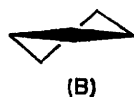
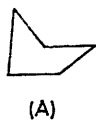


Properties and Reactions of 1,3-Oxathiolans. Part IV.¹ Conformational Analysis of 2-Alkyl-4-methyl- and 2-Alkyl-2,4-dimethyl-1,3-oxathiolans with the Aid of ¹H Nuclear Magnetic Resonance Spectroscopy and Chemical Equilibration

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Several 2-alkyl-4-methyl- and 2-alkyl-2,4-dimethyl-1,3-oxathiolans have been prepared and their conformational properties clarified by examination of acid-catalysed equilibrations of diastereoisomers and with the aid of 100 and 220 MHz ¹H n.m.r. spectroscopy. The data accord best with a moderately flexible envelope conformation which shows certain characteristic features.

CONFORMATIONAL analysis of five-membered rings has progressed relatively slowly though it has been paid increasing attention since it became clear that biased 'envelope' (A) and/or 'half-chair' (B) forms are not



necessarily adequate models for describing the conformational properties of a given five-membered ring.¹⁻⁶ Eliel *et al.*² pointed out that 1,3-dioxolans have a highly

¹ Part III, R. Keskinen, A. Nikkilä, and K. Pihlaja, *Tetrahedron*, 1972, **28**, 3943.

² W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1970, **92**, 5394.

³ R. Keskinen, A. Nikkilä, and K. Pihlaja, *J.C.S. Perkin II*, 1973, 1376.

⁴ L. A. Sternson, D. A. Coviello, and R. S. Egan, *J. Amer. Chem. Soc.*, 1971, **93**, 6529.

flexible five-membered ring where only the most bulky substituents have specific steric interactions. Pihlaja *et al.* recently³ discussed the conformations of 2,4-di-alkyl- and 2-alkyl-2,4-dimethyl-1,3-dithiolans. According to their results³ and those of Sternson *et al.*⁴ the 1,3-dithiolan ring is more puckered than that of 1,3-dioxolan although no clear-cut minimum energy conformation could be defined. However, the ¹H n.m.r. data^{3,4} were not contrary to earlier reports based on X-ray analysis⁷ and vibrational spectra,⁸ which suggest a half-chair conformation for the 1,3-dithiolan ring.

⁵ D. J. Pasto, F. M. Klein, and T. W. Doyle, *J. Amer. Chem. Soc.*, 1967, **89**, 4368.

⁶ G. E. Wilson, jun., M. G. Huang, and F. A. Bovey, *J. Amer. Chem. Soc.*, 1970, **92**, 5907.

⁷ C. Altona, H. R. Buys, and E. Havinga, *Rec. Trav. chim.*, 1966, **85**, 973.

⁸ (a) K. B. Wiberg, 'Computer Programming for Chemists,' Benjamin, New York, 1965, pp. 189-195; (b) the iterative sub-program: J. J. Kankare, personal communication.

Our previous report¹ dealt with the conformational energies and the most probable conformations of 2-alkyl-5-methyl- and 2-alkyl-2,5-dimethyl-1,3-oxathiolans. In that context we explained our results with the

testing of our views¹ on the conformational properties of alkyl-substituted 1,3-oxathiolans. (1) They are easy to synthesize from aldehydes (or ketones) and 2-mercapto-propanol. (2) If the conclusions regarding the 2-alkyl-

TABLE I
Equilibria between isomeric 2,4-dimethyl- and 2-alkyl-2,4-dimethyl-1,3-oxathiolans at different temperatures

1,3-Oxathiolans	5° K ^a	25° K ^a	45° K ^a	65° K ^a
2,4-Me ₂ (<i>trans</i> ⇌ <i>cis</i>)	0.938 ± 0.015 ^b	0.942 ± 0.019 ^b	0.947 ± 0.011 ^b	
2-Et-2,4-Me ₂ ^c	1.057 ± 0.016	1.070 ± 0.013	1.081 ± 0.014	
2-Pr ⁱ -2,4-Me ₂ ^c	1.094 ± 0.024	1.101 ± 0.021	1.108 ± 0.014	
2-Bu ^t -2,4-Me ₂ ^c	1.549 ± 0.035 ^d	1.537 ± 0.036	1.556 ± 0.033	1.580 ± 0.081

^a G.l.c. area ratios. The values shown are the means of 2–3 runs which were analysed 6–12 times. ^b Standard deviation. ^c K = [(I)]/[(II)] = [(*cis*)]/[(*trans*)]. ^d At 35°. Response ratios (r.r.) assumed to be unity. In reality, their values do not differ significantly from unity. Experimentally, r.r. = 1.007 ± 0.002 = (II)/(I) for 2-Prⁱ-2,4-Me₂ and 1.013 ± 0.005 for 2-Bu^t-2,4-Me₂.

aid of an envelope form (A) where the oxygen atom lies at the tip. Pasto *et al.*⁵ came to a similar conclusion in their study on the ¹H n.m.r. spectra of 2-substituted

5-methyl and 2-alkyl-2,5-dimethyl series¹ are correct the conformational properties of the corresponding 4-methyl series should be relatively easy to predict. (3) Chemical equilibration in conjunction with ¹H n.m.r. spectroscopy can again be applied.

