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THE STEREOCHEMISTRY OF *cis*- AND *trans*-3,6-DIMETHYL-*o*-DITHIANE[1]

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Abstract—*cis*- and *trans*-3,6-dimethyl-*o*-dithiane have been prepared from 2,5-dibromohexane through the dithiocyanate and the diisothiouronium salt. Differences in the methylene hydrogen NMR spectra are diagnostic for distinguishing between the two isomers. Evidence is presented which indicates a magnetic anisotropic effect by the S—S bond. A marked difference in the intensity of the UV spectra of the two isomers is noted. There is a direct correspondence between the physical properties of these compounds and the *cis*- and *trans*-1,4-dimethylcyclohexanes.

AS PART of a general study of cyclic disulphides and related compounds *cis*- and *trans*-3,6-dimethyl-*o*-dithiane (I and II) have been synthesized. PMR studies previously have shown that the *o*-dithianes are analogous geometrically to the cyclohexanes.[3,4] In this paper we wish to report on the assignment of structures to the *cis*- and *trans*-3,6-dimethyl-*o*-dithianes based upon their PMR spectra and other physical data and to comment briefly on the stereochemistry of the synthesis of these compounds from 2,5-dibromohexane.

Assignment of configurations to cis- *and* trans-3,6-*dimethyl*-o-*dithiane*

The synthesis of 3,6-dimethyl-*o*-dithiane from 2,5-dibromohexane by classical methods through the dithiol or the dithiocyanate provided advantages over its synthesis from acetonylacetone from which both the yield and quality of the product were poor.[5] From a mixture of *meso* and racemic 2,5-dibromohexane each of these classical methods gave a mixture of the *cis*- and *trans*-3,6-dimethyl-*o*-dithianes which was separated by gas-liquid chromatography. That isomer which was more strongly adsorbed on a polydiethylene glycol succinate column proved to be the *cis*-isomer in agreement with the relative retention volumes of the *cis*- and *trans*-1,4-dimethylcyclohexanes on silicone in a capillary column.[6]

Assignment of structures to the *cis*- and *trans*-isomers could be made on the basis of their NMR spectra (Fig. 1). The most distinguishing difference between the spectra of the two compounds is apparent in the resonance absorption by the methylene

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[3] G. Claeson, G. M. Androes and M. Calvin, *J. Amer. Chem. Soc.* **82**, 4428 (1960); **83**, 4357 (1961).

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protons in the region $\tau \approx 7{\cdot}5$: peak width at one-half peak height for the *trans*-isomer is about 46 c/s whereas for the *cis*-isomer it is only 6 c/s. The difference is a consequence of freezing of the chair form of the *trans*-isomer into a single conformer by the two equatorial methyls, leading to the intricate pattern of spin-spin coupling observed for the rigidly fixed equatorial and axial hydrogens of the methylene groups. The *cis*-isomer, with two energetically equivalent mirror-image conformations, flips rapidly at room temperature leading to a near equivalence for all of the methylene hydrogens.[7] As a consequence the methylene spectrum for the *cis*-isomer, although

