"BABEŞ-BOLYAI" UNIVERSITY CLUJ-NAPOCA
FACULTY OF CHEMISTRY AND CHEMICAL ENGINEERING
ORGANIC CHEMISTRY DEPARTMENT

ANAMARIA ELENA TEREC

Synthesis, Structure and Reactivity of New Spirane, Polyspirane Derivatives and Brominated Compounds with 1,3-Dioxane and 1,3-Oxathiane Units

Ph.D. Thesis
Abstract

Scientific Adviser,
Prof. Univ. Dr. Sorin Mager

JURY

PRESIDENT

Prof. Univ. Dr. Luminița Silaghi-Dumitrescu-Dean of the Faculty of Chemistry and Chemical Engineering, "Babeş-Bolyai" University, Cluj-Napoca

REVIEWERS

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Defence: 29 January, 2003

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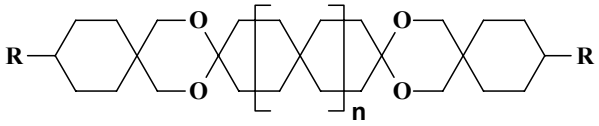
INTRODUCTION

The research work presented in this Ph.D. Thesis is structured in three main parts. The first chapter (Part A) is dedicated to the exhaustive literature investigation of the 1,3-oxathiane derivatives. The most important data concerning the synthesis, stereochemistry, spectral characteristics and reactivity of the derivatives of this heterocycle are reviewed. The original research work was developed in the field of the synthesis and stereochemistry of spiro and polyspiro heterocycles (Part B) and in the field of the stereoselective bromination reaction of bis(1,3-dioxane-2-yl) derivatives (Part C).

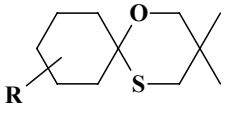
The studies on spiro compounds were focused on the synthesis and the structural investigations of the first reported tetra-, penta– and hexaspiro-1,3-dioxanes I and II and of the spiro-1,3-oxathianes and of first investigated polyspiro-1,3-oxathianes (III and IV).

The aims of the research on the bromination reaction of bis(1,3-dioxane-2-yl) derivatives V were correlated with the study of the diastereoselectivity of this process and of the asymmetric induction of the first brominated chiral centre on the configuration of the chiral centre generated in the second step of the dibromination process.

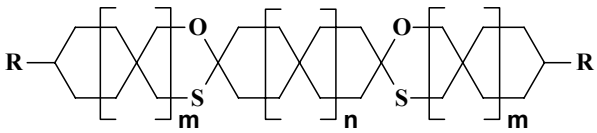
I



II, n = 1,2

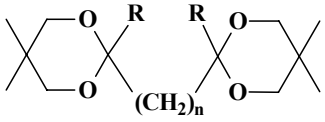


III



IV

n = 0, 1, 2
m = 0, 1



V

n = 1 - 4

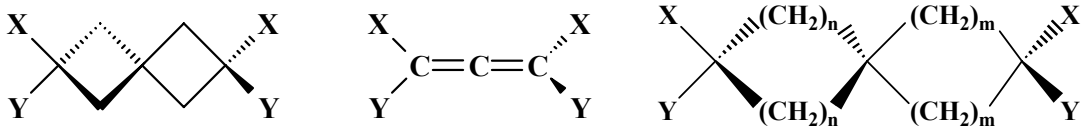
The possibility to describe the peculiar structural features of the investigated spiranes and polyspiranes using the original stereochemistry descriptors proposed in previous works and the versatility of 1,3-dioxane derivatives in the stereoselective dibromination reaction motivated our research in these fields.

PART B: SYNTHESIS AND STRUCTURE OF SPIRO-1,3-DIOXANES AND 1,3-OXATHIANES

1. Stereochemistry of Spiro-Compounds with Six-Membered Rings

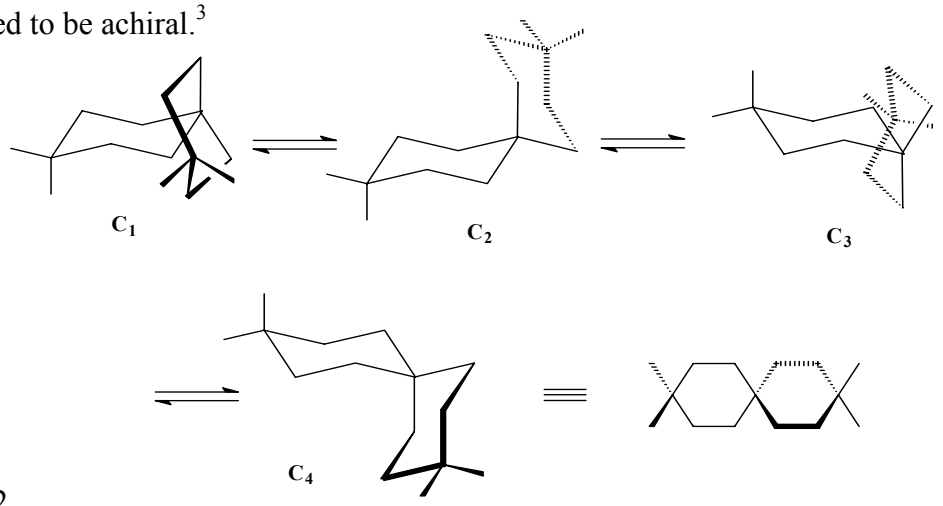
The stereochemistry of spiro[5.5]undecane compounds has complex features because two cyclohexane rings have to be taken into consideration, unlike an early study[1] that analysed the 1-substituted spiro[5.5]undecanes through a simplified model of 2-substituted 1,1-dialkylcyclohexanes.

The chirality of spiro derivatives with planar rings **(a)** is discussed, beside that of allenes **(b)**, as a classical example of axial chirality;[2] but in one condition: the presence of different geminal groups at both ends of the system (X≠Y).



Scheme 1

The spiro junction of the rings forces the disposal of the substituents in orthogonal plans and this provokes the dissymetry of the structure. Other spiro derivatives of type **(c)** were also fitted into this category of compounds with axial chirality if the assumption that the rapid inversion of the rings leads to an average planarity is made, and also if proper substitution is assured. Therefore, the chirality of compounds with [5.5]undecane skeleton was included in this last category (**c**, m=n=2) and the rapid flipping of the cycles would lead to an average structure with planar six-membered ring (scheme 2). And, as in the case of planar spiro systems **(a)** and allenes **(b)**, the compound bearing identical substituents at least at one of the extremities (X=Y) – as well as the unsubstituted spiro[5.5]undecane (X=Y=H) – were considered to be achiral.[3]

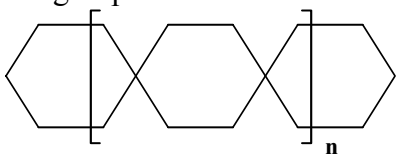


Scheme 2

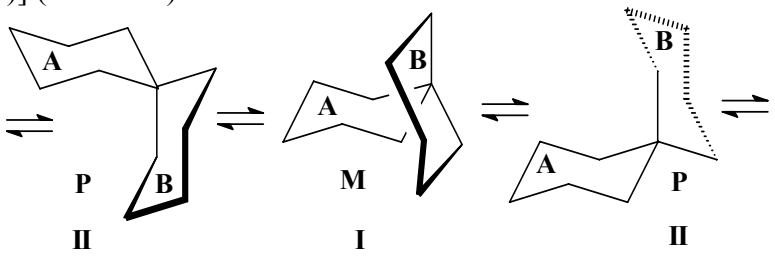
Studying Dreiding models and by means of NMR spectra at low temperature, H.Dodziuk[4] revealed the chirality of the frozen structure of spiro[5.5]undecane. At room temperature, the

rapid flipping of the rings results into an enantiomeric inversion and the chirality of the molecule is not observed. But as the temperature is lowered, the flipping is frozen and an enantiomeric structure may be obtained – conformers $\mathbf{C_1}$ and $\mathbf{C_3}$ and $\mathbf{C_2}$ and $\mathbf{C_4}$, respectively are identical, but $\mathbf{C_1}$ is enantiomeric with $\mathbf{C_2}$ (and $\mathbf{C_3}$ with $\mathbf{C_4}$). So, the author placed this type of compounds in the company of other derivatives (vespirenes, tetramethylazoniaspiro[4.4]nonane) described in the literature[5,6] that exhibit a centre of chirality of the type $C_{a,a,a,a}$ (the spiro atom) bearing four formally identical substituents. As a consequence, the stereochemistry of polyspiro compounds with six-membered rings was discussed as having so many chiral centres of type $C_{a,a,a,a}$ as the number of the spiro joints. Thus, the chirality of spiro compounds with six-membered rings do not fit in the usual classification of chiral elements introduced by Cahn, Ingold and Prelog,[7] nor in the modified form elaborated by Prelog and Helmchen.[8] Hence another classification of the chiral elements has been proposed by the Polish scientists.[9] And recently, the conformational changes of spiro[5.5]undecane derivatives were characterised applying the pseudo-point-group approach.[10]

Previous investigations[11-15] of our group on the structure of the spirane compounds of the type

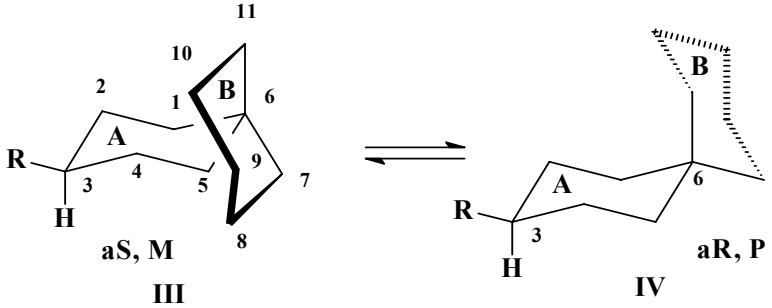


with 1,3-dioxane units (some spiro-, dispiro- and trispiro-1,3-dioxanes) revealed the helical chirality of the spiranes with six membered rings. The helix exhibiting *P* or *M* configuration can turn identical with itself after each fourth six-membered ring. The spiro[5.5]undecane (the helix begins to be built), considered as parent skeleton for the spiranes with six-membered rings, is flexible, the flipping of the rings (A and B) resulting into an enantiomeric inversion [I (*M*) $\rightleftharpoons$ II (*P*)] (scheme 3).



