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Synthesis, stereochemistry and ring–chain tautomerism of some new spiro-1,3-oxathianes

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Abstract—The stereochemistry of new spiro-1,3-oxathiane derivatives has been explored by NMR methods and the molecular structure of one compound established via single crystal by X-ray diffractometry. The investigations revealed flexible, semi-flexible and anancomeric structures and the ring–chain tautomerism of the 1,3-oxathiane heterocycle. © 2001 Elsevier Science Ltd. All rights reserved.

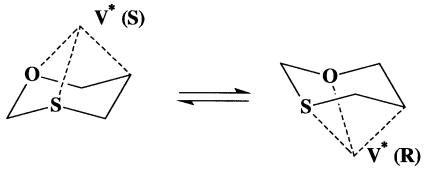
1. Introduction

The stereochemistry of 1,3-oxathiane derivatives reveals peculiar configurational and conformational aspects. The chirality of the 1,3-oxathiane ring[1] is due to a virtual tri-coordinated chiral center (Scheme 1, V*)[2] and the flipping of the heterocycle results in an enantiomeric inversion.

The values measured for many properties of 1,3-oxathiane derivatives (e.g. *A*-values) are close to the average of the values measured for similar 1,3-dioxane and 1,3-dithiane derivatives.[1,3]

Spiro-1,3-oxathianes exhibit in addition to the chiral center belonging to the heterocycle, the characteristic helical and axial chirality of spiro compounds with six-membered rings.[4–6]

Recently,[7] the ring–chain tautomerism of the 1,3-oxathiane ring has been studied, in $CDCl_3$ solution, by NMR spectra, using the data for the equilibration reaction between the *cis* and *trans* isomers of 9-phenyl-5-oxa-1-thia-spiro[5.5]undecane (**3**), and a significant influence of the pH on the rate of the isomerization reaction was observed.

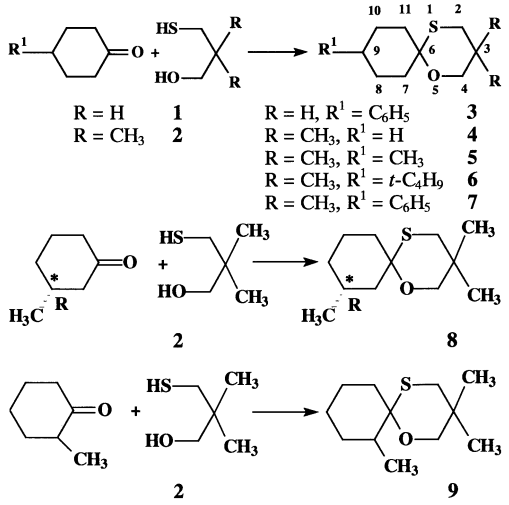


Scheme 1.

This paper investigates the complex configurational and conformational aspects of the stereochemistry of new variously substituted spiro-1,3-oxathianes and develops the already reported results[7–10] concerning the *cis–trans* isomerization of 1,3-oxathiane derivatives.

2. Results and discussion

New spiro-1,3-oxathiane derivatives were obtained by



Scheme 2.

Keywords: spiro-1,3-oxathiane; ring–chain tautomerism; X-ray structure; *cis–trans* isomerization; conformation analysis; kinetic determinations by NMR.

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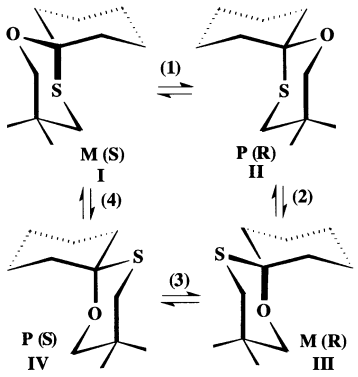


Scheme 3.

the condensation reaction of some cyclohexanones with 3-mercapto-1-propanols **1** and **2** (Scheme 2).

Compound **4** exhibits helical chirality (due to the spiro skeleton) and a virtual triligand chiral center (belonging to the 1,3-oxathiane ring). Four stereoisomers are possible, thereof two diastereoisomeric conformers (Scheme 3): D_1 [I M(S); II P(R)], D_2 [III M(R); IV P(S)]. At room temperature (*rt*) the compound shows a flexible structure, both carbocycle and heterocycle are flipping (Scheme 3) equilibrating all the possible isomers (I–IV). The flipping of the carbocycle (2, 4) determines a diastereomeric equilibration (only the chirality of the spiro skeleton is changed) whereas the flipping of the 1,3-oxathiane ring (1,3) changes both the configurations of the helix and of the virtual chiral center

Table 1. NMR data (δ, ppm; *rt*, CH_2Cl_2) for compounds **3**–**8**

Compound	^{1}H			^{13}C[a]		
	2	4	3-CH_3	2	4	3-CH_3
3-trans[a]	2.92	3.90	–	36.93	61.92	–
4[a]	2.58	3.43	1.05	36.59	70.85	24.95
5-*cis*/**5**-*trans*	2.50/2.59	3.43/3.35	1.02	36.71	71.20/70.90	24.99
6-*cis*/**6**-*trans*	2.52/2.62	3.44/3.36	1.02	36.78	71.30/70.94	24.96
7-*cis*[a]	2.58	3.52	1.08	37.07	71.64	24.37
7-*trans*	2.65	3.43	1.05	37.11	71.37	25.35
8-*cis* (D_3, D_4)	2.63	3.35	1.02, 1.04	44.66	70.96	24.87, 25.14
8-*trans* (D_5, D_6)	2.41, 2.47	3.35, 3.38	0.92, 0.96	45.27	71.01	24.74, 25.14

[a] $CHCl_3$.