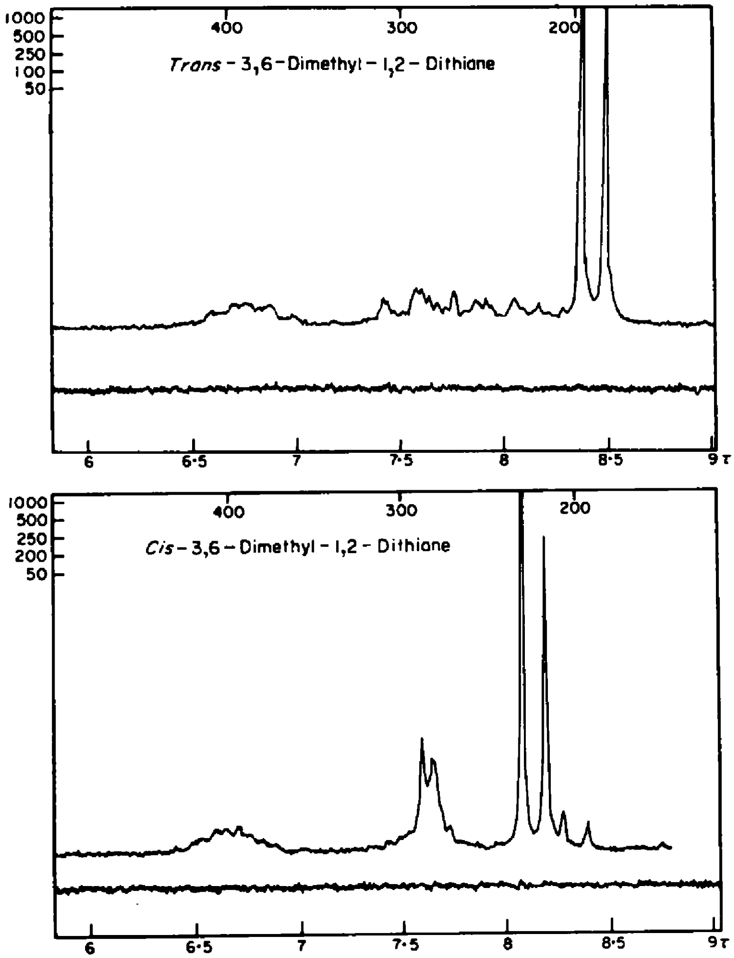

Fig. 1. NMR spectra of 30% solutions of *trans*- and *cis*-3,6-dimethyl-*o*-dithiane in carbon tetrachloride. The *cis*-3,6-dimethyl-*o*-dithiane contained 5% of the *trans*-isomer.

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[7] All of the methylene hydrogens of the *cis*-isomer are, in fact, not in the time-average completely magnetically equivalent. For example, one of the hydrogens of each methylene group makes a dihedral angle of 60° with the adjacent methine hydrogen in both conformations of the ring, whereas the other methylenic hydrogen on each carbon makes an angle with the adjacent methine hydrogen of 60° for one-half the time and 180° for one-half the time.

still complex, is much simpler than that for the *trans*-isomer. Rather similar conclusions concerning *cis*- and *trans*-1,4-dimethylcyclohexane have been drawn from their NMR spectra.[8,9]

Resonance absorption by the methyl hydrogens of the *trans*-isomer is at $\tau = 8{\cdot}35$ ($J = 7{\cdot}0$). If one assumes that the *trans*-isomer exists essentially in a single conformation with both methyls equatorial and takes $\tau = 8{\cdot}35$ as a measure of the chemical shift for an equatorial methyl, one can calculate from the observed τ-value for the methyls of the *cis*-isomer ($\tau = 8{\cdot}14$, $J = 7{\cdot}0$) a τ-value for an axial methyl in the 3-position of the *o*-dithiane ring. As the methyl resonance for the *cis*-isomer is a time-weighted average for the axial and equatorial methyls, the equation[10] $\tau_{cis} = \frac{1}{2}(\tau_E + \tau_A)$ may be used where τ_{cis} = the observed τ for the methyls of the *cis*-isomer, τ_E = the observed τ for an equatorial methyl (τ for the methyls of the *trans*-isomer[11]), and τ_A = the τ of an axial methyl. From this τ_A is found to be 7·93, an extremely low value for a methyl attached to a saturated carbon.[13] In contrast to these results where the hydrogens of an axial methyl in the 3-position of *o*-dithiane are less shielded than those of an equatorial methyl in the same position, the hydrogens of a methyl substituted axially on the cyclohexane ring generally appear to be more highly shielded than are the hydrogens of an equatorial methyl.[8,14] Exceptions which may result from crowding of the axial methyl in cyclohexane systems have been noted.[15] The shift of about 0·42 ppm to lower field for an axial methyl in the 3-position of *o*-dithiane cannot be attributed to increased crowding but must result from deshielding by the magnetically anisotropic S—S bond.

The correspondence between a number of physical properties of the isomeric 3,6-dimethyl-*o*-dithianes and the 1,4-dimethylcyclohexanes is apparent from Table 1.

The molar absorptivity at 2860 A° of *cis*-3,6-dimethyl-*o*-dithiane (321) is almost twice that of the *trans*-isomer (174). The difference in the position of the absorption from that in open-chain disulphides at about 2500 A° results from dihedral strain about the S—S bond in the six-membered ring.[16,17] The higher molar absorptivity for *cis*-3,6-dimethyl-*o*-dithiane with one axial and one equatorial methyl undoubtedly is a consequence of a larger transition moment for this less symmetrical of the two isomers.[18]

The only major difference in the IR spectra of the two isomers were bands at

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[11] The methyl resonance of methylcyclohexane is shifted 0·076 ppm to low field by addition of a *trans*-4-methyl group in *trans*-1,4-dimethylcyclohexane.[12] Clearly a similar shift does not result with the analogous *o*-dithianes since the τ-value for the 3-methyl of 3-methyl-*o*-dithiane is 8·27 (unpublished data) whereas for *trans*-3,6-dimethyl-*o*-dithiane $\tau = 8{\cdot}35$. If one uses 8·27 as a measure of the chemical shift for the equatorial methyl of *cis*-3,6-dimethyl-*o*-dithiane, τ_A is calculated to be 8·01.