Scheme 3

The 3-substituted spiro[5.5]undecane or its heterocycle analogous[11,12] exhibits semiflexible structure, the substituted ring (A) is anancomeric, while the unsubstituted one is flexible (B) (scheme 4).

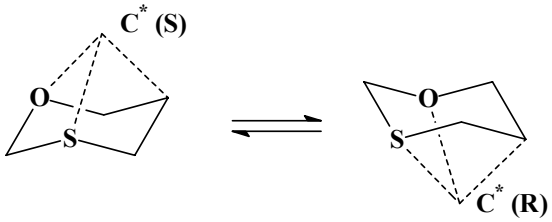


Scheme 4

The flipping of ring B results into an enantiomeric inversion, both axial [C^6-C^9 as chiral axis - the reference groups are R and H at C^3 and the ring B (that can be in front or behind the chiral axis) at C^6] and helical chiralities of the spirane being inverted [III(a*S*, *M*) $\rightleftharpoons$ IV(a*R*, *P*)].

This demonstration will be carried on step-by-step in the stereochemical analysis for the new synthesised tetra-, penta- and hexaspiro 1,3-dioxanes and mono- to hexaspiro-1,3-oxathianes as we discuss the chirality of spiro compounds with six-membered rings in terms of helical and axial chirality.

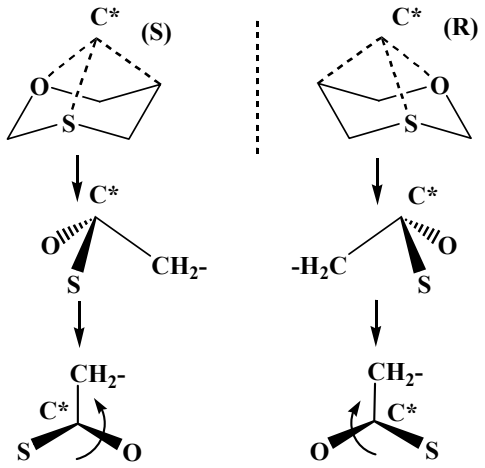
In the case of spiro derivatives with 1,3-oxathiane rings it has to be taken into consideration the fact that the 1,3-oxathiane exhibit a virtual chiral centre[16] (scheme 5).



Scheme 5

The chirality of the chair conformation of 1,3-oxathiane has been reported, the flipping of the heterocycle results into an enantiomeric interconversion.[17]

Specification of the configurations (R or S) for the enantiomers of 1,3-oxathiane is presented below (scheme 7) (the "absent" ligand has the lowest priority and is considered as being behind the plane of the sheet); the order of priority of the ligands is established according to the rules of Cahn, Ingold and Prelog.



Scheme 7

Spiro-1,3-oxathianes exhibit, in addition to the chiral centre belonging to the heterocycle, the characteristic helical and axial chirality of spiro compounds with six-membered rings[11, 12, 15].

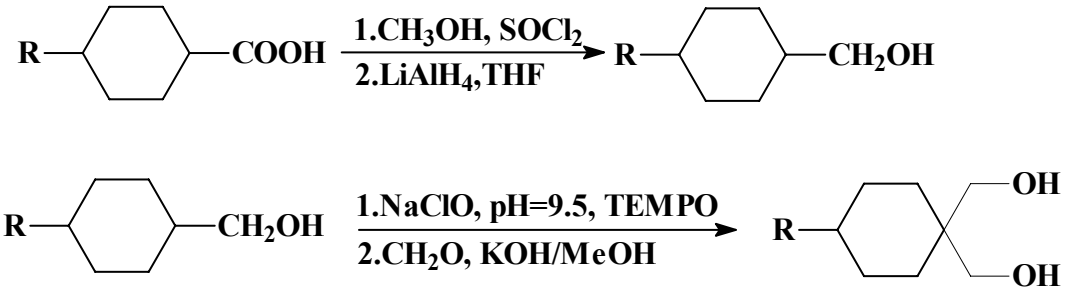
2. Synthesis and Structural Analysis of New Spiro Derivatives Containing 1,3-Dioxane and 1,3-Oxathiane Units

2.1. Synthesis of the Intermediates

The first problem in our work was that most of the reagents needed for these syntheses were not commercially available.

Synthesis of the alcohols (diols or tetrol) implied several steps and the last one is always a reaction of the corresponding aldehyde with formaldehyde in alkaline medium in a Canizzaro-like manner.

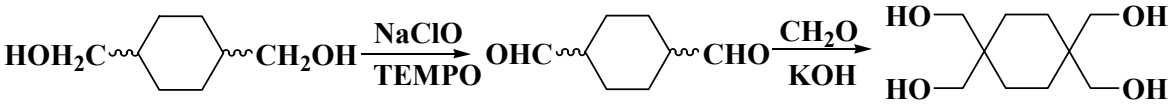
In the synthesis of the diols **8** (R= *t*-C_4H_9) and **9** (R= CH_3) (scheme 8) the starting material was, in both cases, the corresponding carboxylic acid. Bis(hydroxymethyl)cyclohexane **10** was obtained from the commercially available formylcyclohexane.



8 R=*t*-C_4H_9 (39%)
9 R=CH_3 (7%)
10 R=H (89%)

Scheme 8

1,1,4,4-Tetrakis(hydroxymethyl)cyclohexane (**12**) was obtained through the same reaction chain from of commercially available *cis, trans*-1,4-bis(hydroxymethyl)cyclohexanes. This isomers mixture is oxydised to *cis, trans*-cyclohexane-1,4-dicarbaldehyde (**11**) by the previously mentioned method that uses the TEMPO catalyst (2,2,6,6-tetramethylpiperidine-1-oxide) **1**[20] and sodium hypochlorite[21] and finally, after the reaction with formaldehyde, tetrol **12** is obtained in good yield (scheme 9).



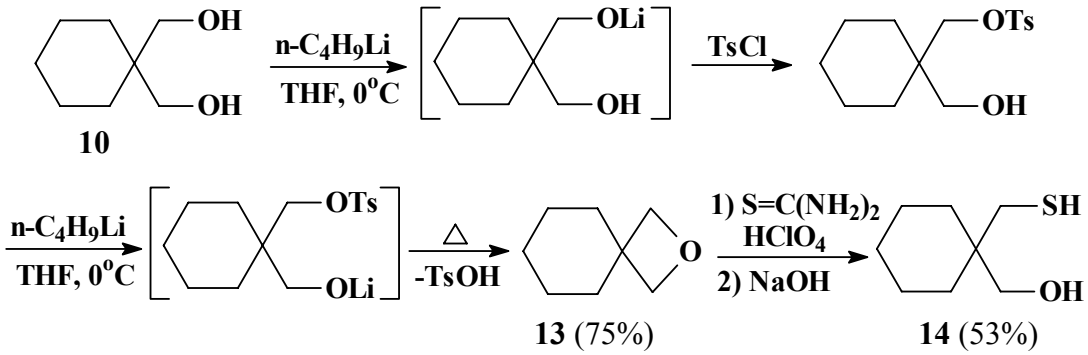
11 (49%) **12** (43%)

Scheme 9

From the diol **10** another starting material was synthesised, namely 1-hydroxymethyl-1-mercaptomethyl-cyclohexane (**14**), in which one of the oxygene atoms in diol is replaced by a sulphur atom (scheme 10). The strategy implies first the formation of 2-oxa-spiro[3.5]nonane (**13**). A one-pot conversion[24] of the 1,3-diol to the oxetane involved the generation of the monolithium salts by treatment with 1 equiv. butyllithium in THF, reaction with 1 equiv. tosyl

chloride to afford the monotosylate that is directly cyclised by further reaction with another equiv. of butyllithium.

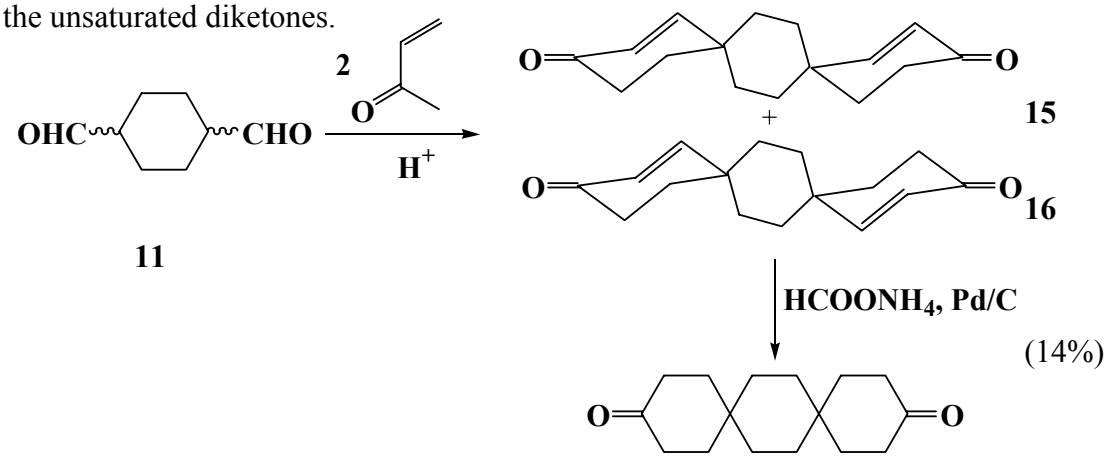
The oxetane is then opened with thiourea as nucleophile with sulphur in the presence of perchloric acid[25] to obtain first the isothiuronium salt (that is not separated from the reaction mixture) and then, after basic hydrolysis, the mercaptopropanol **14**.



Scheme 10

Another issue in the synthesis of intermediates for polypiro compounds was the preparation of the desired spiroketones.

