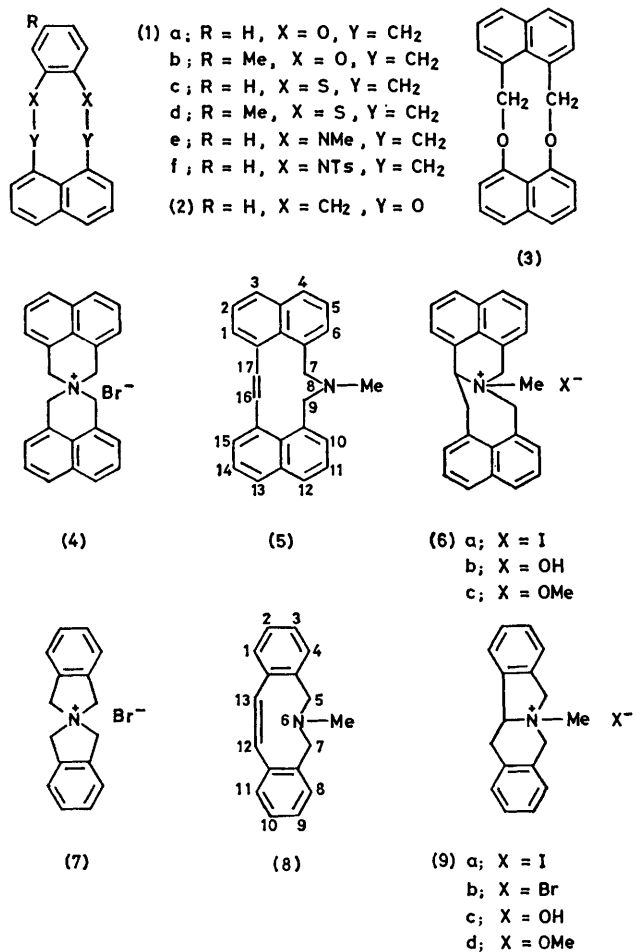


Conformational Behaviour of Medium-sized Rings. Part 5.¹ Transannular Reactions of (16Z)-8,9-Dihydro-8-methyl-7H-dinaphth-[1,8-cd:1',8'-hi]azacycloundecine and (12Z)-6,7-Dihydro-6-methyl-5H-dibenz[*c,g*]azonine. Two Examples of 'Reverse Hofmann Eliminations'

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The olefinic double bonds in the cyclic ene-amines (5) and (8) have been shown to have the *cis*-configuration since two conformational diastereoisomers are formed in each case on quaternisation at nitrogen. The eleven-membered ring ene-amine (5), which is conformationally stable on the ¹H n.m.r. time-scale up to +160 °C, undergoes transannular reactions involving the carbon-carbon double bond and the nitrogen atom in acidic, neutral, and basic media. Although the nine-membered ring ene-amine (8), which is conformationally mobile on the ¹H n.m.r. time-scale at room temperature, also undergoes transannular reactions involving the carbon-carbon double bond and the nitrogen atom in acidic and neutral media, more vigorous reaction conditions are required.

Our interest¹ in the conformational behaviour of the nine-membered ring systems (1a-f) and (2) and the



ten-membered ring system (3) incorporating 1,8-disubstituted naphthalene units as torsionally rigid groups has

led to the preparation of the eleven-membered ring system (5) from the spiro-ammonium salt² (4) by a route analogous to that³ already employed by us⁴ in the synthesis of the nine-membered ring system (8) from the spiro-ammonium salt (7). However, during the synthesis of the eleven-membered ring ene-amine (5) from the spiro-ammonium salt (4) by this route, which involves a Stevens rearrangement and a Hofmann elimination, it was found that (5) undergoes transannular reactions involving the carbon-carbon double bond and the nitrogen atom to afford quaternary ammonium salts (6). This observation prompted us to examine the propensity for the nine-membered ring ene-amine⁴ (8) to undergo transannular reactions as well to give the corresponding quaternary ammonium salts (9). In this paper, we describe the results of these two investigations, one of which has received brief mention in a recent review⁵ on the conformational behaviour of medium-sized ring systems.

EXPERIMENTAL

The general methods are discussed in Part 3.⁴
 2,2-(3H,3'H)-Spirobi-(1H-benz[de]isoquinolinium) Bromide (4).—A 25% ammonia solution (500 ml) was added to a solution of 1,8-bisbromomethylnaphthalene⁶ (80 g) in benzene (800 ml). The mixture was heated (80–85 °C) and stirred in an autoclave for 10 h. On cooling, the crystalline product was collected by filtration and washed with benzene, then with water. Recrystallisation from methanol gave the spiro-ammonium salt (4) (43 g, 84%), m.p. >300° (lit.² m.p. 380°), as needles containing one mole of methanol of crystallisation, which was removed at 0.5 mmHg and 140 °C (Found: C, 71.4; H, 5.0; Br, 20.0; N, 3.65. C₂₄H₂₀BrN requires C, 71.6; H, 5.0; Br, 19.9; N, 3.5%), τ (CF₃CO₂H) 1.88–2.74 (12 H, m, aromatic) and 4.91 (8 H, s, methylene).

