

Preferred Boat Conformations in Unsaturated Sulphur Heterocycles; X-Ray Analysis of *cis*-1,4-Dimethylisothiochroman 2,2-Dioxide

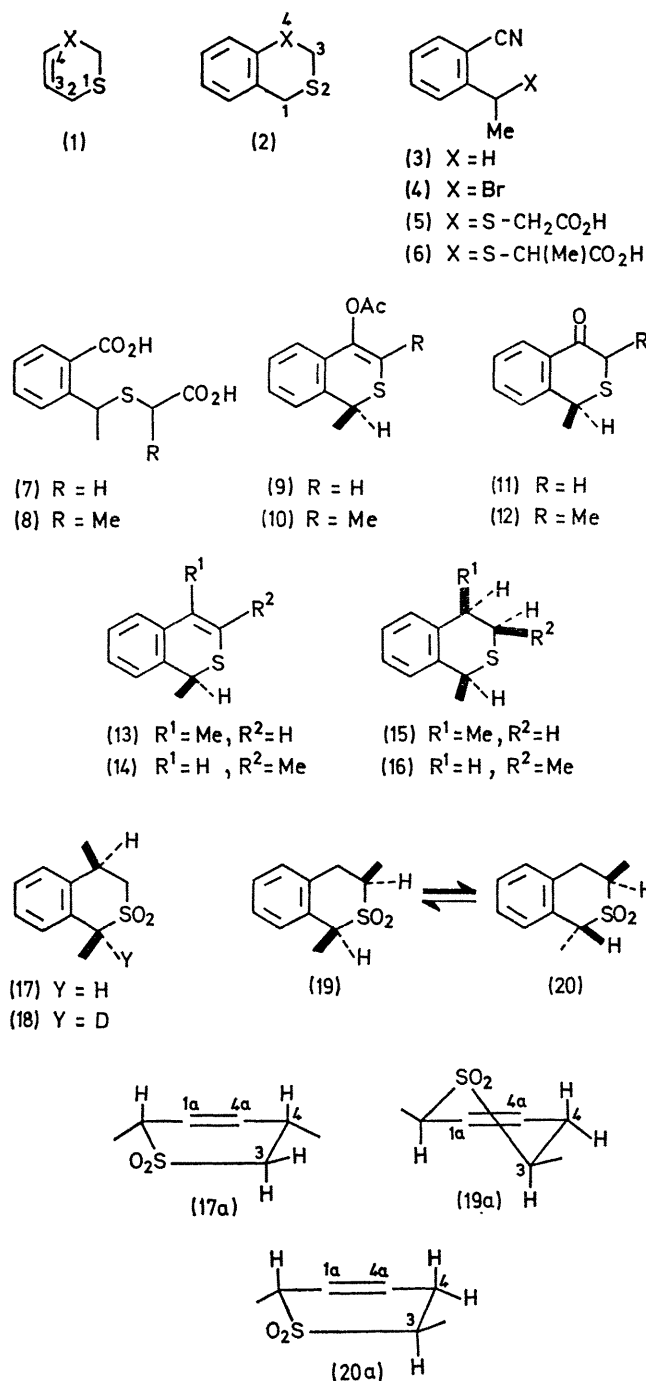
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Summary In the 1,4- and 1,3-dimethylisothiochroman 2,2-dioxides, the *cis*- and *trans*-forms respectively, are shown to be the more thermodynamically stable stereoisomers; a preferred boat conformation is inferred for these compounds and is demonstrated by a crystallographic study of the *cis*-1,4 isomer (**17**).

A PREFERRED boat conformation for the thiacyclohex-3-ene ring has earlier been proposed on kinetic grounds.¹ Examination of molecular models suggests that boat forms in such rings, and similar systems [*e.g.* (**1**; X = CH₂, NH, O, S) or (**2**; X = CH₂, NH, S)], might be subject to less ring strain than the corresponding chair forms. To test this proposition

we have developed stereoselective syntheses of the *cis*-1,4- and *cis*-1,3-dimethylisothiochromans (15) and (16), and their sulphones (17) and (19), and studied their preferred shapes. Thus, *o*-ethylbenzonitrile (3) was treated with *N*-bromo-

