Conformational Behaviour of Medium-sized Rings. Part III.[1] Heterocyclic Analogues of 12,13-Dihydro-11*H*-dibenzo[a,*e*]cyclononene, 6,11,-12,13-Tetrahydro-5*H*-dibenzo[*a*,*e*]cyclononene, and 5,6,7,12,13,14-Hexahydrodibenzo[*a*,*f*]cyclodecene

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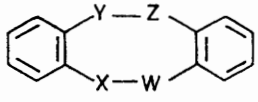
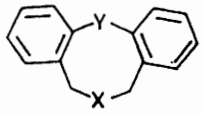
The temperature dependence of the ^{1}H n.m.r. spectra of a number of heterocyclic analogues (3a—c) of 12,13-dihydro-11*H*-dibenzo[*a*,*e*]cyclononene has been interpreted in terms of the interconversion of chair- and boat-like conformations. Conformational analysis on these molecules has been carried out with the aid of strain energy calculations on the thia-analogue (3c); in this case a useful correlation between calculated and experimental activation parameters was found. Variable temperature ^{1}H n.m.r. spectroscopy and strain energy calculations have demonstrated that the heterocyclic analogues (4a–f) and (5a—d) of 6,11,12,13-tetrahydro-5*H*-dibenzo[*a*,*f*]-cyclononene and 5,6,7,12,13,14-hexahydrodibenzo[*a*,*f*]cyclodecene, respectively, all adopt flexible chair-like conformations with C_2 symmetry which undergo an inversion process involving torsion about single bonds.

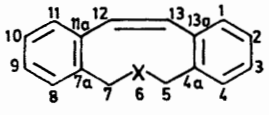
THE recognition [1-5] that 5,6,11,12-tetrahydrodibenzo-[*a*, *e*]cyclo-octene (1; W = X = Y = Z = CH_2) and many heterocyclic derivatives of the '6,8,6' systems (1) and (2) exist in solution in diastereoisomeric Chair † and Boat † conformations has encouraged us to examine the related '6,9,6' and '6,10,6' systems (3)—(5).



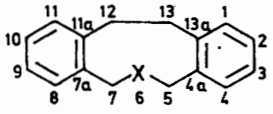
(1)



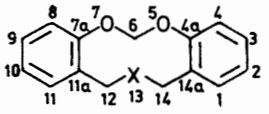
(2)



(3) a; X = NMe
b; X = NCH_2Ph
c; X = S



(4) a; X = NMe
b; X = NCH_2Ph
c; X = NH
d; X = NAc
e; X = S
f; X = SO_2



(5) a; X = NMe
b; X = NCH_2Ph
c; X = S
d; X = SO_2

The *N*-methyl derivative (3a) was prepared by the known route [6] involving (i) a Stevens rearrangement on the spiro-ammonium salt (6) to give the bicyclic amine (7), (ii) formation of the methobromide (8a), (iii) its conversion into the quaternary ammonium hydroxide (8b), and (iv) a Hofmann elimination of (8b). The *N*-benzyl derivative (3b) was prepared by an analogous route [(7) ⟶ (9a) ⟶ (9b) ⟶ (3b)] from the bicyclic amine (7). The cyclic sulphide (3c) was synthesised by the sequence: (i) photochemical transformation of 2,2'-bis-(hydroxymethyl)-*trans*-stilbene (10) [7] into the *cis*-isomer (11), (ii) conversion into the 2,2'-bis(bromomethyl)-*cis*-stilbene (12), and (iii) treatment of the dibromide (12) with sodium sulphide.

The '6,9,6' (4) and '6,10,6' (5) systems were prepared by standard procedures from the dibromides (13b) [7] and (14b) obtained from the diols (13a) [7] and (14a) [8] on treatment with phosphorus tribromide. Bis-(*o*-hydroxymethylphenoxy)methane (14a), reported previously [8] as a product of a base-catalysed methylenation of *o*-hydroxybenzyl alcohol, was obtained from the same starting material by a modified base-catalysed methylenation procedure.[9] The cyclic amines (4a and b) and (5a and b) were prepared by reaction of bis-(*o*-bromomethylphenyl)ethane (13b) and bis-(*o*-bromomethylphenoxy)-methane (14b) respectively with the appropriate amine (methylamine or benzylamine) in benzene. The tetradeuteriated analogue (15), which was required to simplify the ^{1}H n.m.r. spectroscopic investigation performed on the *N*-benzyl derivative (4b), was obtained by an analogous sequence of reactions [(13c) ⟶ (13d) ⟶ (15)]. Catalytic hydrogenolysis of the hydrochloride of the *N*-benzyl derivative (4b) yielded a debenzylated hydrochloride from which the cyclic amine (4c) and the *N*-acetyl derivative (4d) were readily obtained. After these compounds had been prepared, a paper appeared [10] describing the synthesis of the cyclic amine (4c) and its *N*-benzyl derivative (4b) in essentially the same manner.

† The description 'Chair' is non-specific and refers to both of the enantiomeric or degenerate conformations (C and C*) of the rigid chair type. Similarly, the description 'Boat' refers to any conformation of the flexible boat families.

[1] Part II, R. Gellatly, W. D. Ollis, and I. O. Sutherland, preceding paper
[2] Part I, R. Crossley, A. P. Downing, M. Nógrádi, A. Braga de Oliveira, W. D. Ollis, and I. O. Sutherland, *J.C.S. Perkin I*, 1973, 205.
[3] D. Montecalvo, M. St. Jacques, and R. Wasylished, *J. Amer. Chem. Soc.*, 1973, **95**, 2023.
[4] N. L. Allinger and J. T. Sprague, *Tetrahedron*, 1975, **31**, 21.
[5] R. N. Renaud, R. B. Layton, and R. R. Fraser, *Canad. J. Chem.*, 1973, **51**, 3380.
[6] 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.
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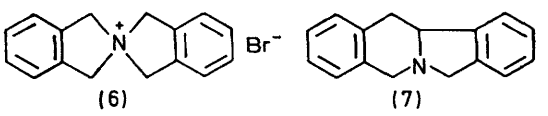
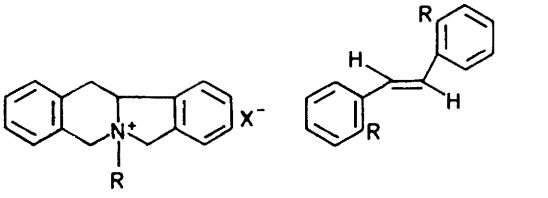
[8] W. Baker, *J. Chem. Soc.*, 1931, 1765.
[9] W. Bonthrone and J. W. Cornforth, *J. Chem. Soc.* (*C*), 1969, 1202.
[10] G. Pala, E. Crescenzi, and G. Bietti, *Tetrahedron*, 1970, **26**, 5789.

The cyclic sulphides (4e) and (5c) were also prepared from the appropriate dibromides (13b) and (14b), respectively, by reaction with sodium sulphide. Oxidation of the

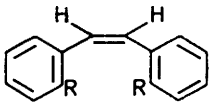


(6) (7)

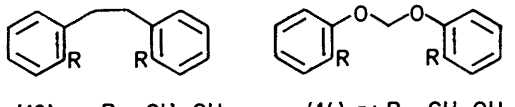


(8) a; R = Me, X = Br
b; R = Me, X = OH
(9) a; R = CH_2Ph, X = Br
b; R = CH_2Ph, X = OH

(10) R = CH_2·OH

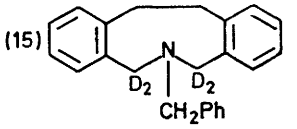


(11) R = CH_2·OH
(12) R = CH_2Br



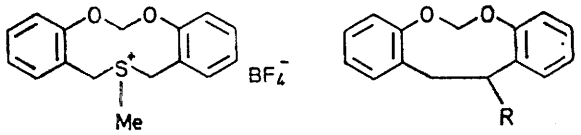
(13) a; R = CH_2·OH
b; R = CH_2Br
c; R = CD_2·OH
d; R = CD_2Br

(14) a; R = CH_2·OH
b; R = CH_2Br



(15)

cyclic sulphides (4e) and (5c) gave the sulphones (4f) and (5d). The dioxonin (17b) was synthesised by the sequence: (i) formation of the sulphonium tetrafluoroborate (16) from the cyclic sulphide (5c), (ii) a Stevens



(16) (17) a; R = SMe
b; R = H

rearrangement on the salt (16) to give the methylthio-derivative (17a), and (iii) desulphurisation of (17a) with Raney nickel.

In this paper, results of studies on the conformational behaviour of the nine-membered ring olefins (3), the '6,9,6' systems (4), (15), and (17b), and the '6,10,6' systems (5) in solution by dynamic ^1H n.m.r. spectroscopy [11] are compared with conclusions reached on the basis of strain energy calculations.[12] The whole investigation has been the subject of two preliminary communications [13] and has also been discussed briefly in a recent review [14] on the conformational behaviour of some medium-sized ring systems.

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. T.l.c. was carried out on glass plates (20 × 5 cm) coated with Merck silica gel G. Developed plates were air-dried, sprayed with cerium(IV) sulphate–sulphuric acid reagent, and heated at about 110 °C. Hopkin and Williams silica gel (M.F.C. grade) was used as chromatographic medium for all column separations. Low resolution mass spectra were determined with an A.E.I MS12 spectrometer, and high resolution spectra with an A.E.I. MS9 spectrometer. I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 137 spectrophotometer [polystyrene (1 603 cm^{-1}) as standard]. ^1H N.m.r. spectra were recorded with a Varian HA 100 spectrometer (tetramethylsilane as 'lock' and internal standard). Theoretical ^1H n.m.r. spectra were calculated with the aid of an ICL 1907 computer.

