Cycloalkylmethyl Radicals. Part 8.[1] A Conformational Study of Dioxa- and Dithia-cyclohexylmethyl Radicals by EPR Spectroscopy

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The conformations of some six-membered oxygen- and sulphur-containing heterocyclic rings have been investigated by EPR spectroscopy using the methylenyl group, $CH_2^•$, directly attached to a ring carbon atom as a 'spin probe'. For the 2-oxacyclohexylmethyl radical the $CH_2^•$ group has a 'conformational free energy' preference for the equatorial position, $-\Delta G^\circ_{273} = 1.4$ kcal mol^{-1}, which is about twice as large as the 0.7 kcal mol^{-1} found previously for cyclohexylmethyl. The equatorial preference of the $CH_2^•$ group is still greater in (1,3-dioxan-2-yl)methyl radicals; indeed, even with the *cis*-(5-*tert*-butyl-1,3-dioxan-2-yl)methyl radical the $CH_2^•$ group was equatorial and the *tert*-butyl group axial. The $CH_2^•$ group in (1,3-dioxan-5-yl)methyl also exhibits a strong preference for the equatorial position ($\Delta G^\circ >$ *ca.* 1.5 kcal mol^{-1}), but with *cis*-(2-methyl-1,3-dioxan-5-yl)methyl it is the methyl group which is equatorial and the $CH_2^•$ group axial. These and other axial/equatorial conformational preferences and the rotational conformational preference of the plane of the $CH_2^•$ group with respect to the C_β–H_β bond are rationalized in terms of subtle steric factors which involve 1,3-axial/axial interactions, or lack thereof, and the variation in the lengths of C–C, C–O and C–S bonds.

We have demonstrated[2] that a methylenyl group, $CH_2^•$, directly attached to an alicyclic ring (Fig. 1) can be a very useful 'spin probe' which reports on the conformation(s) populated by the radical. The reason for this is that many of these species have EPR spectra which exhibit significantly different hyperfine splittings (hfs) by the β-H when the $CH_2^•$ moiety is axial (or quasi-axial) compared with the corresponding equatorial (or quasi-equatorial) conformer. This enables conformational analysis to be carried out on cycloalkylmethyl radicals and, in favourable cases, the dynamics of ring inversion or pseudo-rotation processes, can be followed. The advantage of the EPR method, as compared with NMR studies of related molecules, is that dynamic processes with much lower free energy barriers can be quantitatively assessed.

We have reported detailed studies of cyclohexylmethyl[3] and 4-substituted cyclohexylmethyl radicals.[4] For such radicals the preferred conformation of both axial and equatorial $CH_2^•$ groups is that in which the $C_\alpha 2p_z$ orbital containing the unpaired electron (*i.e.*, the SOMO) eclipses the C_β–H_β bond. The difference between the β-H hfs for axial and equatorial $CH_2^•$ groups arises from differences in the barriers to rotation about the C_β–$C_\alpha^•$ bond. The rotation barrier for an axial $CH_2^•$ is greater than for an equatorial $CH_2^•$ owing to non-bonded repulsion of the α-H-atoms by the axial atoms 3- and 5-H on the ring. The higher the C_β–$C_\alpha^•$ rotation barrier the greater is the interaction of the SOMO with the C_β–H_β bond. Hence, axial $CH_2^•$ groups produce larger β-H hfs than do equatorial $CH_2^•$ groups.

Rings which contain heteroatoms and those having different patterns of heteroatom substitution often have markedly different conformational preferences and free energy barriers to conformational transformations, compared with cycloalkanes.[5] We anticipated, therefore, that at least some heteroatom containing six-membered rings with a $CH_2^•$ spin probe would show distinct EPR spectra for an 'axial' and 'equatorial' $CH_2^•$ group. This would be useful for characterizing the conformations of such rings and would further our long term aim of directly deducing ring conformations from EPR data.[2]

Preliminary work with (2-*tert*-butyl-1,3-dioxan-5-yl)methyl radicals showed significant promise.[3] We report herein an extension of our work to oxa-, dioxa- and dithia-cyclohexylmethyl radicals, including alkyl-substituted derivatives.

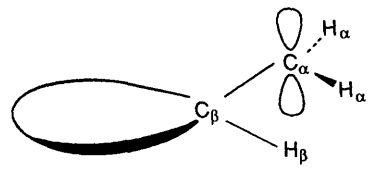
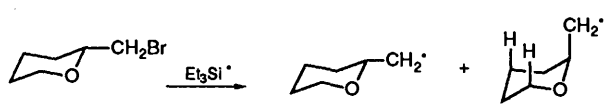


Fig. 1

Results and Discussion

(Tetrahydropyran-2-yl)methyl and (1,3-Dioxan-2-yl)methyl Radicals.—(Tetrahydropyran-2-yl)methyl radicals (**2E** and **2A**) were generated by photolysis of a mixture of (tetrahydropyran-2-yl)methyl bromide (**1**), triethylsilane (or, at higher temperatures, hexamethyldistannane) and di-*tert*-butyl peroxide in the cavity of the EPR spectrometer, with propane, cyclopropane, or *tert*-butylbenzene as solvent.



1 **2E** **2A**

In the temperature range 110–240 K the principal spectrum consisted of a double triplet which had a β-H hfs slightly greater than that found for equatorial cyclohexylmethyl radicals[4] (see Table 1). We attribute this spectrum to the equatorial (tetrahydropyran-2-yl)methyl radical (**2E**). At 280 K the EPR parameters for **2E** were little different from those reported in a study of radicals **2** at 300 K.[6] Long range hfs due to two equivalent hydrogen-atoms were resolved at the lower temperatures (see Table 1).

