CONDENSED SYSTEMS FROM THILANE 1,1-DIOXIDE.

4.* PMR SPECTRA OF cis- AND trans-PERHYDROTHIENO[3,4-d]-OXA(THIA)ZOLE 5,5-DIOXIDES

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Examination of the PMR spectra of eleven bicyclic thiolane 1,1-dioxide derivatives has enabled those features of the spectral parameters characteristic of the cis- and trans-orientation of the two condensed five-membered heterocycles to be established. The proton coupling constants show that the conformation of the 1,1-dioxothiolane ring in both types of compound in solution differs from that in the crystalline state, as determined by x-ray analysis.

Bicyclic compounds are known with both cis- and trans-condensed 1,1-dioxothiolane and other five-membered heterocycles [2]. For example, the less-strained cis-bicyclic systems are obtained by intramolecular cyclization of 4-substituted 2-thiolene 1,1-dioxides [3]. trans-Isomers have been prepared by condensing trans-3,4-disubstituted thiolane 1,1-dioxides under conditions which do not affect the bonds between the ring atoms and the substituents [4, 5]. This behavior has been confirmed by x-ray structural analysis [4, 6].

According to our findings, however, it is possible to convert initially-formed trans-bicycles into the cis-isomers [7, 8]. Consequently, the correctness of the structures assigned to many compounds reported in the literature requires further experimental verification. We here report an attempt to use PMR spectroscopy to determine the mode of ring coupling in condensed thiolane 1,1-dioxides. It was to be hoped that, as a result of the conformational rigidity of bicyclic systems, it would be possible to find a solution to this problem using the known relationships between the vicinal coupling constants and the dihedral angles between the interacting protons [9].

We have obtained the spectra of the compounds (I-XI) (Table 1), in which the protons of the dioxathiolane ring are all nonequivalent, and form an ABCDXY system. The spectrum of the system was resolved into the spectra of the ABX and CDY systems with the addition of the spin coupling of protons X and Y (6a-H and 3a-H in Table 1). In each of the AB and CD spectra of the methylene protons, the low-field signal was attributed to the proton oriented trans- to the heteroatom of the fused ring (the substituent β-effect [10]), and, consequently, cis- to the corresponding angular proton (3a-H or 6a-H). The signals for the latter were assigned on the basis of the electronegativity of the heteroatoms (the greater the electronegativity, the greater the extent of descreening of the protons).

It will be seen from Table 1 that the available set of compounds does not enable any reliable relationship between the chemical shifts and the mode of ring coupling to be established. It is, however, noteworthy that the sums of the differences in the chemical shifts for the methylene protons $\Delta AB + \Delta CD$ for the trans-isomers (0.18-0.32 ppm) are smaller than the corresponding values for the bis-bicycles (0.47-0.71 ppm). This finding is in contrast to that found by the authors for monocyclic thiolane 1,1-dioxides [10].

The geminal constants J_{44} and J_{66} for compounds (I-X) (Table 2) have the usual values for α-methylene protons in thiolane 1,1-dioxides (−13.5 to −15.2 Hz) [10-12], being slightly greater for the cis-compounds. The vicinal constants J_{3a6a} for all the compounds except (XI) lie in the range 8.0-9.5 Hz, and cannot provide a criterion for the assignment of bicyclic compounds to the cis- or trans-series. However, the values of the vicinal constants for

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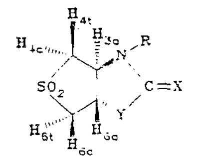
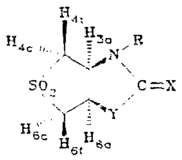
TABLE 1. Chemical Shifts of Protons in the 1,1-Dioxothiolane Ring in cis- and trans-Coupled Bicyclic Sulfones


I–VII


VIII–XI

Compound	R	X	Y	4t-H	4c-H	3a-H	6a-H	6t-H	6c-H
I	H	$NC_6H_5 \cdot HOTs$	O	3,45	3,54	5,11	6,00	3,71	3,90
II	H	$NCH_2C_6H_5 \cdot HOTs$	O	3,43	3,53	5,11	5,93	3,69	3,81
III	H	$NCH_2C_6H_5 \cdot HCl$	O	3,42	3,51	5,05	5,88	3,65	3,74
IV	$COCH_3$	NC_6H_5	O	3,35	3,53	5,25	5,46	3,53	3,45
V	$COCH_3$	O	O	3,33	3,49	5,02	5,33	3,51	3,60
VI	$CH_2C_6H_5$	S	O	3,28	3,50	4,68	5,56	3,53	3,59
VII	H	$NCH_2CH{=}CH_2 \cdot HOTs$	O	3,35	3,55	5,08	5,83	3,67	3,79
VIII	C_6H_5	S	S	3,17	3,49	5,67	4,68	3,58	3,73
IX	C_6H_5	S	O	3,53	3,78	4,71	5,33	3,16	3,52
X	H	NC_6H_5	S	3,42	3,72	5,21	4,58	3,31	3,72
XI	$CH_2C_6H_5$	S	O	3,19	3,58	4,12	4,77	3,67	3,94