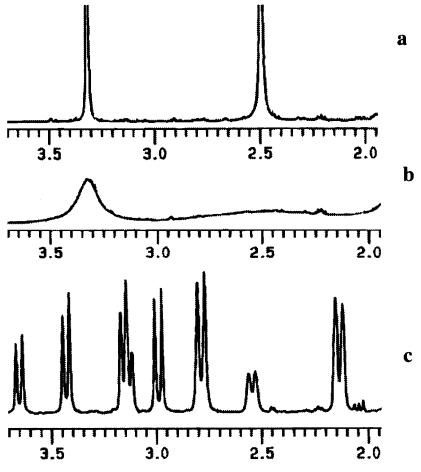


Figure 1. Variable temperature NMR spectra of compound **4** (CD_2Cl_2): (a) 293, (b) 260, and (c) 190 K.

resulting into an enantiomeric inversion. The part of the ^{1}H NMR spectrum (at *rt*, Table 1) belonging to the protons of the heterocycle is very simple (Fig. 1a) displaying one singlet for the protons at position 4 (δ=3.32 ppm) and another one for those at position 2 (δ=2.49 ppm).

At low temperature (190 K) the conformational equilibria are frozen and the ^{1}H NMR spectrum (Table 2, Fig. 1c, coalescence at 260 K, Fig. 1b) exhibits different signals for the two diastereoisomers, as well as for the axial and equatorial protons of the rings. The ratio between D_1 and D_2 (40:60) has been determined from the values of the integrals of the signals belonging to the protons of the 1,3-oxathiane ring (D_1: δ_{2eq}=2.12, δ_{4eq}=3.65, δ_{2ax}=2.78, δ_{4ax}=3.13; D_2: δ_{2eq}=2.12, δ_{4eq}=3.42, δ_{2ax}=2.99, δ_{4ax}=3.16 ppm). In agreement with the literature data that show a higher *A* value (on the cyclohexane ring) for an alkylmercapto than for an alkoxy

Table 2. ^{1}H NMR data (δ, ppm; CH_2Cl_2) at low temperature for compounds **4**–**8** and at *rt* for **9**

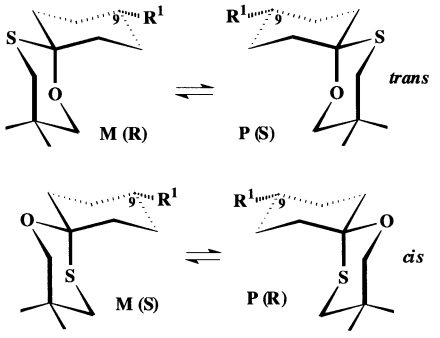
Compound	*T* (K)	Position of protons					
		2-ax	2-eq	4-ax	4-eq	3-CH_3(ax)	3-CH_3(eq)
4 (D_1/D_2)	190	2.78/2.99	2.12	3.13/3.16	3.65/3.42	1.11/1.09	0.88/0.90
5-*cis*, **5**-*trans*	223	2.80/3.00	2.15	3.15	3.64/3.43	1.11	0.80
6-*cis*, **6**-*trans*	213	2.80/2.99	2.14	3.15	3.63/3.43	1.09	0.79
7-*trans*	223	3.04	2.20	3.25	3.51	1.15	0.84
8-*cis* (D_3, D_4)	223	3.01, 3.02	2.14, 2.15	3.14, 3.15	3.43, 3.44	1.12	0.79, 0.80
8-*trans* (D_5, D_6)	223	2.80, 2.83	2.14, 2.16	3.13, 3.15	3.65, 3.66	1.11	0.78, 0.80
9-*cis*[a]	293	2.83	2.18	3.25	3.66	1.20	0.88
9-*trans*	293	2.66	2.14	3.05	3.26	0.93	0.70

[a] $CHCl_3$.

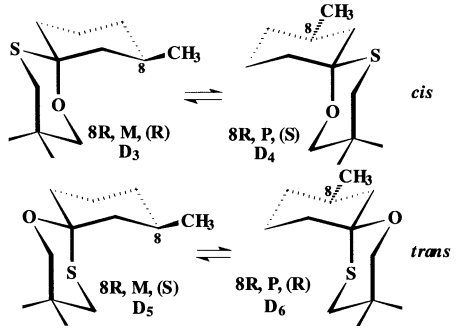
group (A_{SMe}=1 kcal mol^{-1}, A_{OMe}=0.55–0.75 kcal mol^{-1})[11] the diastereoisomer D_2 with the sulphur atom in an equatorial orientation (referred to the cyclohexane ring) was considered as the major isomer.

Compounds **3** and **5**–**9** are obtained as mixtures of *cis* and *trans* isomers (Schemes 4–6). The ratios between the major and minor isomers, determined from the values of the integrals of specific signals measured in the NMR spectra of the crude products (the compound with the sulphur atom in an equatorial orientation was again considered the major one) are almost the same (60:40) for the entire series of investigated compounds.

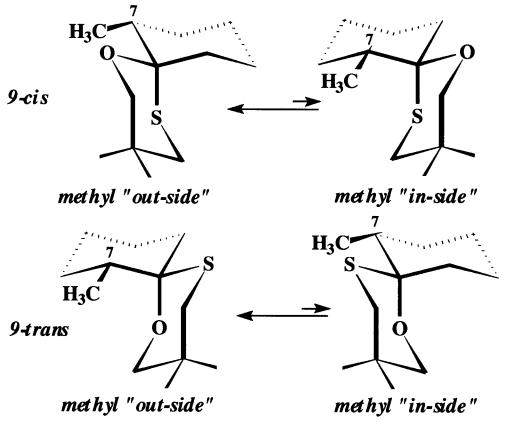
The *cis* and *trans* isomers of **7**, **8** and **9** were separated by flash chromatography.



Scheme 4.



Scheme 5.



Scheme 6.

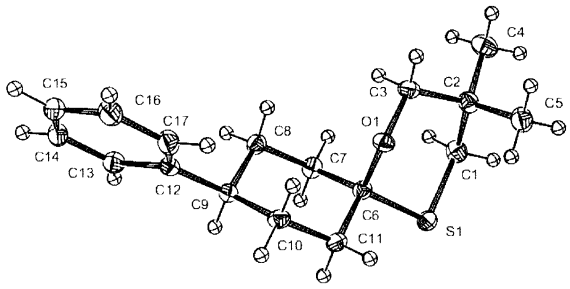


Figure 2. ORTEP diagram of *trans* isomer of compound **7**.

