226 ($M^+ - C_7H_7$) (Found: *m/e*, 317.1776. $C_{22}H_{23}NO$ requires *M*, 317.1780).

(ii) 8,9-Dibenzyl-8-azabicyco[4.3.0]nona-1(6),3-dien-7-one (125 mg) in dry ethanol (25 ml) containing 10% palladium–charcoal (25 mg) was hydrogenated at room temperature for 1 h at atmospheric pressure until uptake corresponded to the reduction of one double bond. The catalyst was filtered off and the ethanol evaporated. T.l.c. of the residue gave the title azabicyclononenone (60 mg, 48%), identical (mass and n.m.r. spectra) with the previous sample.

8,9-*Dibenzyl*-9-*hydroxy*-8-*azabicyclo*[4.3.0]*nonan*-7-*ones* (7) *and* (8).—Ethereal 0.75M-benzylmagnesium chloride (150 ml, 0.05 mol) was added to a stirred solution of *N*-benzyl-*cis*-hexahydrophthalimide (12.1 g, 0.05 mol) in dry ether–benzene (1 : 1; 200 ml) under nitrogen and the mixture was then refluxed for 24 h and then cooled to room temperature. The Grignard complex was decomposed by careful addition of saturated aqueous ammonium chloride (100 ml) and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layers were dried. Evaporation left a solid which was separated into several components by column chromatography using ether–light petroleum (3 : 1) as eluant. The major product was *one isomer* of 8,9-*dibenzyl*-9-*hydroxy*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (isomer A) (1.7 g, 10%), m.p. 101—104°, $\nu_{max.}$ (Nujol) 3 250 (OH) and 1 660 cm^{-1} (C=O), δ 1.0—2.5 (9 H, complex, 4 × ring CH_2 + H-1), 2.62 (1 H, m, $C{\cdot}CH_AH_BPh$, J_{AB} 15 Hz), 2.9—3.2 (2 H, complex, OH + H-6), 3.16 (1 H, m, $C{\cdot}CH_AH_BPh$), 4.4 (1 H, m, $N{\cdot}CH_AH_BPh$, J_{AB} 16 Hz), 4.72 (1 H, m, $N{\cdot}CH_AH_BPh$), and 7.1—7.3 (10 H, complex, 2 × Ph), *m/e* 333 ($M^+ - 2$), 317 ($M^+ - H_2O$), 244 ($M^+ - C_7H_7$), and 226 ($M^+ - C_7H_7 - H_2O$) (Found: C, 78.8; H, 7.6; N, 3.9. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%). The next most abundant product was *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]nonan-7-one (0.8 g, 6%), identified by comparison with an authentic sample (see below). A minor product was a *second isomer* of 8,9-*dibenzyl*-9-*hydroxy*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (isomer B) (0.4 g, 2%), m.p. 117—121°, $\nu_{max.}$ (Nujol) 3 300 (OH) and 1 640 cm^{-1} (C=O), δ 1.2—2.4 (10 H, complex, 4 × ring CH_2 + H-1 + OH), 2.8—3.2 [3 H, complex, $C(OH)CH_2Ph$ + H-6], 4.08 (1 H, m, J_{AB} 16 Hz, NCH_AH_BPh), 4.72 (1 H, m, NCH_AH_BPh), and 7.1—7.4 (10 H, complex, 2 × Ph), *m/e* 333 ($M^+ - 2$), 317 ($M^+ - H_2O$), and 244 ($M^+ - C_7H_7$) (Found: C, 78.8; H, 7.7; N, 4.4. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%).

Preparation of N-*Benzyl*-9-*benzylidene*-8-*azabicyclo*[4.3.0]-*nonan*-7-*one* (6).—(i) The crude product mixture from a Grignard reaction identical in scale and procedure with that described above was refluxed in benzene (350 ml) for 24 h. Evaporation gave an oily solid, which was purified by column chromatography using ether–light petroleum (3 : 1) as eluant, and crystallisation from aqueous ethanol, giving the *azabicyclononanone* (6) (4.0 g, 25%), m.p. 128°, $\nu_{max.}$ ($CHCl_3$) 1 710 and 1 650 cm^{-1}, δ 1.0—2.9 (9 H, complex, 4 × ring CH_2 + H-1), 3.2—3.8 (1 H, m, H-6), 4.68 (1 H, m, J_{AB} 16 Hz, NCH_AH_BPh), 4.88 (1 H, m, NCH_AH_BPh), 5.7 (1 H, s, $C{=}CHPh$), and 7.1—7.3 (10 H, complex, 2 × Ph), *m/e* 317 (M^+) and 226 ($M^+ - C_7H_7$) [Found: C, 83.3; H, 7.3; N, 4.3. $C_{22}H_{23}NO$ requires C, 83.3; H, 7.2(5); N, 4.4%].