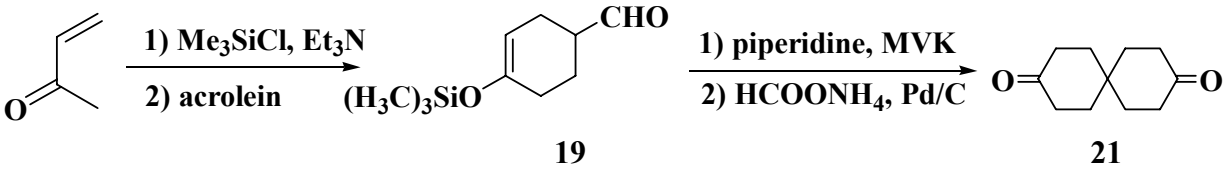
Treatment of **11** with methyl vinyl ketone – in the purpose of achieving an one-pot acid-catalysed spiroannelation of α-alkyl aldehydes and α,β-unsaturated ketones as mentioned in the literature[26] – lead to the dispirodiketenones **15** and **16**[27] (scheme 11). Subsequent hydrogenation of these dienones afforded the dispiro[5.2.5.2]hexadecane-3,12-dione **17** (first described in the literature in 1999) in an overall yield of 6% as mentioned in the literature,[27] the low yield is due to the side products in first two reactions and to the difficult purification of the unsaturated diketones.



Scheme 11

The method presented in the literature for the synthesis of 3,9-diketospiro[5.5]undecane[28] **(21)** starts from 2-methoxybutadiene and it is tedious and inefficient, especially in the purification process. The found original solution to avoid these problems was to replace the group methoxy in 2-methoxy-1,3-butadiene with a silyloxy one. 2-Trimethylsilyloxy-1,3-butadiene is easier to obtain, more rapidly, more stable if the necessary precaution for the silyl derivatives are taken. Still, the yield of this reaction was rather low (35%). The next step

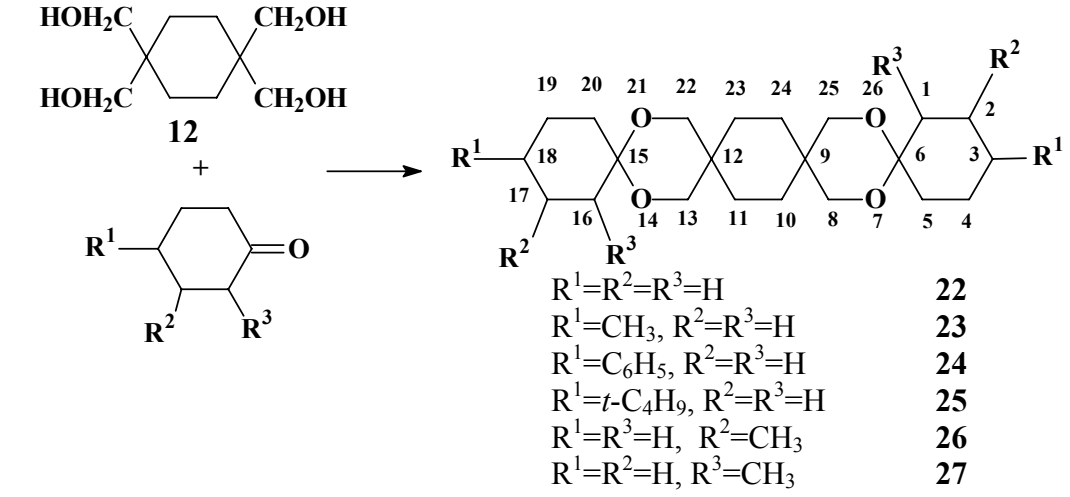
involved a Diels-Alder with acrolein when 1-[(trimethylsilyl)oxy]-4-formyl-l-cyclohexene **(19)** is obtained. The formyl group is then transformed with piperidine into an enamine[31] in order to enhance its reactivity and to avoid the polymerisation in the next step, a Michael spiroannelation that has as final product the desired 3,9-diketospiro[5.5]undecene **(20).** The unsaturated diketone **20** was obtained as a complex mixture that was separated by flash-chromatography and the saturated 3,9-diketospiro[5.5]undecane **(21)** is obtained after hydrogenation.

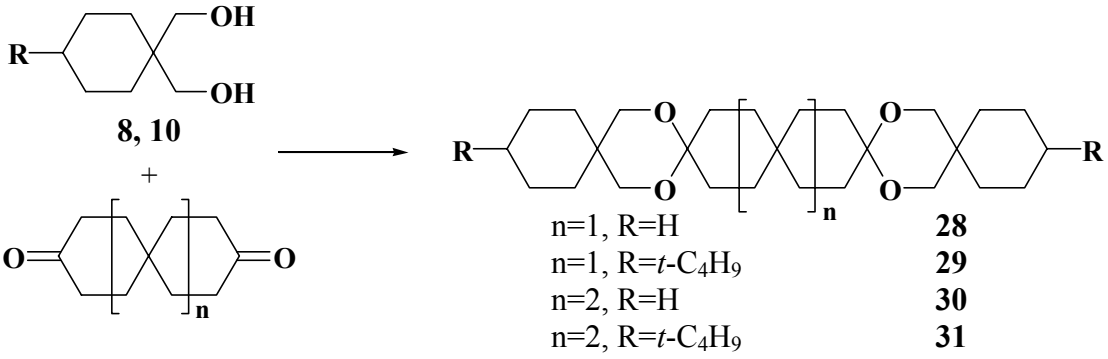


2.2. Synthesis of New Polyspiro-1,3-Dioxanes

New tetraspiro compounds **22-27**[32] were obtained by the condensation of 1,1,4,4-tetrahydroxymethylcyclohexane **12** with several (substituted) cyclohexanones (the optically pure 3-(R)-methylcyclohexanone was used for **26**).

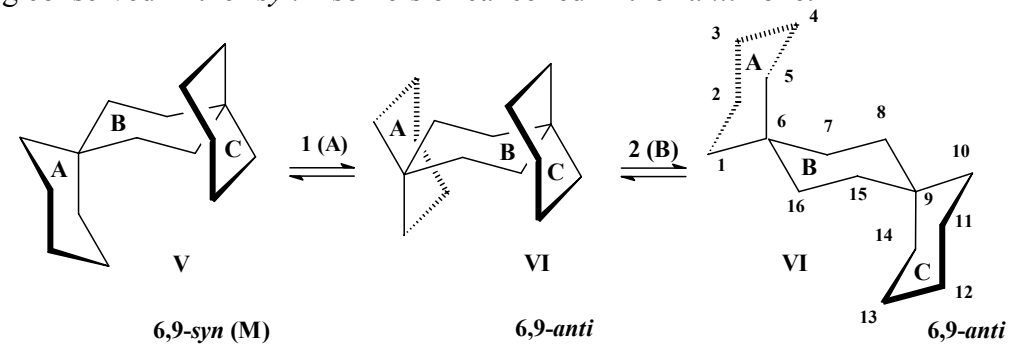
From the reaction in acidic medium (PTSA) between the diols **8** and **10** and 3,9-diketospiro[5.5]undecane **21** and dispiro[5.2.5.2]hexadecane-3,12-dione **17**, respectively new pentaspiro-1,3-dioxane derivatives **28-29** and the hexaspiro-1,3-dioxanes **30** and **31** were obtained.



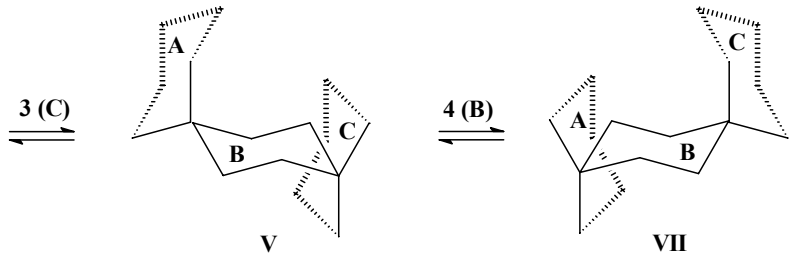


2.3. Structural analysis of the Tetra-, Penta- and Hexaspiro-1,3-Dioxanes

The marginal rings (A and C, Scheme 18) in dispiro[5.2.5.2]hexadecane **33** (or in heterocyclic analogous) show "*syn*" [on the same side of the best plane $C^1C^5C^6$ ($C^9C^{10}C^{14}$) of the middle ring B, structures V and VII] or "*anti*" (on opposite sides, structure VI) dispositions, the helix being conserved in the "*syn*" isomers or cancelled in the "*anti*" one.



33



Scheme 18

The *syn* or *anti* disposition of the rings A and C with reference to ring B in dispirane **33** can be deduced from the value of the dihedral angle $C^1C^2C^4C^5/C^{10}C^{11}C^{13}C^{14}$. If the value of this dihedral angle is close to zero, the rings A and C are *anti* and if the value of this angle is close to 90^o the *syn* disposition of rings A and C must be taken into account.

A comparison of the configuration problems of dispirane **33** with those of [10]helicene is interesting. [10]Helicene can be considered as obtained by the merging of two hexahelicene units. The chirality of [10]helicene can be deduced from the configurations of the jointed units.[33,34] Two units with identical configuration generate *P* or *M* [10]helicene, while the joint of units with different configurations determines a symmetric structure (exhibiting an inversion centre). Similarly, the dispirane **33** is built up by the merging of two monospiro units (rings AB and BC) and the chirality of dispirane is determined by the configurations of the two monospiro entities. If the two units (rings AB and BC) exhibit the same configuration the helix is continued in the whole structure (*P* and *M* "*syn*" isomer) and if they show opposite configurations the chirality of the system is cancelled ("*anti*" isomer; Table 1).

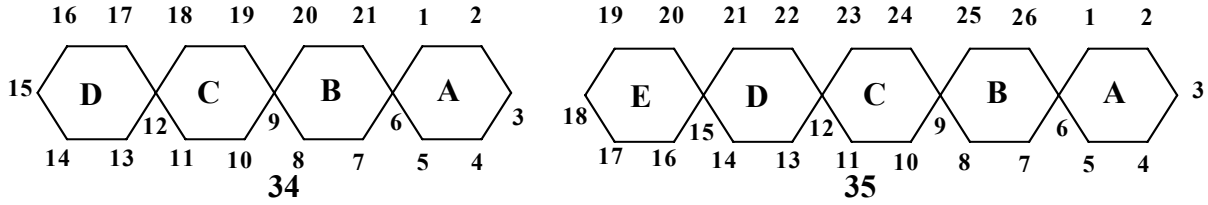
The flipping (steps 1 and 3, Scheme 18) of marginal rings (A or C) changes the configuration of one of the two monospiro constituent units and transforms "*syn*" into "*anti*" isomers and *vice versa*, while the flipping of the middle ring B (steps 2 and 4) changes the configuration of both constituent units and results in a homomeric equilibrium (step 2) in the "*anti*" isomer and in an enantiomeric inversion (step 4) in the "*syn*" ones.