The structure in solid state of the *trans* isomer of **7** was determined by X-ray diffractometry. The ORTEP diagram (Fig. 2) shows chair conformations for both heterocycle and saturated carbocycle. The angle between the plane of the equatorial phenyl group at position 9 (C^{12}–C^{17}) and the reference of the cyclohexane ring $O^1C^6S^1$ is about 30°, showing the different orientation of the phenyl group from the usual bisectional or orthogonal rotamers.[12]

Compounds **3** and **5**–**8** exhibit semiflexible structures, the cyclohexane ring is rigidified by the 'holding group' at positions 9 or 8, whereas the 1,3-oxathiane ring is flipping (Schemes 4 and 5).

The flipping of the heterocycle in the *cis* and *trans* isomers of **3** and **5**–**7** represents an enantiomeric inversion (Scheme 4), while in the *cis* and *trans* isomers of **8** it results in diastereoisomeric equilibria (Scheme 5).

The conformational behavior of these compounds was deduced from the data of NMR spectra recorded at *rt* (Table 1) and at low temperature (Table 2).

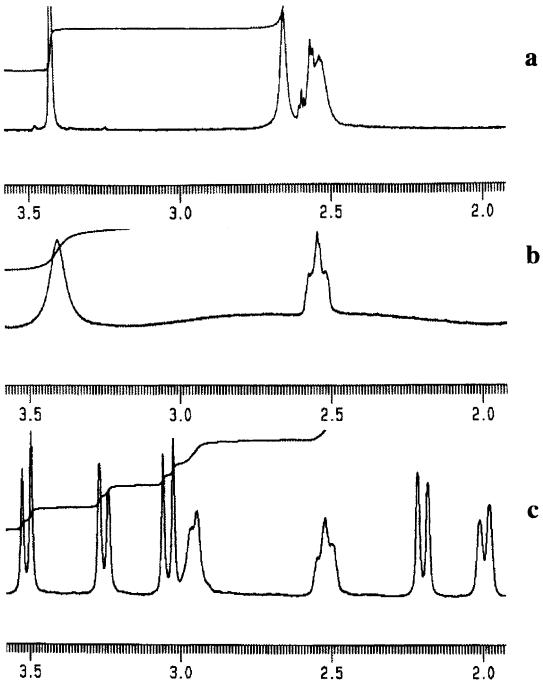


Figure 3. Variable temperature spectra of *trans* isomer of compound **7** (CD_2Cl_2): (a) 298, (b) 263, and (c) 223 K.

The spectrum of the *trans* isomer of compound **7** recorded at *rt* (Table 1, Fig. 3a) exhibits unique signals for the axial and equatorial protons of the heterocycle (δ_2=2.65; δ_4=3.43 ppm) and for the protons of the similar groups ($\delta_{3\text{-Me}}$=1.05 ppm) at position 3 (similar data were observed for all isomers of **3**, **5**–**7**, Table 1).

The flipping of the heterocycle renders equivalent the protons of positions 7 and 11 (8 and 10, too). The equatorial protons at positions 7 and 11 show at *rt* an unique signal at δ=2.56 ppm, that is overlapped with the signal belonging to the proton at position 9. In the low temperature spectrum (223 K, Fig. 3c; coalescence at 263 K, Fig. 3b) the axial and equatorial protons of the heterocycle exhibit different signals. Two doublets for the protons at position 2 (δ_{2eq}=2.20; δ_{2ax}=3.04 ppm), two other ones for those at position 4 (δ_{4eq}=3.51; δ_{4ax}=3.25 ppm) and two signals for the methyl groups at position 3 (δ_{eq}=0.84; δ_{ax}=1.15 ppm) were recorded. The freezing of the flipping of the heterocycle also determines the diastereotopicity of the positions 7 and 11 (8 and 10, respectively). In the low temperature spectrum the signal at δ=2.95 ppm (Fig. 3c) belongs to the equatorial proton at position 11, while the equatorial proton at position 7 shows a signal at δ=1.99 ppm. The differences between the *rt* and low temperature spectra are significant in the case of *cis* and *trans* isomers of compound **8** (Figs. 4 and 5, Tables 1 and 2).

The spectrum at *rt* of the *cis* isomer exhibits one singlet for the protons at position 2 and another one for those at position 4 (δ_2=2.63; δ_4=3.35 ppm, a tendency of these signals to split into AB systems can be observed, Fig. 4a). The

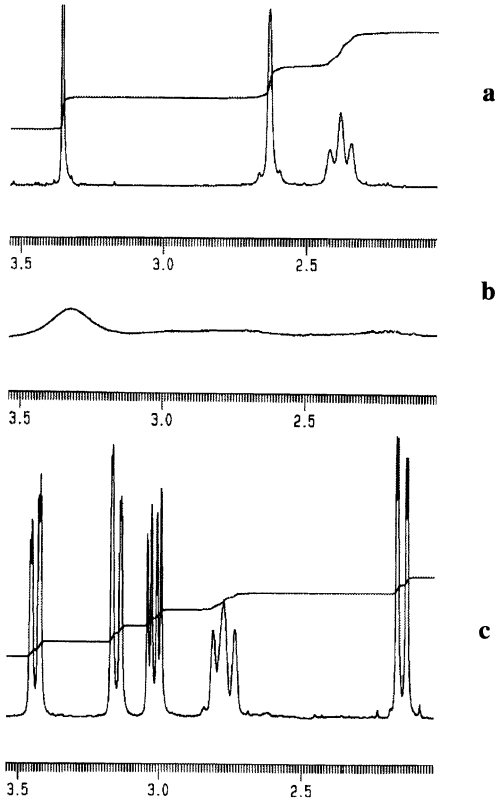


Figure 4. Variable temperature spectra of *cis* isomer of compound **8** (CD_2Cl_2): (a) 298, (b) 263, and (c) 223 K.