16,16a-Dihydro-7H,9H-benzo[ef]benz[4,5,6]isoquino[2,1-b]-[2]benzazepine (10).—1M-Phenyl-lithium in ether (75 ml) was added dropwise with stirring during 4 h to a suspension of the spiro-ammonium salt (4) (40 g) in dry ether (300 ml). Initially, the mixture assumed a green colouration which

¹ Part 4, D. J. Brickwood, W. D. Ollis, and J. F. Stoddart, preceding paper.

² S. Hauptmann, P. Hunger, and S. Blaskovits, *J. prakt. Chem.*, 1968, **37**, 72.

³ G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Annalen*, 1951, **572**, 1; J. H. Brewster and R. S. Jones, *J. Org. Chem.*, 1969, **34**, 354.

⁴ W. D. Ollis and J. F. Stoddart, *J.C.S. Perkin I*, 1976, 926.

⁵ W. D. Ollis, J. F. Stoddart, and I. O. Sutherland, *Tetrahedron*, 1974, **30**, 1903.

⁶ E. D. Bergmann and J. Szmuskovicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2760.

disappeared after stirring for 16 h. Water was added to destroy excess of phenyl-lithium and the mixture was filtered. The white solid was washed repeatedly with ether and the combined ethereal extracts were dried (MgSO_4). Reduction of the volume of the ethereal solution to ca. 300 ml by distillation followed by cooling gave needles of the *bicyclic amine* (10) (12.8 g, 40%), m.p. 148—150° [Found: M (mass spec.), 321. $\text{C}_{24}\text{H}_{19}\text{N}$ requires M , 321], τ (CDCl_3) 2.24—2.92 (12 H, m, aromatic) and 5.30—6.28 (7 H, 2AB systems and ABX system, methine and methylene protons).

16,16a-Dihydro-8-methyl-7H,9H-benzo[ef]benz[4,5,6]isoquinolo[2,1-b][2]benzazepinium Iodide (6a).—Methyl iodide (30 ml) was added to the bicyclic amine (10) (10 g) in ether (200 ml) and benzene (100 ml) and the solution was stirred for 16 h. The precipitated salt was collected by filtration and washed with ether. Recrystallisation from methanol gave yellow needles of the *methiodide* (6a) (13.3 g, 92%), m.p. 262—270° (decomp.), containing methanol of crystallisation, which was removed at 5 mmHg and 215 °C (Found: C, 64.5; H, 4.7; I, 27.1; N, 2.9. $\text{C}_{25}\text{H}_{22}\text{IN}$ requires C, 64.8; H, 4.8; I, 27.4; N, 3.0%), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.83—2.65 (12 H, m, aromatic), 4.18—6.63 (7 H, 2AB systems and ABX system, methine and methylene protons), and 6.75 (3 H, s, Me).

(16Z)-8,9-Dihydro-8-methyl-7H-dinaphth[1,8-cd:1'8'-hi]-azacycloundecine (5) and 16a-Methyl-16,16a-dihydro-7H,9H-benzo[ef]benz[4,5,6]isoquinolo[2,1-b][2]benzazepine (11).—Silver oxide (5 g) was added to the bicyclic methiodide (6a) (10 g) in methanol (62 ml) and water (13 ml). The mixture was stirred for 16 h at room temperature and then the precipitated silver salts were removed by filtration and washed with methanol. Methanol was removed from the filtrate under vacuum without heating. The quaternary ammonium salt was dissolved in dry toluene (250 ml) and the solution was heated under reflux for 2 h in a Dean-Stark apparatus in order to remove water formed. Toluene was then distilled off under reduced pressure and the crystalline residue was recrystallised, first from light petroleum (b.p. 60—80 °C) and then from ethyl acetate, yielding colourless crystals of the *cyclic ene-amine* (5) (1.7 g, 24%), m.p. 197° [Found: C, 89.6; H, 6.55; N, 3.95; M (mass spec.), 335. $\text{C}_{25}\text{H}_{21}\text{N}$ requires C, 89.5; H, 6.3; N, 4.2%; M , 335], τ (CDCl_3) 2.27—2.83 (12 H, m, aromatic), 2.87 (2 H, s, olefinic), 4.87 and 6.79 (4 H, 2 × AX systems, J_{AX} 12.4 Hz, ArCH_2N), and 8.62 (3 H, s, Me). A second product, isolated by column chromatography on silica gel using ethyl acetate—light petroleum (b.p. 60—80 °C) (1 : 3) as eluant, was the *rearrangement product* (11) (100 mg, 1%) [Found: M (mass spec.), 335. $\text{C}_{25}\text{H}_{21}\text{N}$ requires M , 335], τ (CDCl_3) 2.18—2.96 (12 H, m, aromatic), 5.26 and 6.26, 5.50 and 5.93, and 6.12 and 6.40 (6 H, 3 × AB systems with J_{AB} 16.0, 17.0, and 16.0 Hz, respectively, methylene protons), and 8.34 (3 H, s, Me).