TABLE 2
Thermodynamic quantities for the isomer equilibria

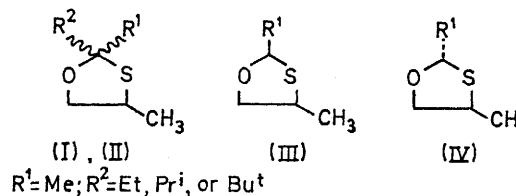
Equilibrium	ΔH°/ J mol ⁻¹	ΔS°/ J mol ⁻¹ K ⁻¹	-ΔG°(298)/ J mol ⁻¹
2,4-Me ₂ (<i>trans</i> ⇌ <i>cis</i>)	176 ± 18 ^a	0.10 ± 0.06	-146
2-Et-2,4-Me ₂	413 ± 5	1.95 ± 0.02	167
(II) ⇌ (I)			
2-Pr ⁱ -2,4-Me ₂	234 ± 9	1.59 ± 0.03	238
(II) ⇌ (I)			
2-Bu ^t -2,4-Me ₂	572 ± 42	5.49 ± 0.13	1063
(II) ⇌ (I)			

^a Only standard errors shown.

1,3-oxathiolans. However, Wilson *et al.*,⁶ who also investigated the conformational properties of 2-substituted 1,3-oxathiolans using ¹H n.m.r. techniques,

RESULTS AND DISCUSSION

The 1,3-oxathiolans studied [(I)–(IV)] were prepared by acid-catalysed condensation of 2-mercapto-propanol



with the appropriate aldehydes or ketones. The diastereoisomers of the 2-alkyl-4-methyl-1,3-oxathiolans

TABLE 3
Chemical shifts [δ (p.p.m.)]

1,3-Oxathiolan	δ _{H(2)}	δ _{H(4)}	δ _{H(5)}	δ _{H(5')}	δ _{Me(2)}	δ _{Me(4)}	δ _{R(2)}
<i>cis</i> -2,4-Me ₂ ^a	5.18	3.60	3.82	3.89	1.60	1.33	
<i>trans</i> -2,4-Me ₂ ^a	5.29	3.68	4.28	3.35	1.54	1.36	
<i>cis</i> -2-Et-4-Me ^a	5.04	3.58	3.83	3.89		1.33	1.01, ^c 1.90 ^d
<i>trans</i> -2-Et-4-Me ^a	5.14	3.61	4.27	3.38		1.33	0.98, ^c 1.77 ^d
<i>cis</i> -2-Pr ⁱ -4-Me ^a	4.89	3.51	3.80	3.89		1.32	1.02, ^c 1.00, ^e 1.99 ^f
<i>trans</i> -2-Pr ⁱ -4-Me ^a	5.00	3.55	4.26	3.34		1.31	0.98, ^c 0.95, ^e 1.96 ^f
2,2,4-Me ₃ ^g		3.57	4.07	3.66	1.58, 1.52	1.26	
2-Et-2,4-Me ₂ (I) ^a		3.57	4.16	3.69	1.55 ^b	1.32	0.98, ^c 1.82 ^d
2-Et-2,4-Me ₂ (II) ^a		3.63	4.14	3.75	1.61 ^b	1.34	1.01, ^c 1.90 ^d
2-Pr ⁱ -2,4-Me ₂ (I) ^h		3.41	4.09	3.55	1.44	1.24	0.89, ^e 0.87, ^e 1.90 ^f
2-Pr ⁱ -2,4-Me ₂ (II) ^h		3.49	4.04	3.68	1.40	1.26	0.97, ^e 0.94, ^e 2.03 ^f
2-Bu ^t -2,4-Me ₂ (I) ^g		3.505	4.33	3.62	1.60	1.33	1.02
2-Bu ^t -2,4-Me ₂ (II) ^g		3.49	4.08	3.78	1.50	1.28	1.04

^a Solvent CDCl₃. ^b These signals are not unequivocally assigned. ^c CH₃ in Et. ^d CH₂ in Et. ^e CH₃ in Prⁱ. ^f CH in Prⁱ. ^g Solvent CCl₄; 220 MHz. ^h Solvent CCl₄; 100 MHz and 4-Me decoupled.

concluded that C(5) is the tip atom in the most favoured conformation.

In general, the steric requirements of the substituents together with those of the ring seem to confine the five-membered ring to certain definite energy minima⁷⁻⁹ whose position, in the pseudorotation circuit of the ring, depends on the number and size of the substituents.¹⁻⁶ For several reasons 2-alkyl-4-methyl- and 2-alkyl-2,4-dimethyl-1,3-oxathiolans seemed suitable for further

with the exception of the *cis*- and *trans*-2,4-dimethyl compounds were unresolved with all available analytical columns. The diastereoisomers of 2-alkyl-2,4-dimethyl-1,3-oxathiolans, with the exception of the 2-ethyl compound, could be separated by preparative g.l.c. The

⁹ (a) R. C. Cookson and T. A. Crabb, *Tetrahedron Letters*, 1961, 679; (b) R. C. Cookson, J. J. Frankel, J. Hudec, and T. A. Crabb, *Tetrahedron Suppl. No. 7*, 1966, 355; (c) R. C. Cookson and T. A. Crabb, *Tetrahedron*, 1968, **24**, 2385; (d) R. Cahill, R. C. Cookson, and T. A. Crabb, *ibid.*, 1969, **25**, 4681.