5,7,11b,12-Tetrahydroisoindolo[2,1-b]*isoquinoline* (7).—N-Phenyl-lithium solution (65 ml) was added dropwise with stirring to a suspension of 2,2'-spirobi-isoindolinium bromide (6) [m.p. 304—305° (lit.,[6] 295°)] (20 g) in ether (50 ml) so as to maintain gentle refluxing. The mixture was then heated under reflux for a further 3 h. On cooling, the excess of phenyl-lithium was decomposed with water, after which the ether layer was separated and extracted with N-sulphuric acid (200 ml). The crude product precipitated on neutralisation of the extract with sodium hydroxide solution. Recrystallisation from methanol–ether yielded the isoindoloisoquinoline (7) as needles (5.2 g, 36%), m.p. 109—110° (lit.,[6] 109—110°), τ ($CDCl_3$) 2.60—2.90 (8 H, m, aromatic) and 5.50—7.18 (7 H, two AB systems, $ArCH_2N$, overlapping with an ABC system, $ArCH_2{\cdot}CHAr$).

5,7,11b,12-Tetrahydro-6-methylisoindolo[2,1-b]*isoquinolinium Bromides* (8a).—A solution of the bicyclic amine (7) (560 mg) in ether (10 ml) containing methyl bromide (1.2 g) was heated at 45° in a sealed tube for 3 h. On cooling, the crude product was filtered off and fractionally crystallised from methanol–acetone (1 : 3) by addition of small amounts of ether. Methobromide A had m.p. 245° (lit.,[6] 242—242.5°), $\nu_{max.}$ (Nujol) 1 420, 1 161, 1 077, 995, 962, 900, 780, 770, 739, and 718 cm^{-1}. Methobromide B had m.p. 173—175 °C (lit.,[6] 122—124°) (Found: C, 62.55, H, 5.85; Br, 25.3; N, 4.15. Calc. for $C_{17}H_{18}BrN$: C, 64.55; H, 5.75; Br, 25.25; N, 4.45%), $\nu_{max.}$ (Nujol) 1 430, 1 161, 1 076, 969, 943, 919, 896, 771, 760, 744, 730, and 712 cm^{-1}.

6,7-Dihydro-6-methyl-5H-dibenz[c,g]*azonine* (3a).—A solution of isomer A (150 mg) of the methobromide (8a) in water (20 ml) was stirred at room temperature with silver oxide (1 g) overnight. The mixture was filtered, and the filtrate concentrated to give the quaternary ammonium

[11] For reviews see: G. Binsch, *Topics Stereochem.*, 1968, **3**, 97; I. O. Sutherland, *Ann. Reports N.M.R. Spectroscopy*, 1971, **4**, 71.
[12] K. B. Wiberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1070.
[13] W. D. Ollis and J. F. Stoddart, *Angew. Chem. Internat. Edn.*, 1974, **13**, 728, 730.
[14] W. D. Ollis, J. F. Stoddart, and I. O. Sutherland, *Tetrahedron*, 1974, **30**, 1903.

hydroxide (8b), which was pyrolysed at 140 °C in a sublimation apparatus at 15 mmHg to yield the crude product. Recrystallisation from aqueous methanol gave the dibenzazonine (3a) as needles (57 mg, 51%), m.p. 59—60° (lit.,[6] 59—61°) (Found: M^+, 235.1355. Calc. for $C_{17}H_{17}N$: M, 235.1361). For ^1H n.m.r. data see Table 1.

6-Benzyl-6,7-dihydro-5H-dibenz[c,g]*azonine* (3b).—A solution of the bicyclic amine (7) (500 mg) and benzyl bromide (4 ml) in ether (25 ml) was heated under reflux for 3 h. On cooling, the supernatant was removed by decantation from the crystalline product which coated the side of the flask. Water (50 ml) and silver oxide (2.0 g) were added to this product and the mixture was stirred overnight at room temperature, then filtered. The filtrate was concentrated and the crystalline residue was pyrolysed at 120 °C in a sublimation apparatus to yield the crude product. Recrystallisation from aqueous methanol gave the *dibenzazonine* (3b) as needles (458 mg, 65%), m.p. 109—111° (Found: C, 88.0; H, 6.95; N, 4.55%; M^+, 311. $C_{23}H_{21}N$ requires C, 88.7; H, 6.8; N, 4.5%; M, 311). For ^1H n.m.r. data see Table 1.

2,2′-Bis(hydroxymethyl)-trans-stilbene (10).—Dimethyl *trans*-stilbene-2,2′-dicarboxylate [m.p. 102—103° (lit.,[7] 101—102°)] (10 g) was added gradually to a solution of lithium aluminium hydride (2.5 g) in dry ether (150 ml). The mixture was refluxed for 30 min before being decomposed with ice and dilute sulphuric acid. The ether layer yielded a crystalline product which was recrystallised from ethanol to give the *diol* (10) (5.79 g, 66%), m.p. 160—161° (lit.,[7] m.p. 162°), τ (CD_3SOCD_3) 2.42—2.78 (10 H, m, aromatic and olefinic) and 5.30 (4 H, s, 2 × CH_2·OH).

2,2′-Bis(hydroxymethyl)-cis-stilbene (11).—A solution of the *trans*-isomer (10) (1.0 g) in methanol (200 ml) in a quartz vessel was irradiated for 3 h with a Hanovia 150 W medium-pressure mercury vapour lamp. T.l.c. on silica gel in benzene–ether (1 : 1) indicated the presence of one major product running slower than the *trans*-isomer (10) together with several very minor components. The major product was purified by column chromatography on silica gel with benzene–ether (1 : 1) as eluant. Recrystallisation from aqueous ethanol afforded the cis-*isomer* (11) (182 mg, 18%), m.p. 113—114° (Found: C, 78.8; H, 6.65%; M^+, 240. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%; M, 240), τ (CD_3SOCD_3) 2.25—3.26 (10 H, m, aromatic and olefinic) and 5.50 (4 H, s, 2 × CH_2OH).

2,2′-Bis(bromomethyl)-cis-stilbene (12).—Phosphorus tribromide (0.25 ml) was added at room temperature to a solution of 2,2′-bis(hydroxymethyl)-*cis*-stilbene (11) (100 mg) in anhydrous benzene (3 ml). The mixture was heated at 60 °C for 1 h, cooled, washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and concentrated to an oil which crystallised. Recrystallisation from benzene–light petroleum (b.p. 60—80°) afforded the *dibromide* (12) (119 mg, 78%), m.p. 125—127° (Found: M^+, 365.9436. $C_{16}H_{14}{}^{79}Br^{81}Br$ requires M, 365.9443), τ ($CDCl_3$) 2.60—3.15 (10 H, m, aromatic and olefinic) and 5.47 (4 H, s, 2 × CH_2Br).

5,7-Dihydrodibenzo[c,g]*thionin* (3c).—Sodium sulphide (120 mg) and 2,2′-bis(bromomethyl)-*cis*-stilbene (12) (100 mg) were refluxed in methanol (50 ml) for 1 h. T.l.c. indicated that the reaction was complete, and so the methanol was evaporated off and the residue was extracted with hot chloroform. The oil obtained from the extract was extracted twice with cold ethanol, affording a crystalline product after evaporation of the ethanol. Recrystallisation from methanol gave the *dibenzothionin* (3c) as prisms (23 mg, 35%), m.p. 101—103°, (Found: M^+, 238.0815. $C_{16}H_{14}S$ requires M, 238.0816). For ^1H n.m.r. data see Table 1.

Bis-(o-bromomethylphenyl)ethane (13b).—Compound (13b), m.p. 137—138° (lit.,[7] 137—138°), was prepared by the published method [7] from bis-(*o*-hydroxymethylphenyl)ethane (13a); τ ($CDCl_3$) 2.50—3.00 (8 H, m, aromatic), 5.54 (4 H, s, 2 × CH_2Br), and 6.92 (4 H, s, CH_2CH_2).

Bis-(o-hydroxy[$^2H_2$]*methylphenyl)ethane* (13c).—Compound (13c), m.p. 152—153° [lit.,[7] 151° for bis-(*o*-hydroxymethylphenyl)ethane (13a)], was prepared from dimethyl 2,2′-ethylenedibenzoate [7] by reduction with lithium aluminium deuteride as described [7] for the reduction of this compound with lithium aluminium hydride; τ (CD_3SOCD_3) 2.60—3.04 (8 H, m, aromatic), 5.16 (2 H, s, 2 × OH), and 7.15 (4H, s, CH_2·CH_2). Compound (13a) shows τ (CD_3SOCD_3) 5.12 (2 H, t, J 5.6 Hz, 2 × OH), and 5.62 (4 H, d, J 5.6 Hz, 2 × CH_2·OH).

Bis-(o-bromo[$^2H_2$]*methylphenyl)ethane* (13d).—Phosphorus tribromide (0.5 ml) was added slowly at room temperature to a suspension of the deuteriated diol (13c) (624 mg) in anhydrous benzene (10 ml) which contained a drop of pyridine. The mixture was heated at 60° C for 2 h, cooled, washed with water and saturated sodium hydrogen carbonate solution successively, and concentrated to a crystalline residue. Recrystallisation from benzene yielded the *dibromide* (13d) (590 mg, 63%), m.p. 137—138°, τ ($CDCl_3$) 2.50—3.00 (8 H, m, aromatic) and 6.91 (4 H, s, CH_2·CH_2).

Bis-(o-hydroxymethylphenoxy)methane (14a).—Dichloromethane was added dropwise with stirring during 2 h in an atmosphere of nitrogen to a mixture of *o*-hydroxybenzyl alcohol (25 g), powdered sodium hydroxide (25 g), and dimethyl sulphoxide (250 ml) heated on a steam-bath. After stirring at 100 °C for a further 1 h, the mixture was cooled and poured into water (800 ml). The precipitate was filtered off and the filtrate was extracted with ether (1 l). The ether layer was washed several times with water and the precipitate was dissolved in the ethereal solution. After drying (Na_2SO_4), the solution was concentrated and the crystalline residue was recrystallised from benzene–light petroleum (b.p. 60—80°) affording the diether (14a) (8.1 mg, 31%), m.p. 117—118° (lit.,[8] 118°) (Found: C, 69.4; H, 6.2. Calc. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2%), τ (CD_3SOCD_3–D_2O) 2.71—3.31 (8 H, m, aromatic), 4.33 (2 H, s, O·CH_2·O), and 5.76 (4 H, s, 2 × CH_2·OH).