Reaction of the *Cyclic Ene-amine* (5) with Trifluoroacetic Acid.—When the ^1H n.m.r. spectrum of the ene-amine (5) was recorded immediately after dissolution in trifluoroacetic acid, evidence for the formation of two *N*-protonated conformational isomers (12) in the approximate ratio 3 : 1 was obtained: τ (major isomer) ($\text{CF}_3\text{CO}_2\text{H}$) 1.89—2.62 (12 H, m, aromatic), 3.89 (2 H, br d, J_{gem} 13.8, $J_{\text{CH}_2\text{NH}} < 1.0$ Hz, methylene protons), 5.56 (2 H, q, J_{gem} 13.8, $J_{\text{CH}_2\text{NH}}$ 10.0 Hz, methylene protons), and 7.65 (3 H, d, J_{MeNH} 5.8 Hz, Me); τ (minor isomer) ($\text{CF}_3\text{CO}_2\text{H}$) 1.89—2.62 (12 H, m, aromatic), 4.98 (2 H, q, J_{gem} 14.0, $J_{\text{CH}_2\text{NH}}$ 8.0 Hz, methylene protons), 5.28 (2 H, q, J_{gem} 14.0, $J_{\text{CH}_2\text{NH}}$ 4.0 Hz, methylene protons), and 6.72 (3 H, d, J_{MeNH} 5.0 Hz, Me). During 2 days at

room temperature the minor isomer was completely converted into the major isomer.

N-Oxides (13) of the *Ene-amine* (5).—The ene-amine (5) (334 mg) dissolved in chloroform (50 ml) was added gradually to *m*-chloroperbenzoic acid (357 mg) in ether (18 ml) maintained below 5 °C by immersion in an ice-bath. After 24 h, sodium hydroxide solution (20 ml; 10%) was added and the chloroform layer was separated and dried (MgSO_4). Evaporation of the chloroform under vacuum at room temperature afforded an oil. Two conformationally isomeric *N-oxides* (13) were separated by preparative t.l.c. on silica gel using methanol as eluant. The faster moving component was the major isomer (50 mg, 14%), m.p. 116—118° (decomp.) [Found: M (mass spec.), 351.1624. $\text{C}_{25}\text{H}_{21}\text{NO}$ requires M , 351.1623], τ (CDCl_3) 2.36 (2 H, s, olefinic), 2.38—3.15 (12 H, m, aromatic), 3.58 and 5.40 (4 H, 2 × AB systems, J_{AB} 14.8 Hz, methylene protons), and 6.42 (3 H, s, Me); the minor isomer (20 mg, 6%) had m.p. 126—127° (decomp.) [Found: M (mass spec.), 351.1631. $\text{C}_{25}\text{H}_{21}\text{NO}$ requires M , 351.1623], τ (CDCl_3) 2.45 (2 H, s, olefinic), 1.75—3.30 (12 H, m, aromatic), 4.13 and 5.58 (4 H, 2 × AB systems, J_{AB} 12.7 Hz, methylene protons), and 6.34 (3 H, s, Me).

Reaction of the *Ene-amine* (5) with Hydroiodic Acid.—Hydroiodic acid (0.1 ml) was added to the ene-amine (5) (100 mg) dissolved in ethanol (30 ml) and the mixture was stirred at room temperature for 2 h. The yellow precipitate was collected and recrystallised from methanol to give yellow needles of the *bicyclic methiodide* (6a) (100 mg, 72%), m.p. 270° (decomp.), containing methanol of crystallisation which was removed at 5 mmHg and 215 °C (Found: C, 64.7; H, 5.0; N, 2.8. $\text{C}_{25}\text{H}_{22}\text{IN}$ requires C, 64.8; H, 4.8; N, 3.0%). The ^1H n.m.r. spectrum in $\text{CF}_3\text{CO}_2\text{H}$ was identical with that already described.