TABLE 2. Coupling Constants for 1,1-Dioxothiolane Ring Protons in (I-XI)

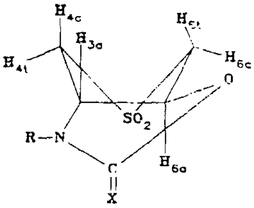
Compound	Coupling constant, Hz							
	J_{4t4c}	J_{4t3a}	J_{4c3a}	J_{3a6a}	J_{6a6t}	J_{6a6c}	J_{6t6c}	J_{4t6c}
I	−14,0	1,2	6,2	9,4	6,0	2,0	−15,2	2,0
II	−14,4	1,5	6,0	9,2	5,6	2,0	−15.2	—
III	−14,7	1,5	6,4	9,2	5,8	2,0	−15,0	—
IV	−14,4	1,9	7,5	8,7	4,8	1,8	−14,9	2,5
V	−14,4	1,5	7,2	9,0	5,1	1,5	−14,4	2,4
VI	−14,4	7,0	1,3	9,2	2,5	5,3	−14,5	—
VII	−14,3	2,0	6,4	8,5	5,7	2,0	−15,0	—
VIII	−14,3	3,1	6,9	9,3	5,9	8,5	−14,0	—
IX	−14,0	3,8	7,0	8,2	7,0	8,4	−14,0	—
X	−13,6	4,0	8,0	8,0	8,0	8,0	−13,6	—
XI	−10,9	13,0	6,3	13,0	12,7	6,8	−10,6	—

the methylene protons depend on the mode of ring coupling. In all the compounds believed to possess the trans-structure, the sets consist of two average (5.0-7.5 Hz) and two small (1.5-2.5 Hz) constants, and for each of the ABX subsystems J_{AX} is small and J_{BX} average, or the reverse. In the bis-bicycles, only one of the four coupling constants for the methylene protons is relatively small (3.1-4.0 Hz), the rest being fairly large (5.9-8.5 Hz).

If calculation of the AB and CD subspectra is difficult for any reason (for example, as a result of the presence in this region of side signals), the width of the multiplets for the methine protons can serve as a criterion for assignment to the cis- or trans-series. The distance between the outer components of each of them is equal to the sum of the three constants J_{XY} + J_{AX} (or J_{CY}) + J_{BX}(J_{DY}). As a result of the differences in the values of the two last, the breadth of the multiplets for the 3a- and 6a-H protons is 15.3-18.1 Hz for trans-coupled (I-VII) and 19.3-24.0 Hz for cis-coupled compounds (VIII-X). Coupling constants for the 3a-H and NH protons in (I-III), (VII), and (X) are not seen in the spectrum, as has been reported previously for biotin and other cyclic ureas [13].

The constants for the bicyclic compound (XI) merit separate consideration. The set of constants undoubtedly corresponds to that for cis-fused compounds, although the values of most of the constants are unusual. This could be due to the marked distortion of the molecular geometry in (XI) as compared with the other cis-fused compounds (VIII-X).

The dihedral angles between the interacting protons of the 1,1-dioxothiolane ring were found for all the compounds. The calculations were carried out using the modified Karplus equation [9] and the values of the appropriate vicinal coupling constants. The dihedral angles for the trans-compounds (I-V) and (VII), calculated from J_{3a4c}, J_{3a6a}, and J_{6a6c}, were found to be 25, 170, and 260°, respectively. The diagram shows the molecular configuration corresponding to these angles. The dioxothiolane ring is close to the envelope configuration, with the sulfur atom departing from the plane. The oxazolidine ring is also nonplanar. The proposed configuration for the trans-fused compounds in solution is in accordance with the high values of the remote constants J_{4t6c} in (I), (IV), and (V). This is impossible for the conformation found for 1,3-dimethyl-2-oxo-trans-perhydrothieno[3,4-d]-imidazole 5,5-dioxide [4]. In the case of (VI), the set of vicinal constants corresponds to this conformation, except that the heteroatoms of the oxazolidine ring should change places. In (IV), the proton with chemical shift 3.45 ppm is assigned the cis-orientation with respect to 6a-H, although this is not in accordance with the β-effect. Otherwise, it would not be possible to select reasonable values for the dihedral angles which would correspond to the observed coupling constants.



The vicinal coupling constants for the cis-compounds correspond to the adoption of a conformation for the 1,1-dioxothiolane ring close to the envelope form, with atoms $C_{(3a)}$ (VIII), $C_{(4)}$ (IX), and $C_{(6)}$ (X) standing out from the plane toward the second ring. These conformations differ from those found by x-ray diffraction analysis [6] for (VIII), namely, the envelope conformation with the sulfur atom standing out from the plane toward the thiazolidine ring, the absence of screened coupling of protons 3a- and 6a-H, and, consequently, nonplanarity of the 1,3-diheterocycle. These conformers are clearly preferred in solution. In the case of (XI), the constants for the methylene protons are in good agreement with the envelope conformation in which the sulfur atom stands out from the plane on the opposite side to the oxazolidine ring. However, the experimental values for J_{3a6a} are much greater than the value of 9.5 Hz calculated for a dihedral angle of 0°. Further, the remote constant J_{4c6s} expected for the assumed envelope conformation is not present in the spectrum. This casts doubt on the stability of the Karplus equation in this case, and requires further structural study.