Bis-(o-bromomethylphenoxy)methane (14b).—Phosphorus tribromide (2.5 ml) was added to a suspension of the diol (14a) (4.5 g) in anhydrous benzene (50 ml). The diol dissolved within a few minutes at room temperature. The mixture was then heated for 15 min at 40 °C, cooled, washed with water, sodium hydrogen carbonate solution, and water again, dried (Na_2SO_4), and concentrated. Recrystallisation of the residue from light petroleum (b.p. 60—80°) afforded the *dibromide* (4.8 g, 73%), m.p. 125—127° (Found: C, 46.8; H, 3.9; Br, 41.2%; M^+, 386. $C_{15}H_{14}Br_2O_2$ requires C, 46.7; H, 3.65; Br, 41.4%; M, 386), τ ($CDCl_3$) 2.54—3.10 (8 H, m, aromatic), 4.10 (2 H, s, O·CH_2·O), and 5.46 (4 H, s, 2 × CH_2Br).

6,7,12,13-Tetrahydro-6-methyl-5H-dibenz[c,g]*azonine* (4a).—A solution of methylamine (30%) in ethanol (3 ml) was added dropwise with stirring to a solution of the dibromide (13b) (500 mg) in benzene (10 ml) over 1 h at room temperature. The mixture was stirred under reflux for 3 h, cooled, and filtered to remove methylamine hydrobromide. The filtrate was washed with water, dried (Na_2SO_4), and concen-

trated to an oil. Vacuum sublimation (water-pump pressure) at 90—100 °C yielded a crystalline product which was recrystallised from aqueous ethanol to give the *dibenzazonine* (4a) (180 mg, 55%), m.p. 63—65° (Found: C, 85.8; H, 7.8; N; 6.05%; M^+, 237. $C_{17}H_{19}N$ requires C, 86.0; H, 8.05; N, 5.9%; *M*, 237). For ^1H n.m.r. data see Table 4.

6-*Benzyl*-6,7,12,13-*tetrahydro*-5H-*dibenz*[c,g]*azonine* (4b).—A solution of benzylamine (1.5 g) in anhydrous benzene (20 ml) was added dropwise with stirring at room temperature to a solution of the dibromide (13b) (1.65 g) in anhydrous benzene (20 ml) over 1 h. The mixture was stirred under reflux for 3 h, cooled, and filtered to remove benzylamine hydrobromide. After washing with water, the filtrate was dried (Na_2SO_4) and concentrated. Extraction of the oily residue with ether yielded a crystalline product. Recrystallisation from ethanol gave the dibenzazonine (4b) as needles (420 mg, 30%), m.p. 108—110° (lit.,[10] 109.5—110°) (Found: C, 88.2; H, 7.4; N, 4.55%; M^+, 313.1822. Calc. for $C_{23}H_{23}N$: C, 88.1; H, 7.4; N, 4.45%; *M*, 313.1830). For ^1H n.m.r. data see Table 4.

The azonine (4b) (217 mg) was dissolved in benzene and converted into its hydrochloride (246 mg, 98%) by treatment with hydrogen chloride gas; m.p. 245—247° (from methanol–ether) (lit.,[10] 246—247°) (Found: C, 78.4; H, 7.1; Cl, 10.05; N, 3.75. $C_{23}H_{24}ClN$ requires C, 78.9; H, 6.9; Cl, 10.15; N, 4.0%).

6-*Benzyl*-6,7,12,13-*tetrahydro*-5H-[5,5,7,7-$^2H_4$]*dibenz*[c,g]-*azonine* (15).—A solution of benzylamine (450 mg) in anhydrous benzene (20 ml) was treated with the deuteriated dibromide (13d) (500 mg) in anhydrous benzene (20 ml), as described for the preparation of the azonine (4b), to yield the *deuteriated azonine* (15) as needles (238 mg, 55%), m.p. 109—110° (from ethanol) (Found: M^+, 317. $C_{23}H_{19}D_4N$ requires *M*, 317). For ^1H n.m.r. data see Table 4.

6,7,12,13-*Tetrahydro*-5H-*dibenz*[c,g]*azonine* (4c).—A solution of the hydrochloride (1.18 g) of the benzyldibenzazonine (4b) in ethanol (150 ml) was hydrogenated over 10% palladium–carbon (100 mg) at room temperature for 1 h. Filtration, concentration, and recrystallisation from methanol–ether yielded the hydrochloride (435 mg, 50%), m.p. 267—268° (lit.,[9] 268—268.5°), of the azonine (4c). Addition of sodium hydroxide solution gave the dibenzazonine (4c) as a precipitate, which crystallised from aqueous methanol as needles, m.p. 149—150° (lit.,[10] 152.5°) (Found: C, 86.0; H, 7.95; N, 6.45. Calc. for $C_{16}H_{17}N$: C, 86.1; H, 7.65; N, 6.25%). For ^1H n.m.r. data see Table 4. A sample of the 6-deuterio-derivative for variable temperature ^1H n.m.r. spectroscopy was obtained by recrystallisation of the amine (4c) from CD_3OD–D_2O.

6-*Acetyl*-6,7,12,13-*tetrahydro*-5H-*dibenz*[c,g]*azonine* (4d).—The hydrochloride (100 mg) of the dibenzazonine (4c) was dissolved in water (20 ml), and acetic anhydride (0.5 ml) in water (5 ml) was added dropwise with stirring. After 1 h, the mixture was extracted with chloroform and the extract was concentrated to a crystalline residue. Recrystallisation from light petroleum (b.p. 60—80°) gave the *acetyldibenzazonine* (4d) as long needles (48 mg, 47%), m.p. 143—145° (Found: C, 81.7; H, 7.45; N, 5.35%; M^+, 265. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%; *M*, 265). For ^1H n.m.r. data see Table 4.

5,7,12,13-*Tetrahydrodibenzo*[c,g]*thionin* (4e).—Sodium sulphide dihydrate (1.14 g) was added to a solution of the dibromide (13b) (730 mg) in methanol (200 ml) and the mixture was heated under reflux for 4 h. On cooling, t.l.c. on silica gel in benzene–light petroleum (b.p. 60—80°) (1 : 1) indicated that the reaction was complete. The methanol was removed and the residue was extracted with boiling ether. Although the ethereal solution yielded a crystalline solid, the product was impure. Column chromatography on silica gel with benzene–light petroleum (b.p. 60—80°) (1 : 1) as eluant gave the *dibenzothionin* (4e) (183 mg, 24%), m.p. 110—111° (from methanol) (Found: C, 78.9; H, 6.7; S, 13.1%; M^+, 240.0979. $C_{16}H_{16}S$ requires C, 79.8; H, 6.7; S, 13.35%; *M*, 240.0973). For ^1H n.m.r. data see Table 4.

5,7,12,13-*Tetrahydrodibenzo*[c,g]*thionin* 6,6-*Dioxide* (4f).—A solution of 30% hydrogen peroxide (1 ml) was added to a solution of the sulphide (4e) (60 mg) in glacial acetic acid (2.5 ml). After 4 days at 5°, the crystalline product was filtered off. Recrystallisation from methanol yielded the *dioxide* (4f) (50 mg, 74%), m.p. 220—221° (Found: C, 70.4; H, 6.1; S, 12.0%; M^+, 272. $C_{16}H_{16}SO_2$ requires C, 70.6; H, 5.9; S, 11.75%; *M*, 272). For ^1H n.m.r. data see Table 4.

13,14-*Dihydro*-13-*methyl*-12H-*dibenzo*[d,i][1,3,7]*dioxazecine* (5a).—A 30% solution of methylamine in ethanol (10 ml) was added dropwise with stirring to a solution of the dibromide (14b) (3 g) in benzene (25 ml) over 1 h at room temperature. The mixture was refluxed for 2 h, cooled, and filtered to remove methylamine hydrobromide (1.3 g). The filtrate was washed with water, dried (Na_2SO_4), and concentrated to an oil. T.l.c. of this product on silica gel in benzene–ether (1 : 1) indicated the presence of a fast moving component and several slower moving components. The fastest moving component was purified by distillation at 0.05 mmHg; the fraction which distilled over in the range 120—130 °C was collected. Although this product (950 mg, 48%), which migrated as one component on t.l.c., could not be obtained crystalline, the spectroscopic evidence suggested it was the *dibenzodioxazecine* (5a) (Found: M^+, 255.1255. $C_{16}H_{17}NO_2$ requires *M*, 255.1259). For ^1H n.m.r. data see Table 7.

The free base (5a) (105 mg) was dissolved in ether and converted into the *hydrochloride* (110 mg, 81%) by treatment with hydrogen chloride gas; m.p. 235—236° (from ethanol) (Found: C, 65.9; H, 6.45; Cl, 11.85; N, 4.9; $C_{16}H_{18}ClNO_2$ requires C, 65.9; H, 6.22; Cl, 12.15; N, 4.8%).

13-*Benzyl*-13,14-*dihydro*-12H-*dibenzo*[d,i][1,3,7]*dioxazecine* (5b).—A solution of benzylamine (1.07 g) in anhydrous benzene (15 ml) was added dropwise with stirring to a solution of the dibromide (14b) (1.16 g) in anhydrous benzene over 1 h at room temperature. The mixture was refluxed for 3 h, cooled, and filtered to remove benzylamine hydrobromide. After washing with water, the filtrate was dried (Na_2SO_4) and concentrated to an oily residue, which had crystallised after two months. Recrystallisation from ethanol yielded the *dibenzodioxazecine* (5b) (670 mg, 68%), m.p. 95—97° (Found: M^+, 331.1572. $C_{22}H_{21}NO_2$ requires *M*, 331.1566). For ^1H n.m.r. data see Table 7.

The free base (5b) (87 mg) was dissolved in ether and converted into the *hydrochloride* (93 mg, 93%) by treatment with hydrogen chloride gas; m.p. 245—246° (from ethanol) (Found: C, 71.6; H, 6.05; Cl, 9.55; N, 3.7. $C_{22}H_{22}ClNO_2$ requires C, 71.8; H, 6.05; Cl, 9.65; N, 3.8%).