Reaction of the *Ene-amine* (5) with Aqueous Methanol.—The ene-amine (5) (30 mg) was stirred in methanol (15 ml) and water (7.5 ml) at room temperature for 48 h. Water and methanol were removed on a rotary evaporator at room temperature. A ^1H n.m.r. spectrum of the residue in $\text{CF}_3\text{CO}_2\text{H}$ indicated the presence of the bicyclic hydroxide/methoxide (6b/c) and the *N*-protonated species (12) in the approximate ratio 1 : 2. Evidence that the *N*-protonated species (12) arises from reaction of unchanged ene-amine (5) with trifluoroacetic acid was obtained by extracting the remainder of the residue with chloroform and recording the ^1H n.m.r. spectrum of the extract in CDCl_3 . This spectrum indicated the presence of unchanged ene-amine (5) in the original residue.

In a second experiment the ene-amine (5) (20 mg) was stirred in methanol (10 ml) and water (5 ml) at room temperature for 48 h. Water and methanol were removed on a rotary evaporator at room temperature and the residue was dissolved in hot ethanol. Amberlite C.G. 400 resin (I-form) (300 mg) was added and the mixture was heated under reflux for 0.5 h. A yellow gum was obtained from the filtrate after evaporation of the ethanol. Trituration of this gummy material with ethanol afforded a solid which, upon recrystallisation from methanol, yielded yellow needles of the *bicyclic methiodide* (6a) (5 mg, 18%), m.p. 268° (decomp.), containing methanol of crystallisation which was removed at 5 mmHg and 215 °C (Found: C, 64.8; H, 4.95; N, 2.85. Calc. for $\text{C}_{25}\text{H}_{22}\text{IN}$: C, 64.8; H, 4.8; N, 3.0%). The ^1H n.m.r. spectrum in $\text{CF}_3\text{CO}_2\text{H}$ was identical with that already described.

Reaction of the *Ene-amine* (5) with Aqueous Methanol at pH 10.—The ene-amine (5) (30 mg) was stirred in methanol (15

ml) and water (7.5 ml) adjusted to pH 10 by addition of ammonia solution. After stirring for 48 h at room temperature, water and methanol were removed; a ^1H n.m.r. spectrum of the residue in $\text{CF}_3\text{CO}_2\text{H}$ indicated the presence of the bicyclic hydroxide/methoxide (6b/c) and *N*-protonated species (12) in the approximate ratio 1 : 2.

Reaction of (12*Z*)-6,7-Dihydro-6-methyl-5H-dibenz[*c,g*]-azonine (8) in Trifluoroacetic Acid.—When the ^1H n.m.r. spectrum of the ene-amine 3,4 (8) was recorded immediately after dissolution in trifluoroacetic acid, evidence for the formation of two *N*-protonated conformational isomers of (14) in the approximate ratio 4 : 3 was obtained: τ (major isomer) ($\text{CF}_3\text{CO}_2\text{H}$ at -10°C) 7.09 (d, J_{MeNH} 5.6 Hz, Me); τ (minor isomer) ($\text{CF}_3\text{CO}_2\text{H}$ at -10°C) 6.58 (d, J_{MeNH} 5.6 Hz, Me). The remainder of the ^1H n.m.r. spectrum consisted of two sets of overlapping multiplets: τ 2.40–3.20 (aromatic and olefinic protons) and 4.90–5.80 (methylene protons). At room temperature all signals were considerably broadened, indicating that conformational interconversion was reasonably fast on the n.m.r. time-scale.

***N*-Oxide (15) of the Ene-amine (8).**—The ene-amine 3,4 (8) (233 mg) dissolved in chloroform (10 ml) was added gradually to a solution of *m*-chloroperbenzoic acid (357 mg) in ether (20 ml) maintained below 5°C by immersion in an ice-bath. After 24 h, sodium hydroxide solution (5 ml; 10%) was added and the chloroform layer was separated and dried (MgSO_4). Evaporation under vacuum at room temperature afforded the *N*-oxide (15) (200 mg, 75%), m.p. $135\text{--}140^\circ$ [Found: *M* (mass spec.), 251. $\text{C}_{17}\text{H}_{17}\text{NO}$ requires *M*, 251], τ (CDCl_3) 2.62–3.14 (10 H, m, aromatic and olefinic), 5.18 and 5.30 (4 H, 2 \times AB systems, J_{AB} 13.0 Hz, methylene protons), and 6.82 (3 H, s, Me).