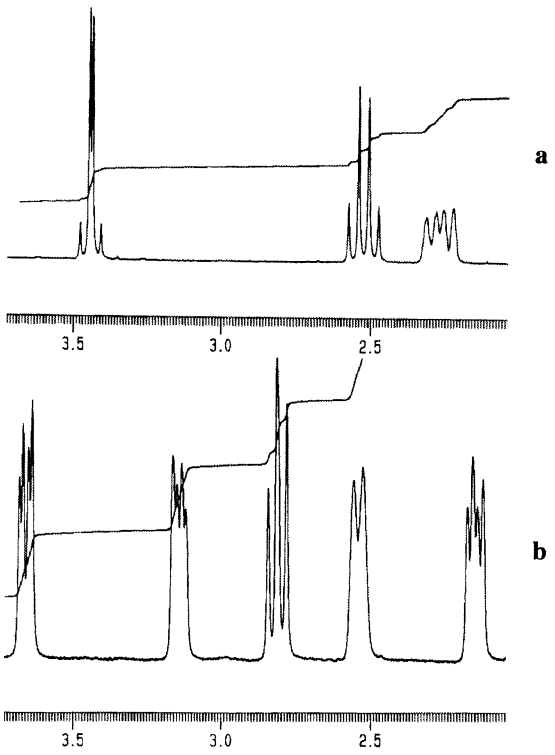
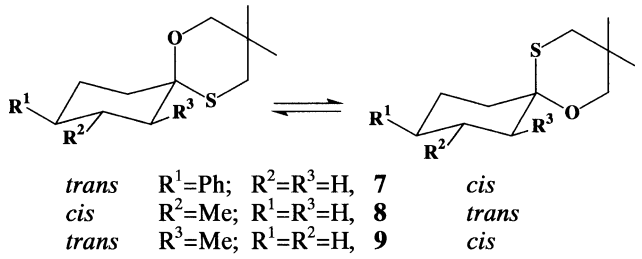


Fig. 5. Variable temperature spectra of *trans* isomer of compound **8** (CD_2Cl_2): (a) 298, (b) 223 K.

spectrum of *trans* isomer at *rt* exhibits for the protons of the heterocycle two AB systems (Fig. 5a). The chiral carbon atom at position 8 determines the diastereotopicity of the two protons at positions 2 and 4, respectively and despite the flipping of the 1,3-oxathiane ring different signals are recorded for these protons (δ_2=2.41; $\delta_{2'}$=2.47 ppm; δ_4=3.35; $\delta_{4'}$=3.38 ppm). The chiral center at position 8 also determines the diastereotopicity of the methyl groups at position 3, two close signals being recorded for the protons of these groups in the spectra (at *rt*) of each isomer (Table 2). The spectra of **8**-*cis* and **8**-*trans* isomers run at low temperature (223 K) exhibit two sets of signals corresponding to the two frozen diastereoisomers of *cis* (D_3, D_4, Scheme 5) and *trans* (D_5, D_6, Scheme 5) isomers. The significant differences of chemical shifts observed between the signals of the protons of each position (2 or 4) correspond to the differences of magnetic environments for equatorial and axial protons. The differences between the chemical shifts of the signals belonging to the protons of the equatorial and axial methyl groups at position 3 observed in the low temperature spectra are significantly higher than the differences recorded between the signals of these protons at *rt* (Tables 1 and 2) showing the significant modifications of the conformational behavior of the molecules.

The *cis* and *trans* isomers of **9** exhibit anancomeric structures (Scheme 6), the equatorial methyl group at position 7 is a 'holding group' for the cyclohexane conformation and for that of the 1,3-oxathiane ring, too. The conformational equilibria due to the flipping of the heterocycle are shifted towards the conformers 'methyl out-side'. The steric hindrance in the 'methyl in-side' conformer is very high and determines the rigidity of the heterocycle (similar data



Scheme 7.

were already reported for analogous 1,3-dioxane derivatives).[13] The NMR spectra (Table 2) of the *cis* and *trans* isomers of **9** (at *rt*), exhibits different signals for the axial and equatorial protons at positions 2 and 4 as well as for the protons of the methyl groups at position 3. The pattern of these spectra (at *rt*) is close to that of the spectra of **5**–**7** run at low temperature (Table 2). In order to make the assignment of the signals belonging to the protons of position 2 NOE experiments were performed with the *cis* isomer of **9**. The irradiation of the signal belonging to the more deshielded methyl group at position 3 (δ=1.20 ppm) showed a strong influence in the NOEDiff spectrum on the more shielded signal (δ=2.18 ppm), while the irradiation of the protons of the more shielded methyl group at position 3 (δ=0.88 ppm) showed a weak influence on the signals of both protons in position 2 (δ=2.18 and δ=2.83 ppm). The results of these experiments show the higher deshielding for the axial protons at position 2 and for the axial methyl group at position 3.

Investigations concerning the ring–chain tautomerism of the 1,3-oxathiane ring were performed with compounds **7**, **8** and **9**, using the data of *trans–cis* isomers equilibrations (Scheme 7). These equilibria involve the opening of the heterocycle in one of the isomers (to a 'chain' form) and the re-closure of the ring to give the other configuration isomer. The kinetic parameters of the isomerization reactions in $CDCl_3$ were determined by NMR, recording the ^1H NMR spectra of the same sample over several periods of time (Table 3) and by measuring the ratio between the isomers using the intensities of specific signals. The collecting of data (Table 3) was faster at the beginning of the process and for the calculation of ratios mean values of the integrals were used. The reaction was considered to be first order and the pH (3.28) of the solvent was fitted (with gaseous dry HCl) to obtain a convenient 'time scale' for the process. The experimental conditions and results (calculated with relations 1 and 2) are shown in Table 4.

$$\ln \frac{x_e}{x_e - x} = (k_1 + k_{-1})t \quad (1)$$

$$\frac{k_1}{k_{-1}} = K \quad (2)$$

In Eqs. (1) and (2) k_1 and k_{-1} are the forward and reverse reaction rate constants, K is the equilibrium constant, x_e is the concentration of the *cis* isomer for **7** and **8** and of *trans* isomer for **9** at equilibrium and x is the concentration of the same isomer at the t time. The k values (Table 4) are similar, the rate of the isomerization reaction is not strongly influenced by the position of the substituents.