Table 1. Possible stereoisomers of spiro compounds with six-membered-rings.

Isomer	Orientation of the rings	AB	BC	CD	DE	Helix
I		*M*				*M*
II		*P*				*P*
V	6,9-*syn*	*M*	*M*			*M*
VI	6,9-*anti*	*P(M)*	*M(P)*			
VII	6,9-*syn*	*P*	*P*			*P*
VIII	6,9-*syn*-9,12-*syn*	*M*	*M*	*M*		*M*
IX	6,9-*syn*-9,12-*syn*	*P*	*P*	*P*		*P*
X	6,9-*syn*-9,12-*anti*	*P*	*P*	*M*		*P*
XI	6,9-*syn*-9,12-*anti*	*M*	*M*	*P*		*M*
XII	6,9-*anti*-9,12-*anti*	*P*	*M*	*P*		*P*
XIII	6,9-*anti*-9,12-*anti*	*M*	*P*	*M*		*M*
XIV	6,9-*syn*-9,12-*syn*-12,15-*syn*	*P*	*P*	*P*	*P*	*P*
XV	6,9-*syn*-9,12-*syn*-12,15-*syn*	*M*	*M*	*M*	*M*	*M*
XVI	6,9-*syn*-9,12-*syn*-12,15-*anti*	*P*	*P*	*P*	*M*	*P*
XVII	6,9-*anti*-9,12-*syn*-12,15-*syn*	*P*	*M*	*M*	*M*	*M*
XVIII	6,9-*anti*-9,12-*syn*-12,15-*anti*	*M*	*P*	*P*	*M*	*P*
XIX	6,9-*anti*-9,12-*syn*-12,15-*anti*	*P*	*M*	*M*	*P*	*M*
XX	6,9-*syn*-9,12-*anti*-12,15-*anti*	*P*	*P*	*M*	*P*	*P*
XXI	6,9-*syn*-9,12-*anti*-12,15-*anti*	*M*	*M*	*P*	*M*	*M*
XXII	6,9-*syn*-9,12-*anti*-12,15-*syn*	*M(P)*	*M(P)*	*P(M)*	*P(M)*	
XXIII	6,9-*anti*-9,12-*anti*-12,15-*anti*	*M(P)*	*P(M)*	*M(P)*	*P(M)*	

The parent trispirane **34** or tetraspirane **35** (Scheme 19) or their analogous heterocycles can be built up from three, respectively four monospiro units being possible the existence of six, respectively ten isomers (Table 1).

The *syn* or *anti* orientations of the rings of the tetraspirane **35** can be deduced as mentioned before for **33** from the values of the angles $C^1C^2C^4C^5/C^{10}C^{11}C^{23}C^{24}$; $C^7C^8C^{25}C^{26}/C^{13}C^{14}C^{21}C^{22}$ and $C^{16}C^{17}C^{19}C^{20}/C^{10}C^{11}C^{23}C^{24}$.



Scheme 19

All the possible isomers of trispirane **34** are chiral, whereas the polyspiro skeleton in tetraspirane **35** exhibits two isomers with higher symmetry (both showing an inversion centre). The configuration problems of polyspiranes, as those of polyhelicenes (formed by multiply joined hexahelicene units or linked [*n*]helicene[35]) are correlated with the odd or even number of spiro joined structural units. It is to be observed that when odd numbers of spiro-units are joined (or odd numbers of hexahelicene units form the polyhelicene) all the possible structures of the polyspiranes (polyhelicenes) are chiral, whereas the polyspiranes with even

numbers of spiro units (or polyhelicenes with even numbers of hexahelicene units) exhibit achiral isomers (with centre of inversion).

Few data concerning the solid-state molecular structure of polyspiranes exhibiting six-membered rings (dispiranes[36], trispiranes[37-39] and tetraspiranes[27]) have been reported. In all data reported until now the polyspiranes display rings of different sizes and to our knowledge no X-ray diffractometry data for tetraspiranes exhibiting only six-membered rings have yet been reported.

Considering the complexity of configurational and conformational problems in the stereochemistry of spiranes with six-membered rings it has been considered of interest to continue the structural studies on the stereochemistry of polyspiranes and to perform the synthesis and NMR and X-ray investigations of some new tetraspiro-1,3-dioxanes.

Compound **22** exhibits flexible structure, the flipping of cyclohexane or 1,3-dioxane rings determines the equilibration of all possible isomers (ten isomers, as for **33**, six of them being diastereoisomers, Table 1). The ^{1}H NMR spectrum of **22** recorded at *rt* is quite simple, the protons of the 1,3-dioxane rings, rendered equivalent by the flexibility of the molecule, exhibit one singlet at δ = 3.55 ppm. The spectrum run at low temperature (223 K in CD_2Cl_2, this temperature barrier is dictated by the low solubility of the compound in all usual NMR solvents) shows for the protons of the heterocycles a broad band between δ 3.25-3.75 ppm. The shape of this signal (band) denotes the proximity of the coalescence and the incurrent imminent freezing of the flipping of the rings.

The molecular structure of **22** (ORTEP diagrams, Figure 1) established in solid state by X-ray diffractometry shows chair conformations for both the cyclohexane and 1,3-dioxane rings.

The crystal contains two kinds of molecules corresponding to the centrosymmetric structures 6,9-*anti*-9,12-*anti*-12,15-*anti* and 6,9-*syn*-9,12-*anti*-12,15-*syn*. The structures were best solved for a 1:1 ratio between the two conformers. The disposition of the rings was deduced from the calculated values of the reference dihedral angles.

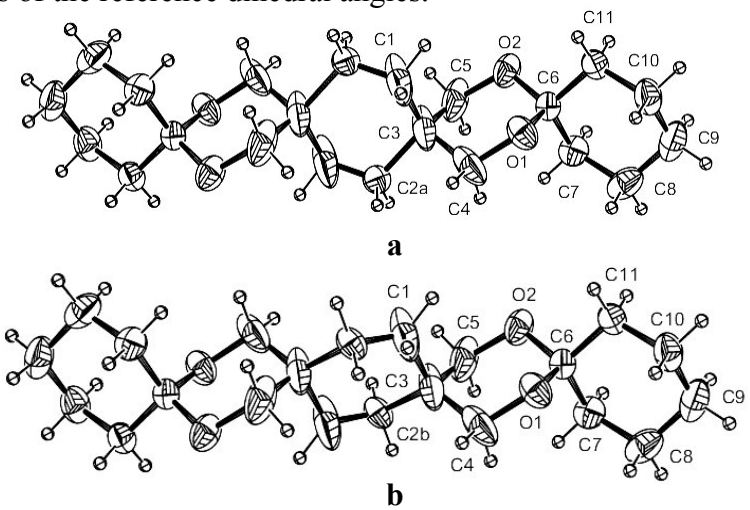
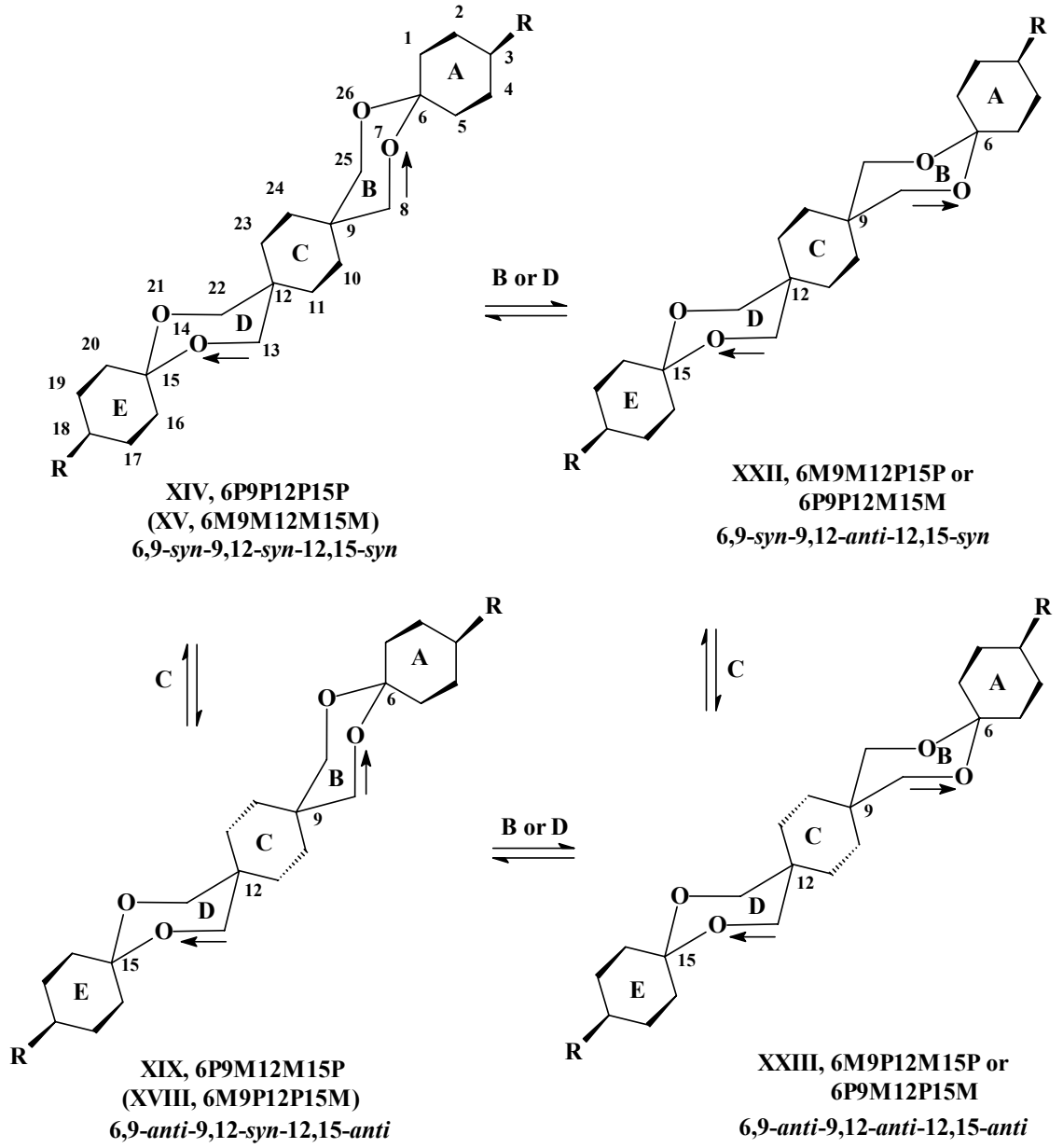


Figure 1. ORTEP diagrams for **22** (a: 6,9-*anti*-9,12-*anti*-12,15-*anti*; b: 6,9-*syn*-9,12-*anti*-12,15-*syn* isomers).