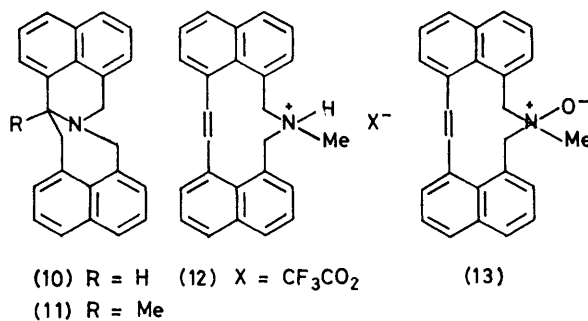
Reaction of the Ene-amine (8) with Hydroiodic Acid.—Hydroiodic acid (0.1 ml) was added to the ene-amine 3,4 (8) (100 mg) dissolved in ethanol (30 ml) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated off under vacuum at room temperature; the ^1H n.m.r. spectrum of the residue in trifluoroacetic acid indicated the presence of the bicyclic methiodide (9a) [τ ($\text{CF}_3\text{CO}_2\text{H}$) 2.35–2.85 (8 H, m, aromatic), 4.65–4.85 (1 H, t, H-11b), 5.06 and 5.33 (4 H, 2 \times s, C-5 and C-7 methylene protons), 6.05–6.87 (2 H, octet, C-12 methylene protons), and 6.55 (3 H, s, Me)] and was identical with that obtained for the bicyclic methobromide A (9b) [τ ($\text{CF}_3\text{CO}_2\text{H}$) 2.40–2.90 (8 H, m, aromatic), 4.66–4.84 (1 H, t, H-11b), 5.05 and 5.32 (4 H, 2 \times s, C-5 and C-7 methylene protons), 6.08–6.90 (2 H, octet, C-12 methylene protons), and 6.54 (3 H, s, Me)] reported in Part 3.⁴

Reaction of the Ene-amine (8) with Aqueous Methanol.—The ene-amine 3,4 (8) (20 mg) was stirred in methanol (10 ml) and water (5 ml) at room temperature for 48 h. T.l.c. on silica gel (ether as eluant) indicated that the starting material was largely unchanged. The solution was then heated under reflux for 2 h, during which time all the olefin (8) reacted (t.l.c.). Water and methanol were removed; a ^1H n.m.r. spectrum of the residue in trifluoroacetic acid indicated the presence of the bicyclic hydroxide/methoxide (9c/d) [τ ($\text{CF}_3\text{CO}_2\text{H}$) 2.40–2.90 (8 H, m, aromatic), 4.66–4.86 (1 H, t, H-11b), 5.04 and 5.33 (4 H, 2 \times s, C-5 and C-7 methylene protons), 6.06–6.90 (2 H, octet, C-12 methylene protons), and 6.54 (3 H, s, Me)] as the only product.

RESULTS AND DISCUSSION

The eleven-membered ring ene-amine (5) was prepared by a route involving (i) a Stevens rearrangement on the

spiro-ammonium salt 2 (4) to give the bicyclic amine (10), (ii) formation of the methiodide (6a), and (iii) its conversion into the quaternary ammonium hydroxide (6b). Initial attempts to pyrolyse the hydroxide (6b) were unsuccessful; starting material was invariably recovered. However, when the hydroxide (6b) was heated under reflux with dry toluene in a Dean–Stark apparatus, reaction proceeded smoothly to give the eleven-membered ring ene-amine (5) as the major (elimination) product and the Stevens rearrangement product (11) as the minor component of the dehydration. Compound (5) was shown to be conformationally stable on the ^1H n.m.r. time-scale: the AX system observed for the ring methylene protons on C-7 and C-9 remained discrete and sharp up to $+160^\circ\text{C}$ in nitrobenzene solution. This means that the free energy of activation for ring inversion in compound (5) must be in excess of 27 kcal mol^{-1} .



In the knowledge that the cyclic ene-amine (5) has a reasonably rigid conformation, it proved possible to show that the olefinic double bond has the *cis*-configuration in this eleven-membered ring compound. Examination of the ^{13}C satellite signals associated with the olefinic resonance at τ 2.87 in the ^1H n.m.r. spectrum revealed a vicinal coupling constant of *ca.* 10 Hz for the olefinic protons, and so compound (5) was tentatively assigned the *cis*-configuration [(5a) in Figure 1. Unambiguous evidence for this follows from (i) the identification of *two* conformational diastereoisomers* (Figure 2) of the *N*-protonated salt (12) in the ^1H n.m.r. spectrum of the cyclic ene-amine (5) recorded in trifluoroacetic acid under conditions of kinetic control and (ii) the isolation of two crystalline conformational diastereoisomers* (Figure 2) of the *N*-oxide (13) of the cyclic ene-amine (5). Figure 1 draws attention to the fact that whereas the *cis*-isomer (5a) has diastereotopic faces (A and B) associated with