12H,14H-*Dibenzo*[d,i][1,3,7]*dioxathiecin* (5c).—Sodium sulphide dihydrate (627 mg) was added to a solution of the dibromide (14b) (420 mg) in methanol (30 ml) and the mixture was heated under reflux for 6 h. On cooling, t.l.c. on silica gel in benzene–light petroleum (b.p. 60—80°) (1 : 1)

indicated the reaction was complete. Apart from a fast moving component there were several slower moving components. The sulphide (5c), which corresponded to the fast moving component, was obtained pure by silica gel column chromatography with benzene–light petroleum (b.p. 60—80°) (1 : 1) as eluant. Recrystallisation from methanol at 5 °C yielded the *dibenzodioxathiecin* (5c) as prisms (97 mg, 25%), m.p. 103—104° (Found: C, 70.2; H, 5.7; S, 12.95%; M^+, 258. $C_{15}H_{14}O_2S$ requires C, 69.8; H, 5.46; S, 12.4%; *M*, 258). For ^{1}H n.m.r. data see Table 7.

12H,14H-*Dibenzo*[d,i][1,3,7]*dioxathiecin* 13,13-*Dioxide* (5d).—A 30% solution of hydrogen peroxide (1 ml) was added to a solution of the sulphide (5c) (50 mg) in glacial acetic acid (2.5 ml). After 2 days at 5°, the crystalline product was filtered off and recrystallised from aqueous ethanol to yield the *dioxide* (5d) as needles (43 mg, 77%), m.p. 239—240° (Found: C, 61.8; H, 4.85; S, 11.25%; M^+, 290. $C_{15}H_{14}O_4S$ requires C, 62.1; H, 4.85; S, 11.05%; *M*, 290). For ^{1}H n.m.r. data see Table 7.

13-*Methyl*-12H,14H-*dibenzo*[d,i][1,3,7]*dioxathiecin*-13-*ium Tetrafluoroborate* (16).—The sulphide (5c) (592 mg) was dissolved in nitromethane (10 ml) and methyl iodide and silver tetrafluoroborate (450 mg) were added. The mixture was stirred at room temperature for 3 h during which time silver iodide was precipitated. After addition of dichloromethane (100 ml), the silver iodide was filtered off and the filtrate was concentrated to an oil which crystallised. Recrystallisation from ethanol yielded the *tetrafluoroborate* (16) (603 mg, 73%), m.p. 179—181° (Found: C, 53.4; H, 4.65; S, 9.1. $C_{16}H_{17}BF_4O_2S$ requires C, 53.4; H, 4.75; S, 8.9%).

12,13-*Dihydro*-12-*methylthiodibenzo*[d,h][1,3]*dioxonin* (17a).—The tetrafluoroborate (16) (500 mg) was suspended in dry tetrahydrofuran (10 ml) and sodium hydride (50 mg) was added. A white precipitate of sodium tetrafluoroborate was formed while the mixture was stirred at room temperature. After 3 h, t.l.c. on silica gel in benzene–light petroleum (b.p. 60—80°) (1 : 1) indicated the reaction was complete. The mixture was filtered and the filtrate concentrated to give an oil which was distilled at 0.05 mmHg. The fraction which distilled over in the range 120—130 °C was the *dibenzodioxonin* (17a) (284 mg, 41%) (Found: C, 69.6; H, 5.75; S, 11.3%; M^+, 272. $C_{16}H_{16}O_2S$ requires C, 70.6; H, 5.9; S, 11.75%; *M*, 272).

12,13-*Dihydrodibenzo*[d,h][1,3]*dioxonin* (17b).—The sulphide (17a) (35 mg) in ethanol (25 ml) was heated under reflux with Raney nickel (100 mg). After 2 h, t.l.c. on silica gel in benzene–light petroleum (b.p. 60—80°) (1 : 1) indicated that the reaction had gone to completion to give one product. Concentration of the filtrate obtained after removal of the catalyst yielded the *dibenzodioxonin* (17b), which crystallised from aqueous methanol as prisms (20 mg, 69%), m.p. 128—129° (Found: C, 79.7; H, 6.15%; M^+, 226. $C_{15}H_{14}O_2$ requires C, 79.6; H, 6.25%; *M*, 226). For ^{1}H n.m.r. data see Table 4.

Determination of Rates of Conformational Change by ^{1}H *N.m.r. Spectroscopy*.—The methods used have been fully described.[1,2] The computer programs (coded in FORTRAN IV) used to generate theoretical line shapes are described [1,2] for the general methods I—III.

Method I. A program (I) for exchange of nuclei between two unequally populated sites, A and B, with no mutual coupling. The *N*-methyl group of compound (3a) and the *N*-benzylic methylene group of compound (3b) both gave two singlet signals of unequal intensities at low temperatures † and so spectral line shapes were simulated by using this program. Calculated and observed spectra are shown in Figures 1 and 2 for compounds (3a and b), respectively. The analysis of the spectra for compound (3b) was carried out in conjunction with program III (see later).

Method II. A program (II) for exchange of nuclei between two sites, A and B, with equal populations and a mutual coupling constant. This program was used to simulate the spectral line shapes of the single AB system exhibited by the C-5 and C-7 methylene protons of the cyclic sulphide (3c) at low temperatures.

Method III. A program (III) for the case in which nuclei are exchanged between the pairs of sites A1 and B1, A2 and B2, A1 and A2, and B1 and B2 of two AB systems. This program was used to simulate the spectral line shapes associated with the C-5 and C-7 methylene protons of the cyclic amines (3a and b) at low temperatures. In both cases, the exchange rate (k_2) between the sites A2 and B2 was fast compared with the exchange rates (k_{12}) and (k_{21}) between the sites A1 and A2, and B1 and B2, and the exchange rate (k_1) between the sites A1 and B1. Thus, nuclei in sites A2 and B2 give rise to a single line (AB2) at the average site chemical shift, whereas nuclei in sites A1 and B1 give rise to a typical four-line AB system. Calculated and observed spectra are shown in Figures 1 and 2 for compounds (3a and b), respectively.

Method IV. For compounds (4a, b, and d—f), and (5a—d) site exchange rate constants, k_c, were calculated at coalescence temperatures, T_c, by using the approximate relationship (i), which is suitable for exchange of nuclei between two sites A and B with equal populations and chemical shifts, ν_A and ν_B, respectively, and a mutual coupling constant, J_{AB}.

$$k_c = \pi[(\nu_A - \nu_B)^2 + 6J_{AB}^2]^{\frac{1}{2}}/2^{\frac{1}{2}} \quad \text{(i)}$$

Strain Energy Calculations.—These were carried out by using a program (coded in FORTRAN) based upon the 'steepest descent' minimisation procedure of Wiberg.[12] Details of the force field employed have been given in a recent review.[14]

RESULTS AND DISCUSSION

In the '6,9,6' systems, which are heterocyclic analogues (3 a—c) of 12,13-dihydro-11*H*-dibenzo[*a*, *e*]cyclononene, similarities in conformational behaviour with that of the '6,8,6' systems (2) are observed. The temperature-dependent ^{1}H n.m.r. spectra of the cyclic amines (3a and b) demonstrate that two diastereoisomeric conformations are populated in solution. In each case, at low temperatures, the C-5 and C-7 methylene protons exhibit (i) an AB system assignable to a relatively rigid conformation and (ii) a singlet associated with a rapidly inverting conformation. These signals coalesce to an AB system as the temperature is increased and then to a

† This observation is consistent with ground state conformations for compound (3b) having C_s or averaged C_s symmetry where the *N*-benzylic methylene protons are homotopic [*cf.* the situation which pertains in compounds (4b) and (5b) with ground state conformations having local C_2 symmetry and demonstrably diastereotopic *N*-benzylic methylene protons]. This requirement necessitates that the olefinic bond in compound (3b) has the *cis*-configuration. The close similarities in the conformational behaviour and ^{1}H n.m.r. spectra of the two cyclic amines (3a and b) imply that compound (3a) also has the *cis*-configuration associated with its double bond.

singlet at higher temperatures. Two exchange processes can therefore be identified by line-shape analysis (Figures 1 and 2) and may be associated with conformational interconversion of the two diastereoisomeric conformations and slow inversion of one of these diastereoisomers with its enantiomer. The other rapidly inverting conformation constitutes the minor one and in the case of the cyclic sulphide (3c) it is not observable by ^{1}H n.m.r. spectroscopy where coalescence of a single AB system characterises the temperature-dependent spectra. In the low temperature spectra of the cyclic amines (3a and b), two singlets of unequal intensity are observed for the *N*-methyl protons of (3a) and also for the *N*-benzylic methylene protons of (3b).† Their coalescence behaviour permits independent line-shape analysis of the interconversion processes involving the two diastereoisomeric conformations. The spectral changes associated with the signals for the C-5 and C-7 methylene protons, and where relevant with those for the *N*-methyl and *N*-benzylic methylene protons, are summarised in Tables 1 and 2. Table 1 gives the chemical shifts and coupling constants of the high- and the low-temperature spectra. Table 2 gives details of the site exchanges affecting the signal line shapes and some thermodynamic parameters associated with the conformational changes. These are derived by comparison (see Figures 1 and 2) of observed and calculated spectra over a range of temperatures by methods I—III (see Experimental section). Good agreement is attained for the thermodynamic parameters associated with the interconversion processes involving the two diastereoisomeric conformations of compounds (3a and b) by using methods I and III on signals arising from two different ^{1}H n.m.r. probes.