(ii) Benzene (20 ml) containing isomer A of 8,9-dibenzyl-9-hydroxy-8-azabicyclo[4.3.0]nonan-7-one (150 mg) was refluxed for 2 h. The reaction was followed by t.l.c. and was complete after 2 h. Evaporation, and recrystallisation of the residue from aqueous ethanol gave *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]nonan-7-one (90 mg, 63%), m.p. 128°, identical (i.r., n.m.r., and mass spectra) with the two previous samples.

(iii) Dehydration of isomer B by the same procedure required 24 h and gave the benzylidene compound, m.p. 128°, in 53% yield.

Reaction of N-*Benzyl*-cis-1,2,3,6-*tetrahydrophthalimide with Benzylmagnesium Chloride, followed by a Neutral Work-up*.—Reaction of *N*-benzyl-*cis*-1,2,3,6-tetrahydrophthalimide (12.0 g, 0.05 mol) with benzylmagnesium chloride (0.15 mol) using the same procedure and work-up as for the preparation of the benzylidene compound (6) by method (i) gave an oil which was separated by preliminary column chromatography, followed by t.l.c., using in each case ether–light petroleum (3 : 1) as the solvent system, into two products. The oily product was N-*benzyl*-9-*benzylidene*-8-*azabicyclo*[4.3.0]*non*-3-*en*-7-*one* (1.7 g, 11%), $\nu_{max.}$ (film) 1 710 and 1 640 cm^{-1}, δ 1.5—3.8 (6 H, complex, ring protons), 4.58 (1 H, m, J_{AB} 15 Hz, NCH_AH_BPh), 4.93 (1 H, m, NCH_AH_BPh), 5.67 (1 H, s, $C{=}CHPh$), 5.7—5.9 (2 H, m, CH=CH), and 7.1—7.3 (10 H,

complex, 2 × Ph), *m/e* 315 (M^+) and 244 ($M^+ - C_7H_7$) [Found: C, 83.6; H, 6.9(5); N, 4.3. $C_{22}H_{21}NO$ requires C, 83.8; H, 6.7; N, 4.4%]. Crystalline 8,9-dibenzyl-8-azabicyclo[4.3.0]nona-1(6),3-dien-7-one (1.3 g, 8%), identical (m.p. and i.r., n.m.r., and mass spectra) with the previous sample, was also isolated.

Isomerisation of Compound (6) *to* (5; Y = NCH_2Ph).—2M-Hydrochloric acid (10 ml) was added to *N*-benzyl-9-benzylidene-8-azabicyclo[4.3.0]nonan-7-one (14 mg) in toluene (3 ml). The mixture was stirred at room temperature for 3 h and then extracted with ether. The extracts were dried and evaporated leaving an oil, shown by its behaviour on t.l.c. to be 8,9-dibenzyl-8-azabicyclo[4.3.0]non-1(6)-en-7-one (10 mg, 71%). With ether–light petroleum (1 : 1) as the solvent for development (6) has R_F 0.8 whereas (5; Y = NCH_2Ph) has R_F 0.4.

cis,cis-8,9-*Dibenzyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (10; Y = NCH_2Ph).— *N*-Benzyl-9-benzylidene-8-azabicyclo-[4.3.0]nonan-7-one (1.5 g) in dry ethanol (250 ml) containing 10% palladium–charcoal (15 mg) was hydrogenated at room temperature and atmospheric pressure until uptake corresponded to the reduction of one double bond. The catalyst was filtered off and the solution evaporated, leaving an oil which was purified by column chromatography, using ether–light petroleum (1 : 1) as eluant, to give cis,cis-8,9-*dibenzyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (1.3 g, 97%), m.p. 89°, $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1}, δ 1.0—1.9 (8 H, complex, 4 × ring CH_2), 1.9—2.2 (1 H, m, $J_{1,9}$ 5 Hz, H-1), 2.2—2.66 (2 H, m, CHC_XH_A-H_BPh and H-6), 2.9—3.2 (1 H, m, $CH_XCH_AH_BPh$), 3.6—3.8 (1 H, m, CH_XCH_2Ph), 4.14 (1 H, *m*, J_{AB} 15 Hz, NCH_AH_BPh), 4.96 (1 H, m, NCH_AH_BPh), and 6.9—7.4 (10 H, complex, 2 × Ph), *m/e* 319 (M^+) and 228 ($M^+ - C_7H_7$) [Found: C, 82.9; H, 8.0; N, 4.2. $C_{22}H_{25}NO$ requires C, 82.7(5); H, 7.8; N, 4.4%].