3. Conclusions

The investigations of the stereochemistry of spiro-1,3-oxathianes, performed by complex NMR experiments and by the first molecular structure of a spiro-1,3-oxathiane, revealed the preference of the heterocycle in solid state and in solution for the chair conformation and the influence of the chirality of the heterocycle and of the spiro skeleton on the representative number of stereoisomers. The *rt* NMR spectra showed flexible structure for the spirane with unsubstituted carbocycle, semiflexible structures for the compounds bearing substituents at the 8 and 9 positions and an anancomeric structure for the compound substituted at position 7. The low temperature spectra demonstrated the freezing of the flipping of the rings and the anancomeric behavior of the molecules at these temperatures. The kinetic parameters of the ring–chain tautomerism of 7-, 8- and 9-substituted spiro compounds were found to be similar.

Table 3. Data (time/ratio of isomers) of the kinetic measurements for the *trans–cis* equilibria in **7**, **8** and *cis–trans* equilibrium in **9**

Nr	**7**		**8**		**9**	
	Time (min)	Ratio *cis/trans*	Time (min)	Ratio *cis/trans*	Time (min)	Ratio *trans/cis*
1	17	1:10.9	26	1:2.20	26	1:7.10
2	42	1:6.46	42	1:1.69	45	1:4.38
3	72	1:5.90	62	1:1.40	61	1:3.17
4	108	1:3.26	80	1:1.13	76	1:2.55
5	142	1:2.79	97	1:1.00	93	1:2.10
6	174	1:2.30	122	1:0.89	145	1:1.87
7	221	1:2.05	143	1:0.82	279	1:1.21
8	At equilibrium	1:1.50	At equilibrium	1:0.66	At equilibrium	1:0.66

Table 4. Kinetic parameters (k_1, k_{-1}; mol l^{-1} min^{-1}) for isomerizations of **7**–**9**

Compound	Starting isomer	Initial concentration (mol l^{-1})	K	$k_1 \times 10^3$	$k_1 \times 10^3$
7	*Trans*	3.4×10^{-2}	1.43	4.24	2.96
8	*Trans*	4.3×10^{-2}	0.625	7.37	11.8
9	*Cis*	4.8×10^{-2}	0.69	2.63	3.81

4. Experimental

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded using CD_2Cl_2 ($CDCl_3$) as solvent in 5 mm tubes on a Bruker AM 400 (Varian Gemini 300) NMR spectrometer equipped with a dual ^{13}C–^{1}H (multinuclear) head operating at 400 (300) MHz for protons and 100 (75) MHz for carbon atoms. IR spectra were recorded on a JASCO FT-IR 615 spectrometer. Melting points were measured with a Kleinfeld APOTEC melting point apparatus and are uncorrected. Elemental analyses were obtained at the University of Medicine and Pharmaceutics, Cluj-Napoca. Their results agreed favorably with the calculated values. Thin-layer chromatography was performed on Merck silica gel 60 F 254. Silica gel Merck (40–63 μm) was used for flash chromatography.

4.2. X-Ray crystallographic study

Crystal data and data-collection information are summarized in Table 5.

The sample was studied on an automatic diffractometer CAD4 NONIUS[14] with graphite monochromatized Mo-$K\alpha$ radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. After Lorenz and polarization corrections the structure was solved with SIR-97[15] which reveals the non-hydrogen atoms of the compound. After anisotropic refinement a Fourier difference reveals many hydrogen atoms. The whole structure was refined with SHELXL97[16] by the full-matrix least-square techniques.

Atomic scattering factors from International Tables for X-ray Crystallography.[17] Ortep views were realized with PLATON98[18] and Ortep-3 for windows.[19] All the calculations were performed on a Pentium NT Server computer.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-162845. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int. code: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

4.3. General procedure for the synthesis of new compounds 3–9

A solution of 3-mercapto-propan-1-ols **1** or **2** (11 mmol), the corresponding cyclohexanone (5 mmol) and *p*-toluenesulphonic acid (0.05 g, 0.29 mmol) in 20 ml of toluene was refluxed and the water generated in the reaction was removed using a Dean–Stark trap. When the theoretical water was separated, after cooling at *rt*, the catalyst was neutralized (under stirring) with excess 0.1 M KOH (in order to remove the remaining thiol). The organic layer was then washed twice with water (20 ml). After drying (with Na_2SO_4), the toluene was removed and the oxathianes were purified by vacuum distillation and/or by flash-chromatography (details given below).

4.3.1. 9-Phenyl-5-oxa-1-thia-spiro[5.5]undecan (3). White crystals, mixture of *trans* and *cis* isomers (60:40), subjected to column chromatography, (*n*-hexane/ethyl acetate=12:1, ΔR_f=0.10, *trans* isomer with R_f=0.40 and *cis* isomer with R_f=0.30). Yield 54% (0.67 g).

trans Isomer. Solid, white crystals, mp=129°C. Yield 21% (0.26 g). ^{1}H NMR ($CDCl_3$): 1.60–2.00 (8H, overlapped peaks, 3-CH_2, 7-CH_{ax}, 8-CH_2, 10-CH_2, 11-CH_{ax}), 2.43–2.65 (3H, overlapped peaks, 7-CH_{eq}, 9-CH, 11-CH_{eq}), 2.92 (2H, t, 2-CH_2, ^3J=5.8 Hz), 3.90 (2H, t, 4-CH_2, ^3J=5.5 Hz), 7.15–7.40 (5H, m, aromatic protons); ^{13}C NMR ($CDCl_3$): 25.58 (C-3), 29.07 (C-8, C-10), 36.57 (C-7, C-11), 36.93 (C-2), 43.78 (C-9), 61.12 (C-4), 86.97 (C-6), 126.12, 126.92, 128.40 (tertiary aromatic carbon atoms). IR (KBr) 3078, 3055, 3022, 2947, 2921, 2863, 2853, 1716, 1599, 1490, 1448, 1431, 1372, 1300, 1276, 1187, 1163, 1115, 1080, 1046, 1033, 1027, 997, 942, 929, 910, 847, 786, 763, 705, 535 cm^{-1}. Anal. Calcd for $C_{15}H_{20}OS$ (248.12): C, 72.54; H, 8.12; S, 12.91. Found: C, 72.63; H, 8.05; S, 13.08.