TABLE 1

Temperature-dependent ^{1}H n.m.r. spectral parameters (100 MHz) for compounds (3a—c) in $CDCl_3$

Compound	X	Temp. (°C)	Group	Chemical shift (τ) (coupling constant in Hz) [a]
(3a)	NCH_3	−31	$ArCH_2N$	5.82 (A1), 6.22 (B1) (J 13.9)
			$ArCH_2N$	6.23 (AB2)
			CH_3N	7.62(s) (A), 7.70(s) (B)
			$ArCH$	3.60(s) [b]
		+30	$ArCH_2N$	5.86 (A12), 6.26 (B12) (J 13.9)
			CH_3N	7.64(s) (AB)
		+68	$ArCH_2N$	6.12(s) (AB12)
			CH_3N	7.64(s) (AB)
(3b)	NCH_2Ph	−20	$ArCH_2N$	5.84 (A1), 6.08 (B1) (J 13.9)
			$ArCH_2N$	6.17(s) (AB2)
			$PhCH_2N$	6.23(s) (A), 6.48(s) (B)
			$ArCH$	3.58(s) [b]
		+45	$ArCH_2N$	6.08(s) (AB12)
			$PhCH_2N$	6.28(s) (AB)
(3c)	S	−10	$ArCH_2S$	5.93 (A1), 6.34 (B1) (J 14.2)
		+40	$ArCH_2S$	6.16 (AB1)

[a] The designations A1, B1 *etc.* correspond to the site exchanges cited in Table 2. Sites are designated A and B for uncoupled two-site systems. Sites that represent two time-averaged signals are designated AB. Sites are designated A1 and B1 for coupled AB systems. Sites are designated A1, B1, A2, and B2 for four-site systems where there is coupling in the form of two AB systems. Sites that represent two time-averaged signals are designated AB1 (average of A1 and B1), A12 (average of A1 and A2), *etc.* [b] The signal for the minor conformation. The signal for the olefinic protons in the major conformation is masked by the signals for the aromatic protons.

Examination of molecular models of compounds (3) and strain energy calculations on the cyclic sulphide (3c) direct attention to two types of conformation which are relatively free from angle strain and torsional strain. The first of these is a rigid chair-like conformation (18) with C_s symmetry (Chair). Protons H_1 and H_2 [see (18)] of the C-5 and C-7 methylene groups undergo exchange between sites A1 and B1 during the conformational inversion (18a) ⇌ (18b). Thus, it is necessary to consider the degenerate conformations (18a) and (18b) separately and so they will be designated C and C* in the discussion that follows. Conformations are also conveniently [1,2,14] described by using the usual + and − notation [15] for torsion angles and referring in turn to the bonds 4a,5, 5,6, 6,7, 7,7a, 11a,12, and 13,13a in compounds (3). Accordingly, the signs of these torsion angles are listed below all conformational diagrams used in this paper.

TABLE 2

Site exchanges and thermodynamic parameters associated with conformational changes in compounds (3a—c)

Compd.	X	Program	Site exchanges [a]	p_1	p_2	ΔG^0/ kcal mol^{-1}	$\Delta G^\ddagger$/ kcal mol^{-1}	Process	Comments
(3a)	NCH_3	III	A1 ⟶ A2; B1 ⟶ B2	0.905	0.095	1.13 (−22 °C)	15.9	C ⟶ Boat	Assumed k(A2 ⇌ B2) ⟶ ∞
			A1 ⇌ B1				16.3	C ⇌ C*	
		I	A ⟶ B				15.4	C ⟶ Boat	
(3b)	NCH_2Ph	I + III	A1 ⟶ A2; B1 ⟶ B2	0.860	0.140	0.84 (−42 °C)	14.9	C ⟶ Boat	Assumed k(A2 ⇌ B2) ⟶ ∞
			A1 ⇌ B1				16.1	C ⇌ C*	
			A ⟶ B				14.9	C ⟶ Boat	
(3c)	S	II	A1 ⇌ B1	>0.98	<0.02	>2.11 (0 °C)	15.5	C ⇌ C*	

[a] Details of chemical shifts and coupling constants are given in Table 1. The AB system A1B1 refers to the C-5 and C-7 methylene protons of the Chair (major) conformation and the singlet AB2 to the Boat (minor) conformation.

† The same footnote as on page 930.

[15] W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521; J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537; 1962, **84**, 3355; 1964, **86**, 4854; 1967, **89**, 7036, 7043, 7047.

conformations can be distinguished on account of their symmetry. They are (i) the pair of boat conformations

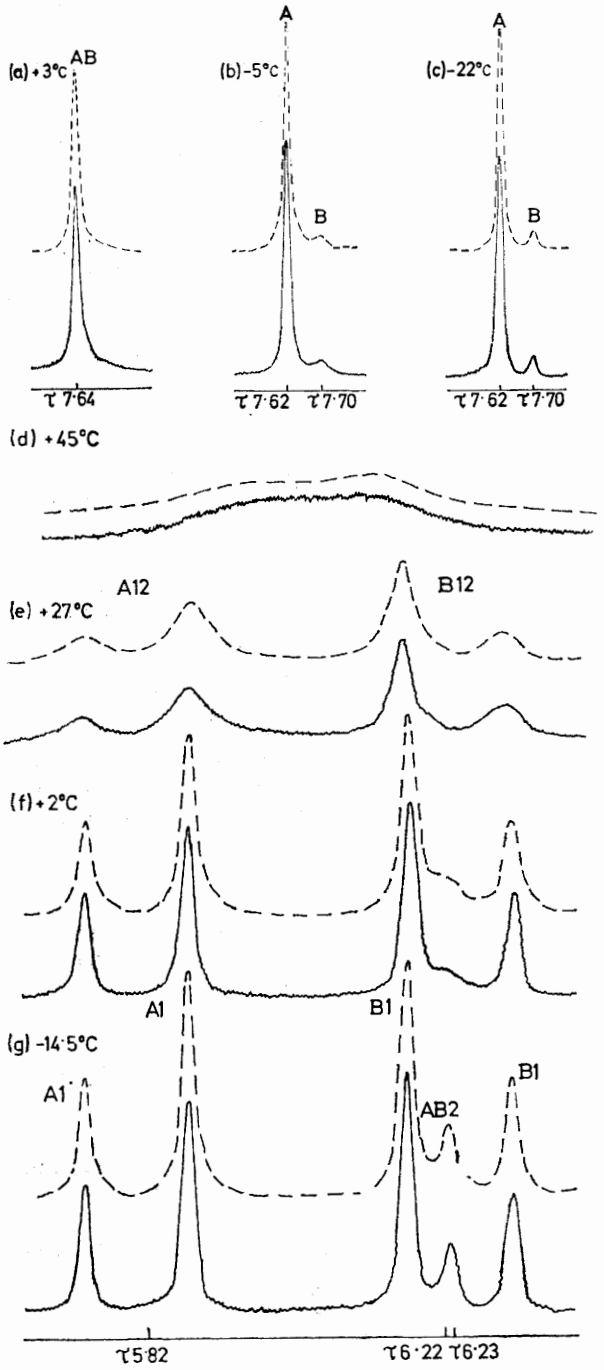


FIGURE 1 Observed (full line) and computed (broken line) spectra of the *N*-methyl protons of the *N*-methyl derivative (3a): (a) At +3 °C, $k_{AB} = 3.0\ s^{-1}$, p_A 0.905, p_B 0.095; (b) at −5 °C, $k_{AB} = 1.2\ s^{-1}$, p_A 0.905, p_B 0.095; (c) at −22 °C, $k_{AB} = 0.23\ s^{-1}$, p_A 0.905, p_B 0.095.

Observed (full line) and computed (broken line) spectra of the C-5 and C-7 methylene protons of the *N*-methyl derivative (3a): (d) At +45 °C, $k_1 = 58\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, $k_{12} = 120\ s^{-1}$, p_1 0.905, p_2 0.095; (e) at +27 °C, $k_1 = 1.0\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, $k_{12} = 21\ s^{-1}$, p_1 0.905, p_2 0.095; (f) at +2 °C, $k_1 = 0\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, $k_{12} = 1.0\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, $k_{12} = 1.0\ s^{-1}$, p_1 0.905, p_2 0.095; (g) at −14.5 °C, $k_1 = 0\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, $k_{12} = 0.14\ s^{-1}$, p_1 0.905, p_2 0.095

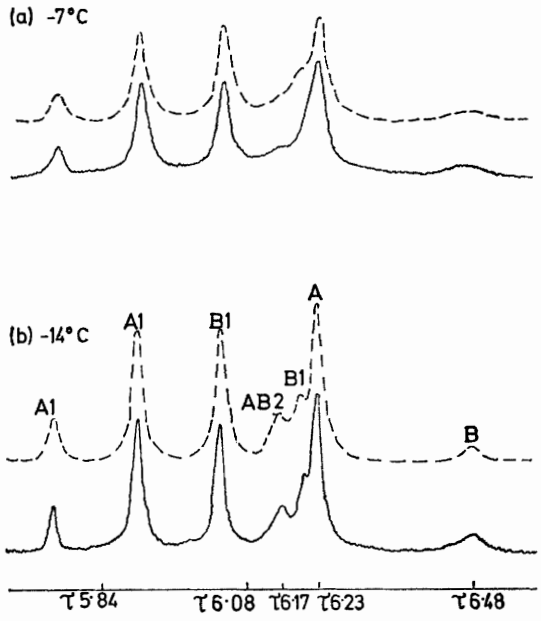
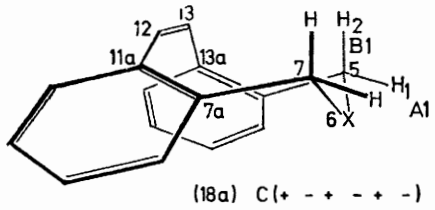
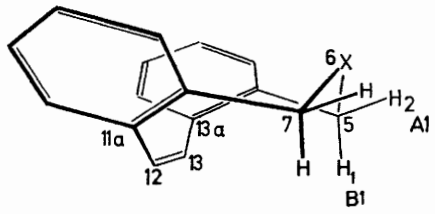


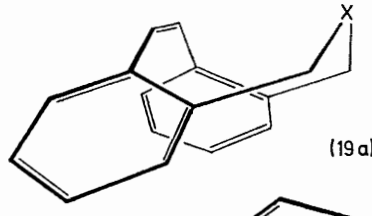
FIGURE 2 Observed (full line) and computed (broken line) spectra of the *N*-benzylic methylene protons and the C-5 and C-7 methylene protons of the *N*-benzyl derivative (3b): (a) At −7 °C, $k_1 = 0\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, $k_{12} = 3.0\ s^{-1}$, $k_{AB} = 3.0\ s^{-1}$, $p_1 \equiv p_A = 0.86$, $p_2 \equiv p_B = 0.14$; (b) at −14 °C, $k_1 = 0\ s^{-1}$, $k_2 = 100\ 000\ s^{-1}$, k_{12} 0.66 s^{-1}, $k_{AB} = 0.66\ s^{-1}$, $p_1 \equiv p_A = 0.86$, $p_2 \equiv p_B = 0.14$