Compounds **23-27** exhibit semiflexible structures. In **23-25** the rings A and E are anancomeric and rings B, C and D are flipping.

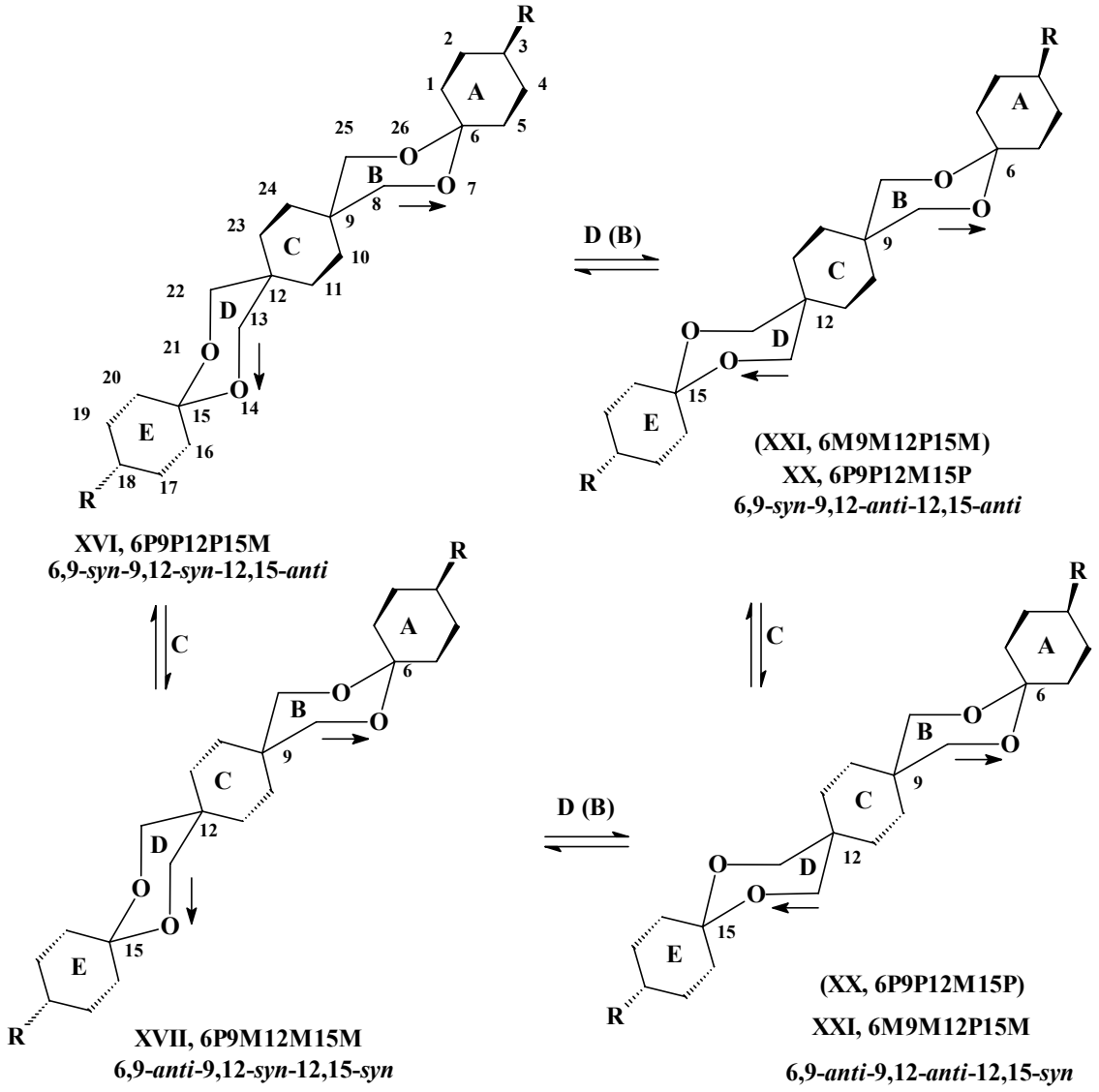
Compounds **23-25** exhibit two separable diastereoisomers. The flipping of the rings (B, C and D, scheme 20) in the major diastereoisomer D_1 leads to an equilibrium between structures XIV, XV, XVIII, XIX, XXII and XXIII (Table 1).

In the other isomer (D_2) the equilibria are running among the structures XVI, XVII, XX and XXI (Scheme 21).



Scheme 20 **diastereoisomer D_1**

To convert one of the structures of D_1 into one of the structures of D_2 it is necessary to break bonds and to remake bonds. *Per contra* the possible enantiomers (XIV, XV; XVIII, XIX for D_1 and XVI, XVII; XX, XXI for D_2) are equilibrated by the flipping of the rings.



Scheme 21 **diastereoisomer D_2**

This situation is different in the case of trispiro-1,3-dioxanes with semiflexible structures when the flipping of the middle part of the molecule is bringing in conformational equilibrium the possible diastereoisomers, but the enantiomers of the compounds are separable.[12,15] The case of tetraspiranes with semiflexible structure is similar with that of dispiro-1,3-dioxanes[13] that exhibit separable diastereoisomers and conformationally equilibrated enantiomers.

The ratio between the two diastereoisomers of **23-25** is about D_1:D_2 = 4:1 (estimated from NMR spectra).

The magnetic environments of the similar protons and similar carbon atoms in the two diastereoisomers (D_1 and D_2) are very close and in the NMR spectra of the mixture of diastereoisomers the majority of the signals are not separated. However, for the protons and carbon atoms of the heterocycles (positions 8, 13, 22, 25) very close, but separated signals, are observed. As an example, the ^{1}H NMR spectrum of **24** exhibits for the protons of each diastereotopic positions of the heterocycles two very close signals ($\delta_{8,22}$ = 3.60 and 3.61, $\delta_{13,25}$ = 3.64 and 3.62 ppm, Figure 2a).

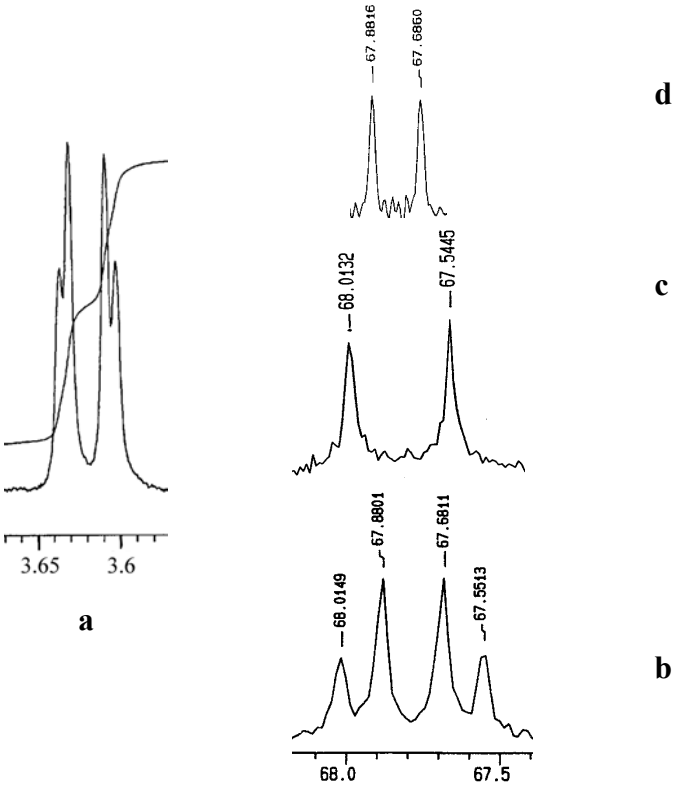


Figure 2. NMR spectra (fragments) of **24** (75 MHz, $CDCl_3$, a: ^1H NMR, mixture of D_1 and D_2, b: ^{13}C NMR, mixture of D_1 and D_2, c: ^{13}C NMR of D_1, d: ^{13}C NMR of D_2).

The ^{13}C NMR spectrum also exhibits two sets of signals for the carbon atoms of these positions ($\delta_{8,22}$ = 67.54 and 67.69, $\delta_{13,25}$ = 68.01 and 67.88 ppm, Figure 2b). The two diastereoisomers of **24** have been separated by flash chromatography (dichloromethane : diethylether = 5:1). The NMR spectra of the separated isomers showed unique sets of signals (*e.g.*, for the carbon atoms of positions 8, 22 and 13, 25 respectively, Figures 2c and 2d).

The molecular structure of the minor isomer (D_2) of **24** was investigated by X-ray diffractometry. The ORTEP diagram (Figure 5) shows the preference in solid state of the polyspiro skeleton for the 6,9-*anti*-9,12-*anti*-12,15-*syn* structure. The orientation of the phenyl groups (at positions 3 and 18) is intermediary (dihedral angles $\alpha = O^{26}C^6O^7$ / C^{27}-C^{32} = 68.1° and $\beta = O^{14}C^{15}O^{21}$ / C^{33}-C^{38} = 65.7°) to that observed in the typical bisectional (α, β = 0°) and orthogonal (α, β = 90°) rotamers.[40]

The variable temperature NMR experiments run with **23-25** showed [at low temperatures (*e.g.*, for **25** the coalescence is close to 213 K, Figure 6)] the freezing of the flipping of the rings B, C and D.