The *cis* isomer was not separated as a pure compound.

4.3.2. 3,3-Dimethyl-5-oxa-1-thia-spiro[5.5]undecan (4). Colorless liquid, bp=75–78°C/0.5 mmHg. Yield 75% (0.75 g). ^{1}H NMR ($CDCl_3$): 1.05 (6H, s, 3-CH_3), 1.36–1.47 (2H, m, 9-CH_2), 1.49–1.65 (4H, m, 8-CH_2, 10-CH_2), 1.80–2.01 (4H, m, 7-CH_2, 11-CH_2), 2.58 (2H, s, 2-CH_2), 3.43 (2H, s, 4-CH_2); ^{13}C NMR ($CDCl_3$): 22.35 (C-8, C-10), 24.95 (3-*C*H_3), 25.74 (C-9), 28.06 (C-3), 36.26

Table 5. Crystal data and data collection information for **7**-*trans*

Parameters	Values	Parameters	Values
Empirical formula	$C_{17}H_{24}OS$	Z	8
Formula weight	276.42	D_{calc} (g cm^{-3})	1.205
Temperature (K)	293(2)	Absorption coefficient (mm^{-1})	0.203
Wavelength (Å)	0.71069	F(000)	1200
Crystal system	Orthorombic	Crystal size (mm)	0.35×0.30×0.28
Space group	*Pbca*	θ range for data collection (°)	1.78–27.48
Unit cell dimension		Reflections collected	3493
a (Å)	10.9880(1)	Independent reflections	3493 [R_{int}=0.0000]
b (Å)	22.9420(2)	Data/restraints/parameters	3493:0:173
c (Å)	12.0860(3)	Goodness-of-fit on F^2	0.999
α (°)	90	Final R indices [$F^2>2\sigma(F^2)$]	R_1=0.0379, wR_2=0.1050
β (°)	90	R indices (all data)	R_1=0.0512, wR_2=0.1157
γ (°)	90	Largest difference	
Volume (Å^3)	3046.72(8)	peak and hole (eÅ^{-3})	0.375 and −0.274

(C-7, C-11), 36.59 (C-2), 70.85 (C-4), 81.60 (C-6). IR (neat, film) 2935, 2860, 1469, 1445, 1362, 1307, 1274, 1247, 1144, 1074, 1020, 946, 831 cm^{-1}. Anal. Calcd for $C_{11}H_{20}OS$ (200.33): C, 65.95; H, 10.06; S, 16.00. Found C, 66.08; H, 9.90; S, 15.88.

4.3.3. 3,3,9-Trimethyl-5-oxa-1-thia-spiro[5.5]undecan (5). Colorless liquid, bp=85°C/0.5 mmHg, mixture of *trans* and *cis* isomers (60:40). Yield 78% (0.83). ^1H NMR (CD_2Cl_2): 0.85 (3H, d, 9-CH_3, J=6.3 Hz)^t, 0.87 (3H, d, 9-CH_3, J=6.3 Hz)^c, 1.02 (6H, s, 3-CH_3), 1.14–1.26 (2H, m, 8-CH_{ax}, 10-CH_{ax}), 1.31–1.62 (5H, overlapped peaks, 7-CH_{ax}, 8-CH_{eq}, 9-CH_{ax}, 10-CH_{eq}, 11-CH_{ax}), 2.24 (2H, d (overlapped ddd), 7-CH_{eq}, 11-CH_{eq}, ^2J=^3J=$^3J'$=13 Hz)^c, 2.36 (2H, d (overlapped ddd), 7-CH_{eq}, 11-CH_{eq}, ^2J=^3J=$^3J'$=13 Hz)^t, 2.50 (2H, s, 2-CH_2)^c, 2.59 (2H, s, 2-CH_2)^t, 3.35 (2H, s, 4-CH_2)^t, 3.43 (2H, s, 4-CH_2)^c; ^{13}C NMR ($CDCl_3$): 21.69 (9-CH_3)^c, 22.11 (9-CH_3)^t, 24.99 (3-CH_3), 27.94 (C-3)^t, 28.32 (C-3)^c, 30.18 (C-8, C-10)^t, 31.30 (C-8, C-10)^c, 31.96 (C-9)^t, 32.15 (C-9)^c, 35.97 (C-7, C-11), 36.71 (C-2), 70.90 (C-4)^t, 71.20 (C-4)^c, 80.20 (C-6)^t, 82.94 (C-6)^c. IR (neat, film) 2950, 2925, 2867, 1457, 1441, 1363, 1308, 1264, 1241, 1147, 1074, 1025, 976, 853 cm^{-1}. Anal. Calcd for $C_{12}H_{22}OS$ (214.36): C, 67.24; H, 10.34; S, 14.96. Found: C, 67.02; H, 10.51; S, 15.03.

c and *t* signals belonging to the *cis* and *trans* isomers, respectively.

4.3.4. 9-*tert*-Butyl-3,3-dimethyl-5-oxa-1-thia-spiro[5.5]-undecan (6). White crystals, mp=66–86°C, mixture of *trans* and *cis* isomers (60:40). Yield 77% (0.98 g). ^1H NMR (CD_2Cl_2): 0.84 (9H, s, 9-C(CH_3)$_3$), 1.02 (6H, s, 3-CH_3), 1.23–1.67 (7H, overlapped peaks, 7-CH_{ax}, 8-CH_2, 9-CH, 10-CH_2, 11-CH_{ax}), 2.33 (2H, m, 7-CH_{eq}, 11-CH_{eq})^c, 2.46 (2H, m, 7-CH_{eq}, 11-CH_{eq})^t, 2.52 (2H, s, 2-CH_2)^c, 2.62 (2H, s, 2-CH_2)^t, 3.36 (2H, s, 4-CH_2)^t, 3.44 (2H, s, 4-CH_2)^c; ^{13}C NMR 400($CDCl_3$): 22.65 (C-8, C-10)^t, 23.93 (C-8, C-10)^c, 24.96 (3-CH_3), 27.61 (9-C(CH_3)$_3$)^t, 27.66 (9-C(CH_3)$_3$)^c, 28.35 (C-3), 32.31 (9-C(CH_3)$_3$)^c, 32.43 (9-C(CH_3)$_3$)^t, 36.50 (C-7, C-11), 36.78 (C-2), 47.66 (C-9)^t, 47.89 (C-9)^c, 70.94 (C-4)^t, 71.30 (C-4)^c, 80.06 (C-6)^c, 83.20 (C-6)^t. IR (KBr) 2953, 2949, 2869, 2854, 1471, 1435, 1365, 1306, 1280, 1246, 1185, 1078, 1056, 1030, 952, 926, 860, 806, 608 cm^{-1}. Anal. Calcd for $C_{15}H_{28}OS$ (256.44): C, 70.25; H, 11.01; S, 12.50. Found: C, 70.13; H, 10.84; S, 12.71.

c and *t* signals belonging to the *cis* and *trans* isomers, respectively.