In the temperature range 260–285 K a second radical was observed with a much less intense double triplet splitting pattern. This radical had a much larger β-H hfs (Table 1) and

Table 1 EPR hyperfine splittings for oxa-, dioxa-, dithia-cyclohexylmethyl and related radicals

Radical	T/K	Ring conformation[a]	Torsion conformation[b]	Hfs/mT		
				$2H_\alpha$	H_β	Other
Cyclohexylmethyl[c]	140	E	Fig. 3	2.15	3.04	0.096 (4H)
2E	140	E	Fig. 3	2.27	3.45	0.11 (2H)
6E	160	E	Fig. 3	2.27	2.57	0.04 (2H)
trans-**8E**	153	E	Fig. 3	2.27	2.51	*ca.* 0.03 (2H)[d]
cis-**8E**	153	E	Fig. 3	2.27	2.51	*ca.* 0.03 (2H)[d]
trans-**7E**	163	E	Fig. 3	2.27	2.54	0.031 (2H)
cis-**7E**	163	E	Fig. 3	2.27	2.54	*e*
10E	200	E	Fig. 6	2.20	1.80	0.11 (4H)
trans-**12E**	200	E	Fig. 6	2.21	1.77	0.11 (4H)
trans-**14E**	140	E	Fig. 6	2.22	1.65	0.12 (4H)
trans-**16E**	160	E	Fig. 3	2.19	2.43	0.08 (4H)
Cyclohexylmethyl[c]	184	A	Fig. 3	2.15	4.12	
2A	260	A	Fig. 3	2.27	3.72	
cis-**12A**	200	A	FR	2.22	2.20	0.28 (2H), 0.08 (2H)
cis-**14A**	140	A	FR	2.22	1.98	0.28 (2H), 0.08 (2H)
cis-**16A**	160	A	Fig. 3	2.18	3.04	0.16 (2H), 0.07 (2H)

[a] Chair conformation with the $CH_2^\bullet$ group equatorial (E) or axial (A). [b] Conformation about the C_β–$C_\alpha^\bullet$ bond; eclipsed, Fig. 3, or bisected, Fig. 6; FR indicates free rotation. [c] From ref. 4. [d] The first derivative spectrum shows essentially the same incompletely resolved fine structure as for *trans*-**7E** on first derivative. For *trans*-**7E** the spectrum was strong and second derivative scans resolved this fine structure. [e] Overlap of this spectrum with that due to *trans*-**7E** obscured any other H hfs.

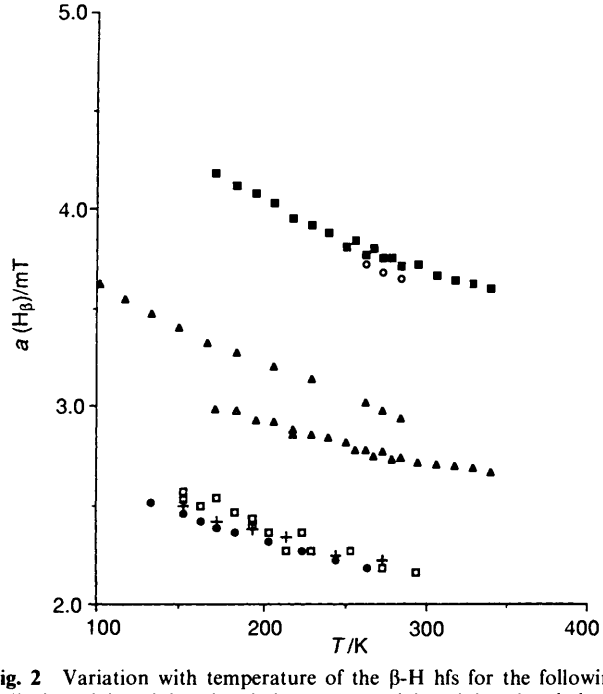


Fig. 2 Variation with temperature of the β-H hfs for the following radicals: axial cyclohexylmethyl, ■; equatorial cyclohexylmethyl, △; axial (tetrahydropyran-2-yl)methyl, **2A**, ○; equatorial (tetrahydropyran-2-yl)methyl, **2E**, ▲; (1,3-dioxan-2-yl)methyl, **6E**, □; (5-methyl-1,3-dioxan-2-yl)methyl, (*cis*/*trans* mixture), +; *cis*-(5-*tert*-butyl-1,3-dioxan-2-yl)methyl, *cis*-(**8E**), ●

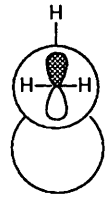


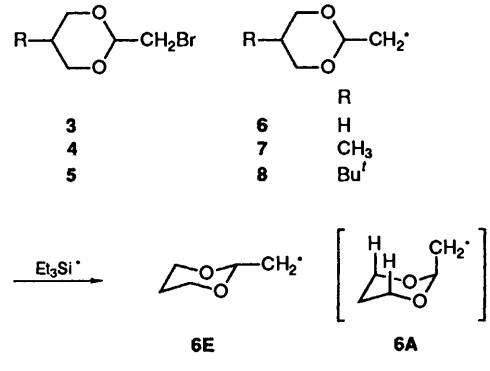
Fig. 3

therefore we assign to it the axial[2–4] conformation of the (tetrahydropyran-2-yl)methyl radical **2A**.

The β-H hfs of both **2E** and **2A** decreased with increasing temperature (Fig. 2) which indicates that the preferred torsional conformation about the C_β–$C_\alpha^\bullet$ bond is that given in Fig. 3 in which the SOMO eclipses the C_β–H bond. This is the same conformation as that preferred by axial and equatorial cyclohexylmethyl radicals.[2–4]

The relative concentration of the axial conformer **2A** was difficult to estimate because of the low intensity of its EPR signal, particularly at low temperatures where the [**2A**]/[**2E**] ratio decreases. At higher temperatures this ratio increases but the spectra become weaker. However, at 273 K the ratio of conformers could be measured, and [**2A**]/[**2E**] = 0.075 ± 0.01. From this ratio we derive a 'conformational free energy' for the $CH_2^\bullet$ group: $-\Delta G^\circ_{273}$ = 1.4 ± 0.2 kcal mol^{-1} (1 cal = 4.184 J). This value is significantly greater than that found for a $CH_2^\bullet$ group attached to a cyclohexane ring,[4] for which $-\Delta G^\circ_{300}$ = 0.71 kcal mol^{-1}. The larger conformational energy for the $CH_2^\bullet$ group on the tetrahydropyran ring can be attributed to the fact that C–O bonds are shorter than C–C bonds and this places the $CH_2^\bullet$ group closer to the *syn* axial hydrogens on C-4 and C-6 (*cf.* structure **2A**). As a consequence, 1,3-steric repulsions are greater in **2A** than in axial cyclohexylmethyl radicals and hence **2A** is more destabilized relative to **2E** than is the case for the corresponding cyclohexylmethyls.

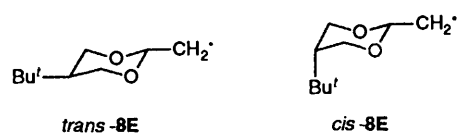
The EPR spectra of the radicals generated from three 2-bromomethyl-1,3-dioxanes **3**–**5**, were also examined. The parent compound **3** gave only a single radical the spectral parameters for which (Table 1) allow it to be assigned an equatorial conformation **6E**. None of the axial conformer **6A** could be detected at any temperature. We can therefore deduce that the



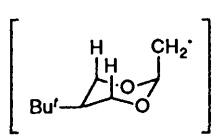
conformational free energy of the $CH_2^{\bullet}$ group, $-\Delta G^{\circ}$, is $>ca.$ 1.5 kcal mol^{-1}. It will be obvious that 1,3-steric repulsions from the axial hydrogens on C-4 and C-6 will be greater for **6A** than for **2A** because the presence of two oxygen atoms in **6A** will bring the $CH_2^{\bullet}$ group into closer proximity with the indicated *syn*-axial hydrogens than is the case for **2A**. Consequently, the **[6A]/[6E]** ratio will be even smaller than the **[2A]/[2E]** ratio, the concentration of **6A** being less than the detection limit of the spectrometer.

