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CONFORMATION AND CONFIGURATIONAL ASSIGNMENT OF CIS AND TRANS 3,4-DIMETHYL-6-*t*-BUTYL-5,6-DIHYDRO-2*H*-THIOPYRAN-S-OXIDES AND S-METHYL CATIONS

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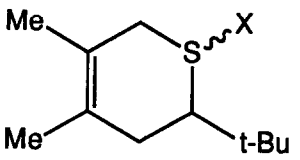
Abstract *The assignment of the cis and trans configuration of 3,4-dimethyl-6-t-butyl-5,6-dihydro-2H-thiopyran-S-oxides and S-Methyl cations is made by* ^{13}C *and* ^{17}O *NMR, and by force field calculations It is shown that the preferred conformation of all compounds is the half chair and that a previous configurational assignment of the S-oxides should be reversed*

This report describes the configurational assignment and the conformation of *cis* and *trans* 3,4-dimethyl-6-*t*-butyl-5,6-dihydro-2*H*-thiopyran-S-oxides (**1a,1b**) and S-Methyl cations (**2a,2b**), made by ^{13}C and ^{17}O NMR, and by force field calculations The present investigation is part of a more extensive study on the structure and the stereochemistry of 5,6-dihydro-2*H*-thiopyran derivatives obtained by cycloaddition of thiocarbonyl compounds and their oxides with dienes[1-2]



X = O (**1a,1b**)
X = CH_3 (**2a,2b**)

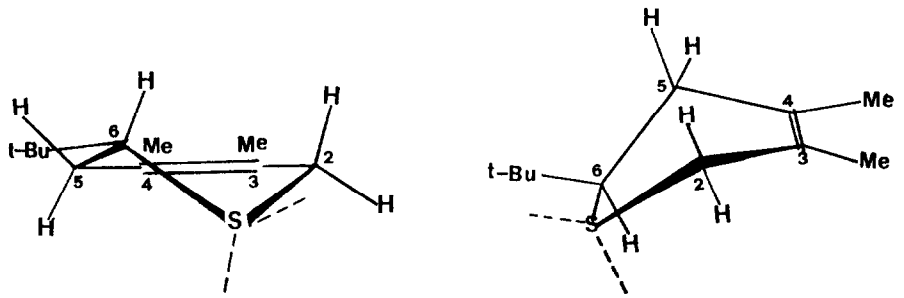
The literature on the conformational preferences of 5,6-dihydro-2*H*-thiopyran derivatives is scarce, in spite of the fact that these compounds are intermediates in the synthesis of important natural products [3-4] According to a recent IR and Raman study the 5,6-dihydro-2*H*-thiopyran ring is nonplanar and the half chair is the minimum energy conformation[5] However, for substituted 5,6-dihydro-2*H*-thiopyrans the preferred conformation is reported to be either boat or half chair, depending on the substitution pattern[6-9]

We will show that the preferred conformation of the S-oxides and S-Methyl cations examined here is the half chair and that a previously reported[1] configurational assignment of the *cis* and *trans* S-oxides should be reversed

Results and discussion

Table 1 gives the ^{13}C and ^{17}O NMR chemical shifts of **1a,1b** and the ^{13}C chemical shifts of **2a,2b** Table 2 gives the results of MM2 force field calculations of the conformation of **2a,2b** and, for comparison, also of the starting sulfide Force field calculations were not carried out on **1a** and **1b**, since, for this kind of molecules, the torsional force constants between the S^+-O^- group and the double bond are not available

The proton chemical shifts of **1a** and **1b** have already been reported[1] However, 2D carbon-proton correlated spectroscopy shows that the previous assignment of the H-5,H-5' and H-6 protons of one of the isomers is incorrect (see the experimental section) In **1a,1b** and **2a,2b** the *t*-butyl group is equatorial, as proved by the fact that the proton H-6 always has one large (11-12 Hz) *axial-axial* and one small (4-5 Hz) *axial-equatorial* ^3J(H-6,H-5) coupling constant and is, consequently, axial The geminal ^2J(H-2,H-2') coupling constants are 17 0 and 17 5 for **1a** and **2a**, respectively, and 15 0 Hz for both **1b** and **2b** No variations are observed in the proton spectrum of all compounds in the temperature range $-90°C \leqslant T \leqslant +100°C$ This indicates that there is a high degree of conformational homogeneity in all compounds, due to the biasing effect of the bulky t-butyl group Unfortunately, this makes the proton-proton coupling constants