The low temperature spectra of these compounds are very complex and they are not well-solved, due on one hand to the six possible diastereoisomers and on the other hand to the different axial and equatorial positions of the protons of the rings. These spectra exhibit for the protons of the heterocycles (instead of the two singlets recorded at *rt*), four or five groups of large signals between 3 and 4 ppm (for example, for the major isomer (D_1) of **24** the ^1H

NMR (a) and the COSY (b) spectra at 193 K of these protons are presented in Figure 7). These modifications of the spectra prove the freezing of the flipping of the middle part of the tetraspirane.

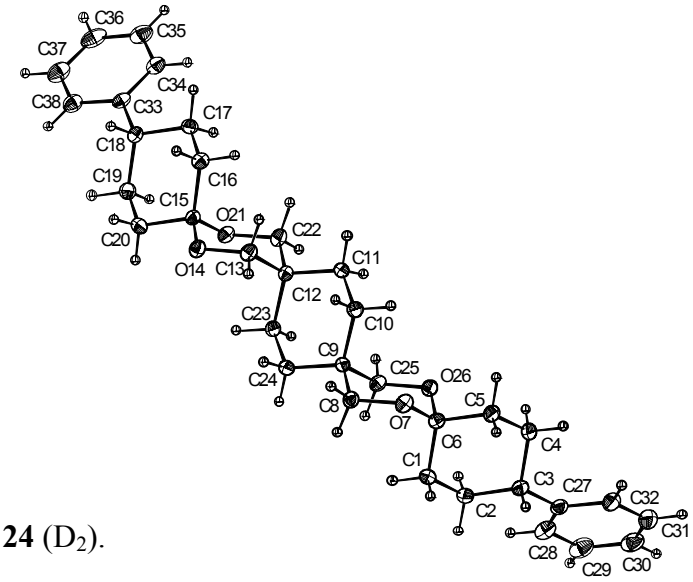


Figure 5. ORTEP diagram of **24** (D_2).

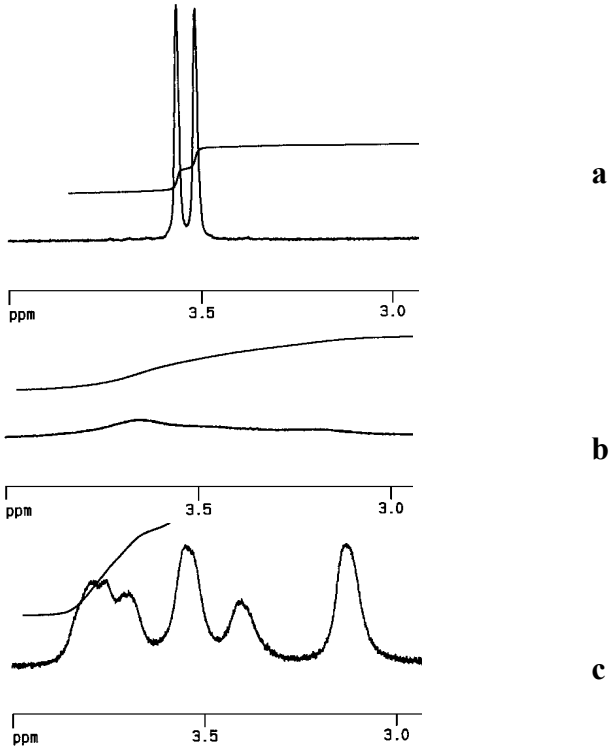
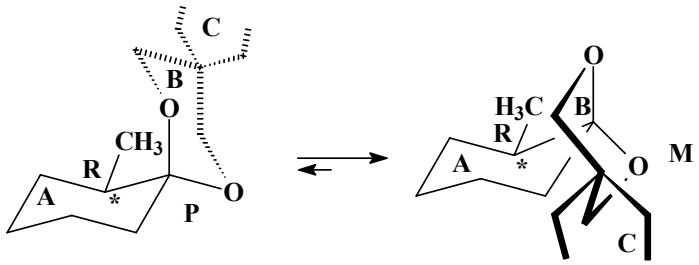


Figure 6. Variable temperature ^{1}H NMR spectra (fragments) of **25** (400 MHz, CD_2Cl_2, a: 273 K, b: 213 K, c: 193 K).

The stereochemistry of **26** (2*R*, 17*R* isomer, pure 3(*R*)-methylcyclohexanone was used as starting material) is similar to that of **23-25**. The marginal rings (A and E) are anancomeric while the middle part of the spirane is flipping. The conformational behaviour of the compound is deduced from the NMR spectra run at *rt* and at low temperature (similar modifications with those observed for **23-25** are recorded).

The synthesis of **27** was performed using the racemic ketone. A mixture of *like* and *unlike* isomers was obtained. The equatorial methyl groups in positions 1 and 16 determine, besides the anancomericity of rings A and E, the anancomericity of neighbouring rings B and D, too (Scheme 22).[14] Both *like* and *unlike* isomers exhibit semiflexible structures: the middle ring C is flipping, while the other rings (A, B, D, E) are anancomeric. The configuration of the chiral centres determines the configuration of the neighbouring spiro units (AB and DE). A chiral centre exhibiting *R* configuration is correlated with an *M* configuration of the close spiro unit and the *S* configuration of the chiral centre involves the *P* configuration of the neighbouring spiro unit (Scheme 22).



Scheme 22

Two separable diastereoisomers for the *like* isomer (D_3, D_4; Table 5, Scheme 23) and two other ones for the *unlike* structure (D_5, D_6) are possible. In the synthesis of **27** (yield 62 %) the diastereoisomer D_5 (of the *unlike* compound) is the main product (about 70 %) and it was separated by crystallisation.

Table 5. Possible stereoisomers of **27**.

Isomer	Type	Configuration at C^1 and C^{16}	Configuration of spiro units AB (6)	BC (9)	CD (12)	DE (15)	Arrangements of the polyspiro skeleton
XXIV	*like*	1*R*16*R*	*M*	*M*	*M*	*M*	6,9-*syn*-9,12-*syn*-12,15-*syn*
XXV	*like*	1*S*16*S*	*P*	*P*	*P*	*P*	6,9-*syn*-9,12-*syn*-12,15-*syn*
XXVI	*like*	1*R*16*R*	*M*	*P*	*P*	*M*	6,9-*anti*-9,12-*syn*-12,15-*anti*
XXVII	*like*	1*S*16*S*	*P*	*M*	*M*	*P*	6,9-*anti*-9,12-*syn*-12,15-*anti*
XXVIII	*like*	1*R*16*R*	*M*	*P*	*M*	*M*	6,9-*anti*-9,12-*anti*-12,15-*syn*
XXIX	*like*	1*S*16*S*	*P*	*M*	*P*	*P*	6,9-*anti*-9,12-*anti*-12,15-*syn*
XXX	*unlike*	1*R*16*S*	*M*	*M*	*P*	*P*	6,9-*syn*-9,12-*anti*-12,15-*syn*
XXXI	*unlike*	1*R*16*S*	*M*	*P*	*M*	*P*	6,9-*anti*-9,12-*anti*-12,15-*anti*
XXXII	*unlike*	1*R*16*S*	*M*	*M*	*M*	*P*	6,9-*syn*-9,12-*syn*-12,15-*anti*
XXXIII	*unlike*	1*R*16*S*	*M*	*P*	*P*	*P*	6,9-*anti*-9,12-*syn*-12,15-*syn*

D_3 | **XXIV, 6M9M12M15M** $\overset{C}{\rightleftharpoons}$ **XXVI, 6M9P12P15M**

XXV, 6P9P12P15P $\overset{C}{\rightleftharpoons}$ **XXVII, 6P9M12M15P**

D_4 (flipping of ring C in XXVIII and XXIX results into a homomeric inversion)

D_5 **XXX, 6M9M12P15P** $\overset{C}{\rightleftharpoons}$ **XXXI, 6M9P12M15P**

D_6 **XXXII, 6M9M12M15P** $\overset{C}{\rightleftharpoons}$ **XXXIII, 6M9P12P15P**

Scheme 23

The structure of this compound was assumed by the molecular structure determined by X-ray diffractometry and from NMR spectra (Figures 9 and 10). The ORTEP diagram and the calculated reference angles show the centrosymmetric 6,9-*anti*-9,12-*anti*-12,15-*anti* structure in solid state of the isolated isomer. The ^{1}H NMR spectrum of **27** run at *rt* is not similar with that of compounds **23-26**, different signals being obtained for the axial and equatorial protons of the heterocycles (Figure 10).

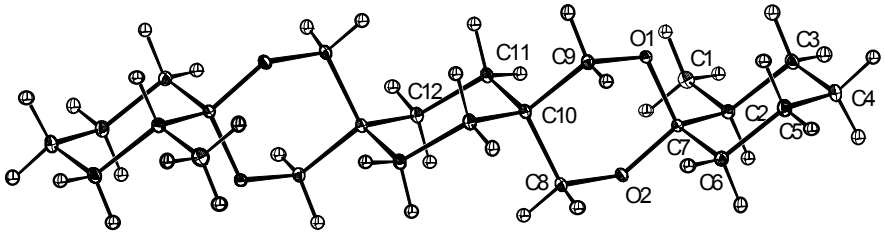


Figure 9. ORTEP diagram of **27** (D_5).