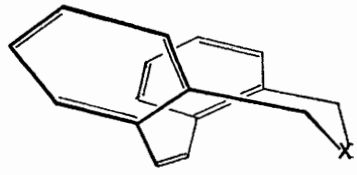
(18a) C(+ − + − + −)



(18b) C* (− + − + − +)

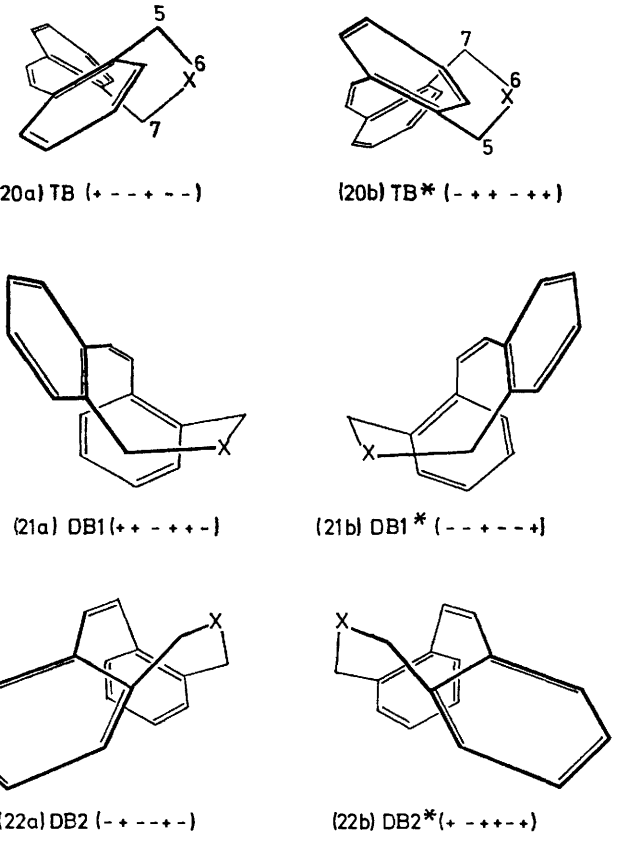


(19a) B(++ − − + −)



(19b) B*(− − + + − +)

B and B* (19a and b) with C_s symmetry and (ii) the pair of twist-boat conformations TB and TB* (20a and b) with C_2 symmetry.† These conformations are interconvertible by a pseudorotational process which involves asymmetric distorted-boat conformations DB1, DB1*, DB2, and DB2* [(21a and b) and (22a and b)].‡



The relative energies of the C, B, TB, and DB conformational types depend upon the nature of the group X in compounds (3). Strain energy calculations (Table 3) on the cyclic sulphide (3c) indicate that the C (18a and b) and DB [(21a and b) and (22a and b)] conformational

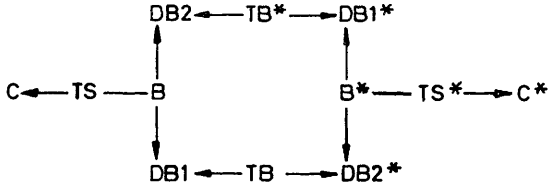


FIGURE 3 Conformational changes in the heterocyclic analogues (3) of 12,13-dihydro-11*H*-dibenzo[*a*,*e*]cyclononene

types correspond to ground state conformations. The DB conformations [(21a and b) and (22a and b)] are situated geometrically between B (19a and b) and TB (20a and b) conformations in the conformational itinerary depicted in Figure 3 and are characterised by torsion angles of *ca.* 45 and 98° about the 5,6- and 6,7-bonds, respectively, in the cyclic sulphide (3c). The strain energy calculations (Table 3) show that the C_s conformations B and B* (19a and b) are destabilised, as expected, by nonbonded interactions involving the sulphur atom and the olefinic double bond. The calculations show that these nonbonded interactions are partially relaxed and instead the strain manifests itself in angle strain. Although the C_2 conformations TB and TB* (20a and b) are stabilised by increased conjugation of the olefinic double bonds with the aromatic rings, they experience large contributions to angle strain in the region of the olefinic double bond as well as out-of-plane deformation of the aromatic rings. The destabilising features of the B (19) and TB (20) conformations are progressively reduced by the pseudorotational process that converts them both into DB conformations [(21) and (22)], corresponding to the minimum energy Boat conformations. In the DB conformations [(21) and (22)] both nonbonded interactions and angle strain are minimised at the expense of a slight increase in torsional strain associated with either the 5,6- or 6,7-bonds. In contrast with the '6,8,6' systems (2),[1] in the '6,9,6' systems (3) the minimum energy Boat conformations [(21) and (22)] lie closer to the B conformations (19) than to the TB conformations (20).

With the identity of the ground state conformations established, it is necessary to consider pathways by which they might undergo inversion and interconversion processes. Strain energy calculations indicate that the DB conformations [(21) and (22)] can undergo inversion by means of B (19) and TB (20) transition state conformations. However, the rate-limiting process for DB $\rightleftharpoons$ DB* inversion must be associated with the higher energy TB (20) transition state conformation.

Strain energy calculations on trial geometries indicate that the transition state TS conformation (23) for Chair $\rightleftharpoons$ Boat interconversion is characterised by coplanarity of atoms 4a, 5, 6, 7, and 7a, and thus has C_s symmetry. This situation contrasts with the transition state of C_1 symmetry which was identified [1] by strain energy calculations for 5,7-dihydro-12*H*-dibenzo[*c*,*f*]thiocin (2; X = S, Y = CH_2) and 6-methyl-5,6,7,12-tetrahydrodibenz[*c*,*f*]azocine (2; X = NMe, Y = CH_2). In the case of the cyclic sulphide (3c), the torsional rigidity associated with the olefinic double bond appears to be responsible for the preservation of C_s symmetry in the TS conformation (23). This transition state conformation lies on the pathways C $\rightleftharpoons$ B and C* $\rightleftharpoons$ B* and is characterised by appreciable contributions from angle strain, torsional strain, and out-of-plane deformations of the aromatic rings.

The conformational itinerary in Figure 3 associates the ground state conformations (C, DB1, DB2 and their degenerate or enantiomeric partners C*, DB1*, DB2*) with the transition states (B, TB, TS and B*, TB*, TS*).

† The conformational types TB and TB* (20a and b) do not have C_2 symmetry when X = NR. However, if the substituent R on nitrogen is ignored then this conformation has local C_2 symmetry.

‡ There is an infinite number of distorted-boat conformations. The descriptions DB1 and DB2 and the conformational diagrams (21) and (22) correspond to the minimum energy boat conformations for compounds (3).

TABLE 3

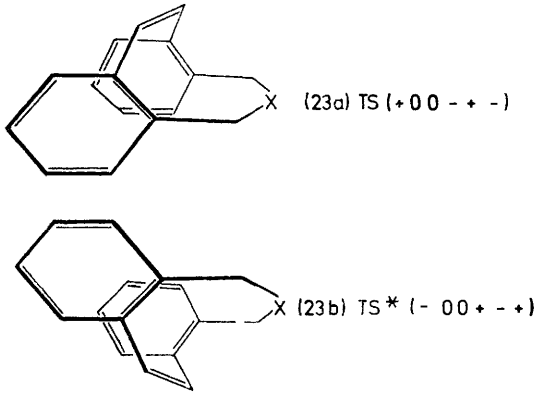
Calculated strain energies (E_T/kcal mol^{-1}) of various conformations of 5,7-dihydrodibenzo[*c*,*g*]thionin (3c)

Conformation	E_r [a-c]	E_θ [a-c]	E_ϕ [d]	E_δ [e]	E_{nb} [f]	E_T
C≡C* (18) [g]	0.23	0.82	1.41	0.09	−1.16	1.40
B≡B* (19) [g]	1.20	4.42	0.78	0.80	1.97	9.18
TB≡TB* (20) [h]	2.32	13.92	−6.26	4.11	0.01	14.09
DB1≡DB1*≡DB2≡DB2* [(21), (22)] [i]	0.94	3.45	0.93	0.14	0.79	6.24
TS≡TS* (23) [g j]	2.68	7.03	5.57	3.86	−1.64	17.50

[a] The following energy terms (J. F. Stoddart, ' Organic Chemistry, Series One, Structure Determination in Organic Chemistry,' ed. W. D. Ollis, Butterworths, London, 1973, p. 1) have been used: E_r (bond length strain), E_θ (angle strain), E_ϕ (torsional strain), E_δ (out-of-plane strain in aromatic rings), E_{nb} (non-bonded interactional strain); total strain energy $E_T = E_r + E_\theta + E_\phi + E_\delta + E_{nb}$. [b] Calculations based upon the following force constants. Bond length strain: Aromatic k_{CC} 1 120, k_{CH} 727; Aliphatic k_{CC} 663, k_{CH} 688, k_{CS} 451; Olefinic k_{CC} 1 380, k_{CH} 764 kcal mol^{-1} Å^{-2}. Angle strain: Aromatic k_{CCC} 144, k_{CCH} 108; Aliphatic k_{CCC} 115, k_{CCH} 94, k_{HCH} 74, k_{SCH} 89, k_{CSC} 100; Olefinic k_{CCC} 144, k_{CCH} 108 kcal mol^{-1} radian^{-2}; all angle strain reduced by a factor of 0.7. [c] Calculations based upon the following equilibrium bond lengths and bond angles: Aromatic C–C 1.395, C–H 1.09; Aliphatic C–C 1.54, Ar–C 1.50, C–S 1.80, C–H 1.09; Olefinic C=C 1.33, C–H 1.09 Å. Aromatic $\widehat{CCC}$ 120°, $\widehat{CCH}$ 120°; Aliphatic $\widehat{CCC}$ 111.5°, $\widehat{SCC}$ 111.5°, $\widehat{CSC}$ 98.5°, $\widehat{CCH}$ 109.5°, $\widehat{HCH}$ 106°, $\widehat{SCH}$ 108.5°; Olefinic $\widehat{CCC}$ 120°, CCH 120°. [d] The torsional strain associated with C–S bonds was treated as a three-fold barrier of height 2.1 kcal mol^{-1}. That associated with the C=C bond was treated as a two-fold barrier of height 65 kcal mol^{-1}. Conjugation energy of 5 kcal mol^{-1} for the double bond with each aromatic ring was also included in the calculations. Aromatic C···C bond twisting was calculated according to Boyd *et al.* (see footnote *e*). [e] Out-of-plane strain associated with aromatic rings was calculated according to Boyd *et al.* (R. H. Boyd, *J. Chem. Phys.*, 1968, **49**, 2574; C. Shieh, D. McNally, and R. H. Boyd, *Tetrahedron*, 1969, **29**, 3653). [f] Non-bonded interactions based upon the Hill equation as summarised in E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, ' Conformational Analysis,' ch. 7, Wiley–Interscience, New York, 1965. [g] C_s symmetry. [h] C_2 symmetry. [i] $\phi_{56} = +48°$ and $\phi_{67} = -98°$ in DB1. [j] Defined by holding atoms 4a, 5, 6, 7, and 7a coplanar.