Mixtures of *cis*- and *trans*-2-bromomethyl-5-methyl-1,3-dioxane (**4**) and 5-*tert*-butyl-1,3-dioxane (**5**) were obtained by condensation of the appropriate diol with bromoacetaldehyde dimethyl acetal (see the Experimental section). For **5** a good separation of the *cis* and *trans* isomers was achieved by column chromatography. However, neither this technique nor preparative GLC, gave a good separation of the two **4** isomers.

Bromide *trans*-**5** must be essentially all di-equatorial. The EPR spectrum obtained by bromine atom abstraction from this compound was very similar to that obtained by bromine abstraction from **3**. With a β-H hfs = 2.51 mT at 153 K this radical must have an equatorial $CH_2^{\bullet}$ group, *trans*-**8E**. Interestingly, bromine abstraction from *cis*-**5** gave an EPR spectrum which was indistinguishable from that obtained from *trans*-**5** (see Table 1). The radical formed from *cis*-**5** must therefore have its $CH_2^{\bullet}$ group in the equatorial position and the bulky *tert*-butyl group axial, *i.e.*, the radical is *cis*-**8E** and is not **8A**.



trans-**8E** *cis*-**8E**



8A

The *cis*-**8E** conformation is not without precedent. Thus, Eliel[7,8] and Riddell[9] and their co-workers have studied a series of 2,5-dialkyl-1,3-dioxanes by NMR spectroscopy and showed that the 2-substituent monopolizes the equatorial orientation, even when the 5-substituent is the *tert*-butyl group. For example, *cis*-2-methyl-5-*tert*-butyl-1,3-dioxane, which is structurally very similar to the radical derived from *cis*-**5**, exists mainly as the conformation with the *tert*-butyl group axial. The steric repulsion of the group at C-2 due to the *syn*-axial hydrogens on C-4 and C-6 in **8A** seriously destabilizes this conformer. However, the axial *tert*-butyl group in **8A** does not experience a similar effect because oxygen atoms occupy the analogous sites. For this reason, the *cis*-**8** conformer is lower in energy than **8A**.

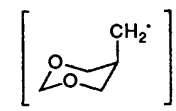
As would be expected in view of the foregoing, bromine atom abstraction from the *trans*-**4**/*cis*-**4** mixture appeared to show the EPR spectrum of only a single radical with a β-H hfs = 2.54 mT. We presume that both the *trans* and the *cis* bromides yield radicals with equatorial $CH_2^{\bullet}$ groups and hence have indistinguishable spectra; *i.e.*, the two radicals from **4** adopt conformations analogous to *cis*- and *trans*-**8E**.

The β-H hfs for all the 1,3-dioxan-2-yl radicals decrease with an increase in temperature (Fig. 1). These radicals therefore adopt the eclipsed torsional conformation (Fig. 3).

Attempts to prepare the dithia-analogues of **3**–**5** were unsuccessful; the prospective bromides dehydrobrominated extremely rapidly and only the corresponding alkenes could be isolated.

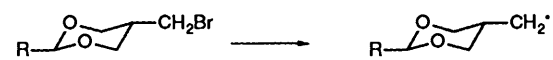
(1,3-Dioxan-5-yl)methyl Radicals.—Bromine abstraction from 5-bromomethyl-1,3-dioxane, **9** gave rise to an EPR spectrum showing only one doublet of triplets with a β-H hfs = 1.80 mT at 200 K and long range splitting from four hydrogens (Table 1). We attribute this spectrum to the equatorial radical **10E**. The axial conformer **10A** could not be detected at any temperature, which again implies that $-\Delta G^{\circ} > ca.$ 1.5 kcal mol^{-1}.

9 **10E**



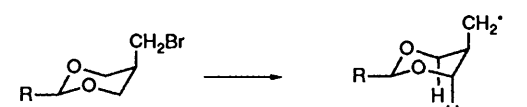
10A

That the equatorial and axial conformers of this class of radicals actually do have readily distinguishable EPR spectra was shown by an examination of the 2-methyl and 2-*tert*-butyl[3] derivatives. The *trans*-2-methyl compound, *trans*-**11**, and *trans*-2-*tert*-butyl compound, *trans*-**13**, both of which exist in the di-equatorial conformation, gave EPR spectra with small β-H hfs (*ca.* 1.6 mT at 140 K, but similar to that found for **10E** at 200 K; see below and Table 1). This confirms that **11** and **13** give the equatorial radicals **12E** and **14E**, respectively.



trans-**11** *trans*-**12E** R = CH_3
trans-**13** *trans*-**14E** R = Bu^t

The corresponding *cis*-2-methyl compound, *cis*-**11**, and *cis*-2-*tert*-butyl compound, *cis*-**13**, gave EPR spectra, *cis*-**12A** and *cis*-**14A**, respectively, which were readily distinguishable from those derived from the *trans* bromides by having larger β-H hfs (*ca.* 2.0 mT at 140 K) and by having different long range splitting patterns (see Table 1). It is obvious that in these radicals the 2-methyl and 2-*tert*-butyl substituents will adopt the equatorial position in order to escape the steric effect of the axial hydrogens on C-4 and C-6 that they would encounter if they were to adopt an axial position. Fig. 4 illustrates the major differences between the EPR spectra of the equatorial and axial radicals **14E** and **14A**.



cis-**11** *cis*-**12E** R = CH_3
cis-**13** *cis*-**14E** R = Bu^t

The EPR spectra of (1,3-dioxan-5-yl)methyl radicals reveal a number of unexpected conformational features. In these radicals an axial $CH_2^{\bullet}$ group does not experience a strong 1,3-steric repulsion by *syn* axial hydrogens at the 1 and 3 positions on the ring. It is therefore surprising that we could not detect **10A**, while our estimate that $-\Delta G^{\circ} > 1.5$ kcal mol^{-1} for the 5-$CH_2^{\bullet}$ group attached to this ring must be contrasted with the smaller values of $-\Delta G^{\circ}$ found for cyclohexylmethyl (0.7 kcal mol^{-1})[4] and (tetrahydropyran-2-yl)methyl (**2**, 1.4 kcal mol^{-1}), and for both of the last named radicals there are 1,3-steric interactions due to *syn* axial hydrogens. In addition, we had anticipated that *cis*-**11** would yield a mixture of axial, *cis*-**12A**, and equatorial, *cis*-**12E**, radicals because the steric demands of