Hence, criteria have been found for the establishment of the mutual orientation of the two rings in cis- and trans-fused thiolane 1,1-dioxides from their PMR spectra. The most reliable and readily determined feature characteristic of trans-fused compounds is the presence of small (less than 2.5 Hz) vicinal coupling constants for the protons of each methylene group in the 1,1-dioxothiolane ring with the angular methine proton. In addition, the trans-isomers show a smaller width of the multiplets for the methine protons, and a greater difference in the shifts of the methylene protons than do the cis-isomers. The vicinal coupling constants show that in solution the compounds have conformations differing from that found by x-ray analysis for the crystalline state.

EXPERIMENTAL

PMR spectra were obtained on Bruker VP-200 and Varian VXR-300 spectrometers in $DMSO-D_6$ at room temperature under standard conditions, internal standard HMDS. Assignment of the multiplets for the methylene protons was made by homonuclear double resonance, and their chemical shifts were calculated using the formulas for ABX systems [14]. IR spectra were obtained on a UR-20 spectrometer in KBr disks.

The range of possible values for the dihedral angles φ_{HH} in each ethane fragment of the molecule in (I-XI) was measured from molecular models. These values were refined graphically from the angular dependence of the appropriate coupling constants [9]. The values for the electronegativity (EN) of the substituents required for the calculations were found from the EN for the elements [15] using the relationship given in [9]. The EN of the sulfonyl group was taken to be 3.0 on the basis of the correlation between the chemical shifts of the protons and the EN of the substituents [15]. The range of dihedral angles on varying EN_{SO_2} between 2.5 and 3.3 was no greater than 10°.

The preparation of compounds (I), (II), and (VII) has been reported in [5], and of (VIII) in [6]. The new compounds gave satisfactory analyses.

trans-2-Benzyliminoperhydrothieno[3,4-d]oxazole 5,5-dioxide hydrochloride (III), and trans-3-acetyl-2-oxoperhydrothieno[3,4-d]oxazole 5,5-dioxide (V) were obtained by hydrolysis of trans-2-benzylimino-3-acetylperhydrothieno[3,4-d]oxazole 5,5-dioxide with 15% HCl and 50% aqueous acetic acid, respectively [16].

trans-2-Phenylimino-3-acetylperhydrothieno[3,4-d]oxazole 5,5-Dioxide (IV, $C_{13}H_{15}N_2O_4S$). To a solution of 3.9 g (20 mmoles) of the tosylate (I) in 50 ml of water, heated to 70°C, was added 2.0 ml (20 mmoles) of acetic anhydride, followed by the careful addition of 2.0 g of sodium acetate tetrahydrate in 10 ml of water. The solid which separated was washed with 50 ml of alcohol and 50 ml of ether. Crystallization from alcohol gave 1.8 g (62%) of product, mp 176.0-177.5°C. Obtained similarly in 72% yield was trans-2-benzylimino-3-acetylperhydrothieno[3,4-d]oxazole 5,5-dioxide, the starting material for compounds (III) and (V).

trans-3-Benzyl-2-thioxoperhydrothieno[3,4-d]oxazole 5,5-dioxide (VI, $C_{12}H_{13}NO_3S_2$) was obtained from trans-3-hydroxy-4-benzylaminothiolane 1,1-dioxide and thiophosgene as described in [7]. Yield 32%, mp 248°C (from acetone). IR spectrum: 1490, 1320, 1305, 1240, 1115, and 700 cm^{-1}. trans-Fusion of the rings was confirmed kinetically [17].

cis-2-Thioxo-3-phenylperhydrothieno[3,4-d]oxazole 5,5-Dioxide (IX, $C_{11}H_{11}NO_3S_2$). To a solution of 1.34 g (10 mmoles) of 4-hydroxy-2-thiolene 1,1-dioxide in 50 ml of toluene was added 1.35 g (10 mmoles) of phenyl isothiocyanate and 0.2 ml of pyridine. The mixture was boiled for 1 h, cooled, and the solid filtered off and crystallized from 50% aqueous DMF to give 2.21 g (82%) of (IX), mp 248°C. IR spectrum: 1490, 1450, 1320, 1290, 1115, and 700 cm^{-1}.

cis-2-Phenyliminoperhydrothieno[3,4-d]thiazole 5,5-dioxide (X) was obtained by treating a hot aqueous solution of the appropriate salt [3] with one equivalent of sodium hydroxide (2 moles/liter).

cis-3-Benzyl-2-thioxoperhydrothieno[3,4-d]oxazole 5,5-dioxide (XI, $C_{12}H_{13}NO_3S_2$) was obtained from cis-3-hydroxy-4-benzylaminothiolane 1,1-dioxide and thiophosgene as described in [7], yield 35%, mp 227°C (from acetone). IR spectrum: 1315, 1250, 1115, and 740 cm^{-1}. cis-Fusion of the rings was confirmed kinetically [17].

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