4.3.5. 3,3-Dimethyl-9-phenyl-5-oxa-1-thia-spiro[5.5]undecan (7). White crystals, mixture of *trans* and *cis* isomers (60:40), subjected to column chromatography (*n*-hexane/ethyl acetate=12:1, ΔR_f=0.09, *trans* isomer with R_f=0.40 and *cis* isomer with R_f=0.31). Yield 62% (0.86 g).

trans Isomer. Solid, white crystals, mp=76–76.5°C. Yield 21%(0.29 g). ^1H NMR (CD_2Cl_2): 1.05 (6H, s, 3-CH_3), 1.63–1.78 (6H, overlapped peaks, 7-CH_{ax}, 8-CH_2, 10-CH_2, 11-CH_{ax}), 2.53–2.60 (3H, overlapped peaks, 7-CH_{eq}, 9-CH, 11-CH_{eq}), 2.65 (2H, s, 2-CH_2), 3.43 (2H, s, 4-CH_2), 7.15–7.29 (5H, m, aromatic protons); ^{13}C NMR ($CDCl_3$): 25.35 (3-CH_3), 28.34 (C-3), 29.67 (C-8, C-10), 36.53 (C-7, C-11), 37.11 (C-2), 44.19 (C-9), 71.37 (C-4), 79.99 (C-6), 126.47, 127.28, 128.76 (tertiary aromatic carbon atoms), 147.21 (quaternary aromatic carbon atom). IR (KBr) 3080, 3058, 3024, 2943, 2928, 2860, 2855, 1600, 1585, 1493, 1446, 1430, 1398, 1365, 1306, 1260, 1168, 1125, 1067, 1022, 1007, 940, 855, 797, 756, 700, 529 cm^{-1}. Anal. Calcd for $C_{17}H_{24}OS$ (276.43): C, 73.86; H, 8.75; S, 11.60. Found: C, 73.98; H, 8.81; S, 11.51.

cis Isomer. Solid, white crystals, mp=85–86°C. Yield 17% (0.15 g). ^1H NMR ($CDCl_3$): 1.08 (6H, s, 3-CH_3), 1.55–1.91 (7H, overlapped peaks, 7-CH_{ax}, 8-CH_2, 9-CH, 10-CH_2, 11-CH_{ax}), 2.42–2.58 (2H, overlapped peaks, 7-CH_{eq}, 11-CH_{eq}), 2.58 (2 H, s, 2-CH_2), 3.52 (2H, s, 4-CH_2), 7.15–7.35 (5H, m, aromatic protons); ^{13}C NMR ($CDCl_3$): 24.37 (3-CH_3), 28.30 (C-3), 30.95 (C-8, C-10), 36.46 (C-7, C-11), 37.07 (C-2), 44.37 (C-9), 71.64 (C-4), 82.97 (C-6), 126.49, 127.24, 128.73 (tertiary aromatic carbon atoms), 146.74 (quaternary aromatic carbon atom). IR (KBr) 3080, 3058, 3026, 2956, 2926, 2860, 2854, 1600, 1581, 1492, 1447, 1388, 1361, 1308, 1262, 1230, 1168, 1103, 1078, 1029, 947, 891, 867, 844, 801, 754, 698, 608, 528 cm^{-1}. Anal. Calcd for $C_{17}H_{24}OS$ (276.43): C, 73.86; H, 8.75; S, 11.60. Found: C, 74.06; H, 8.78; S, 11.59.

4.3.6. 3,3,8-Trimethyl-5-oxa-1-thia-spiro[5.5]undecan (8). Colorless liquid, mixture of *trans* and *cis* isomers (40:60), subjected to column chromatography (petroleum ether/ethyl acetate=14:1, ΔR_f=0.13, *cis* isomer with R_f=0.68 and *trans* isomer with R_f=0.55). Yield 76% (0.81 g).

cis Isomer. Colorless liquid, bp=95–96°C/0.1 mmHg. Yield 27% (0.29 g). ^1H NMR (CD_2Cl_2): 0.87 (3H, d, 8-CH_3, J=6.5 Hz), 0.88 (1H, m, 10-CH_{ax}), 1.02 (3H, s, 3-CH_{3eq}), 1.04 (3H, s, 3-CH_{3ax}), 1.12 (1H, dd, 7-CH_{ax}, ^2J=^3J=11.9 Hz), 1.35 (1H, m, 11-CH_{ax}), 1.48–1.68 (4H, overlapped peaks, 8-CH_{ax}, 9-CH_{ax}, 9-CH_{eq}, 10-CH_{eq}), 2.38 (2H, m, 7-CH_{eq}, 11-CH_{eq}), 2.63 (2H, s, 2-CH_2), 3.35 (2H, s, 4-CH_2); ^{13}C NMR ($CDCl_3$): 21.63 (8-CH_3), 22.27 (C-9), 24.87 (3-CH_{3eq}), 25.14 (3-CH_{3ax}), 27.84 (C-8), 28.36 (C-3), 34.44 (C-10), 35.37 (C-11), 36.64 (C-7), 44.66 (C-2), 70.96 (C-4), 80.76 (C-6). IR (neat, film) 2950, 2928, 2866, 1469, 1442, 1363, 1310, 1266, 1251, 1149, 1091, 1071, 1049, 965, 939, 884, 862, 818 cm^{-1}. Anal. Calcd for $C_{12}H_{22}OS$ (214.36): C, 67.24; H, 10.34; S, 14.96. Found: C, 67.21; H, 10.43; S, 14.99.