isomers were characterized by physical constants, n.m.r., and chemical equilibration. Equilibrations were carried out in ether solution using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as acid catalyst. Equilibrated samples were analysed by g.l.c. to obtain equilibrium constants at various temperatures, from

Configurational Assignments.—The configurational assignments for the 2,4-disubstituted 1,3-oxathiolans were based on the n.m.r. parameters only. In the case of 2,4-dimethyl-1,3-oxathiolans the analytical conditions employed in equilibrium measurements were very similar

TABLE 4
Coupling constants (J/Hz) for the various compounds

1,3-Oxathiolan	$J_{55'}$	J_{cis}	J_{trans}	$J_{H(2)(R2)}$	$J_{(H4)Me(4)}$
<i>cis</i> -2,4-Me ₂ ^a	-8.97	5.23	2.49	5.8	6.5
<i>trans</i> -2,4-Me ₂ ^a	-9.18	5.87	8.62	5.9	6.8
<i>cis</i> -2-Et-4-Me ^a	-9.11	5.07	2.64	5.8	6.4
<i>trans</i> -2-Et-4-Me ^a	-9.03	5.57	8.47	5.95	6.6
<i>cis</i> -2-Pr ^l -4-Me ^a	-9.01	5.12	2.39	6.45	6.4
<i>trans</i> -2-Pr ^l -4-Me ^a	-8.97	5.65	8.81	6.6	6.9
2,2,4-Me ₃ ^b	-9.11	5.07	5.55		6.5
2-Et-2,4-Me ₂ (I) ^a	-9.12	5.20	6.92		6.4
2-Et-2,4-Me ₂ (II) ^a	-9.20	5.08	5.02		6.6
2-Pr ^l -2,4-Me ₂ (I) ^c	-9.22	5.38	8.38		6.2
2-Pr ^l -2,4-Me ₂ (II) ^c	-8.94	5.08	4.47		6.8
2-Bu ^t -2,4-Me ₂ (I) ^b	-9.21	5.09	10.22		6.5
2-Bu ^t -2,4-Me ₂ (II) ^b	-9.20	5.20	3.36		6.7

^a 220 MHz; CDCl_3 . ^b 220 MHz; CCl_4 . ^c 100 MHz; CCl_4 and 4-Me decoupled. $J_{cis} = J_{45}$ and $J_{trans} = J_{4'5'}$; $J_{55'}$, J_{cis} , and J_{trans} are accurate within ± 0.05 Hz.

TABLE 5

Relative population of the two possible conformer families of *trans*-2,5- and *trans*-2,4-dialkyl-1,3-oxathiolans in carbon tetrachloride and the corresponding free energy differences at 306 K. The values of J_{13} and J_{24} were obtained from the corresponding *cis*-isomers ¹

Compound	J_{obs}/Hz	J_{24}/Hz	J_{13}/Hz	κ_{IVa} or κ_{VIa}	$K = \frac{[(VIa)]}{[(IVb)]}$ or $\frac{[(IVb)]}{[(IVa)]}$	$-\Delta G^\circ/\text{J mol}^{-1}$
<i>trans</i> -2,5-Me ₂	6.69 ¹	9.78 ¹	2.49	0.576	1.36	778
<i>trans</i> -2-Et-5-Me	6.63 ¹	9.98 ¹	2.64	0.544	1.19	448
<i>trans</i> -2-Pr ^l -5-Me	6.32 ¹	10.00 ¹	2.39	0.516	1.07	163
<i>trans</i> -2-Bu ^t -5-Me	4.70 ^a	10.08 ^a	2.2 ^b	0.317	0.465	-1950
<i>trans</i> -2,4-Me ₂	8.62	9.78 ¹	2.49	0.159	5.29	4238
<i>trans</i> -2-Et-4-Me	8.47	9.98 ¹	2.64	0.206	3.86	3435
<i>trans</i> -2-Pr ^l -4-Me	8.81	10.00 ¹	2.39	0.156	5.40	4289

^a Unpublished results. ^b Estimated.^{5,6}

which enthalpy, entropy, and free energy differences between the isomers were derived by the method of least squares.

TABLE 6

Energy contributions of different pseudoaxial interactions in 1,3-oxathiolans

Alkyl group	Conformational energy/kJ mol ⁻¹ (method)	References
5a-Me	4.81 (CE, J_{45})	1
	5.10 (CE, J_{45})	This work, 1
	4.06 (CE)	11
2a-Me	4.64 (CE); 4.90 (J_{45})	1
	4.31 (CE, J_{45} : 2,5-series); 4.23 (J_{45} : 2,4-series)	This work, 1
	4.73 (CS)	5
2a-Et	4.85 (CE); 4.98 (J_{45})	1
	4.64 (CE, J_{45} : 2,5-series); 3.73 (J_{45} : 2,4-series)	This work, 1
	4.85 (CS)	5
2a-Pr ^l	5.69 (J_{45})	1
	4.94 (CE, J_{45} : 2,5-series); 4.27 (J_{45} : 2,4-series)	This work, 1
	8.41 (CS) ^a	5
2a-Bu ^t	8.4 (CE)	1
	8.58 (CE)	11
	7.07 (CE, J_{45} : 2,5-series)	This work, 1

CE = chemical equilibration, J_{45} = vicinal coupling constants, and CS = chemical shifts.