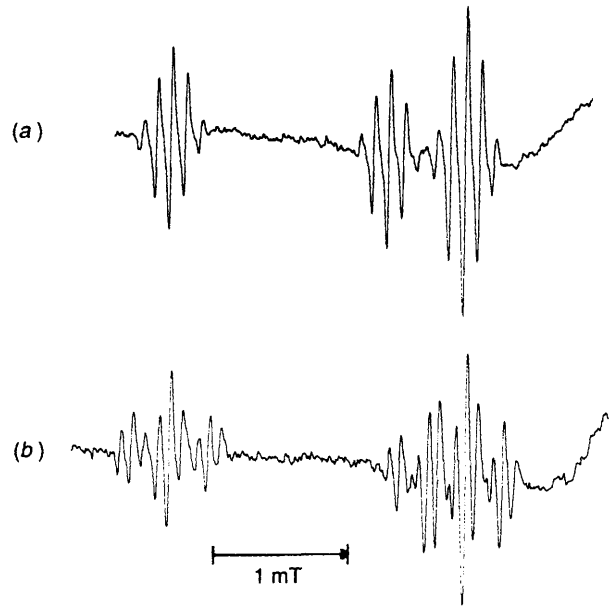
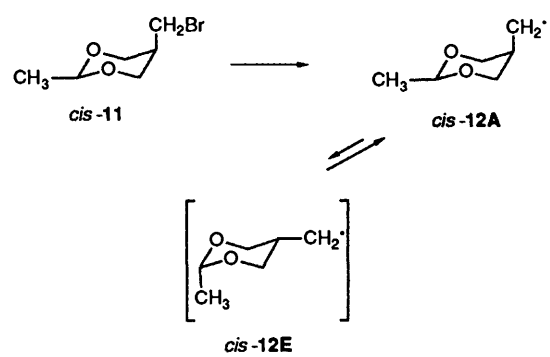


Fig. 4 Low-field halves of 9.4 GHz EPR spectra of: (*a*) *trans*-(2-*tert*-butyl-1,3-dioxan-5-yl)methyl radical (**12E**) in cyclopropane at 150 K; (*b*) *cis*-(2-*tert*-butyl-1,3-dioxan-5-yl)methyl radical **14E** in cyclopropane at 100 K

CH_3 and CH_2• when in the axial position must tend to 'balance out'. However, no trace of *cis*-**12E** could be detected. The equatorial preference of the CH_3 group must therefore be substantially greater than that of the CH_2• group in this radical. Again, we attribute these conformational effects to the fact that C–O bonds are shorter than C–C bonds.



The temperature dependence of the β-H hfs for **10E**, **12E** and **14E** and for **12A** and **14A** are shown in Fig. 5. For the three equatorial radicals the β-H hfs are below the free rotation limit and increase with an increase in temperature. Thus, in contrast with equatorial cyclohexylmethyl radicals, with **2E**, and with **6E**–**8E**, the preferred torsional conformations of **10E**, **12E** and **14E** are bisected (Fig. 6), with the C_β–H bond lying in the nodal plane of the SOMO.

The conformational 'switch' (from Fig. 3 to Fig. 6) is clearly related to the replacement by oxygen of the two ring CH_2• groups at the 3 and 5 positions with respect to the $C_\alpha H_2$• group, *i.e.* cyclohexylmethyl radicals, and **2E**, **6E**, **7E** and **8E** have two CH_2 groups whereas **10E**, **12E** and **14E** have two oxygen atoms in these positions. The bisected conformation of the latter radicals can reasonably be attributed to the ease with which their β-H's can 'tip' inwards towards the ring [Fig. 7(*a*)]. This relative lack of resistance to ring distortion in Fig. 7(*a*) compared with Fig. 7(*b*) permits the switch to the bisected conformation which, when adopted, relieves repulsion between the two α-hydrogen atoms, H_α, and the two equatorial hydrogen atoms, H_{eq}, attached to the γ-carbon atoms in the ring, Fig. 8(*a*). In those radicals under

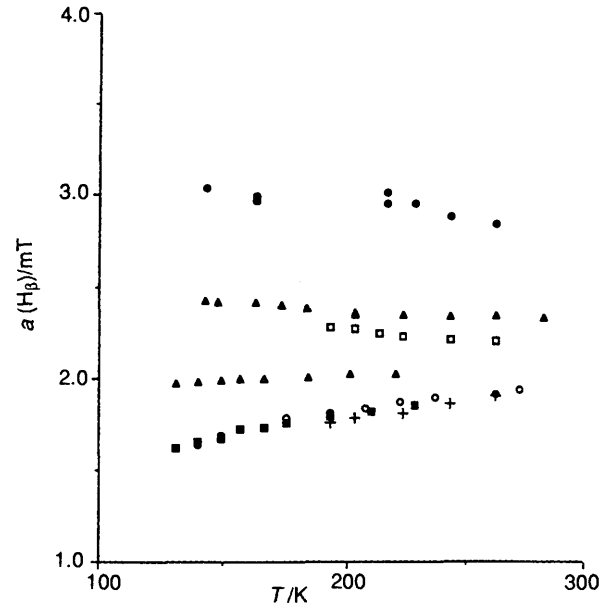


Fig. 5 Variation with temperature of the β-H hfs for the following radicals; (1,3-dioxan-5-yl)methyl, **10E**, ○; *cis*-(2-methyl-1,3-dioxan-5-yl)methyl, *cis*-**12A**, □; *trans*-(2-methyl-1,3-dioxan-5-yl)methyl, *trans*-**12E**, +; *cis*-(2-*tert*-butyl-1,3-dioxan-5-yl)methyl, *cis*-**14A**, △; *trans*-(2-*tert*-butyl-1,3-dioxan-5-yl)methyl, *trans*-**14E**, ■; *cis*-(2-*tert*-butyl-1,3-dithian-5-yl)methyl, *cis*-**16A**, ●; *trans*-(2-*tert*-butyl-1,3-dithian-5-yl)-methyl, *trans*-**16E**, ▲