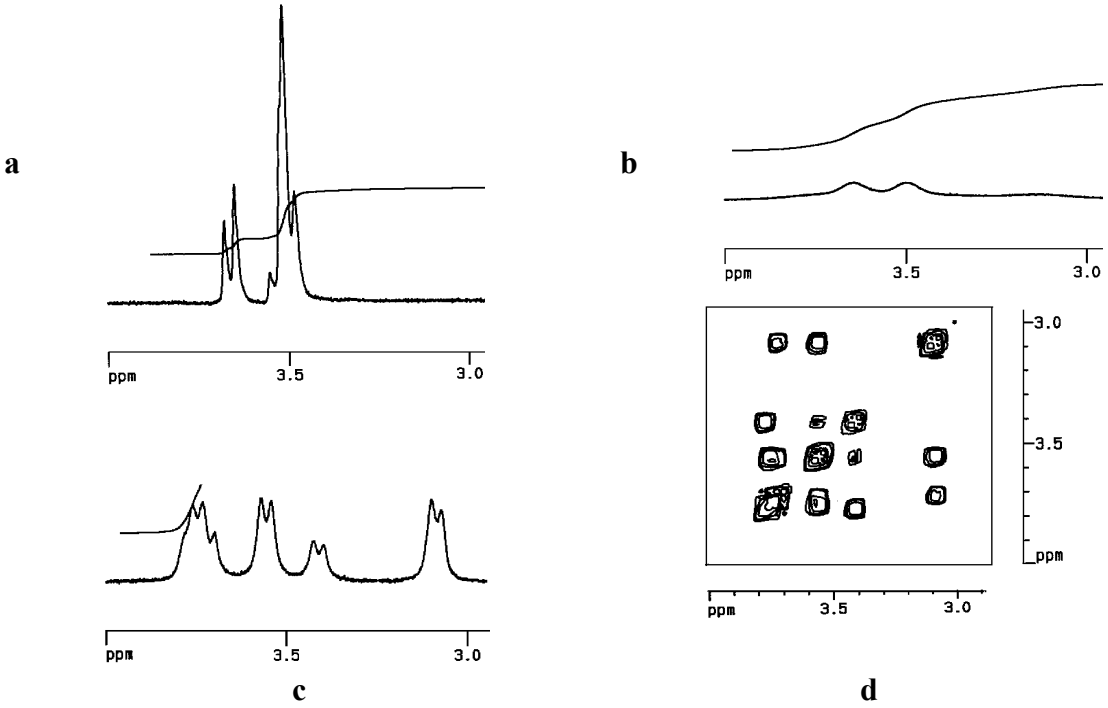
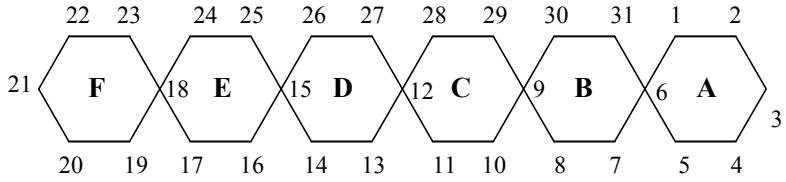


Figure 10. Variable temperature NMR spectra (fragments) of **27** (400 MHz, CD_2Cl_2, a: 273 K, b: 223 K, c: 203 K, d: COSY spectrum at 203 K).

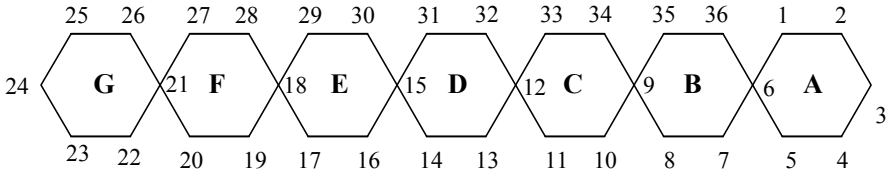
The flipping of ring C determines the recording (at *rt*) of signals belonging to average magnetic environments and the measured differences of chemical shifts between the axial and equatorial protons of the heterocycles are smaller than usual.[40] In the low temperature spectrum (203 K, coalescence at 223 K, Figure 10) the protons of the heterocycles exhibit two sets of signals with close intensities. These signals belong to the two frozen structures of D_5 [6,9-*anti*-9,12-*anti*-12,15-*anti* (XXXI) and 6,9-*syn*-9,12-*anti*-12,15-*syn* (XXX)]. The theoretically eight doublets are overlapped into four signals. As can be deduced from the

intensities of the signals and from the COSY spectrum (Figure 10d) in the more deshielded signal (δ = 3.73 ppm) there are three overlapped doublets, while the signals at δ = 3.57 ppm and δ = 3.09 ppm are both obtained by the overlapping of two doublets. The supplementary coupling between the signals at δ = 3.57 ppm and at δ = 3.41 ppm (observed in the COSY spectrum) is probably due to the characteristic long range coupling between the equatorial protons at the positions 4 and 6 of the 1,3-dioxane ring.

The parent pentaspirane **36** or hexaspirane **37** or their analogues heterocycles can be further built up from five or six monospiro units, respectively. A number of 20 possible isomers can be described in the first case, while for **37** the number of isomers goes up to 36.



36



37

All the possible isomers of pentaspirane **36** are chiral (odd number of spiro units are joined), while for the hexaspirane **37** with five joined spiro units there are four achiral isomers.

The pentaspirane **28** exhibits flexible structure, the flipping of cyclohexane or 1,3-dioxane rings determines the equilibration of all possible isomers (20 isomers, as for **36**). The ^{1}H NMR spectrum of **28** recorded at *rt* is simple, the protons of the 1,3-dioxane rings, rendered equivalent by the flexibility of the molecule, exhibit one singlet at δ = 3.54 ppm and only two more signals appear – a broad triplet (overlapped peaks, an AA'BB' system with an estimated vicinal constant ^{3}J=6.0 Hz) at δ=1.69 ppm for the eight protons at positions 10, 14, 26 and 29 and a group of signals for all the other 28 cyclohexane protons at δ=1.25-1.45 ppm. The spectrum run at low temperature (180 K in CD_2Cl_2) shows for the protons of the heterocycles a broad band between δ=3.25-3.75 ppm (coalescence at 211K). The shape of this signal (band) denotes the incurrent freezing of the flipping of the rings.

The substituted pentaspirane **29** exhibit semiflexible structure, the *tert*-butyl goups at positions 3 and 21 are holding groups. Therefore, the rings A and F are anancomeric and rings B, C, D and E are flipping.

Compounds **29** exhibit two separable enantiomers. As in the case of trispiro-1,3-dioxanes, the flipping of the interior rings brings in conformational equilibrium the possible diastereomers.

In ^{1}H NMR there are two singlets for the protons in the 1,3-dioxane rings at δ=3.67 and δ=3.38 ppm, respectively. Once again, the spectrum run at low temperature (180 K in CD_2Cl_2) did not show yet the freezing of the flipping of the rings and for the protons of the heterocycles a broad band between δ=3.10-3.90 ppm is present (coalescence at 187 K).

The hexaspirane **30** exhibit flexible structure, all the possible isomers (36 as for **37**) are equilibrated by the flipping of the cyclohexane and 1,3-dioxane rings.

Just as in the case of **28**, the ^{1}H NMR spectrum of **30** is very simple, only one singlet at δ=3.46 ppm for the eight protons from the 1,3-dioxane rings, again a triplet (overlapped peaks, an AA'BB' system, ^3J=6.0 Hz) at δ=1.60 ppm for the protons at positions 10, 17, 29 and 34 and a group of signals for the rest of the protons at δ=1.18-1.35 ppm.

The structure of this compound was also confirmed by the appearance in the EI spectra of the molecular peak (500.4).

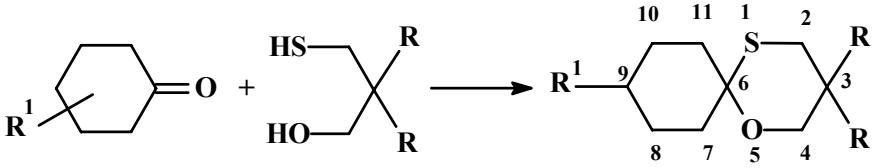
When in positions 3, 24 there are *tert*-butyl groups, they are anancomeric groups and compound **31** exhibit semiflexible structure. The marginal rings A and G are anancomeric and the other rings (B, C, D, E and F) are flipping.

Compound **31** is presented as a pair of diastereomers. It was not possible to identify or to separate the two diastereomers, there is only one set of signals in the NMR spectra of the reaction mixture. This is probably due to the fact that the differences in the structure of the two isomers are too small and also the large molecular weight did not allow their study through classical methods used to identify the diastereomers (GC-MS for example). In our attempt to discriminate the two isomers, we have run some ^{1}H NMR spectra in the presence of lanthanide shift reagents ($Eu(FOD)_3$, $Pr(FOD)_3$), but no significant result was obtained.

The structure of **31** was also confirmed by the appearance in the EI spectra of the molecular peak (612.5). The ^{1}H NMR spectrum of **31** is almost identical to that of **29**, there is only one more singlet at δ=1.29 ppmfor the protons from the middle part of the spirane (positions 13, 14, 31, 32).

2.4. Synthesis of New Spiro- and Polyspiro-1,3-Oxathianes

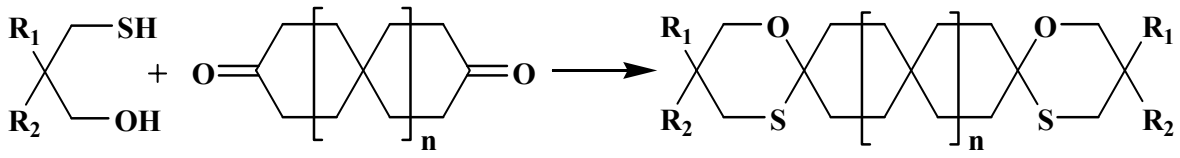
New spiro-1,3-oxathiane derivatives **40-46**[41] were obtained by the condensation reaction of some cyclohexanones with 3-mercapto-1-propanols **38** and **39** (Scheme 24).



R = H	**38**	R = H, R^1 = 9-C_6H_5	**40**
R = CH_3	**39**	R = CH_3, R^1 = H	**41**
		R = CH_3, R^1 = 9-CH_3	**42**
		R = CH_3, R^1 = 9-*t*-C_4H_9	**43**
		R = CH_3, R^1 = 9-C_6H_5	**44**
		R = CH_3, R^1 = 8-CH_3	**45**
		R = CH_3, R^1 = 7-CH_3	**46**

Scheme 24

New poly (di-, tri-, tetra-, penta- and hexa-) spiro-1,3-oxathianes were also obtained from the appropriate diketones and mercaptopropanols (scheme 25).