^a This seems to be an overestimate.

to those employed for the 2,5-dimethyl derivatives.¹ Hence, it was concluded that in both cases the *cis*-form had the shorter retention time. In the case of 2-alkyl-2,4-dimethyl-1,3-oxathiolans the situation was simpler. Inspection of molecular models readily showed that the *cis*-2,4-Me₂ isomer should have a greater J_{trans} (vicinal) coupling constant, the magnitude of which should increase when the size of the 2-alkyl group increases. Similarly, the J_{trans} value of the other isomer (*trans*-2,4-Me₂) should decrease with increasing size of the 2-alkyl group. Accordingly, the isomer having the shorter retention time is the *cis*-2,4-Me₂ derivative (I) (Tables 1, 2, and 5). Other available evidence agrees with this conclusion.

Chemical Equilibration.—In the case of 2-alkyl-5-methyl-1,3-oxathiolans the most probable conformations for the *cis* \rightleftharpoons *trans* equilibrium are shown in equation (1). Similarly, the equilibria for the 2,4-dialkyl series are described by equation (2). In all conformations [equations (1) and (2)] the oxygen atom lies at the tip but these conformations may be distorted more or less towards the envelope form where C(5) is the flap atom.

In the (IVa) form of *trans*-2-alkyl-4-methyl-1,3-oxathiolans there exists a pseudoaxial 2-alkyl group whereas in the other conformation [(IVb)] both alkyl groups are pseudoequatorially orientated. Thus (IVb) predomin-

ates in at least 80% depending on the values of the conformational energies of the 2-pseudoaxial alkyl groups¹ (see Tables 5 and 6). The predominance of the same ring conformation in both the 2,5-dialkyl and the 2,4-dialkyl series implies that the steric requirements of the 1,3-oxathiolan ring are as important as those of the substituents. We shall discuss in more detail the justification of the conformational equations (1) and (2) when dealing with the n.m.r. results.

which accords with equations (1) and (2). In the *cis*-2,4-Me₂ derivatives (I) the predominance of conformation (Ib), where the 2-methyl group is pseudoaxial, increases with increasing size of the second 2-alkyl group. In the *trans*-2,4-Me₂ series conformation (IIa), which includes a pseudoequatorial alkyl group, becomes more and more favoured when the size of the alkyl group increases. These conclusions, based on the inspection of molecular models, are supported by the magnitude of the vicinal

TABLE 7

Relative population of the two possible conformer families of *cis*- and *trans*-2,4-Me₂-2-alkyl-1,3-oxathiolans in CCl₄ and the corresponding free energy differences at 306 K. The values of J_{13} and J_{24} were obtained from the 2-alkyl-*trans*-2,5-Me₂-1 and *cis*-2,4-dialkyl-1,3-oxathiolans

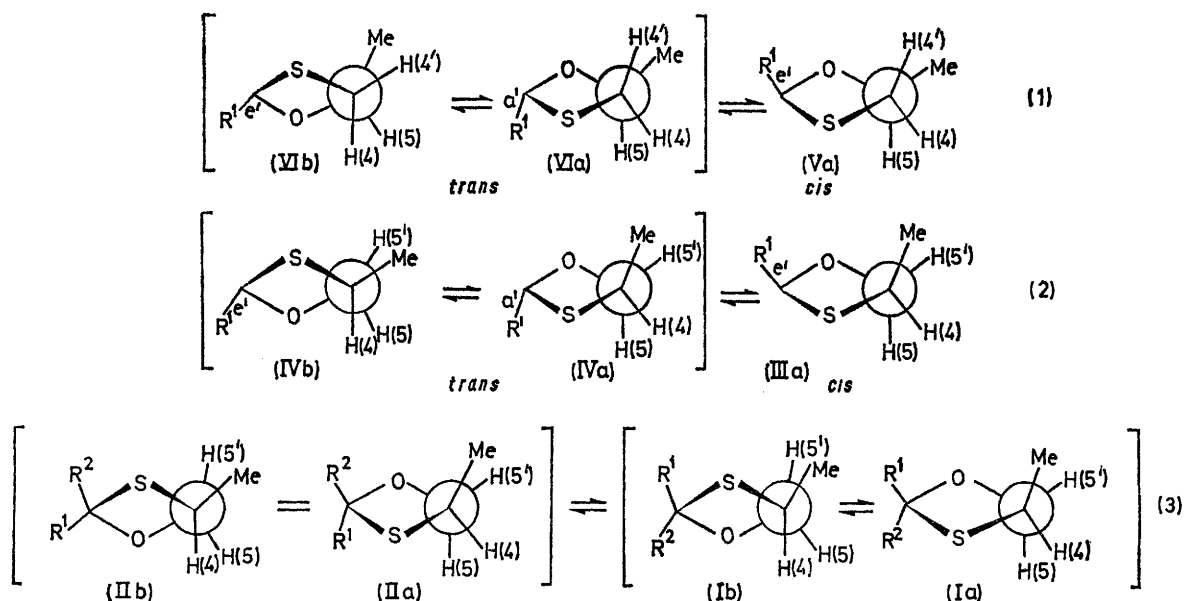
Compound	J_{obs}/Hz	J_{24}/Hz	J_{13}/Hz	α_{Ia} or α_{IIa}	$K = \frac{[(\text{Ia})]}{[(\text{Ib})]} \text{ or } \frac{[(\text{IIa})]}{[(\text{IIb})]}$	$-\Delta G^\circ(306)/\text{J mol}^{-1}$
2-Et- <i>cis</i> -2,4-Me ₂ (I) ^a	6.92	10.14	2.64	0.429	0.751	-728
2-Pr ¹ - <i>cis</i> -2,4-Me ₂ (I)	8.38	10.23	2.39	0.236	0.309	-2987
2-Bu ¹ - <i>cis</i> -2,4-Me ₂ (I)	10.22	10.64	2.2 ^b	0.050	0.053	-7489
2-Et- <i>trans</i> -2,4-Me ₂ (II) ^a	5.02	10.14	2.64	0.683	2.15	1946
2-Pr ¹ - <i>trans</i> -2,4-Me ₂ (II)	4.47	10.23	2.39	0.735	2.77	2594
2-Bu ¹ - <i>trans</i> -2,4-Me ₂ (II)	3.36	10.64	2.2 ^b	0.863	6.30	4682