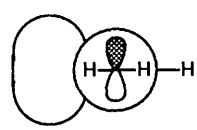


Fig. 6

Fig. 7

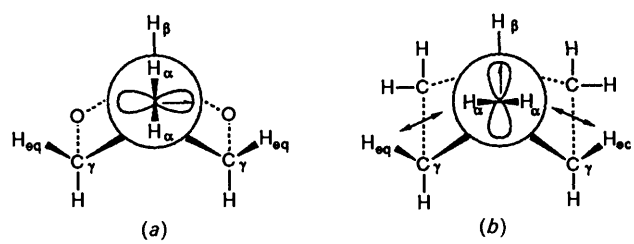


Fig. 8

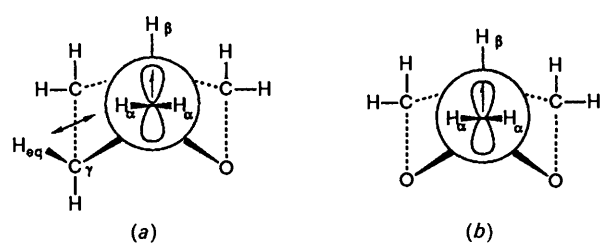


Fig. 9

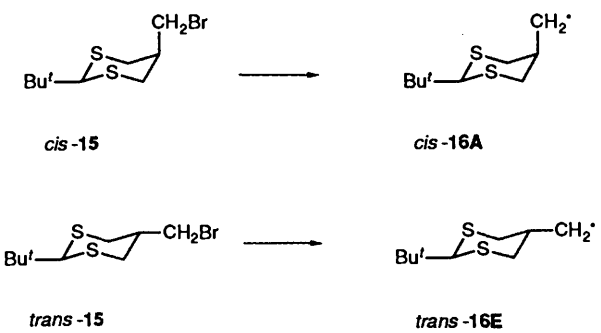
consideration which adopt the eclipsed conformation, Fig. 3, the destabilizing repulsion (signified by ⟷) between the two α-H's and the two γ-H_{eq} in cyclohexylmethyl radicals [Fig. 8(*b*)] will be reduced (presumably by nearly a factor of two) in the (tetrahydropyran-2-yl)methyl radical **2E**, *cf.* Fig. 9(*a*), and will be essentially eliminated in the (1,3-dioxan-2-yl)methyl radicals **6E**

and *cis*- and *trans*-**7E** and **8E**, *cf.* Fig. 9(*b*). Thus, there is a decrease in the destabilization of (eclipsed) equatorial radicals along the series: cyclohexylmethyl > **2E** > **6E**, **7E** and **8E**. This provides a very simple explanation as to why the conformational free energy preference of the $CH_2^•$ group for the equatorial position increases along the same series, *viz.*, $-\Delta G^\circ = 0.71$, 1.4 and > 1.5 kcal mol^{-1} for cyclohexylmethyl, **1** and **3**, respectively.

It will be clear that both the equatorial/axial preference of the $CH_2^•$ group and the eclipsed/bisected $>C_\beta H–C_\alpha H_2^•$ torsional preference in cyclohexylmethyl and related heteroatom-substituted radicals are determined by rather subtle factors involving only small energy differences. As a consequence, it is not surprising to find that conformational 'switching' occurs rather readily.

In the case of the axial (1,3-dioxan-2-yl)methyl radicals, *cis*-**12A** and *cis*-**14A**, the magnitude of the β-H hfs and the absence of any significant temperature dependence (Fig. 5) indicates that there is virtually free rotation about the $C_\beta–C_\alpha^•$ bond. The difference in free energy between the eclipsed, Fig. 3, and bisected, Fig. 6, torsional conformers of these two radicals must therefore be negligible.

(1,3-*Dithian*-5-*yl*)*methyl Radicals*.—Bromine atom abstraction from *cis*-bromomethyl-2-*tert*-butyl-1,3-dithiane, *cis*-**15** and its *trans* isomer, *trans*-**15**, yielded the corresponding *cis*-**16A** and *trans*-**16E** radicals, which could be clearly distinguished by the



magnitude of their β-H hfs (Table 1). The temperature dependence of the β-H hfs of *cis*-**16A** and *trans*-**16E** (Fig. 5) shows that both radicals have a slight preference for the eclipsed torsional conformation, Fig. 3. This is the torsional conformation adopted by equatorial and axial cyclohexylmethyl radicals but it differs from the conformational preferences expressed by the structurally analogous dioxane radicals, *viz.*, the bisected species, Fig. 6, for the equatorial radicals, **10E**, **12E** and **14E**, and free rotation for the axial radicals, **12A** and **14A** (*vide infra* and Table 1). The smaller magnitudes of the β-H hfs found for *cis*-**16A** and *trans*-**16E** compared with that for equatorial and axial cyclohexylmethyl radicals, respectively (Table 1), indicates that the barrier to rotation about the $C_\beta–C_\alpha^•$ bond is lower in the dithiane radicals. This is to be expected for the reasons outlined in our earlier discussion of the steric factors which cause the conformational preferences of the equatorial and axial dioxane radicals, **9**, **11** and **13** to be quite different from those of cyclohexylmethyl radicals. The differences that our $CH_2^•$ spin probe detects in torsional and in equatorial–axial conformational preferences between cyclohexane rings and six-membered rings containing oxygen or sulphur points to a subtle balance of (steric) forces in these radicals.

Conclusions

For every six-membered ring system studied to date the corresponding cycloalkylmethyl radicals show major differences in the β-H hfs of the equatorial and axial conformers. For the cyclohexylmethyl and cyclohexenylmethyl[10] systems the dynamics of ring interconversion could be followed. For the oxygen and sulphur substituted rings, this was prevented either because the preference for one conformer was too strong or because the ring inversion barrier was too high for study in the temperature range accessible to EPR spectroscopy.

Experimental

EPR spectra were recorded on Bruker ER 200D and Varian E104 spectrometers with samples which had been degassed by several freeze–pump–thaw cycles. These samples were sealed in 4 mm o.d. Spectrosil tubes and were irradiated in the cavity of the EPR spectrometer with light from a 500 W super pressure mercury lamp. ^{1}H NMR spectra were recorded on 60 MHz Varian EM 360, 80 MHz Bruker WP 80 and/or 300 MHz Bruker AM 300 spectrometers in $CDCl_3$ as solvent with Me_4Si as internal standard. Coupling constants *J* are given in Hz. Mass spectra were recorded on a Hewlett-Packard 5970 A Mass Selective Detector with an HP-Ultra I fused silica capillary GC column (10 m × 0.2 mm i.d., OV-101 type, cross-linked, bonded phase). Column chromatographic purifications used Merck grade 60 silica gel (230–400 mesh, 60 Å, Aldrich).