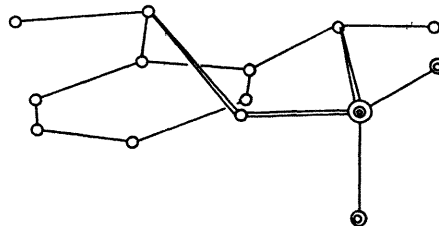


succinimide, and the resulting bromoethylbenzonitrile² (4) was converted into the thio-acids (5) and (6) by reaction with thioacetic and thiolactic acid, respectively, in alkali. After hydrolysis to the di-acids (7) and (8), cyclisation using

Ac₂O-NaOAc afforded the enol acetates (9) and (10), which were readily hydrolysed by base to the isothiochroman-4-ones (11) and (12). Treatment of the ketone (11) with MeMgI followed by dehydration (P₂O₅) gave the 1,4-dimethylisothiochromene (13), while the 1,3-dimethylisothiochromene (14) was obtained by borohydride-reduction of ketone (12) and subsequent elimination of water (P₂O₅). Hydrogenation of the isothiochromenes (13) and (14) over palladium (40 atmos.; 80°) afforded the desired *cis*-1,4- and *cis*-1,3-dimethylisothiochromans (15) and (16) respectively, hydrogen addition taking place from the less hindered side, with high stereoselectivity. In neither case could *trans*-products be detected, chromatographically, spectroscopically, or through derivatives. The corresponding *cis*-sulphones (17) and (19) were prepared by permanganate-oxidation of the isothiochromans.

If the heterocyclic ring of the 1,4-dimethyl-sulphone (17) assumed a quasi-chair conformation, then it would be expected that the *cis*-isomer (*ax*-*eq*) would be less stable than the *trans* (*eq*-*eq*) isomer. However the *cis*-arrangement is preferred, since no epimerisation at C-1 could be detected in aqueous NaOH-pyridine, although the 1-deuteriated product (18) was obtained from D₂O-NaOD-pyridine. Similarly a quasi-chair conformation for the *cis*-1,3-dimethyl-sulphone (19) would orientate both methyl groups into the equatorial arrangement. However, the sulphone (19) equilibrates in pyridine-aqueous alkali to a mixture in which the *trans*-1,3-isomer (20) predominates (*ca.* 2:1 by n.m.r.). This information suggests that boat conformers are preferred for the sulphones (17) and (20), with the *cis*-1,4- and *trans*-1,3-substituents equatorial. As a test of this finding we have made a crystallographic study of *cis*-1,4-dimethylisothiochroman 2,2-dioxide (17).

The sulphone (17), C₁₁H₁₄O₂S, crystallised from aqueous ethanol, m.p. 119–120°, space group *P*2₁/*c*, with *a* = 8.44, *b* = 15.90, *c* = 8.22 Å; β = 114° 22'; *Z* = 4. *X*-Ray intensities were measured on a linear diffractometer, with 1320 reflections considered observed. The sulphur atom was located in a Patterson synthesis, and used to phase the observed intensities. A Fourier map with these data revealed all the non-hydrogen atoms. The structure was refined by block diagonal least-squares, and continued to *R* = 8.1%, omitting hydrogens and using anisotropic temperature factors for all included atoms. The final structure is shown in the Figure and clearly reveals a



FIGURE

classical boat conformation. It seems likely that the length of the C-S bonds [C(1)-S, 1.82, C(3)-S, 1.79 Å] and the C-S-C angle (103.4°, less than the tetrahedral angle) contribute to strain in the more flattened quasi-chair form, which is relieved in the boat shape.

The n.m.r. spectra of the *cis*-1,4- and *trans*-1,3-sulphones

(17a) and (20a) are in accordance with this; for both compounds $J_{3ax-4ax} = 12$ Hz. The former spectrum is essentially temperature independent in the range -100 to $+100^\circ$. The *cis*-1,3-dimethylsulphone (19) might take up a boat form with an axial and an equatorial methyl group, or adopt a quasi-chair conformation with both methyl groups

equatorial. N.m.r. spectroscopy supports the latter (19a), since the spectrum hardly changes in the range -100 to $+100^\circ$, giving no evidence for rapid conformational equilibration, and the coupling constants $J_{3ax-4ax} = 10$ and $J_{3ax-4eq} = 4$ Hz point to an axial orientation of H-3.

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