cis,cis-9-*Benzyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (10; Y = NH).—8,9-Dibenzyl-8-azabicyclo[4.3.0]nonan-7-one (100 mg) and methanesulphonic acid (2 ml) were heated together at 110 °C for 48 h. The mixture was then cooled, poured into ice–water (500 ml), and extracted with ether. The ethereal layer was separated, dried, and evaporated, leaving an oil which after column chromatography using ether as eluant gave 9-*benzyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (20 mg, 35%), m.p. 101—103°, which ran as a single spot on t.l.c. and had $\nu_{max.}$ ($CHCl_3$) 3 440 (NH) and 1 690 cm^{-1} (C=O), δ 1.0—1.9 (8 H, complex, 4 × ring CH_2), 2.0—2.8 (4 H, complex, CH_2Ph, H-1, and H-6), 3.84 (1 H, m, H-9), 5.30br (1 H, s, NH), and 7.0—7.4 (5 H, m, Ph), *m/e* 228 ($M^+ - 1$) [Found: *m/e* ($M^+ - 1$), 228.1393. $C_{15}H_{18}NO$ (*i.e.* $M^+ - 1$) requires *m/e*, 228.1388].

9-*Benzyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one* (5; Y = NH).—Debenzylation of 8,9-dibenzyl-8-azabicyclo[4.3.0]-non-1(6)-en-7-one by the procedure described above gave a 34% yield of 9-*benzyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one*, m.p. 160—161°, which ran as a single spot on t.l.c. and had $\nu_{max.}$ ($CHCl_3$) 3 450 (NH) and 1 685 cm^{-1} (C=O), δ 1.5—2.3 (8 H, complex, 4 × ring CH_2), 2.3—2.6 (1 H, m, CH_XCH_A-H_BPh), 2.9—3.2 (1 H, m, $CH_XCH_AH_BPh$), 4.0—4.2 (1 H, m, CH_XCH_2Ph), 5.84br (1 H, s, NH), and 7.0—7.4 (5 H, m, Ph), *m/e* 227 (M^+) (Found: *m/e*, 227.1310. $C_{15}H_{17}NO$ requires *M*, 227.1310).

9,9-*Dibenzyl*-8-*oxabicyclo*[4.3.0]*non*-3-*en*-7-*one*.— Ethereal 0.25M-benzylmagnesium chloride (200 ml, 0.05 mol) was added to a solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (7.6 g, 0.05 mol) in dry ether–benzene (1 : 1; 200 ml) at room temperature during 0.25 h. The mixture was then refluxed for 5 h and cooled. The Grignard complex was decomposed by the addition of an excess of 2M-hydrochloric acid, and the organic layer was separated. The aqueous layer was extracted twice with ether and the organic layers were then combined, washed with saturated aqueous sodium hydrogen carbonate, and dried. Evaporation left an oil, from which, by column chromatography using ether–light petroleum (1 : 1) as eluant, 9,9-*dibenzyl*-8-*oxabicyclo*[4.3.0]-*non*-3-*en*-7-*one* (0.4 g, 3%), m.p. 90°, $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1} (γ-lactone), δ 2.0—2.3 (5 H, complex, 2 × ring CH_2 + H-1), 2.5—3.3 (5 H, complex, 2 × CH_AH_BPh + H-6), 5.82 (2 H, m, CH=CH), and 7.0—7.4 (10 H, complex, 2 × Ph), *m/e* 318 (M^+) and 227 ($M^+ - C_7H_7$) [Found: C, 82.9; H, 7.1(5). $C_{21}H_{22}O_3$ requires C, 83.0; H, 6.9%], was isolated.

9-*Benzyl*-3,4-*dimethyl*-8-*oxabicyclo*[4.3.0]*non*-3-*en*-7-*one* (11; R^1 = Me, R^2 = Ph).—2,3-Dimethylbuta-1,3-diene (1.0 ml) and δ-phenyl-Δ^1-angelica lactone [5-benzylfuran-2(5H)-one] (0.5 g) were heated together in a sealed tube at 200 °C for 24 h. Column chromatography, using ether–light petroleum (1 : 1) as eluant, gave 9-*benzyl*-3,4-*dimethyl*-8-*oxabicyclo*[4.3.0]*non*-3-*en*-7-*one* (0.25 g, 33%), m.p. 84—86°, $\nu_{max.}$ (film) 1 765 cm^{-1}, δ 1.6 (6 H, s, 2 × Me), 1.9—2.7 (6 H, complex, 2 × ring CH_2, H-1, and H-6), 2.75—3.15 (2 H, m, $CH_XCH_AH_BPh$), 4.2—4.4 (1 H, m, CH_XCH_2Ph), and 7.0—7.3 (5 H, m, Ph), *m/e* 256 (M^+) and 165 ($M^+ - C_7H_7$) (Found: C, 79.4; H, 7.8. $C_{17}H_{20}O_2$ requires C, 79.7; H, 7.8%).