* Proof of the configurational assignment is contained in the observation that *two* conformational diastereoisomers are formed in both reactions. Although conformational assignments are immaterial as regards this particular argument, it is tempting to speculate that the *major* conformational diastereoisomers (see Experimental section) formed from (5) on (i) *N*-protonation under kinetic control and (ii) *N*-oxide formation are the *exo*-isomers (see Figure 2), *exo*-(12) and *exo*-(13), respectively. In each case, formation of these isomers follows from attack of (5) by the reagents in the more sterically accessible manner. Coupling constant data (see Experimental section) for the trifluoroacetates (12) and chemical shift data (see Experimental section) for the *N*-oxides (13) lend some support to these *tentative* conformational assignments.

quaternisation at nitrogen and so can give rise to diastereoisomeric products, the *trans*-isomer (5b) has homotopic faces (C) associated with quaternisation at nitrogen

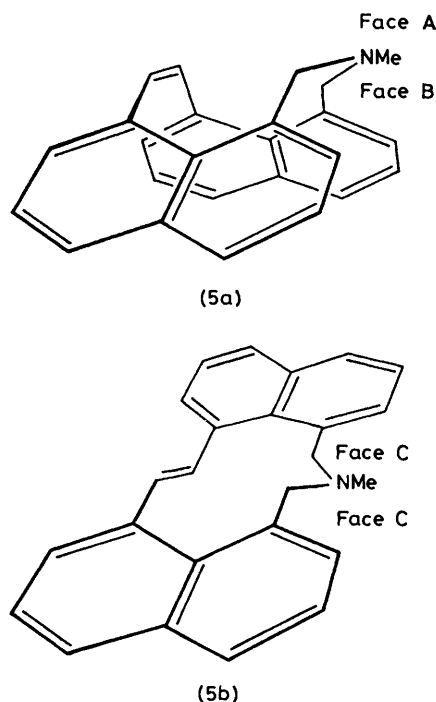


FIGURE 1 The *cis*-(5a) and *trans*-(5b) isomers of the cyclic ene-amine (5). The *cis*-isomer (5a) with C_s symmetry has diastereotopic faces (A and B) associated with quaternisation at nitrogen. The *trans*-isomer (5b), with C_2 symmetry has homotopic faces (C) associated with quaternisation at nitrogen

and so would give rise to only one product. It follows that the configuration of the olefinic double bond in (5) is *cis* (*Z*). The ^1H n.m.r. spectroscopic identification of conformationally diastereoisomeric trifluoroacetates (12) and the isolation of conformationally diastereoisomeric *N*-oxides (13) indicate that the barriers to conformational interconversion in both cases are greater than *ca.* 25 kcal mol $^{-1}$ [*cf.* the high energy barrier to ring inversion of (5) to which attention has already been drawn].

The difficulty experienced in carrying out a Hofmann elimination on the quaternary ammonium hydroxide (6b) unless water is simultaneously removed from the reaction vessel suggests that the reverse reaction [(5) + H $_2$ O \rightarrow (6b)] is favoured. In fact, the cyclic ene-amine (5) undergoes reactions in acidic, neutral, and basic media to give quaternary ammonium salts. The experiments which substantiate these claims are as follows. (i) Treatment of an ethanolic solution of (5) with hydroiodic acid at room temperature for 2 h afforded the bicyclic ammonium methiodide (6a) in 72% yield. When (5) was stirred, either (ii) in aqueous methanol at room temperature for 48 h, or (iii) in aqueous methanol adjusted to pH 10 by addition of ammonium hydroxide at room temperature for 48 h, ^1H n.m.r. spectroscopy in trifluoroacetic acid of the residues remaining after re-

moval of the solvents indicated the presence of transannular products (6b,c) and unchanged cyclic ene-amine (5) in the approximate ratio 1 : 2 in each case. Since the unchanged cyclic ene-amine (5) is transformed quantitatively into the *N*-protonated salt (12) on addition of trifluoroacetic acid (see above), the presence of (5) in the residues from experiments (ii) and (iii) was confirmed by ^1H n.m.r. spectroscopy (solvent deuteriochloroform) of chloroform extracts of the residues. In addition, experiment (ii) was repeated and the bicyclic ammonium hydroxide/methoxide (6b/c) formed during the transannular reaction was characterised as the bicyclic ammonium methiodide (6a) after treatment of the mixture with an anion-exchange resin in the iodide form.