2-*Bromomethyltetrahydropyran* (**1**).—A commercial sample (Aldrich) of this compound was purified by standard methods before use.

2-*Bromomethyl*-1,3-*dioxane* (**3**).—A mixture of bromoacetaldehyde dimethyl acetal (5.0 g, 0.03 mol), propane-1,3-diol (2.3 g, 0.03 mol) and toluene-*p*-sulphonic acid (50 mg) in chloroform (75 cm^3) was heated for 1 h and the solvent was then distilled off. The residue was distilled (Kugelrohr) at 140 °C/20 Torr * to give **3** (4.3 g, 79%); δ_H(60 MHz) 1.2–1.6 (1 H, m), 1.7–2.5 (1 H, m). 3.3 (2 H, d, *J* 7), 3.5–4.4 (4 H, m) and 4.7 (2 H, t, *J* 6); *m*/*z* (%) 182, 180 (0.2, M$^+$), 123, 121 (10), 96, 94 (7), 87 (100), 59 (14), 43 (11) and 41 (11).

cis- *and* trans-2-*Bromomethyl*-5-*methyl*-1,3-*dioxane* (**4**).—A mixture of 2-methylpropane-1,3-diol (2.0 g, 0.022 mol), bromoacetaldehyde dimethyl acetal (4.0 g, 0.024 mol) and toluene-*p*-sulphonic acid (100 mg) in benzene (50 cm^3) was refluxed for 3 h in a Dean and Stark separator. A mixture of water and diethyl ether (50 cm^3) was added, the organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to give crude product (4.5 g) which was chromatographed on silica gel. Separation of the two isomers was not achieved with any solvent system. Attempts to separate *cis*-**4** from *trans*-**4** by preparative GLC were also unsuccessful. ^{1}H NMR spectroscopy of the mixture showed; δ_H(200 MHz) 0.71–0.74 and 1.28–1.31 (3 H, 2d, *J* 3), 1.5–2.25 (1 H, 2m), 3.34–4.16 (6 H, d, *J* 2 and m) and 4.63–4.74 (1 H, 2t, *J* 4). *cis*- and *trans*-**4** were separated satisfactorily only on the analytical chromatograph of the coupled GC–MS. By analogy with the *tert*-butyl-substituted compounds, *cis*- and *trans*-**5**, the first eluted component was the *cis*-isomer, *cis*-**4**: (20 rel. %), *m*/*z* 195, 193 (4, *M* − H$^+$), 125 (9), 123 (18), 121 (6), 101 (100), 55 (52), 43(19), 42 (52) and 41 (24) and the second eluted was the *trans*-isomer, *trans*-**4**: (80 rel. %), *m*/*z* (%) 195, 193 (6, M − H$^+$), 125 (9), 123 (15), 121 (6), 102 (6), 101 (100), 55 (47), 43 (21), 42 (55) and 41 (26).

cis- *and* trans-2-*Bromomethyl*-5-tert-*butyl*-1,3-*dioxane*, cis- *and* trans-**5**.—Diethyl 2-*tert*-butylmalonate (20 g, 0.09 mol) was reduced with $LiAlH_4$ (4 g, 0.1 mol) in diethyl ether (45 cm^3) to give 2-*tert*-butylpropane-1,3-diol (16 g, 66%) as a white solid,

* 1 Torr = (101 325/760) Pa.

m.p. 59–60 °C (lit.,[11] 57–58 °C). This diol (1.3 g, 0.01 mol) was dissolved in benzene (25 cm^3) to which was added toluene-*p*-sulphonic acid (0.13 g) and bromoacetaldehyde dimethyl acetal (1.2 g, 0.01 mol). The resulting solution was refluxed for 2 h in a Dean and Stark separator, poured onto ice, extracted with diethyl ether (3 × 30 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a mixture of *cis*- and *trans*-2-bromomethyl-5-*tert*-butyl-1,3-dioxane (1.7 g, 72%) as a pale yellow oil. δ_H(200 MHz) 0.90 and 1.06 (9 H, 2s), 1.83 (1 H, s), 3.31–3.37 (2 H, dd, *J* 4 and 2), 3.59–3.70 and 3.87–3.95 (2 H, t, *J* 5.5 and dd, *J* 6 and 2), 4.17–4.25 and 4.30–4.36 (2 H, dd, *J* 6 and 2, and d, *J* 6) and 4.60–4.64 and 4.77–4.81 (1 H, 2t, *J* 2). The two isomers were separated by column chromatography using ethyl acetate–hexane (0.5%). The first eluted isomer was *cis*-**5** which could only be obtained in 50% purity. Fortunately, GC–MS analysis (*vide infra*) showed no trace of contamination by the *trans* isomer. The second eluted isomer was *trans*-**5** which was obtained in pure form as a pale yellow oil (0.2 g) (Found: C, 45.8; H, 7.20. $C_9H_{17}BrO_2$ requires C, 45.58; H, 7.23%); δ_H(200 MHz) 0.89 (9 H, s), 1.83 (1 H, s), 3.36–3.41 (2 H, d, *J* 5), 3.58–3.69 (2 H, t, *J* 11), 4.16–4.24 (2 H, dd, *J* 6 and 3) and 4.59–4.63 (1 H, t, *J* 2). *cis*- and *trans*-**5** were readily separated by GC–MS with the former compound again eluting first. *cis*-**5** (17 rel. %), *m*/*z* (%) 237, 235 (2, $M - H^+$), 143 (100), 69 (49), 57 (77) and 41 (47). *trans*-**5** (83 rel. %) 237, 235 (3, $M - H^+$), 143 (100), 69 (69), 57 (62) and 41 (44).