9-*Benzyl*-8-*oxabicyclo*[4.3.0]*non*-3-*en*-7-*one* (11; R^1 = H, R^2 = Ph).—Buta-1,3-diene (3.0 ml) and δ-phenyl-Δ^1-angelica lactone [5-benzylfuran-2(5H)-one] (1.0 g) were heated together in a sealed tube for 24 h at 200 °C. Column chromatography, using ether–light petroleum (1 : 1) as the eluant, then gave 9-*benzyl*-8-*oxabicyclo*[4.3.0]*non*-3-*en*-7-*one* (0.45 g, 34%), as an oil which ran as a single spot on t.l.c. and had $\nu_{max.}$ (film) 1 775 cm^{-1}, δ 1.9—2.8 (6 H, complex, 2 × ring CH_2, H-1 and -6), 2.8—3.2 (2 H, m, $CH_XCH_AH_BPh$), 4.2—4.4 (1 H, m, $J_{1,9}$ 4.5 Hz, CH_XCH_2Ph), 5.6—5.8 (2 H, m, CH=CH), and 7.1—7.4 (5 H, m, Ph), *m/e* 228 (M^+) and 137 ($M^+ - C_7H_7$) (Found: *m/e*, 228.1150. $C_{15}H_{16}O_2$ requires *M*, 228.1150).

9-*Benzyl*-8-*oxabicyclo*[4.3.0]*nonan*-7-*one* (10; Y = O).—9-Benzyl-8-oxabicyclo[4.3.0]non-3-en-7-one (120 mg) in dry ethanol (25 ml) containing 10% palladium–charcoal (12 mg) was hydrogenated at room temperature and atmospheric pressure until uptake corresponded to reduction of one double bond. The catalyst was filtered off, and the solution evaporated, leaving an oil which was purified by column chromatography, using ether–light petroleum (1 : 1) as eluant, to give 9-*benzyl*-8-*oxabicyclo*[4.3.0]*nonan*-7-*one* (90 mg, 75%) as a yellow oil, $\nu_{max.}$ (CCl_4) 1 780 cm^{-1}, δ 1.2—2.6 (10 H, complex, 4 × ring CH_2, H-1 and -6), 2.75—3.1 (2 H, m, $CH_XCH_AH_BPh$), 4.2—4.4 (1 H, m, CH_XCH_2Ph), and 7.1—7.4 (5 H, m, Ph), *m/e* 230 (M^+) and 139 ($M^+ - C_7H_7$) (Found: C, 78.0; H, 8.0. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.8%).

8,9-*Dibenzyl*-6-*methyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one*.—Diisopropylamine (304 mg, 3.12 mmol) in dry [28] tetrahydrofuran (5 ml) was added slowly to 15% butyl-lithium in hexane (2 ml, 3.12 mmol) under dry, oxygen-free nitrogen at −70 °C, and the solution was then stirred for 0.5 h to generate lithium di-isopropylamide. 8,9-Dibenzyl-8-

[28] D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, ' Purification of Laboratory Chemicals,' Pergamon, Oxford, 1966, p. 262; L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 1140.

azabicyclo[4.3.0]nonan-7-one (10; Y = NCH_2Ph) (500 mg, 1.56 mmol) in dry [28] tetrahydrofuran (5 ml) was then added dropwise to the solution of lithium di-isopropylamide at −70 °C, under nitrogen, and the mixture was stirred at −70 °C for 0.5 h to complete the formation of the anion from (10; Y = NCH_2Ph). Iodomethane (282 mg, 2 mmol) in dry [28] tetrahydrofuran (5 ml) was then added slowly, and the mixture was allowed to warm up to −30 °C during 1 h. The mixture was stirred at −30 °C for 3 h and then treated with an excess of 2M hydrochloric acid. Extraction with ether gave an oil, which was purified by column chromatography, using ether–light petroleum (1 : 1) as eluant, to give 8,9-*dibenzyl*-6-*methyl*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (300 mg, 57%), m.p. 85—86°, $\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1}, δ 1.02 (3 H, s, Me), 1.0—1.9 (8 H, complex, 4 × ring CH_2), 2.2—2.4 (1 H, m, H-1), 2.5—3.2 (2 H, m, J_{AB} 14 Hz, CH_X-CH_AH_BPh), 3.8—4.0 (1 H, m, CH_XCH_2Ph), 4.05 (1 H, m, J_{AB} 15 Hz, NCH_AH_BPh), 5.05 (1 H, m, NCH_AH_BPh), and 7.0—7.4 (10 H, complex, 2 × Ph), *m/e* 333 (M^+) and 242 ($M^+ - C_7H_7$) (Found: C, 82.9; H, 8.4; N, 4.2. $C_{23}H_{27}NO$ requires C, 82.9; H, 8.1; N, 4.2%).