All the evidence from the reactions of the cyclic ene-amine (5) with proton donors suggests that *N*-protonated salts (12) are the products of kinetic control whereas the bicyclic ammonium salts (6) formed as a result of transannular reactions (Figure 3), which may be described as 'reverse Hofmann eliminations,' are the thermodynamically more stable products. It is interesting that (5) undergoes transannular reactions in neutral and basic

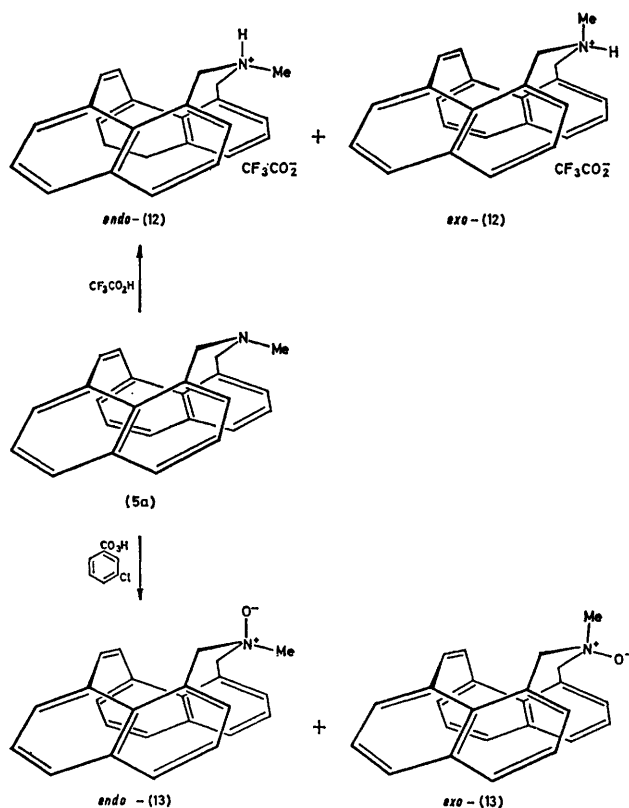


FIGURE 2 The formation of conformational diastereoisomers from the cyclic ene-amine (5) on (i) treatment with trifluoroacetic acid to give the trifluoroacetates, *endo*-(12) and *exo*-(12), and on (ii) oxidation with *m*-chloroperbenzoic acid to give the *N*-oxides, *endo*-(13) and *exo*-(13)

media, as well as in acidic media. Although transannular reactions between carbon-oxygen double bonds* and

* Transannular reactions between carbon-nitrogen double bonds and nitrogen atoms, although not so common, are known.⁷

⁷ L. Brzechffa, M. K. Eberle, and G. G. Kahle, *J. Org. Chem.*, 1975, **40**, 3062.

nitrogen atoms in amino-ketones are well known,⁸ relatively few transannular reactions between carbon-carbon double bonds and nitrogen atoms are known⁹⁻¹⁶ and most¹²⁻¹⁵ require an acid catalyst. However, there are isolated examples of transannular reactions between carbon-carbon double bonds and nitrogen occurring in neutral⁹ and basic¹⁰ media. In the present case, the propensity for the cyclic ene-amine (5) to undergo transannular reactions is not surprising in view of the ability of 7,12-dihydropleiadenes¹⁷ and 7*H*,14*H*-cyclo-octa[1,2,3-*de*;5,6,7-*d'e'*]dinaphthalene¹⁸ to exhibit transannular interactions and reactions associated with functionality at the *peri*-positions. However, to our knowledge, the transannular reactions described here are the first examples involving a carbon-carbon double bond and a nitrogen atom in a medium-sized ring incorporating two naphthalene residues. Attempts to carry out oxygen-transfer reactions on the *N*-oxides (13)

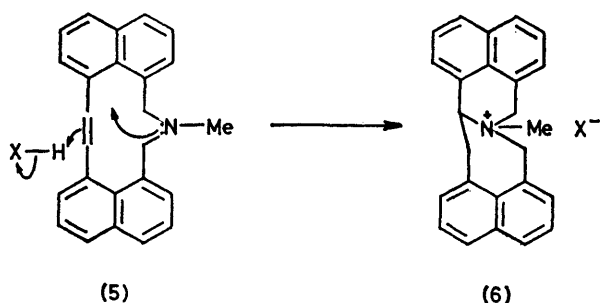
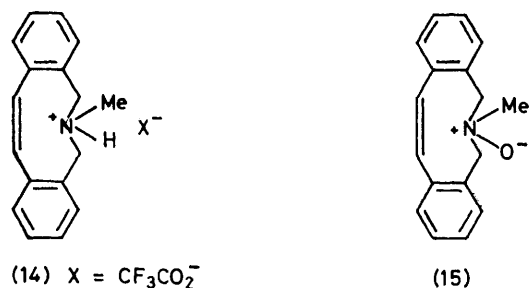


FIGURE 3 Transannular reactions of the cyclic ene-amine (5)

in strongly acidic media similar to those reported^{11,19} for *ortho*-alkenyl-dimethylbenzylamine oxides were unsuccessful.

Next, it was of interest to discover if the nine-membered ring ene-amine (8), whose conformational behaviour was discussed in Part 3,⁴ exhibited transannular reactions.