5-*Bromomethyl*-1,3-*dioxane* (**9**).—Diethyl bis(hydroxymethyl)malonate (22.0 g, 0.1 mol), paraformaldehyde (9.60 g, 0.3 mol) and toluene-*p*-sulphonic acid (0.2 g) were dissolved in ethanol (50 cm^3) and benzene (250 cm^3). The solution was refluxed for 1 h. The water produced was removed azeotropically by distilling out the benzene and ethanol. The residue was distilled on a Buchi Kugelrohr to give 5,5-diethoxycarbonyl-1,3-dioxane (18.5 g, 80%); δ_H(300 MHz), 1.3 (6 H, t, *J* 8), 4.2 (4 H, q, *J* 8), 4.3 (4 H, s) and 4.8 (2 H, s). 5,5-Diethoxycarbonyl-1,3-dioxane (18.4 g, 79 mmol) was added to KOH (25.1 g) in ethanol (210 cm^3) and the solution was refluxed for 1 h. Successive 30 cm^3 portions of ethanol were distilled out and replaced with water. When *ca.* 210 cm^3 of distillate had been collected, the remaining solution was cooled in ice and conc. HCl was added dropwise, with stirring, until it was acidic. The solution was extracted with diethyl ether (3 × 100 cm^3), the extracts were combined, dried (Na_2SO_4), decolourized (charcoal) and the solvent was evaporated to give 1,3-dioxane-5,5-dicarboxylic acid (8.5 g, 60%); δ_H(80 MHz), 4.2 (4 H, s), 4.8 (2 H, s) and 4.9 (2 H, br s). 1,3-Dioxane-5,5-dicarboxylic acid (8.35 g, 47 mmol) was refluxed in anhydrous pyridine for 1.5 h. The solution was cooled over ice–salt while 20% HCl (50 cm^3) was added dropwise. The acidic solution was extracted with diethyl ether (3 × 50 cm^3). The extracts were combined and washed with 10% HCl (30 cm^3) then saturated NaCl (30 cm^3), dried ($MgSO_4$), and evaporated to give 1,3-dioxane-5-carboxylic acid (4.20 g, 68%); δ_H(80 MHz), 2.7 (1 H, m), 3.7–4.2 (4 H, ABX, δ_A 3.8, δ_B 4.0, J_{AX} 7, J_{BX} 5, J_{AB} 12), 4.6 (1 H, d, *J* 7), 4.8 (1 H, d, *J* 7) and 3.2–5.0 (1 H, br s). 1,3-Dioxane-5-carboxylic acid (2.64 g, 20 mmol) in the minimum volume of ether was added to ice-cold $LiAlH_4$ (2.00 g) in dry diethyl ether (20 cm^3). The suspension was then refluxed for 3 h, cooled, water was added and the ether layer was decanted. Dilute sulphuric acid was added to the aqueous layer which was then extracted several times with ether. The ether fractions were combined, dried (Na_2SO_4) and evaporated. The residual oil was distilled on a Buchi Kugelrohr to give 5-hydroxymethyl-1,3-dioxane (1.14 g, 48%) as a colourless oil; δ_H(80 MHz), 1.9 (1 H, m), 2.9 (1 H, br s), 3.7 (2 H, d, *J* 7), 3.6–4.1 (4 H, ABX, δ_A 3.7, δ_B 4.0, J_{AX} 6, J_{BX} 4, J_{AB} 11) and 4.8 (2 H, AB, degenerate). This ^1H NMR spectrum was in satisfactory agreement with the literature.[12] 5-Hydroxymethyl-1,3-dioxane (1.70 g, 14 mmol) and carbon tetrabromide (4.78 g, 14 mmol) were dissolved in benzene (7 cm^3), heated to 60 °C and stirred while triphenylphosphine (3.77 g, 14 mmol) was added in small portions. The solvent was evaporated and the product was distilled directly out of the residue on a Buchi Kugelrohr to give 5-bromomethyl-1,3-dioxane (**9**): (1.82 g, 72%); δ_H(60 MHz) 2.1 (1 H, m), 3.5 (2 H, d, *J* 7), 3.6–4.2 (4 H, ABX, δ_A 4.1, δ_B 3.8, J_{AX} 4, J_{BX} 5, J_{AB} 12 Hz) and 4.75 (2 H, s). This ^1H NMR spectrum was also in satisfactory agreement with the literature.[12]

cis- *and* trans-5-*Bromomethyl*-2-*methyl*-1,3-*dioxane*, cis- *and* trans-**11**.—Diethyl bis(hydroxymethyl) malonate (22.0 g, 100 mmol), the acetal (23.6 g, 200 mmol) and toluene-*p*-sulphonic acid (0.2 g) were mixed and heated to 80 °C in a distillation apparatus. The ethanol formed, and the excess acetal, were removed by distillation. The residue was distilled under reduced pressure to give 5,5-diethoxycarbonyl-2-methyl-1,3-dioxane (22.47 g, 91%), b.p. 146 °C/15 Torr; δ_H(80 MHz) 1.2 (3 H, t, *J* 7), 1.3 (3 H, t, *J* 7), 1.3 (3 H, d, *J* 2), 3.8 (1 H, t, *J* 1), 4.0 (1 H, t, *J* 1), 4.2 (2 H, q, *J* 7), 4.3 (2 H, q, *J* 7 Hz), 4.6 (2 H, m) and 4.7 (1 H, t, *J* 1). 5,5-Diethoxycarbonyl-2-methyl-1,3-dioxane (22.4 g, 91 mmol) was added to NaOH (21.8 g) in ethanol (180 cm^3) and the solution was refluxed for 1 h. Ethanol was removed by distillation in 30 cm^3 portions and was progressively replaced with water. When virtually all the ethanol had been removed, the aqueous solution was cooled in ice and acidified with conc. HCl. The acidic solution was extracted with diethyl ether (3 × 100 cm^3). The ether extracts were combined, dried ($MgSO_4$), decolourized (charcoal) and evaporated to give 2-methyl-1,3-dioxane-5,5-dicarboxylic acid (12.6 g, 73%); δ_H(300 MHz) 1.2 (3 H, d, *J* 4), 3.9 (2 H, d, *J* 12), 4.4 (2 H, d, *J* 12), 4.7 (1 H, q, *J* 4) and 13.3 (2 H, br s). 2-Methyl-1,3-dioxane-5,5-dicarboxylic acid (13.00 g, 68 mmol) was stirred and refluxed in anhydrous pyridine (15 cm^3) for 1 h. The solution was cooled in ice–salt and 20% aqueous HCl (75 cm^3) was added dropwise. The acidic solution was extracted with ether (3 × 100 cm^3), the ether layers were combined, dried ($MgSO_4$), decolourized (charcoal) and evaporated to give a mixture of *cis*- and *trans*-2-methyl-1,3-dioxane-5-carboxylic acid (3.46 g, 35%). ^1H NMR spectroscopic analysis indicated that the mixture was *ca.* 70% *trans* isomer; δ_H(300 MHz) 1.2 (3 H, d, *J* 5), 2.5 (1 H, m), 3.5 (1 H, bs), 3.6–4.2 (ABX, δ_A 4.1, δ_B 3.7, J_{AX} 5, J_{BX} 11, J_{AB} 11) and 4.6 (1 H, q, *J* 5) and 30% *cis* isomer; δ_H(300 MHz) 1.1 (3 H, d, *J* 5), 2.3 (1 H, m), 3.3 (1 H, br s), 3.8 (2 H, d, *J* 11), 4.3 (2 H, d, *J* 11) and 4.6 (1 H, q, *J* 5). The mixture of 2-methyl-1,3-dioxane-5-carboxylic acids (3.40 g, 23 mmol) was dissolved in dry diethyl ether (20 cm^3) and added to ice-cold $LiAlH_4$ in dry diethyl ether (40 cm^3). The suspension was then refluxed for 3 h, water was added and the ether layer was decanted. Dilute sulphuric acid was added to the aqueous layer which was then extracted several times with ether. The ether layers were combined, dried (Na_2SO_4) and evaporated to leave an oil (2.91 g after distillation on a Buchi Kugelrohr). This oil, together with carbon tetrabromide (7.30 g), were dissolved in benzene (11 cm^3) and heated to 60 °C when triphenylphosphine (5.76 g) was added slowly. The solvent was evaporated and *cis*- and *trans*-5-bromomethyl-2-methyl-1,3-dioxane were distilled directly out of the residue (1.8 g, 40%). GLC and NMR spectroscopic analyses indicated that the mixture was 58% *cis*-5-bromomethyl-2-methyl-1,3-dioxane, *cis*-**11**; δ_H(80 MHz) 1.3 (3 H, d, *J* 5), 1.6–1.9 (1 H, m), 3.8 (2 H, d, *J* 8), 3.9–4.2 (4 H, m) and 4.7 (1 H, q, *J* 5) and 42% *trans*-5-bromomethyl-2-methyl-1,3-dioxane, *trans*-**11**; δ_H(80 MHz) 1.3 (3 H, d, *J* 5), 2.1–2.6 (1 H, m), 3.1 (2 H, d, *J* 7), 3.3–4.3 (4 H, ABX, δ_A 4.2, δ_B 3.4, J_{AX} 5, J_{BX} 11, J_{AB} 11) and 4.6 (1 H, q, *J* 5 Hz). These ^1H NMR spectra are in agreement with the literature.[12] The two isomers were separated by preparative GLC on a 3 m × 1 cm FFAP column at 110 °C.