When a solution of the anion from (10; Y = NCH_2Ph) (250 mg), prepared as described above, was quenched with water (5 ml), extraction with ether gave material (200 mg) which ran as a single spot on analytical t.l.c., and which was identified spectroscopically as (10; Y = NCH_2Ph).

8,9-*Dibenzyl*-6-*hydroxy*-8-*azabicyclo*[4.3.0]*nonan*-7-*one*.—A solution of the lithium salt of (10; Y = NCH_2Ph) (3.12 mmol) in hexane–dry [28] tetrahydrofuran (1 : 5; 24 ml), prepared as described above, was added dropwise with stirring to dry ether (100 ml) at 0 °C into which dry oxygen was being bubbled. The stirring was continued for 0.5 h and the solvents were then evaporated off. The resultant solid was washed with aqueous sodium sulphite until a starch-iodide test showed the absence of peroxides in the washings. The solid was then taken up in dichloromethane and the solution dried. Evaporation, and column chromatography of the residue using ether–light petroleum (3 : 1) as eluant, then gave 8,9-*dibenzyl*-6-*hydroxy*-8-*azabicyclo*[4.3.0]*nonan*-7-*one* (300 mg, 29%), m.p. 158—160°, $\nu_{max.}$ ($CHCl_3$) 3 350 (OH) and 1 675 cm^{-1} (C=O), δ 1.0—2.0 (8 H, complex, 4 × ring CH_2), 2.2—2.4 (1 H, m, H-1), 2.45—3.15 (2 H, m, J_{AB} 15 Hz, $CH_XH_AH_B$Ph), 3.4—3.8br (1 H, s, O*H* exchangeable), 4.04 (1 H, m, J_{AB} 15 Hz, NCH_AH_BPh), 4.1—4.3 (1 H, m, CH_X-CH_2Ph), 4.95 (1 H, m, NCH_AH_BPh), and 6.8—7.4 (10 H, complex, 2 × Ph), *m/e* 335 (M^+) and 244 ($M^+ - C_7H_7$) (Found: C, 78.8; H, 7.7; N, 4.1. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%).

4-*Methyl*-7-*oxo*-8-*oxabicyclo*[4.3.0]*non*-2-*en*-5-*carboxylic Acid* (13).—Hexa-2,4-dien-1-ol (4.2 g) and maleic anhydride (4.2 g) were heated together in refluxing benzene (100 ml) for 48 h. Evaporation, and recrystallisation of the residue from toluene gave the *acid* (4.7 g, 56%), m.p. 159—161°, $\nu_{max.}$ (Nujol) 3 260 (OH), 1 765 (lactone CO), and 1 730 cm^{-1} (CO_2H), δ [$(CD_3)_2CO$] 1.15 (3 H, d, *J* 7 Hz, Me), 2.5—3.5 (4 H, complex, 4 × ring CH), 4.0—4.5 (2 H, m, J_{AB} 9 Hz, CH_X·CH_AH_B·O), 5.5—6.0 (2 H, m, CH=CH), and 8.5—9.0br (1 H, s, CO_2H), *m/e* 196 (M^+) and 178 ($M^+ - H_2O$) [Found: C, 61.2; H, 6.1(5). $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.1%].

trans,cis,trans-2-*Methyl*-7,9-*dioxo*-8-*oxabicyclo*[4.3.0]*non*-3-*en*-5-*ylmethyl Acetate* (12; R = Ac, Y = O).—Maleic anhydride (1.0 g, 0.01 mol) and hexa-2,4-dienyl acetate (1.4 g, 0.01 mol) were stirred together and warmed to 50 °C until stirring was no longer possible. Crystallisation from toluene then gave the *ester* (1.6 g, 67%), m.p. 103—105°, $\nu_{max.}$ ($CHCl_3$) 1 855 and 1 780 (CO·O·CO) and 1 740 cm^{-1} (OAc), δ 1.43 (3 H, *J* 7 Hz, CH*Me*), 2.06 (3 H, s, OCOMe), 2.3—2.8 (2 H, complex, H-2 and -5), 3.24—3.64 (2 H, complex, H-1 and -6), 4.4—4.7 (2 H, m, CH_X·CH_AH_B·O), and 5.6—5.9 (2 H, m, CH=CH), *m/e* 239 ($M^+ + 1$), 179 (M^+ − OAc), and 151 (M^+ − OAc − CO) (Found: C, 60.7; H, 5.8. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%).