It is now necessary to relate the results obtained (Table 3) from strain energy calculations on the cyclic sulphide (3c) to the temperature-dependent ^{1}H n.m.r. spectral characteristics of compounds (3) and the thermodynamic parameters associated with the conformational interconversion and inversion processes.

The calculated strain energy difference ($\Delta E_T < 8$ kcal mol^{-1}) between the DB [(21) and (22)] and TB (20) conformations (Table 3) in the cyclic sulphide (3c) implies that the DB ⇌ DB* inversion in compounds (3) must involve a relatively low energy barrier and an inversion process which is fast on the n.m.r. time scale even at −100 °C. Thus, the spectral characteristics associated with rapid inversion in the cyclic amines (3a and b) can be ascribed to Boat conformations. The calculated strain energy difference (ΔE_T 16.1 kcal mol^{-1}) between the C (19) and TS (23) conformations (Table 3) is in good



agreement with the observed free energy of activation ($\Delta G^\ddagger$ 15.5 kcal mol^{-1}) for C ⇌ C* inversion in the cyclic sulphide. The calculated strain energy difference (ΔE_T 4.8 kcal mol^{-1}) between the C (18) and DB [(21) and (22)] conformations (Table 3) is consistent with the failure to observe any Boat conformation signals in the low-temperature ^{1}H n.m.r. spectra of the cyclic sulphide (3c). The fact that both the *N*-methyl derivative (3a) ($\Delta G^\ddagger$ 16.3 kcal mol^{-1}) and the *N*-benzyl derivative (3b) ($\Delta G^\ddagger$ 16.1 kcal mol^{-1}) undergo C ⇌ C* inversion *via* flexible boat conformations as detectable intermediates in their ^{1}H n.m.r. spectra below 0 °C probably reflects the decreased destabilisation of the DB conformation [(21) and (22)] when nitrogen replaces sulphur at C-6. In principle, the free energy of activation for C → Boat interconversion should be reduced by *RT* ln 2 relative to that for C ⇌ C* inversion since $k_{C \rightleftharpoons C^*} = 0.5\ k_{C \rightarrow Boat}$ if the inversion process involves intermediate Boat conformations. Qualitatively, this feature is evident in both the *N*-methyl derivative (3a) ($\Delta G^\ddagger_{C \rightarrow Boat}$ 15.4—15.9 kcal mol^{-1}) and the *N*-benzyl derivative (3b) ($\Delta G^\ddagger_{C \rightarrow Boat}$ 14.9 kcal mol^{-1}) where the only criterion exercised in the determination of $k_{C \rightarrow Boat}$ by line-shape analysis using two different ^{1}H n.m.r. probes was the match between observed and calculated spectra.

The ' 6,9,6 ' systems (4) show a completely different kind of conformational behaviour from the nine-membered ring olefins (3). At low temperatures, the ^{1}H n.m.r. spectra of compounds (4a, b, e, and f) show a single AB system associated with either *homotopic* or *enantiotopic* C-5 and C-7 methylene groups. In all cases, this AB system coalesces to a singlet as the temperature is increased. In contrast, the temperature-dependent ^{1}H n.m.r. spectra of the cyclic amide (4d) are characterised by the occurrence of two different exchange processes. Two equal intensity AB systems associated with diastereotopic C-5 and C-7 methylene groups at low temperatures coalesce to give two well-resolved singlets at room temperature which eventually broaden and coalesce at high temperatures. The C-5 and C-7 methylene groups are diastereotopic because of slow amide bond

rotation and hence give rise to two AB systems in the temperature range where ring inversion is observed [*cf.* Abraham *et al.* (footnote *e*, Table 4)]. At room temperature, where ring inversion is fast on the ^1H n.m.r. timescale, the C-5 and C-7 methylene groups are still diastereotopic on account of slow amide bond rotation and thus give rise to two singlets. These singlets coalesce into one singlet at higher temperatures where hindered amide bond rotation is observed. The spectral changes associated with the signals for the C-5 and C-7 methylene protons, and where relevant with those for the *N*-acetyl, *N*-benzylic methylene, and *N*-methyl protons are summarised in Tables 4 and 5. Table 4 gives chemical shifts and coupling constants of the high- and low-temperature spectra. Table 5 records the spectral data which permit calculation by method IV (see Experimental section) of the rate constants at the coalescence temperatures and the associated free energies of activation for the conformational changes.

TABLE 4

Temperature dependent ^1H n.m.r. spectral parameters (100 MHz) for compounds (4a, b, and d—f), and (17b)

Compound	X	Solvent	Temp. (°C)	Group	Chemical shift (τ) (coupling constant in Hz) [a]
(4a)	NCH_3	$CDCl_3$–CS_2 (1 : 1)	−70	$ArCH_2N$	6.53 (A1), 6.73 (B1) (J_{AB} 13.5)
				$ArCH_2C$	6.70—7.46 (m) [b]
				CH_3N	7.36 (s)
			+30	$ArCH_2N$	6.86 (s) (AB1)
				$ArCH_2C$	7.11 (s)
				CH_3N	7.45 (s)
(4b)	NCH_2Ph [c]	$CDCl_3$–CS_2 (1 : 2)	−70	$ArCH_2C$	6.69—7.59 (m) [d]
				$PhCH_2N$	5.84 (A1), 6.52 (B1) (J_{AB} 12.5)
			+30	$ArCH_2C$	6.71 (s)
				$PhCH_2N$	6.24 (s) (AB1)
(4d)	$NCOCH_3$	CS_2	−70	$ArCH_2N$ [e]	4.60 (A1), 6.91 (B1) (J_{AB} 13.5)
					5.55 (A2), 6.31 (B2) (J_{AB} 14.5)
				$ArCH_2C$	6.49—7.59 (m) [d]
				CH_3CON	7.64 (s)
			−30	$ArCH_2N$ [e]	5.66 (s) (AB1),[f] 5.82 (s) (AB2)
				$ArCH_2C$	7.03 (s)
				CH_3CON	7.65 (s)
(4e)	S	$CDCl_3$–CS_2 (1 : 1)	−70	$ArCH_2S$	6.54 (A1), 6.80 (B1) (J_{AB} 13.5)
				$ArCH_2S$	6.60—7.80 (m) [b]
			+30	$ArCH_2S$	6.74 (s) (AB1)
				$ArCH_2C$	7.15 (s)
(4f)	SO_2	$CDCl_3$	−30	$ArCH_2SO_2$	5.94 (A1), 6.18 (B1) (J_{AB} 13.8)
				$ArCH_2C$	6.45—7.70 (m) [b]
			+40	$ArCH_2SO_2$	6.00br (s) (AB1)
				$ArCH_2C$	6.45br (s)
(17b)		$CDCl_3$–CS_2 (1 : 1)	−90	$ArCH_2C$	6.80—7.50 (m) [b]
				OCH_2O	4.50 (s)
			+30	$ArCH_2C$	7.04 (s)
				OCH_2O	4.48 (s)

[a] The designations A1, B1, *etc.* correspond to the site exchanges cited in Table 5. See footnote *a* in Table 1 for further details. [b] AA'BB' system. [c] ^1H N.m.r. spectra were recorded for the tetradeuterio-derivative (15) at low temperatures because of overlapping of the signals for the C-5 and C-7 methylene protons and the benzylic methylene protons in the parent compound (4b). [d] ABCD system. [e] Two sets of signals are observed for the C-5 and C-7 methylene protons as a result of slow amide bond rotation rendering these methylene groups diastereotopic in the temperature range where ring inversion is observed (*cf.* R. J. Abraham, L. J. Kricka, and A. Ledwith, *J.C.S. Chem. Comm.*, 1973, 282). [f] These singlets begin to show extensive line broadening above +30 °C in $CDCl_3$.

TABLE 5

Free energies of activation for ring inversion (C_2 chair $\rightleftharpoons$ C_2 chair*) in compounds (4a, b, and d—f),and (17b)

Compound	X	Prochiral group	$(\nu_A - \nu_B)$/Hz [a]	J_{AB}/Hz	T_c/K	k_c [b]/s^{-1}	$\Delta G^{\ddagger}$ (at T_c)/ kcal mol^{-1}
(4a)	NCH_3	$ArCH_2N$	20.5	13.5	214	87	9.8
(4b)	NCH_2Ph	$PhCH_2N$	68.0 [c]	12.5 [c]	217 [c]	166	10.4
(4d)	$NCOCH_3$	$ArCH_2N$ [d]	23.0	13.5	215	516	9.8
			76.0 [e]	14.5 [e]	208 [e]	186	9.9
(4e)	S	$ArCH_2S$	25.8	13.5	231	93	11.3
(4f)	SO_2	$ArCH_2SO_2$	23.1	13.8	288	91	13.7
(17b)		$ArCH_2C$ [f]	14.3	14.0	189	83	9.3

[a] Details of chemical shifts are given in Table 4. Protons undergo exchange between sites A1 and B1 unless otherwise stated. [b] Calculated by method IV (see Experimental section). [c] Spectral parameters for the tetradeuterio-derivative (15). [d] Line-shape analysis by use of program I on the high temperature spectra (see footnote *e* in Table 4) indicate that a free energy of activation of 19.3 kcal mol^{-1} can be associated with hindered amide bond rotation. [e] Spectral parameters for site exchange A2 $\rightleftharpoons$ B2. [f] Coalescing AA'BB' system treated as an AB system.