cis *and* trans-5-*Bromomethyl*-2-tert-*butyl*-1,3-*dioxane*, cis- *and* trans-**13**.—The syntheses and isolation of pure samples of both of these compounds have been described previously.[3]

cis- *and* trans-5-*Bromomethyl*-2-tert-*butyl*-1,3-*dithiane*, cis- *and* trans-**15**.—Dihydroasparagusic acid[13] (13.7 g, 0.09 mol) and toluene-*p*-sulphonic acid (1.3 g, 6 mmol) in 137 cm^3 methanol were refluxed for 18 h. The methanol was evaporated off and the residue was dissolved in diethyl ether, washed with water and brine, and dried (Na_2SO_4). Filtration and evaporation gave dihydroasparagusic acid methyl ester as a yellow liquid (12.5 g, 84%); *m/z* (%) 166 (34, M^+), 134 (15), 106 (11), 100 (23), 73 (100), 61 (22) and 55 (79). This ester (12.5 g, 0.075 mol), toluene-*p*-sulphonic acid (1.2 g, 6 mmol) and trimethylacetaldehyde (10 cm^3, 0.09 mol) were dissolved in benzene (125 cm^3) and refluxed for 18 h in a Dean and Stark separator under nitrogen. The methanol was evaporated and the residue was dissolved in diethyl ether (200 cm^3). Subsequent work-up with a water and brine wash, drying (Na_2SO_4), filtration and evaporation gave a mixture of *cis*- and *trans*-2-*tert*-butyl-1,3-dithiane-5-carboxylic acid methyl ester as a yellow oil (15.0 g, 85%); *m/z* (%) 234 (6, M^+), 177 (80), 73 (18), 59 (29), 47 (14) and 41 (100). This ester (11.6 g, 0.05 mol) in diethyl ether (125 cm^3) was added dropwise to a suspension of $LiAlH_4$ (2.0 g, 0.05 mol) in ether (125 cm^3) and the mixture was stirred for 18 h at room temperature under nitrogen, after which time TLC analysis (12% ethyl acetate–hexane) showed none of the starting ester to be present. The reaction mixture was poured slowly onto ice, washed with brine, dried (Na_2SO_4), filtered and evaporated to give a mixture of *cis*- and *trans*-2-*tert*-butyl-5-hydroxymethyl-1,3-dithiane as a colourless oil (10.0 g, 95%); δ_H(60 MHz) 1.1 (9 H, s), 2.0 (2 H, t, *J* 11), 2.2–3.2 (4 H, m), 3.4 (2 H, t, *J* 10) and 3.9 (1 H, br s). This alcohol (5 g, 0.02 mol) and triphenylphosphine (5.7 g, 0.02 mol) were dissolved in freshly distilled methylene dichloride (50 cm^3), cooled to 10 °C and *N*-bromosuccinimide (4.2 g, 0.02 mol) was added in small portions over 1.5 h, after which TLC analysis (3% ethyl acetate–hexane) showed none of the starting alcohol to be present. Evaporation, extraction with hexane (3 × 100 cm^3) and evaporation of the hexane left a solid residue which was a mixture of *cis*-5-bromomethyl-2-*tert*-butyl-1,3-dithiane, *cis*- and *trans*-**15** (4.0 g, 66%). The whole of this material was subjected to column chromatography (0.5% ethyl acetate–hexane), in which *cis*-**15** (0.2 g) was eluted first followed by *trans*-**15** (0.75 g), both as white solids. *cis*-**15**: m.p. 59.6–60.0 °C (Found: C, 40.2; H, 6.5. $C_9H_{17}BrS_2$ requires C, 40.14; H, 6.36%); *m/z* (%) 270, 268 (12, M^+), 212 (100), 210 (93), 148 (11), 55 (14) and 41 (22); δ_H(200 MHz) 1.13 (9 H, s), 2.22 (1 H, m), 2.99–3.23 (4 H, dq, *J* 9, 2), 3.90, 3.94 (2 H, d, *J* 3.6) and 3.97 (1 H, s). *trans*-**15**: m.p. 58.6–59.0 °C (Found: C, 40.5; H, 6.5. $C_9H_{17}BrS_2$ requires C, 40.14; H, 6.36%); *m/z* (%) 270, 268 (9, M^+), 212 (100), 210 (94), 55 (21), 45 (28) and 41 (35); δ_H(200 MHz) 1.15 (9 H, s), 2.22 (1 H, m), 2.65 (2 H, t, *J* 12.5), 2.95–3.05 (2 H, dd, *J* 10 and 2.5) and 3.30–3.37 (2 H, d, *J* 7) and 3.92 (1 H, s).

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