N-*Benzyl*-cis,cis,cis-5-*hydroxymethyl*-2-*methyl*-8-*azabicyclo*-[4.3.0]*non*-3-*ene*-7,9-*dione* (14).—*trans,cis,trans*-2-Methyl-7,9-dioxo-8-oxabicyclo[4.3.0]non-3-en-5-ylmethyl acetate (4.8 g, 0.02 mol) was melted in a flask fitted for distillation and stirred at 190—200 °C while benzylamine (4.4 g, 0.04 mol) was added dropwise; water and the excess of benzylamine were distilled off. After 2 h at 200 °C the melt was poured out and the product was purified by column chromatography using ether as eluant, giving the *alcohol* (14) (4.3 g, 75%) as an oil, $\nu_{max.}$ (film) 3 450 (OH), 1 775, and 1 700 cm^{-1}, δ 1.35 (3 H, d, *J* 7 Hz, CH*Me*), 2.0—3.0 (5 H, complex, 4 × ring CH + OH), 3.6—4.0 (2 H, m, $CH_XCH_AH_B$·O), 4.65 (2 H, s, NCH_2Ph), 5.7 (2 H, m, CH=CH), and 7.1—7.4 (5 H, m. Ph), *m/e* 285 (M^+) and 267 ($M^+ - H_2O$) (Found: C, 71.9; H, 6.9; N, 5.2. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.7; N, 4.9%).

N-*Benzyl*-trans,cis,trans-5-*hydroxymethyl*-2-*methyl*-8-*azabicyclo*[4.3.0]*non*-3-*ene*-7,9-*dione* (12; R = H, Y = NCH_2Ph).—Hexa-2,4-dien-1-ol (1.0 g) and *N*-benzylmaleimide (1.9 g) were heated together in refluxing benzene (10 ml) for 18 h. Evaporation left the crude product, which after purification by column chromatography using ether as eluant yielded the *alcohol* (12; R = H, Y = NCH_2Ph) (2.4 g, 84%) as an oil, which ran as a single spot on t.l.c. and had $\nu_{max.}$ (film) 3 440 (OH), 1 765, and 1 690 cm^{-1}, δ 1.44 (3 H, d, *J* 7 Hz, CH*Me*), 2.30—2.60 (2 H, complex, H-2 and -5), 2.90—3.5 (3 H, complex, H-1, H-6, and OH), 3.8—4.0 (2 H, m, CH_X·CH_AH_B·O), 4.57 (2 H, s, NCH_2Ph), 5.5—5.8 (2 H, m, CH=CH), and 7.0—7.4 (5 H, m, Ph), *m/e* 285 (M^+) (Found: *m/e* 285.1363. $C_{17}H_{19}O_3$ requires *M*, 285.1365).

Isomerisation of the Alcohol (12; R = H, Y = NCH_2Ph) *to* (14).—Compound (12; R = H, Y = NCH_2Ph) (1.4 g, 5 mmol) and benzylamine (0.6 g, 5.1 mmol) were heated together, with stirring, at 190—200 °C for 2 h. Analytical t.l.c. of the residue, using ether as developing solvent, showed that isomerisation was then almost complete [(12; R = H, Y = NCH_2Ph), R_F 0.5; (14), R_F 0.8]. Column chromatography using ether as eluant gave (14) (0.9 g, 64%), identical (i.r., n.m.r., and mass spectra) with the previous sample. No isomerisation was detectable by analytical t.l.c. when (12; R = H, Y = NCH_2Ph) was heated alone at 200 °C for 2 h.

Catalytic Hydrogenation of the Alcohols (12; R = H, Y = NCH_2Ph) *and* (14).—Compound (12; R = H, Y = NCH_2Ph) (1.4 g) in ethanol (25 ml) containing 10% palladium–charcoal (140 mg) was hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off and the solution evaporated, leaving an oil which was purified by column chromatography using ether as eluant to give N-*benzyl*-trans,cis,trans-5-*hydroxymethyl*-2-*methyl*-8-*azabicyclo*[4.3.0]*nonane*-7,9-*dione* (1.0 g, 71%) as an oil, $\nu_{max.}$ (film) 3 440 (OH), 1 730, and 1 690 cm^{-1}, δ 1.14 (3 H, d, *J* 7 Hz, CH*Me*), 1.2—1.7 (4 H, complex, 2 × ring CH_2), 1.8—2.3 (2 H, complex, H-3 and -5), 2.8—3.3 (3 H, complex, H-1, H-6, and OH), 3.5—3.9 (2 H, m, CH_X·CH_AH_B·O), 4.64 (2 H, s, NCH_2Ph), and 7.15—7.5 (5 H, m, Ph) [Found: C, 71.2; H, 7.5; N, 4.7(5). $C_{17}H_{21}NO_3$ requires C, 7.11; H, 7.3; N, 4.9%]. Hydrogenation of (14) under identical conditions