trans Isomer. Solid, white crystals, mp=47–47.5°C. Yield 20% (0.21 g). ^1H NMR 300(CD_2Cl_2): 0.73 (1H, m, 10-CH_{ax}), 0.82 (3H, d, 8-CH_3, J=6.4 Hz), 0.92 (3H, s, 3-CH_{3eq}), 0.96 (3H, s, 3-CH_{3ax}), 1.00 (1H, t (overlapped dd), 7-CH_{ax}, ^2J=^3J=12 Hz), 1.22 (1H, dt (overlapped ddd), 11-CH_{ax}, ^2J=^3J=12 Hz, $^3J'$=4.5 Hz), 1.41–1.69 (4H, overlapped peaks, 8-CH, 9-CH_{ax}, 9-CH_{eq}, 10-CH_{eq}), 2.15 (1H, m, 7-CH_{eq}), 2.21 (1H, m, 11-CH_{eq}), 2.41 (1H, d, 2-CHH$'$, ^2J=13.5 Hz), 2.47 (1H, d, 2-CHH', ^2J=13.5 Hz), 3.35 (1H, d, 4-CHH$'$, ^2J=12 Hz), 3.38 (1H, d, 4-CHH', ^2J=12 Hz); ^{13}C NMR ($CDCl_3$): 22.27 (C-9), 22.76 (8-CH_3), 24.74 (3-CH_{3eq}), 25.14 (3-CH_{3ax}), 28.35 (C-3), 28.39 (C-8), 34.61 (C-10), 35.75 (C-11), 36.80 (C-7), 45.27 (C-2), 71.01 (C-4), 83.28 (C-6). IR (KBr) 2961,

2937, 2855, 1483, 1439, 1351, 1323, 1274, 1265, 1162, 1081, 1066, 1038, 952, 936, 881, 858, 814 cm^{-1}. Anal. Calcd for $C_{12}H_{22}OS$ (214.36): C, 67.24; H, 10.34; S, 14.96. Found: C, 67.32; H, 10.38; S, 15.03.

4.3.7. 3,3,7-Trimethyl-5-oxa-1-thia-spiro[5.5]undecan (9). Colorless liquid, bp=92–94°C/0.1 mmHg, mixture of *trans* and *cis* isomers (60:40), subjected to column chromatography (petroleum ether/ethyl acetate=30:1, ΔR_f=0.10, *trans* isomer with R_f=0.56 and *cis* isomer with R_f=0.46). Yield 75% (0.8 g).

trans Isomer. Colorless liquid. Yield 18% (0.14 g). ^{1}H NMR (CD_2Cl_2): 0.70 (3H, s, 3-CH_{3eq}), 0.88 (3H, d, 7-CH_3, J=6.1 Hz), 0.93 (3H, s, 3-CH_{3ax}), 1.17–1.59 (8H, overlapped peaks, 7-CH, 8-CH_{ax}, 8-CH_{eq}, 9-CH_{ax}, 9-CH_{eq}, 10-CH_{ax}, 10-CH_{eq}, 11-CH_{ax}), 2.14 (1H, d, 2-CH_{eq}, ^2J=13.2 Hz), 2.48 (1H, m, 11-CH_{eq}), 2.66 (1H, d, 2-CH_{ax}, ^2J=13.2 Hz), 3.05 (1H, d, 4-CH_{ax}, ^2J=12 Hz), 3.26 (1H, d, 4-CH_{eq}, ^2J=12 Hz); ^{13}C NMR (CD_2Cl_2): 16.13 (7-CH_3), 22.87 (C-10), 24.16 (3-CH_{3eq}), 26.52 (3-CH_{3ax}), 28.29 (C-9), 30.46 (C-3), 31.11 (C-8), 34.58 (C-11), 37.19 (C-2), 42.26 (C-7), 71.21 (C-4), 84.74 (C-6). IR (neat, film) 2947, 2931, 2861, 1469, 1448, 1388, 1362, 1261, 1250, 1142, 1075, 1021, 1002, 977, 937, 914, 856, 840, 805, 742 cm^{-1}. Anal. Calcd for $C_{12}H_{22}OS$ (214.36): C, 67.24; H, 10.34; S, 14.96. Found: C, 67.47; H, 10.28; S, 15.10.

cis Isomer. Colorless liquid. Yield 12% (0.1 g). ^{1}H NMR ($CDCl_3$): 0.88 (3H, s, 3-CH_{3eq}), 1.13 (3H, d, 7-CH_3, J=6.7 Hz), 1.20 (3H, s, 3-CH_{3ax}), 1.02–1.78 (7H, overlapped peaks, 7-CH, 8-CH_{ax}, 9-CH_{ax}, 9-CH_{eq}, 10-CH_{ax}, 10-CH_{eq}, 11-CH_{ax}), 2.28 (1H, d, 2-CH_{ax}, ^2J=13.1 Hz), 2.45 (1H, m, 11-CH_{eq}), 2.83 (1H, d, 2-CH_{eq}, ^2J=13.1 Hz), 3.25 (1H, d, 4-CH_{ax}, ^2J=12.0 Hz), 3.66 (1H, d, 4-CH_{eq}, ^2J=12.0 Hz); ^{13}C NMR (CD_2Cl_2): 16.14 (7-CH_3), 23.25 (C-10), 23.38 (3-CH_{3eq}), 24.49 (C-9), 26.51 (3-CH_{3ax}), 28.13 (C-3), 30.59 (C-8), 32.44 (C-11), 36.16 (C-2), 42.20 (C-7), 70.72 (C-4), 86.35 (C-6). IR (neat, film) 2953, 2938, 2849, 1457, 1442, 1392, 1370, 1255, 1244, 1150, 1069, 1018, 1001, 979, 942, 909, 849, 833, 808, 744 cm^{-1}. Anal. Calcd for $C_{12}H_{22}OS$ (214.36): C, 67.24; H, 10.34; S, 14.96. Found: C, 67.14; H, 10.32; S, 15.12.

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