First, the assumption⁴ that the olefinic double bond



isomers of the *N*-protonated salt (14) on treatment with trifluoroacetic acid. This was established by ¹H n.m.r. spectroscopy at -10 °C. The line broadening associated with the signals for (14) in trifluoroacetic acid at room

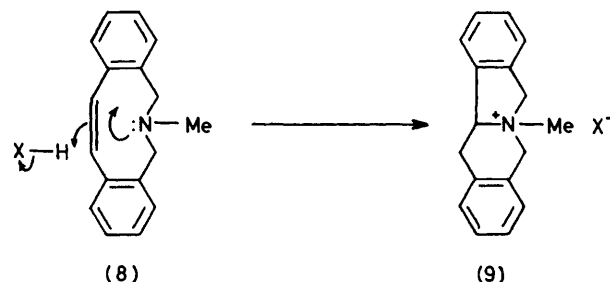


FIGURE 4 Transannular reactions of the cyclic ene-amine (8)

temperature indicates that conformational interconversion of the two diastereoisomers is occurring with a ΔG^\ddagger value of *ca.* 15–20 kcal mol⁻¹. It may be recalled⁴ that chair-chair inversion of the cyclic ene-amine (8) is associated with a ΔG^\ddagger value of 16.3 kcal mol⁻¹. The fact

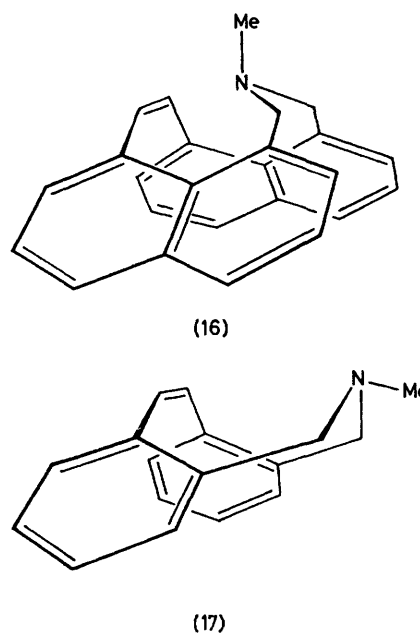


FIGURE 5 The boat conformations (16) and (17) of the cyclic ene-amines (5) and (8), respectively

that only one *N*-oxide (15) was isolated when the cyclic ene-amine (8) was treated with *m*-chloroperbenzoic acid is not unexpected in view of the relatively low energy

has the *cis*-configuration in (8) was proved unambiguously by the fact that (8) forms *two* conformational diastereo-

⁸ J. Sicher, *Progr. Stereochem.*, 1962, **3**, 239.

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¹³ L. A. Paquette and K. M. Scott, *J. Org. Chem.*, 1968, **33**, 2379.

¹⁴ D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Letters*, 1968, 2609; M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, 1969, **25**, 1881.

¹⁵ R. A. Johnson, *J. Org. Chem.*, 1972, **37**, 312.

¹⁶ M. J. Begley and N. Whittaker, *J.C.S. Perkin I*, 1973, 2830; Y. Arata, Y. Ada, S. Yasuda, and M. Hansoka, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2672; P. W. Jeffs and J. D. Scharver, *J. Amer. Chem. Soc.*, 1976, **98**, 4301.

¹⁷ P. T. Lansbury, *Accounts Chem. Res.*, 1969, **2**, 210.

¹⁸ W. C. Agosta, *J. Amer. Chem. Soc.*, 1967, **89**, 3505, 3926.

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barrier that would be associated with the interconversion of conformational diastereoisomers, if indeed two such isomers are formed.

The nine-membered ring ene-amine (8) was found to undergo transannular reactions in two separate experiments. (i) Treatment of an ethanolic solution of (8) with hydroiodic acid at room temperature for 2 h gave a methiodide (9a) which afforded an ^1H n.m.r. spectrum in trifluoroacetic acid identical with that previously obtained ⁴ for one of the methobromides (9b). (ii) When (8) was refluxed in aqueous methanol for 2 h, the ^1H n.m.r. spectrum of the residue in trifluoroacetic acid indicated that (8) had been completely converted into the bicyclic ammonium hydroxide/methoxide (9c/d). In contrast with the eleven-membered ring ene-amine (5), no reaction occurred in aqueous methanol at room tem-

perature. Thus, although the nine-membered ring ene-amine (8) undergoes transannular reactions (Figure 4) more vigorous conditions are required than in the case of the eleven-membered ring ene-amine (5). This result is entirely in accord with expectation. Molecular models indicate (Figure 5) that transition states for transannular reactions developing out of the boat conformation (16) of the nine-membered ring ene-amine (8) are not as favourable as those for transannular reactions developing out of the boat conformation (17) of the eleven-membered ring ene-amine (5).

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