gave a 71% yield of N-*benzyl*-cis,cis,cis-5-*hydroxymethyl*-2-*methyl*-8-*azabicyclo*[4.3.0]*nonane*-7,9-*dione*, as an oil, $\nu_{max.}$ (film) 3 440 (OH), 1 740, and 1 690 cm^{-1}, δ 1.11 (3 H, d, *J* 7 Hz, CH*Me*), 1.2—1.6 (4 H, complex, 2 × ring CH_2), 1.8—2.1 (2 H, complex, H-2 and -5), 2.3—2.9 (3 H, complex, H-1, H-6, and OH), 3.45—3.75 (2 H, m, $CH_X{\cdot}CH_AH_B{\cdot}O$), 4.60 (2 H, s, NCH_2Ph), and 7.1—7.4 (5 H, m, Ph) (Found: C, 71.1; H, 7.3; N, 4.8. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.3; N, 4.9%).

Isomerisation of N-*Benzyl*-trans,cis,trans-5-*hydroxymethyl*-2-*methyl*-8-*azabicyclo*[4.3.0]*nonane*-7,9-*dione*.— *N*-Benzyl-*trans,cis,trans*-5-hydroxymethyl-2-methyl-8-azabicyclo-[4.3.0.]nonane-7,9-dione (262 mg) and benzylamine (100 mg) were heated together at 190 °C for 24 h. Analytical t.l.c. of the residue, using ether as the developing solvent, showed that only the *trans,cis,trans*- (R_F 0.5) and the *cis,cis,cis*-isomers (R_F 0.75) were present. The *cis,cis,cis*-isomer was not equilibrated with the *trans,cis,trans*-isomer under the same conditions.

N-*Benzyl*-cis,cis,cis-2-*methyl*-5-*tetrahydropyranyloxymethyl*-8-*azabicyclo*[4.3.0]*non*-3-*ene*-7,9-*dione*.— *N*-Benzyl-*cis,cis,cis*-5-hydroxymethyl-2-methyl-8-azabicyclo[4.3.0]-non-3-ene-7,9-dione (1.425 g, 5 mmol) and redistilled 2,3-dihydropyran (2.0 g, 27 mmol) in dry dioxan (50 ml), containing toluene-4-sulphonic acid (140 mg) were stirred at room temperature for 2 h. The mixture was then neutralised with dilute sodium hydroxide, and evaporated. The residue was dissolved in ether and the solution was filtered and dried. Evaporation left an oil which was submitted to column chromatography using ether–light petroleum (1 : 1) as eluant, giving N-*benzyl*-cis,cis,cis-2-*methyl*-5-*tetrahydropyranyloxymethyl*-8-*azabicyclo*[4.3.0]*non*-3-*ene*-7,9-*dione* (1.1 g, 60%) as an oil, $\nu_{max.}$ (film) 1 764 and 1 710 cm^{-1}, δ 1.32 (3 H, d, *J* 7 Hz, CH*Me*), 1.14—1.90 (6 H, complex, 3 × CH_2), 2.0—3.1 (4 H, complex, H-1, -2, -5, and -6), 3.4—4.00 (5 H, complex, $CH_2{\cdot}O{\cdot}CH{\cdot}O{\cdot}CH_2$), 4.62 (2 H, s, NCH_2Ph), 5.6—5.9 (2 H, m, CH=CH), and 7.2—7.4 (5 H, m, Ph), *m/e* 284 ($M^+ - C_5H_9O$) and 267 ($M^+ - C_5H_{10}O_2$) [Found: C, 71.3; H, 7.4; N, 3.9. $C_{22}H_{27}NO_4$ requires C, 71.5(5); H, 7.3; N, 3.8%].

The Lactam (15; R^1 = Me, R^2 = CH_2OThp or R^1 = CH_2OThp, R^2 = Me).—Ethereal 0.35M-benzylmagnesium chloride (130 ml; 45 mmol) was refluxed for 15 h with a solution of the above tetrahydropyranyl ether (5.4 g, 15 mmol) in dry ether–benzene (1 : 1; 200 ml). When cold the Grignard complex was carefully decomposed with an excess of 2M-hydrochloric acid, and the organic layer was separated. The aqueous layer was extracted twice with ether, and the combined organic layers were dried. Evaporation left an oil, which was purified by column chromatography, using ether–light petroleum (3 : 1) as eluant, to give 8,9-*dibenzyl*-2(or 5)-*methyl*-5-(*or* 2)-*tetrahydropyranyloxymethyl*-8-*azabicyclo*[4.3.0]*nona*-1(6),3-*dien*-7-*one* (3.6 g, 54%), as an oil, which ran as a single spot on t.l.c., and had $\nu_{max.}$ (film) 1 660 cm^{-1}, δ 1.29 (3 H, d, *J* 7 Hz, CH*Me*), 1.2—1.8 (6 H, complex, 3 × ring CH_2), 2.8—3.8 (8 H, complex, $CHCH_2Ph$, $CH{\cdot}CH_2{\cdot}O{\cdot}CH_2$, H-2, and H-5), 3.88 (1 H, m, J_{AB} 16 Hz, NCH_AH_BPh), 4.2—4.6 (2 H, complex, $CHCH_2Ph$ and $O{\cdot}CH{\cdot}O$), 5.2 (1 H, m, NCH_AH_BPh), 5.5—5.9 (2 H, m, CH=CH), and 6.8—7.4 (10 H, complex, 2 × Ph), *m/e* 443 (M^+) and 252 ($M^+ - C_7H_7$) (Found: *m/e*, 443.2468. $C_{29}H_{33}NO_3$ requires *M*, 443.2460).