*Half chair and boat conformations of 3,4-dimethyl-6-t-butyl-5,6-dihydro-*2H*-thiopyran, with the t-butyl group equatorial The axial and equatorial orientation of the substituent on sulfur in the S-oxides (**1a,1b**) and in the S-methyl cations (**2a,2b**) are indicated by the dashed lines*

of little help in establishing the preferred conformations Indeed, there are no rigid model compounds to which the J values of **1a,1b** and **2a,2b** could be compared and, moreover, the dihedral angles between adjacent protons in the half chair conformation are not dramatically different from those in the boat (see the figure)

Examination of the oxygen and carbon chemical shifts reported in table 1 shows that in the pairs **1a,1b** and **2a,2b** one isomer has the substituent on sulfur which is equatorial and the other which is axial For the sulfoxides this is proved by the comparison of the chemical shifts of the oxygen atom, -14 ppm and 5ppm for **1a** and **1b**, respectively, with those reported for the axial and equatorial isomers of the rigid *trans*-1-thiadecalin (-11 4 and 5 6 ppm)[10] and of several pairs of thiane-S-oxides[11] For the S-Methyl cations the axial and equatorial setting of the substituent on sulfur is proved by the $\delta(^{13}C)$ values of S-$\underline{C}H_3$, 17 5 and 25 2 ppm for **2a** and **2b**, respectively, which are the same as those found for several diastereomeric pairs of axial and equatorial thianium cations [12a-b] (*cf*, for example, the $\delta(^{13}C)$ value of the axial and equatorial isomers of 4-isopropyl-S-methyl-thianium cation, 17 4 and 25 7 ppm, respective-

ly)[12a] On the other hand, the chemical shift difference between the carbons C-2, C-6, C-5 of **1a** and **1b** and between the same carbons of **2a** and **2b** are, in fact, the differences expected on the basis of the β and

Table 1 ^{13}C chemical shifts[a] of **1a,1b,2a,2b** and ^{17}O chemical shifts[b] of **1a,1b.**

	1a	**1b**	**2a**	**2b**
C2	53 8	55 3	39 3	40 6
C3	128 5	129 3	128 0	124 5
C4	115 0	118 8	115 9	120 4
C5	24 8	32 6	27 2	31 1
C6	63 8	71 1	58 5	68 3
CH_3	20 2	19 8	20 0	19 9
	19 6	19 4	19 3	19 8
$\underline{C}(CH_3)_3$	33 6	33 7	34 9	35 2
$C(\underline{C}H_3)_3$	28 3	28 9	28 2	27 6
$S\underline{C}H_3$			17 5	25 2
$S\underline{O}$	-14 0	5 0		

a) In CD_2Cl_2, in ppm from TMS, b) In CD_2Cl_2, in ppm from external deionized water

γ effects exerted by an axial and an equatorial S^+-O^- and S^+-CH_3 group[12a-b] Since, in the axial orientation, S^+-O^- and S^+-CH_3 both give smaller β effects and larger γ effects than in the equatorial orientation[12a-b] , **1a** and **2a** have C-2, C-6 and C-5 resonating at lower frequencies than the corresponding carbons of **1b** and **2b**

However, the knowledge of the axial or equatorial orientation of the substituent on sulfur is *per se* insufficient to assign the configuration of **1a,1b** and **2a,2b** Indeed, the figure shows that the axial or equatorial orientation of the substituent on sulfur leads to opposite configurational assignments, depending on whether the preferred conformation is the half chair or the boat

The large *deshielding* shown by H-5ax ($\delta(^1H)$ = 2 65 ppm) in the isomer which has the S^+-O^- group axial (**1a**) with respect to H-5ax ($\delta(^1H)$ = 2 09 ppm) of the isomer which has the S^+-O^- group equatorial (**1b**) and with respect to the same proton in the sulphide ($\delta(^1H)$ = 2 15 ppm)[1], is a clue to understand the conformation of this isomer In fact, the deshielding experienced by H-5ax in **1a** indicates that this proton and the S^+-O^- group are syn-axial[12c,13-15] . But, H-5ax and the S^+-O^- group in **1a** can be syn-axial only if the conformation is the half chair It follows that **1a** has the *cis* configuration and, in consequence, **1b** has the *trans* Moreover, the *trans* isomer **1b** must be in the half chair conformation to allow both substituents, the t-butyl group and the the oxygen on sulfur, to be equatorial (see the figure)