The observation of isochronous C-5 and C-7 methylene groups in compounds (4a, b, e, and f) at low temperatures requires that the observable ground state conformation must have either C_s or C_2 symmetry. A decision between these two possibilities is provided by the ^1H n.m.r.

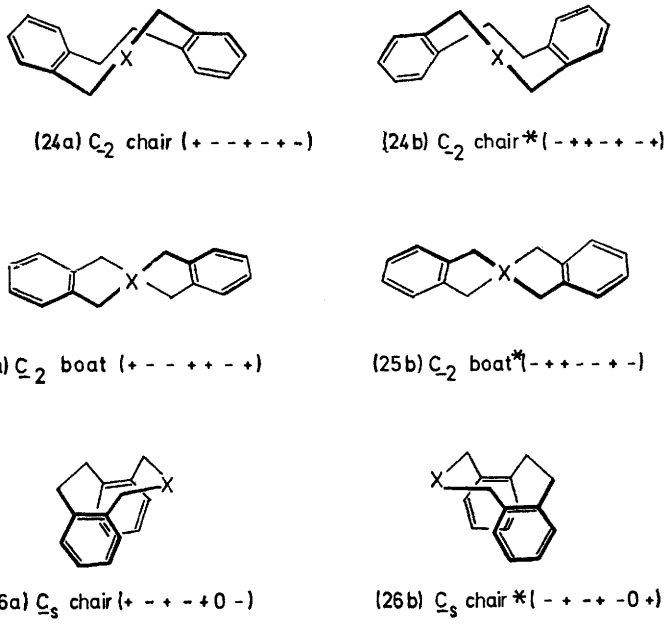
spectrum of the *N*-benzyl derivative (4b), where below −50 °C the benzylic methylene protons give rise to an AB system and are therefore demonstrably diastereotopic. Clearly the ground state of the ' 6,9,6 ' system (4b) must have C_2 symmetry leading to either a C_2 chair (24) or a C_2 boat (25) as the only two possibilities. The notation [15] for torsion angles in these conformations, (Figure 4) involving C_s chair (26) conformations. The transition state geometry has not been characterised by strain energy calculations in this case, but nonetheless it seems likely that the transition state conformation will lie on the pseudorotational itinerary somewhere between the C_2 chair (24) and the C_s chair (26). Boat-like intermediates do not need to be implicated in the C_2

TABLE 6

Calculated strain energies (E_T/kcal mol^{-1})[a] on two conformations of 5,7,12,13-tetrahydrodibenzo[*c*,*g*]thiocin (4e)

Conformation	E_r	E_θ	E_ϕ	E_δ	E_{nb}	E_T
C_2 chair ⇌ C_2 chair* (24a)	0.52	1.34	3.21	0.36	0.77	6.20
C_2 boat ⇌ C_2 boat* (24b)	1.58	4.35	3.60	0.49	2.67	12.70

[a] See footnotes *a*—*f* in Table 3. The torsional strain associated with C–C bonds was treated as a three-fold barrier of height 3.0 kcal mol^{-1}.



and in others in this series, refers in turn to the 4a,5-, 5,6-, 6,7-, 7,7a-, 11a,12-, 12,13-, and 13,13a-bonds. Discrimination in favour of the C_2 chair (24) as the preferred ground state conformation for the ' 6,9,6 ' systems (4) was provided by strain energy calculations (Table 6) on the cyclic sulphide (4e). Extrapolation to the other cases is justifiable since angle strain accounts for much of the destabilisation of the C_2 boat (25) relative to the C_2 chair (24).

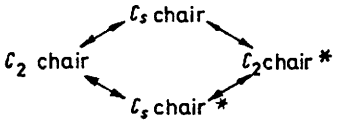


FIGURE 4 Conformational changes in the heterocyclic analogues (4) of 6,7,11,12-tetrahydro-5*H*-dibenzo[*a*,*e*]cyclononene

Examination of molecular models indicates that the C_2 chair (24) is a flexible conformation and that ring inversion can occur by a pseudorotational process chair ⇌ C_2 chair* inversion process. The magnitudes ($\Delta G^\ddagger$ 9.8—13.7 kcal mol^{-1}) of the free energies of activation (Table 5) of this inversion process for compounds (4a—f) are entirely in accord with a process involving torsion about single bonds and contrast with the much higher values ($\Delta G^\ddagger$ 15.5—16.3 kcal mol^{-1}) for the olefinic ' 6,9,6 ' systems (3) where angle strain is an important contributor (Table 3) in the TS conformation (23). The relatively high value ($\Delta G^\ddagger$ 13.7 kcal mol^{-1}) for the sulphone (4f) is mainly due to the much larger steric requirements of the sulphone group in a pseudorotational process.

The ' 6,10,6 ' systems of type (5) are very similar in their conformational behaviour to the ' 6,9,6 ' systems (4). At low temperatures, compounds (5a—d) all exhibit (Table 7) AB systems for their C-12 and C-14 methylene groups and sharp singlets for their dioxymethylene protons. These observations are consistent with conformations having C_2 symmetry. For the *N*-benzyl derivative (5b), two AB systems, one for the C-12

TABLE 7

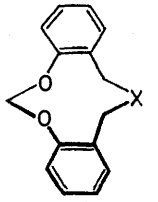
Temperature dependent ^1H n.m.r. spectral parameters (100 MHz) for compounds (5a—d) in $CDCl_3$–CS_2 (1 : 1)

Compound	X	Temp. (°C)	Group	Chemical shifts (τ) (coupling constant in Hz) [a]
(5a)	NCH_3	−60	$ArCH_2N$	6.13 (A1), 6.89 (B1) (J_{AB} 13.5)
			OCH_2O	4.34(s) [b]
			CH_3N	7.39 (s)
		+20	$ArCH_2N$	6.51(s) (AB1)
			OCH_2O	4.37 (s)
			CH_3N	7.43 (s)
(5b)	NCH_2Ph	−60	$ArCH_2N$	6.14 (A1), 6.82 (B1) (J_{AB} 12.5) [c]
			$PhCH_2N$	5.92 (A2), 6.46 (B2) (J_{AB} 13.7) [d]
			OCH_2O	4.32(s) [b]
		+30	$ArCH_2N$	6.44(s) (AB1)
			$PhCH_2N$	6.16(s) (AB2)
(5c)	S	−70	$ArCH_2S$	6.21 (A1), 6.95 (B1) (J_{AB} 14.8)
			OCH_2O	4.29(s) [b]
		+20	$ArCH_2S$	6.59(s) (AB1)
			OCH_2O	4.33(s)
(5d)	SO_2	−50	$ArCH_2SO_2$	5.30 (A1), 6.42 (B1) (J_{AB} 14.3)
			OCH_2O	4.17(s) [b]
		+50	$ArCH_2SO_2$	5.92br (s) (AB1)
			OCH_2O	4.21(s)

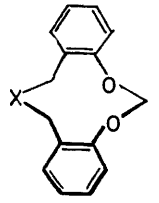
[a] The designations A1, B1 *etc.* correspond to the site exchanges cited in Table 8. See footnote *a* in Table 1 for further details. [b] Indicative of a ground state conformation of C_2 symmetry. [c] Only one AB system is observed although the C-12 and C-13 methylene groups are diastereotopic. [d] Confirmation of a ground state conformation of C_2 symmetry.

by comparison with the '6,9,6' systems (4) is the C_2 chair (27). The notation [15] for torsion angles in this conformation refers in turn to the 4a,5-, 5,6-, 6,7-, 7,7a-, 11a,12-, 12,13-, 13,14, and 14,14a-bonds. The magnitudes ($\Delta G^{\ddagger}$ 10.6—13.1 kcal mol^{-1}) of the free energies of activation (Table 8) for ring inversion (C_2 chair $\rightleftharpoons$ C_2 chair*) are once again entirely in accord with a pseudorotational process.

Strain energy calculations have not been carried out on '6,10,6' systems (27) because of the problems intro-



(27a) C_2 chair (+ − − + − + + −)



(27b) C_2 chair* (− + + − + − − +)

duced by potential p—π conjugative interactions between the oxygen atoms and the aromatic rings, and also by potential 1,3-interactions [16] involving the two oxygen atoms. However, the selection of the C_2 chair (27) as the ground state conformation matches that selected by other investigators [17] for monocyclic *cis,cis*-cyclodeca-1,6-diene derivatives on the basis of conformational analysis.

TABLE 8

Free energies of activation for ring inversion (C_2 chair $\rightleftharpoons$ C_2 chair*) in compounds (5a—d)

Compound	X	Prochiral group	$(\nu_A - \nu_B)$/Hz [a]	J_{AB}/Hz	T_c/K	k_c [b]/s^{-1}	$\Delta G^{\ddagger}$ (at T_c)/ kcal mol^{-1}
(5a)	NCH_3	$ArCH_2N$	75.4	13.5	227	184	10.8
(5b)	NCH_2Ph	$PhCH_2N$	68.6	13.7	237	170	11.3
		$PhCH_2N$	53.6 [c]	12.5 [c]	231 [c]	137	11.1
(5c)	S	$ArCH_2S$	74.0	14.8	223	183	10.6
(5d)	SO_2	$ArCH_2SO_2$	112.0	14.3	277	261	13.1

[a] Details of chemical shifts are given in Table 7. Protons undergo exchange between sites A1 and B1 unless otherwise stated. [b] Calculated by using method IV (see Experimental section). [c] Spectral parameters for site exchange A2 $\rightleftharpoons$ B2.

and C-14 methylene protons † and the other for the benzylic methylene protons, are observed at low temperatures. Thus, the ground state conformation must have C_2 symmetry and the one which has been selected

† The diastereotopicity of the C-12 and C-14 methylene groups is not detectable by ^1H n.m.r. spectroscopy at 100 MHz

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