8,9-*Dibenzyl*-5(or 2)-*hydroxymethyl*-2(or 5)-*methyl*-8-*azabicyclo*[4.3.0]*nona*-1(6),3-*dien*-7-*one*.— 8,9-Dibenzyl-2(or 5)-methyl-5(or 2)-tetrahydropyranyloxymethyl-8-azabicyclo-[4.3.0]nona-1(6),3-dien-7-one (160 mg) was stirred at room temperature for 24 h in methanol (10 ml)–0.1M-hydrochloric acid (10 ml). The mixture was then neutralised with dilute aqueous ammonia and extracted with ether (3 × 50 ml). The extracts were dried and evaporated, leaving an oil which was purified by column chromatography, using ether as eluant, to give 8,9-*dibenzyl*-5(*or* 2)-*hydroxymethyl*-2(or 5)*methyl*-8-*azabicyclo*[4.3.0]*nona*-1(6),3-*dien*-7-*one* (58 mg, 45%), m.p. 116°, $\nu_{max.}$ (Nujol) 3 230 (OH) and 1 645 cm^{-1} (C=O), δ 1.27 (3 H, d, *J* 7 Hz, CH*Me*), 1.66br (1 H, s, OH, exchangeable), 2.94 (2 H, d, *J* 6 Hz, $CH{\cdot}CH_2Ph$), 3.0—3.2 (2 H, complex, H-2 and -5), 3.3—3.5 (2 H, m, $CH{\cdot}CH_2OH$), 4.0 (1 H, m, J_{AB} 16 Hz, NCH_AH_BPh), 4.3 (1 H, t, *J* 6 Hz, $CHCH_2Ph$), 5.12 (1 H, m, NCH_AH_BPh), 5.5—5.9 (2 H, m, CH=CH), and 6.9—7.3 (10 H, complex, 2 × Ph), *m/e* 268 ($M^+ - C_7H_7$) (Found: C, 80.0; H, 7.2; N, 4.1. $C_{24}H_{25}NO_2$ requires C, 80.2; H, 7.0; N, 3.9%).

8,9-*Dibenzyl*-2(or 5)-*methyl*-5(or 2)-*tetrahydropyranyloxymethyl*-8-*azabicyclo*[4.3.0]*non*-1(6)-*en*-7-*one*.— 8,9-Dibenzyl-2-(or 5) methyl-5(or 2)-tetrahydropyranyloxymethyl-8-azabicyclo[4.3.0]nona-1(6),3-dien-7-one (1.0 g) in methanol (175 ml) was hydrogenated over W 1 Raney nickel [29] (1 ml) in an autoclave at 50 °C and 100 atm for 8 h. The mixture was cooled, and the catalyst filtered off. Evaporation gave an oil, which was subjected to column chromatography, using ether–light petroleum (1 : 1) as eluant, and gave 8,9-*dibenzyl*-2(or 5)-*methyl*-5(or 2)-*tetrahydropyranyloxymethyl*-8-*azabicyclo*[4.3.0.]*non*-1(6)-*en*-7-*one* (0.4 g, 40%) as an oil which ran as a single spot on t.l.c. and had $\nu_{max.}$ (film) 1 675 cm^{-1}, δ 1.15 (3 H, d, *J* 7 Hz, CH*Me*), 1.2—1.8 (10 H, complex, 5 × ring CH_2), 2.2—3.7 (8 H, complex, $CHCH_2Ph$, $CH_2{\cdot}O{\cdot}CH{\cdot}O{\cdot}CH_2$, H-1 and -6), 3.85 (1 H, m, J_{AB} 16 Hz, NCH_AH_BPh), 4.1—4.6 (2 H, complex, $O{\cdot}CH{\cdot}O$ and H-9), 5.2 (1 H, *m*, NCH_AH_BPh), and 6.9—7.4 (10 H, complex, 2 × Ph), *m/e* 445 (M^+) and 354 ($M^+ - C_7H_7$) (Found: *m/e*, 445.2615. $C_{29}H_{35}NO_3$ requires *M*, 445.2617).

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