Since the syn-axial effect of a S^+-CH_3 group is negligible [12c] , the same line of reasoning cannot be applied to **2a** and **2b** The fact that the proton-proton couplings of **2a** and **2b** are nearly the same as those of **1a** and **1b** and that the stereoelectronic properties of an S^+-CH_3 and an S^+-O^- group are similar[12c,13] , suggests that the S-Methyl cations should have the same conformation as the S-oxides Further evidence that the preferred conformation of **2a** and **2b** is, in fact, the half chair is provided by the force field calculations reported in table 2 According to force field calculations, the half chair with the *t*-butyl group equatorial is the preferred conformation of both **2a** and **2b**, as well as of the corresponding sulfide It is seen that

in the *cis* isomer - where the tendency of the S-Methyl group to be axial is fulfilled[16] - only the half chair with the *t*-butyl equatorial and the S-Methyl axial is populated In the *trans* isomer - where the S-Methyl group is forced to be equatorial - the strain due to the setting of the substituent on sulfur is insufficient to reverse the preferred conformation, which is still the half chair However, in this case, the calculations predict that other conformers should be populated, although to a much lesser extent. In this respect, it is worth noting that the half chair with the *t*-butyl and the S-Methyl group *both axial* has nearly the same

Table 2. MM2 force field calculated conformational energies (*E, kcal/mol*) and torsional angles (*1234* and *3456, in degrees*) of *3,4*-dimethyl-*6*-*t*-butyl-*5,6*-dihydro-*2H*-thiopyran and the corresponding *cis* and *trans* S-methyl cations

Sulfide			Sulfonium cations							
		E			*E*				*E*	
h c [a] *eq*[b]		11 58	*cis*	h c *eqax*[c]	13 95	*trans*	h c *eqeq*		15 17	
h c. *ax*		14.75		h c *axeq*	21 94		h c *axax*		15 97	
b *eq*		14 69		b *eqeq*	19 93		b *eqax*		16 02	
b *ax*		15.73		b *axax*	21 23		b *axeq*		18 14	
	1234	*3456*			*1234*	*3456*			*1234*	*3456*
h c [c] *eq*	21	15	*cis*	h c *eqax*	20	12	*trans*	h c *eqeq*	27	10
h c *ax*	12	22		h c.*axeq*	13	24		h c. *axax*	10	19
b *eq*	-53	-58		b *eqeq*	-49	54		b *eqax*	-50	57
b *ax*	-51	-54		b *axax*	-51	52		b *axeq*	-52	53

a) h c = half chair, b = boat For homogeneity, the notation *ax* and *eq* instead of *endo* and *exo* is also used for the boat conformation; b) t-butyl; c) t-butyl, methyl

energy as the boat with the *t*-butyl equatorial and the S-Methyl axial Note also that, when the substituents change from the equatorial to the axial orientation the variations of the dihedral angles for the half chair conformation are larger than those for the boat Clearly, the half chair conformation is more capable than the boat to adapt its geometry to the steric requirements of the substituents

Since the preferred conformation for both the *cis* and the *trans* S-Methyl cations is the half chair, it follows that **2a**, the isomer with the S-Methyl group axial, is the *cis* one and **2b**, the isomer with the S-Methyl group equatorial, is the *trans* The invariance of the proton spectrum of **2b** with the temperature suggests that in solution there is a higher degree of conformational homogeneity than predicted by the calculations, possibly due to further stabilization of the preferred conformation by specific solute-solvent interactions

In conclusion, the presence of the *t*-butyl group locks the thiopyran ring in the half chair conformation and the replacement of a lone pair on sulfur by an oxygen atom or a methyl group does not lead to conformational changes This result is contrary to what would have been expected on the basis of the behaviour of other substituted thiopyran derivatives whose preferred conformation is the boat, *cf*, for

example, *cis*-1,4-Dimethylisothiocroman 2,2-dioxide[6] This suggests that, in this kind of compounds, the configurational assignement of the *cis* and *trans* isomers requires the previous determination of the preferred conformations. Finally, the configurational assignement of the S-oxides **1a** and **1b**, already reported[1], must be reversed.