^a In CDCl₃. ^b Estimated.^{5,6}

2,4-Dimethyl-1,3-oxathiolans (III) and (IV).—In this case the experimental entropy difference is practically zero, which means that the *cis*-isomer (slightly less stable; Tables 1 and 2) should possess some conformational mobility. Inspection of molecular models* reveals that the *cis*-form is able to fluctuate more readily than the *trans* about the most probable conformation (IIIa) while still leaving the relative orientations of the 4- and 5-protons nearly unchanged. This libration seems to compensate for the entropy due to mixing of the

coupling constants between 4- and 5-protons (Tables 4 and 7).

In all cases the 2-alkyl-*cis*-2,4-Me₂ isomer (I) had the shorter retention time under the g.l.c. conditions employed. The *trans*-isomers always have slightly lower enthalpy than the *cis*-isomers, an observation in agreement with that made with the corresponding 2-alkyl-2,5-Me₂-1,3-oxathiolans.¹ However, the *cis*-forms are favoured by entropy and thus they are thermodynamically more stable than the *trans*-isomers.



(IVa and b) conformations of the *trans*-isomer (*cf.* n.m.r. results).

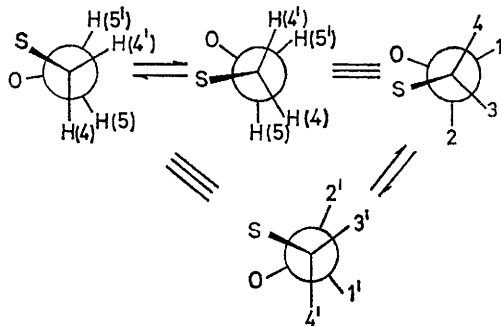
2-Alkyl-2,4-dimethyl-1,3-oxathiolans (I) and (II).—The conformational and epimeric equilibria for the 2-alkyl-2,4-dimethyl series may be illustrated by equation (3)

The small enthalpy and free energy differences are in agreement with the conformational models suggested in equation (3) since there is no widely differing non-bonded interaction on either side of the epimer equilibria.

* Dreiding, FMM, and OMBS models were used.

The *cis*-form (I; $R^1 = \text{Me}$, $R^2 = \text{Bu}^t$) has higher entropy than the *trans*-form (II; $R^1 = \text{Me}$, $R^2 = \text{Bu}^t$). In the light of the values of J_{45} (Tables 4 and 7) this must be at least partly due to more pronounced libration about the most probable conformation (Ib) of the *cis*-isomer.

N.m.r. Spectra.—The ^1H n.m.r. spectra of 2-substituted, 2,2-disubstituted, 2,5-disubstituted, and 2,2,5-trisubstituted 1,3-oxathiolans have been previously investigated.^{1,5,6} Typical H(4)–H(5) vicinal coupling constants extend over the following ranges (Scheme):



SCHEME

J_{14} 4.4–5.8; J_{13} 2.2–3.2; J_{24} 9.6–11.0; J_{23} 3.8–5.5 Hz.*

As stated before we were able to separate only the diastereoisomers of 2-Prⁱ- and 2-Bu^t-2,4-Me₂-1,3-oxathiolans by preparative g.l.c. and hence most of the spectra were recorded on isomer mixtures. To get sufficient resolution most were recorded at 220 MHz or at least at 100 MHz. In this way the spectra for all isomer pairs could be analysed though assignment of some alkyl group signals remained equivocal (Table 3). The chemical shifts of the *cis*- and *trans*-series are in all cases clearly distinguishable and the values of calculated coupling constants (Table 4) are in agreement with the selected most probable conformations. The 4- and 5-protons of the 1,3-oxathiolans studied formed an 'ABX' or 'AMX' system, from which the chemical shifts and coupling constants between these protons are simply resolved and the final parameters computed with the aid of an iterative ABC program.⁸