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Table 1. Properties of *cis*- and *trans*-3,6-dimethyl-*o*-dithiane

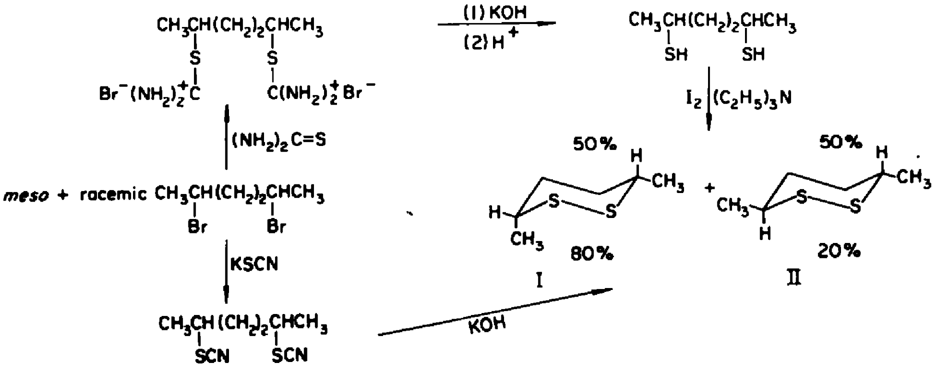
Property being compared	Compound	*cis*-Isomer	*trans*-Isomer
M.p.	Dithiane	−40 – −39·5°[a]	17·1–17·4°
	Cyclohexane[b]	−87·7°	−37·09°
Methylene peak width, NMR	Dithiane[c]	6[a]	46
(c/s at ½ peak height)	Cyclohexane[d]	4·8	19·2
n_D^{25}	Dithiane	1·5409[a]	1·5306
	Cyclohexane[b]	1·4273	1·4185
Relative retention volume, GLC	Dithiane[e]	1·22	1·00
	Cyclohexane[f]	1·22	1·00
λ_{max}	Dithiane[g]	2860 Å	2860 Å
ε	Dithiane[g]	321	174

[a] As determined by GLC, the *cis*-3,6-dimethyl-*o*-dithiane contained 5% of the *trans*-isomer. [b] A. F. Forziati, A. R. Glasgow, Jr., C. B. Willingham, and F. D. Rossini, *J. Research Natl. Bur. Standards* **36**, 129 (1946). [c] At 60 mc/s. [d] At 40 mc/s.[8] [e] At 112° with diethylene glycol succinate polyester on diatomaceous earth. [f] At 51° with silicone in a capillary column.[6] [g] In 95% EtOH.

1045 cm^{-1} and 1100 cm^{-1} present in the spectrum of the *cis*-isomer which were absent from the spectrum of the *trans*-isomer. By analogy with cyclohexane derivatives, these may well result from skeletal vibrations of the less symmetrical *cis*-isomer.[19]

Stereochemistry of the synthesis of cis- *and* trans-3,6-*dimethyl*-o-*dithiane*

The 2,5-dibromohexane from which the dithianes were prepared was a mixture of *meso* and racemic forms. By analytical gas chromatography the mixture was shown to consist of about 80% of one of these isomers and 20% of the other, but the identity of each fraction was not determined. The unfractionated mixture of isomers was used for both syntheses. Reaction of the mixed dibromides through the diisothiouronium salt and the dithiol yielded a 50:50 mixture of *cis*- and *trans*-3,6-dimethyl-*o*-dithiane. Reaction of the same mixed dibromides through the dithiocyanate, a method much to be preferred over the synthesis through the diisothiouronium salt, gave a mixture which contained 80% *cis*- and 20% *trans*-3,6-dimethyl-*o*-dithiane. The composition of the mixed dithianes was determined by gas chromatography and confirmed by comparison of experimental values with the known indices of refraction and molar absorptivities of the pure *trans*-isomer and the 95% pure *cis*-isomer.



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[19] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* (2nd Edition), p. 31. Methuen, London (1958).

One inversion at each of the two asymmetric centres is involved in each sequence of reactions from the dibromide to the dithiane. As a consequence, whether the synthesis is carried out through the dithiocyanate or the diisothiouronium salt, if no racemization occurs the *meso*-dibromide should give *cis*-3,6-dimethyl-*o*-dithiane and the racemic dibromide should give the *trans*-isomer. For two reasons it would be unprofitable at this time to attempt an interpretation of the differences in *cis* : *trans* ratios which resulted from the two different syntheses: (1) it is not known whether the *meso*-2,5-dibromohexane or the racemic compound was the preponderant isomer in the starting mixture, and (2) the yields of products, although good for multi-step syntheses, are not sufficiently high that the ratios of isomers may not have been upset by preferential loss of one isomer during the reactions or isolations.