Experimental Section

Materials The preparation of the S-oxides (**1a, 1b**) has already been reported[1] We have found that a better separation of the two isomers (each isomer about 90% pure) is achieved by repeated elutions on silicagel plates with a mixture made of 48% light petroleum, 48% ethyl acetate and 4% methanol The proton spectra in CD_2Cl_2 were the followings *cis* isomer (**1a**) $\delta(^1H)$,ppm 3.15 (2H, s, H-2ax, H-2eq), 2 65 (1H, t, H-5ax), 2 18 (1H, m, H-6ax), 2.07 (1H, m, H-5eq), 1 77 (3H, s, Me), 1 71 (3H, s, Me), 1 08 (9H, s, t-Bu), *trans* isomer (**1b**) $\delta(^1H)$,ppm 3 44, 3.47 (2H, m (AB), H-2ax, H-2eq), 2 64 (1H, q, H-6ax), 2 43 (1H, q, H-5eq), 2 09 (1H, q, H-5ax), 1 72 (6H, s, Me), 1 34 (9H, s, t-Bu)

The sulphonium salts were obtained as 4 1 mixture of the *cis*, **2a**, and *trans*, **2b**, isomers in the following way 3,4-dimethyl-6-trimethylsilyl-6-*t*-butyl-*2H*-5,6-dihydrothiopyran (0 38 g , 1 48 mmol) was reacted with methyl trifluoromethanesulphonate in anhydrous CH_2Cl_2 (10 ml) at room temperature overnight Evaporation of the solvent gave in quantitative yield 1,3,4-trimethyl-6--*t*-butyl-6-trimethylsilyl-*2H*-5,6-dihydrothiopyranium trifluoromethanesulphonate as a solid, m p 93-95°C (diethylether), which was subjected to the desilylation without further purification This salt (0 31 g , 0 74 mmol) was dissolved in wet CH_3CN (5 ml) and treated with an equimolar amount of CsF for 2 days under argon at room temperature The solvent was removed under vacuum and the residue extracted with diethylether to remove the ring-contracted products formed during the reaction[17] The solid residue was extracted again with CH_2Cl_2, evaporation of the solvent left **2a** and **2b** (0 12 g , 75%) as a thick oil. The proton spectrum of the two isomers in CD_2Cl_2 is the following *cis* isomer (**2a**) $\delta(^1H)$,ppm 4 16 (1H, d, H-2eq), 3 64 (1H, d, H-2ax), 2 5(2H, m, H-5eq,H-5ax), 3 50 (1H, q, H-6), 2 68 (3H, s, S-C<u>H</u>3), 1 80 (6H, s , Me), 1 15 (9H, s, *t*-Butyl), *trans* isomer (**2b**) $\delta(^1H)$,ppm 3 00 (1H, d, H-2ax), 3 89 (1H, d, H-2eq), 2 5 (2H, m, H-5ax,H-5eq), 3 19 (1H, q, H-6), 2 78 (S-C<u>H</u>3), 1 90 (3H, s, Me), 1 84 (3H, s, Me), 1 14 (9H, s, t-Bu)

NMR Spectra Proton and carbon NMR spectra were recorded with a Varian XR-200 or Gemini-300 spectrometer working at 200 and 300 MHz (^1H) and 50 and 75 MHz (^{13}C) Signal assignments were made with the aid of carbon-proton (1D DEPT, 2D HETCOR NMR) correlated spectroscopy The HETCOR spectrum allowed the correct assignment of the proton resonances of **1a** In fact, the proton resonating at 2 65 ppm (H-5ax) should be correlated to the carbon resonating at 24 8 ppm, whereas the proton resonating at 2 18 ppm (H-6) should be correlated to the carbon resonating at 63 8 ppm Proton NMR low temperature experiments were carried out with the Varian Gemini-300 spectrometer using the standard variable temperature equipment, in CD_2Cl_2 (low T) and DMSO-d_6 (high T) The ^{17}O spectra were recorded at 40 67 MHz with a Bruker CXP-300 spectrometer, using a high power probe (no spinning, no lock) and a home-made 15 mm solenoid insert

Computational details Calculations were carried out on a Vax Station 2000 using the Allinger MM2 (87) programme

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