The values of the geminal coupling constants for 1,3-oxathiolans are clearly more negative than those for 1,3-dioxolans but less negative than those for 1,3-dithiolans. In 1,3-dioxolans the geminal coupling constants range from –7.1 to –7.3 Hz,² in 1,3-oxathiolans from –8.9 to –9.2 Hz on the oxygen side and from –9.7 to –10.3 Hz on the sulphur side,¹ whereas in 1,3-dithiolans the range is between –11.2 and –11.5 Hz.³ The great decrease in the J_{gem} values when passing from 1,3-dioxolans to 1,3-dithiolans *via* 1,3-oxathiolans is due to the electronegativity difference between oxygen and sulphur and to the increased puckering of the ring.^{9,10}

* In the following discussion we shall assume that $J_{24} = J_{3'4'}$ and $J_{13} = J_{1'2'}$. Actually, these couplings for the 5- and 4-methyl series may differ somewhat in value though the above assumption is not too crude.

The most informative n.m.r. data are the values of the vicinal coupling constants (Tables 4, 5, and 7). In our earlier report¹ we pointed out that *cis*-2-alkyl-5-methyl-1,3-oxathiolans consist principally of type (Va) conformations, in which the H(4)–H(5) coupling constants correspond to J_{24} and J_{23} [equation (1) and Scheme]. This is true for the 2-alkyl-2,5-dimethyl derivatives also. On the contrary, *trans*-2-alkyl-5-methyl-1,3-oxathiolans were mixtures of two separate (series of) pseudorotamers of which one [(VIa)] has the J_{24} , J_{23} arrangement [Scheme and equation (1)] and the other the J_{13} , J_{14} arrangement. If the 1,3-oxathiolan ring itself has appreciable steric requirements, the most probable conformations of the 2-alkyl-4-methyl derivatives should be like those in equation (2). Accordingly, *cis*-2,4-dialkyl derivatives should have the J_{13} , J_{14} arrangement (Scheme), which is strongly supported by the values of the experimental couplings (Tables 4 and 5). Similarly, *trans*-2,4-dialkyl forms should be mixtures of conformations (IVa and b). The observed values of J_{45} are again in agreement with this conclusion.

The analysis of the spectra of the 5-methyl derivatives¹ did not lead to the value of J_{13} in any case, and hence we carried out some calculations on the conformational equilibria with the aid of the sums of the coupling constants in question.¹ If we now suppose that the *cis*-2,5- and *cis*-2,4-dialkyl derivatives represent 'anacomeric' models for the J_{24} , J_{23} and the J_{13} , J_{14} arrangements (Scheme), respectively, it is possible to estimate the proportions of (VIa and b) or (IVa and b) in both *trans*-series from the expressions (4) and (5). J_{23} and J_{14}

$$\textit{trans-2,5: } J_{\text{obs}} = x_{\text{VIa}}J_{24} + (1 - x_{\text{VIa}})J_{13} \quad (4)$$

$$\textit{trans-2,4: } J_{\text{obs}} = x_{\text{IVa}}J_{13} + (1 - x_{\text{IVa}})J_{24} \quad (5)$$

are so close in value that they cannot be used similarly. However, we want to emphasize before proceeding with the analysis that even the *cis*-isomers may include other conformations [*e.g.* type (Vb)] up to say 10%.

Table 5 presents a summary of the vicinal coupling constants for the *trans*-isomers and the values of J_{24} and J_{13} , which were used in each estimate [equations (4) and (5)]. Also the conformational equilibrium constants and free energy differences for the *trans*-dialkyl derivatives are shown in Table 5.

Taking into account the enthalpy change –4657 J mol^{–1} measured earlier¹ for the *trans* \rightleftharpoons *cis* equilibrium of 2,5-dimethyl-1,3-oxathiolans and the data in Table 5 we were able to estimate the conformational energy for a pseudoaxial 5-methyl group (5104 J mol^{–1}) and for a pseudoaxial 2-methyl group (4326 J mol^{–1}). The enthalpy change¹ for the *trans* \rightleftharpoons *cis* equilibrium of 2-Et-5-Me-1,3-oxathiolans was 4874 J mol^{–1}. Practically, the same value is obtained from the pseudoaxial interactions of a 5-methyl group and a 2-ethyl group (4657 J mol^{–1}; *cf.* Table 5).

¹⁰ M. Anteunis, G. Swaelens, and J. Gelan, *Tetrahedron*, 1971, 27, 1917.

For the conformational energy of a pseudoaxial 2-isopropyl group the data in Table 5 lead to the value $5104 - 163 = 4941 \text{ J mol}^{-1}$. Thus it is evident, as presumed in our previous paper,¹ that the interactions due to pseudoaxial alkyl groups increase in the order $\text{Me} < \text{Et} < \text{Pr}^i < \text{Bu}^t$. For the Bu^t group the value 7054 J mol^{-1} is obtained. All the present estimates are close to those presented earlier (Table 6).¹ It is worth mentioning that our recent results again support the view that the *cis*-forms of the 2- Pr^i -5-Me¹ and 2- Bu^t -5-Me¹¹ derivatives are not strainless in comparison with the *trans*-forms. Moreover, the *trans*-conformations (VIa) may decrease the pseudoaxial character of the 2-alkyl groups by distortion towards the envelope form where C(5) is the flap atom. Thus it is not surprising that their conformational interactions depend on other substitution.