EXPERIMENTAL

2,5-*Dibromohexane*. This compound, prepared[21] from 2,5-hexanediol,[22] was distilled to give an 88% yield of product, b.p. 122–123° (22 mm) n_D^{25} 1·5013 (lit.[21] b.p. 98–100° at 20 mm, n_D^{20} 1·4997–1·4999; n_D^{20} 1·5007 for the racemic isomer[23]).

The 2,5-dibromohexane was subjected to GLC with Apiezon M on Chromosorb P at 110°. With a He flow rate of 50 ml/min two partially separated peaks appeared after 10 and 12 min; the ratio of peak hts was approximately 4:1 respectively.

cis- *and* trans-3,6-*Dimethyl*-1,2-*dithiane*

A. *Via the diisothiouronium salt.* 2,5-Dibromohexane, 160 g (0·66 mole), was added to 152 g (1·98 moles) thiourea in 120 ml water. After 9 hr of reflux, 192 g (3·43 moles) KOH in 345 ml water was added, and hydrolysis was allowed to proceed at reflux in N_2 atm. for 6 hr. The reaction mixture then was cooled and acidified with dil. H_2SO_4. The upper layer was removed, the aqueous layer was extracted with several portions of $CHCl_3$, and the organic phases were combined. The total yield of impure 2,5-*hexanedithiol*, obtained as a pale yellow liquid after removal of solvent by distillation, was 72 g (0·48 mole, 73%). Because of its unpleasant odour and its tendency to polymerize, the dithiol was not purified.

The total quantity of dithiol was dissolved in $CHCl_3$ and 101 g (1·0 mole) of freshly distilled triethylamine was added to the solution.[24] The dithiol was then oxidized under N_2 by addition of a slight exceess of I_2, as evidenced by the colour. The colour was then discharged by addition of a small amount of the $CHCl_3$ solution of the dithiol which had been reserved for this purpose. After the reaction mixture had been washed with water and H_2SO_4 and dried over $MgSO_4$, the solvent was removed by distillation and the 3,6-dimethyl-*o*-dithiane was distilled at 78–79° (5 mm) (lit.[5] b.p. 66–69° at 10 mm) to yield 37·5 g (0·25 mole, 52%) with an n_D^{25} 1·5352 (lit.[5] n_D^{25} 1·5461), λ_{max} 2860 Å ($\varepsilon = 248$) in 95% EtOH. (Found: C, 48·80; H, 8·32; S, 43·00. Calc. for $C_6H_{12}S_2$: C, 48·59; H, 8·16; S, 43·25%.)

The mixed dithianes were chromatographed at 112° through a column containing diethylene glycol succinate polyester on diatomaceous earth. The *trans*-3,6-dimethyl-*o*-dithiane emerged after 14 min with a flow of 60 ml/min of He and was cleanly separated from the *cis*-3,6-dimethyl-*o*-dithiane which emerged after 17 min. Samples for use in determining the physical properites of the two isomers were obtained by about 125 repetitions of the GLC separation on 12μl samples of the mixed isomers. The physical data determined on pure *trans*-3,6-dimethyl-*o*-dithiane and on 95% *cis*-3,6-dimethyl-*o*-dithiane which contained 5% of the trans isomer are recorded in Table 1.[25]

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[25] The NMR spectra were determined by Mr. K. Eisentraut on a Varian Model A-60 instrument using 30% solutions in carbon tetrachloride with tetramethylsilane as the external standard. We wish to acknowledge a grant to Rensselaer from the National Aeronautics and Space Administration which permitted purchase of the instrument.

B. *Via the dithiocyanate.* 2,5-Dibromohexane (96 g, 0·39 mole) was added to a boiling solution of KSCN (78 g, 0·80 mole) in 400 ml absolute MeOH. After refluxing for 5 hr, 77 g (0·65 mole, 81 %) of KBr bromide was separated by filtration. Removal of the solvent by distillation left 75 g (0·38 mole, 95 %) crude 2,5-*dithiocyanatohexane*. The crude dithiocyanate was dissolved in 420 ml MeOH and a solution of 42 g (0·75 mole) KOH in 420 ml MeOH was added.[26–31] The mixture was allowed to stand overnight after which it was poured on ice and extracted with $CHCl_3$. After drying of the extract (Na_2SO_4) and removal of the solvent, the product was distilled to yield 22·1 g (0·150 mole, 38 %) of a mixture of *cis*- and *trans*-3,6-dimethyl-1,2-dithiane, b.p. 60–61° (0·5 mm), n_D^{25} 1·5388 (lit.[5] n_D^{25} 1·5461).

GLC was used to separate the isomers. The amount of *trans*-3,6-dimethyl-1,2-dithiane, which emerged after 14 min, was about one-fourth that of the *cis*-3,6-dimethyl-1,2-dithiane, which emerged after 17 min.

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