In the *trans*-2,4-dialkyl derivatives the free energy difference between conformations (IVa and b) should represent the interaction due to the pseudoaxial 2-alkyl group. The calculated free energy differences [equation (5)] are, however, somewhat smaller than expected on the basis of the above estimates (*cf.* Table 6) though the more stable conformation (IVb) might in addition be favoured by the rotational entropy of the alkyl groups (Et and Pr^i). If, however, C(5) becomes the flap atom, steric hindrance to free rotation of the ethyl and isopropyl groups in conformation (IVa) decreases, and the observed free energy differences represent better the extra enthalpy contributions of the alkyl groups. This conclusion is in agreement with the $J_{\text{H}(2)\text{R}(2)}$ values which are not greatly higher for the *trans*-series.

In general, inspection of molecular models and the values of the vicinal coupling constants of the 2,5- and/or 2,4-dialkyl derivatives reveals that the energy difference between the envelope forms (A) with the oxygen or C(5) as the flap atom is not high enough to 'bias' the ring in either of these conformations. Thus the steric requirements of the substituents may greatly affect the position of the energy minimum.

The values of J_{45} suggest that both isomeric 2-alkyl-2,4-dimethyl-1,3-oxathiolans are mixtures of conformations. Using equations (4) and (5) and the coupling constants shown in Table 7 we calculated the free energy differences between conformations (Ia and b) and conformations (IIa and b).

In the *cis*-2,4-Me₂-2-alkyl series the differences are mainly due to the free energy differences between pseudoaxial 2-alkyl and 2-methyl groups. Also the rotational entropy of the 2-alkyl groups favours conformation (Ib), and hence the respective free energy differences are somewhat greater than expected on the

basis of the results in Tables 5 and 6. In conformation (Ia) the *cis*-2- Bu^t -2,4-Me₂ derivative cannot decrease appreciably the axial character of the Bu^t group without increasing the transannular Me-Me interaction between positions 2 and 4. Thus the large free energy difference, 7.5 kJ mol^{-1} , in this case probably represents the maximum for the conformational energy of a 2- Bu^t group ($4.2 + 7.5 = 11.7 \text{ kJ mol}^{-1}$).^{1,5}

In the *trans*-2,4-Me₂-2-alkyl series the estimated free energy differences (Table 7) are also mainly due to the free energy differences between pseudoaxial 2-alkyl and 2-methyl groups. In all cases conformation (IIb) with a pseudoaxial 2-alkyl group (2-Me pseudoequatorial) is the less stable and its relative amount depends on the size of the alkyl group. However, the estimated free energy differences for the equilibrium (IIb) \rightleftharpoons (IIa) [equations (4) and (5)], especially that of the 2- Bu^t derivative, deviate greatly from those obtained for the corresponding equilibrium (Ib) \rightleftharpoons (Ia) of the *cis*-isomers.

In conformation (IIa) the oxygen atom lies predominantly at the tip since libration towards the conformation with C(5) as the flap atom increases the interaction between 2-R and 4-Me. Similarly, (IIb) has an envelope structure where C(5) is the flap atom and is hence able to decrease the pseudoaxial character of the 2-alkyl group appreciably. In the ethyl case, however, (IIa) still fluctuates more freely than (IIb) and owing to the resulting entropy contribution the former is more favoured than expected on the basis of the results for the *cis*-set (Table 7).

Conclusions.—The results of this study together with those presented earlier support the view that the 1,3-oxathiolan ring is much less flexible than the 1,3-dioxolan ring.^{1,2} Together with the results for the 1,3-dithiolan ring^{3,4} it demonstrates the tendency of a sulphur atom to increase the puckering of the ring. All the collected data are explainable with the aid of envelope structures (A) where either O(1) or C(5) is the flap atom. This postulate is in accordance with the opinion of Pasto *et al.*⁵ and Wilson *et al.*⁶ Although we cannot ascertain whether the ring itself has a clear-cut preference for a certain conformation, the steric requirements of the ring are evident and furthermore the depths of separate energy minima in the conformational motion depend on the substitution pattern of the ring.

As concluded before,¹ a methyl substituent in the 4-position has no great steric demands of its own though further substitution may reflect the effect of this methyl group in the most probable conformation. Though the pseudoaxial character usually decreases the conformational energy as compared with that observed for purely axial alkyl groups¹²⁻¹⁶ the substituents at positions 2 and

¹¹ K. Pihlaja, A. Nikkilä, and R. Keskinen, unpublished results.

¹² K. Pihlaja and P. Äyräs, *Acta Chem. Scand.*, 1970, **24**, 204, 531.

¹³ (a) K. Pihlaja, *Ann. Univ. Turkuensis Ser A* **1**, 1967, No. 114; (b) K. Pihlaja and S. Luoma, *Acta Chem. Scand.*, 1968, **22**, 2401; (c) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 3444.

¹⁴ E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, 1969, **91**, 2703.

¹⁵ P. Pasanen and K. Pihlaja, *Tetrahedron*, 1969, **28**, 2617.

¹⁶ (a) K. Pihlaja, D. M. Jordan, A. Nikkilä, and H. Nikander, *Adv. Mol. Relaxation Processes*, 1973, **6**, 227; (b) K. Pihlaja and A. Tenhosaari, *Suomen Kem.* 1970, **43B**, 175; (c) K. Pihlaja and J. Jalonen, *Org. Mass Spectrometry*, 1971, **5**, 1363; (d) J. Jalonen, P. Pasanen, and K. Pihlaja, *ibid.*, 1973, **7**, 949.

5 of the 1,3-oxathiolan ring show conformational interactions, the magnitude of which varies from 4 to 8 kJ mol⁻¹ (Table 6).

Finally, we emphasize that the 1,3-oxathiolan ring is an example of a five-membered ring where certain conformational models illustrate the real situation better than a freely interconverting circuit of pseudorotamers. However, there still exist several possibilities for pseudolibration, which make complete quantification of the information obtained difficult. No doubt, the most favoured conformations [equations (1)–(3)] have envelope structures where either O(1) or C(5) is the flap atom. The minimum energy conformation may, in reality, be an intermediate between these limiting structures or may be more or less distorted towards the nearest half-chair conformation. This moderate flexibility leads to the situation that the exact conformation depends greatly on the substitution and *vice versa* the conformational energies of pseudoaxial substituents depend on the conformational requirements of the ring and the other substituents.

EXPERIMENTAL

2-Mercaptopropanol (ca. 30%) was prepared from CH₃CH(SH)CO₂H (Fluka AG) by conventional LiAlH₄ reduction, b.p. 55° at 11 mmHg, *n*_D²⁰ 1.4900, *d*₄²⁰ 1.0687 g cm⁻³. 1,3-Oxathiolans were prepared and purified as described previously.¹ The *cis*- and *trans*-forms were separated in the case of 2-Pr^l- and 2-Bu^t-2,4-Me₂ derivatives only (Table 8).¹

Equilibrations.—These were carried out at three or four temperatures and the values of the thermodynamic parameters were calculated by the method of least squares (Tables 1 and 2). Diethyl ether was used as solvent and BF₃·Et₂O as catalyst. The reaction solutions consisted of 10% v/v of the substrate with 10 mole % of catalyst. Before analysis each sample was quenched by addition of methanolic sodium methoxide. In all cases equilibria were established within 6 weeks. If both stereoisomers in question were available (2-Pr^l-2,4-Me₂ and 2-Bu^t-2,4-Me₂) the equilibration was started using samples containing initially one of the two isomeric forms. 2–4 Samples were equilibrated in each case. Equilibria were considered as reached when the same and reproducible area ratios were obtained from both initially *cis*-rich and *trans*-rich samples or two separate samples were formed which were analysed with an interval of at least 2 weeks.

The equilibria were analysed using a Perkin-Elmer F11 gas chromatograph equipped with a 2 m × $\frac{1}{8}$ in column containing 5% Carbowax 20M on Chromosorb G (60–80 mesh). To separate the isomeric 2,4-Me₂- and 2-Et-2,4-Me₂-1,3-oxathiolans a 10 m × $\frac{1}{8}$ in column containing 5% Carbowax 20M and 0.5% KOH on Chromosorb G was used.

TABLE 8

Physical constants of the alkyl-substituted 1,3-oxathiolans prepared

Compound	B.p. [<i>t</i> /°C (<i>p</i> /Torr)]	<i>n</i> _D ²⁰	<i>d</i> ₄ ²⁰ / g cm ⁻³	Yield (%)
(III, IV; R = H)	70–74 (64)	1.4902	1.0860	22
(III, IV; R = Me)	68–70 (64)	1.4720 ^a	1.0189	27
(III, IV; R = Et)	86–88 (63)	1.4718 ^a	0.9963	58
(III, IV; R = Pr ^l)	97–98 (59)	1.4692 ^a	0.9720	53
(I, II; R ¹ = R ² = Me)	69–71 (68)	1.4648	0.9775	53
(I, II; R ¹ = Et, R ² = Me)	80–81 (52)	1.4690 ^a	0.9748	70
(I; R ¹ = Pr ^l , R ² = Me)	87 (50)	1.4692	0.9649	
(II; R ¹ = Pr ^l , R ² = Me)	93–94 (62)	1.4733		51 ^a
(I; R ¹ = Bu ^t , R ² = Me)	109–110 (56) ^a	1.4719	0.9547	35 ^a
(II; R ¹ = Bu ^t , R ² = Me)		1.4776	0.9634	

^a For mixtures of diastereoisomers. The compounds had ¹H n.m.r., i.r., and mass spectra^b in accordance with their structures. ^b Cf. D. J. Pasto, *J. Heterocyclic Chem.*, 1967, **6**, 175.

N.m.r. Spectra.—These were recorded on a Varian HA 100 spectrometer in Finland and on the S.R.C. 220 MHz spectrometers at Runcorn and Harwell. In general, 10% v/v solutions were used and the solvents were CCl₄ or CDCl₃ (Tables 3 and 4).

Spectral analysis. The spectra examined in this work consist of spin-spin multiplets of the AMX or ABX types with extra couplings for three protons due to the methyl substituents. The extra couplings from the methyl groups were always treated on a first-order basis and the final parameters computed using an iterative ABC program on an IBM 1139 computer in Turku.⁸ Finally the analyses of spectra were confirmed by comparison of observed spectra with those generated by the LAOCOON III program on an Elliott 4130 computer in Stirling.

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