38	**47**	$R_1=R_2=H$, n=0	**48**
39	**47**	$R_1=R_2=CH_3$, n=0	**49**
39	**21**	$R_1=R_2=CH_3$, n=1	**50**
14	**47**	R_1, R_2= -$(CH_2)_5$-, n=0	**51**
38	**17**	$R_1=R_2=H$, n=2	**52**
39	**17**	$R_1=R_2=CH_3$, n=2	**53**
14	**21**	R_1, R_2= -$(CH_2)_5$-, n=1	**54**
14	**17**	R_1, R_2= -$(CH_2)_5$-, n=2	**55**

Scheme 25

2.5. Structural analysis of the Spiro- and Polyspiro-1,3-Oxathianes

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.[17,42]

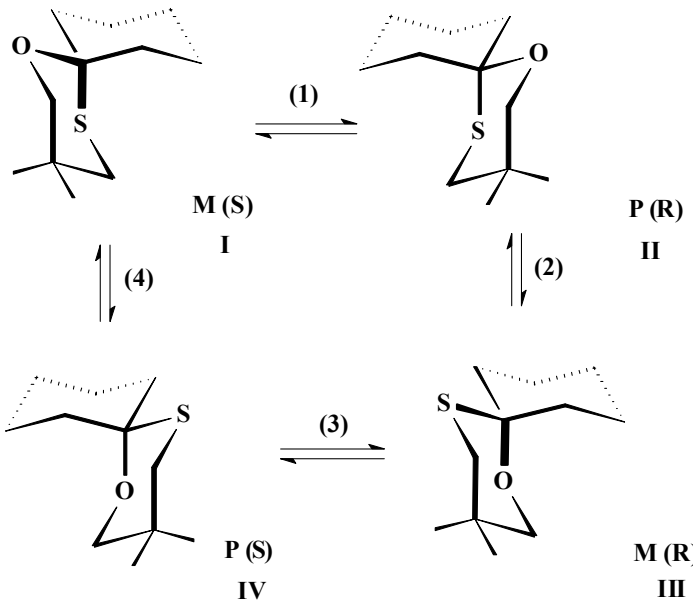
As presented earlier in this chapter, spiro-1,3-oxathianes exhibit the characteristic helical and axial chirality of spiro compounds with six-membered rings in addition to the chiral centre belonging to the heterocycle.[11,12,15]

Recently,[43] 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 (**40**), and a significant influence of the *p*H on the rate of the isomerization reaction was observed.

The complex configurational and conformational aspects of the stereochemistry of new variously substituted spiro 1,3-oxathianes are worth investigating and the already reported results[43-46] concerning the *cis-trans* isomerization of 1,3-oxathiane derivatives may be developed on this substrates.

Compound **41** exhibits helical chirality (due to the spiro skeleton) and a virtual triligand chiral centre (belonging to the 1,3-oxathiane ring). Four stereoisomers are possible, thereof two diastereoisomeric conformers (Scheme 26): D_1 [I *M*(*S*); II *P*(*R*)], D_2 [III *M*(*R*); IV *P*(*S*)]. At room temperature the compound shows a flexible structure, both carbocycle and heterocycle are flipping (Scheme 26) 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 centre resulting into an enantiomeric inversion. The part of the ^{1}H NMR spectrum at *rt* belonging to the protons of the heterocycle is very simple (Figure 11a) 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).



41

Scheme 26

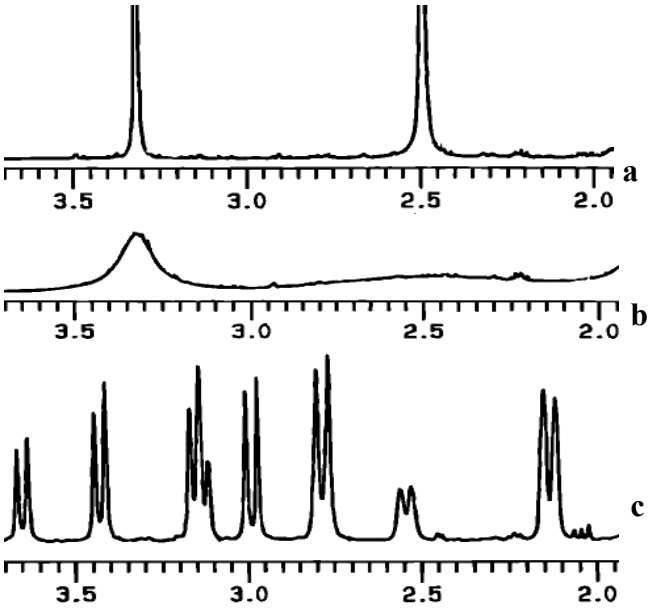


Figure 11. Variable temperature NMR spectra of compound **41** (400 MHz, CD_2Cl_2; a: 293 K, b: 260 K, c: 190 K).

At low temperature (190 K) the conformational equilibria are frozen and the ^1H NMR spectrum (Figure 11c, coalescence at 260 K, Figure 11b) 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} = 3.13, δ_{2ax} = 2.78 , δ_{4ax} = 3.65; D_2: δ_{2eq} = 2.12, δ_{4eq} = 3.16, δ_{2ax} = 2.99 , δ_{4ax} = 3.42 ppm). In agreement with the literature data that show a higher A value (on the cyclohexane ring) for an alkylmercapto than for an alkoxy group (A_{SMe} = 1 kcal/mol, A_{OMe} = 0.55-0.75 kcal/mol)[47] the diastereoisomer D_2 with the sulphur atom in an equatorial orientation (referred to the cyclohexane ring) was considered as the major isomer.

Compounds **40** and **42-46** were obtained as mixtures of *cis* and *trans* isomers (Schemes 27-29). 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 **44**, **45** and **46** were separated by flash chromatography.

The structure in solid state of the *trans* isomer of **44** was determined by X-ray diffractometry. The ORTEP diagram (Figure 13) 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]

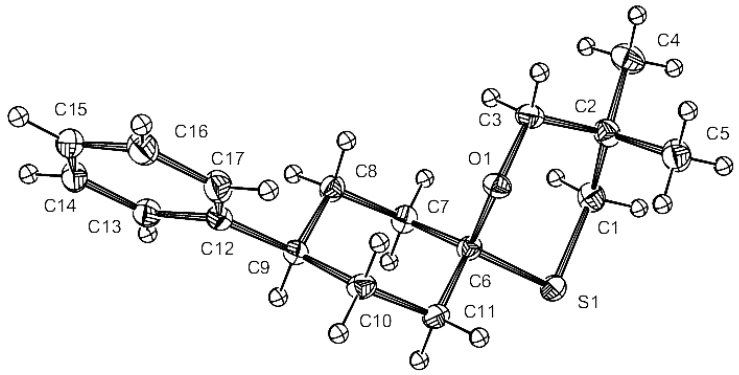
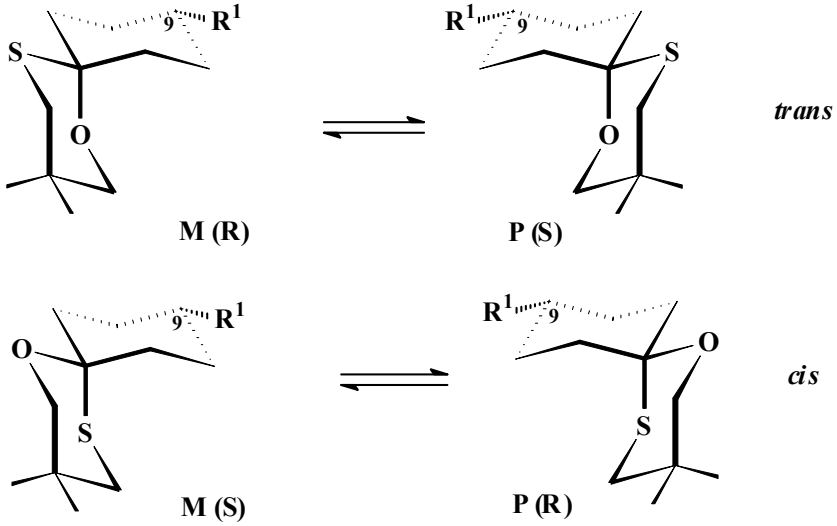


Figure 13. ORTEP diagram of *trans* isomer of compound **44**.

Compounds **40** and **42-45** 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 27 and 28).

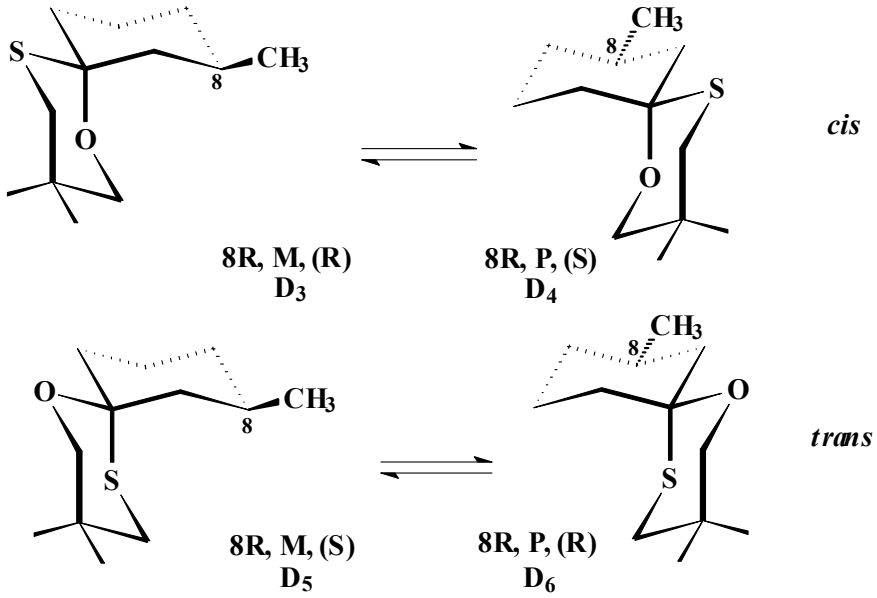


Scheme 27

The flipping of the heterocycle in the *cis* and *trans* isomers of **40** and **42-44** represents an enantiomeric inversion (Scheme 27), while in the *cis* and *trans* isomers of **45** it results in diastereoisomeric equilibria (Scheme 28).

The conformational behaviour of these compounds was deduced from the data of NMR spectra recorded at *rt* and at low temperature.

The spectrum of the *trans* isomer of compound **44** recorded at *rt* (Figure 14a) 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 **40**, **42-44**).



Scheme 28

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, Figure 14c; coalescence at 263 K, Figure 14b) 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_{4ax} = 3.51; δ_{4eq} = 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 (Figure 14c) 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 **45** (Figures 15 and 16).

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, Figure 15a).

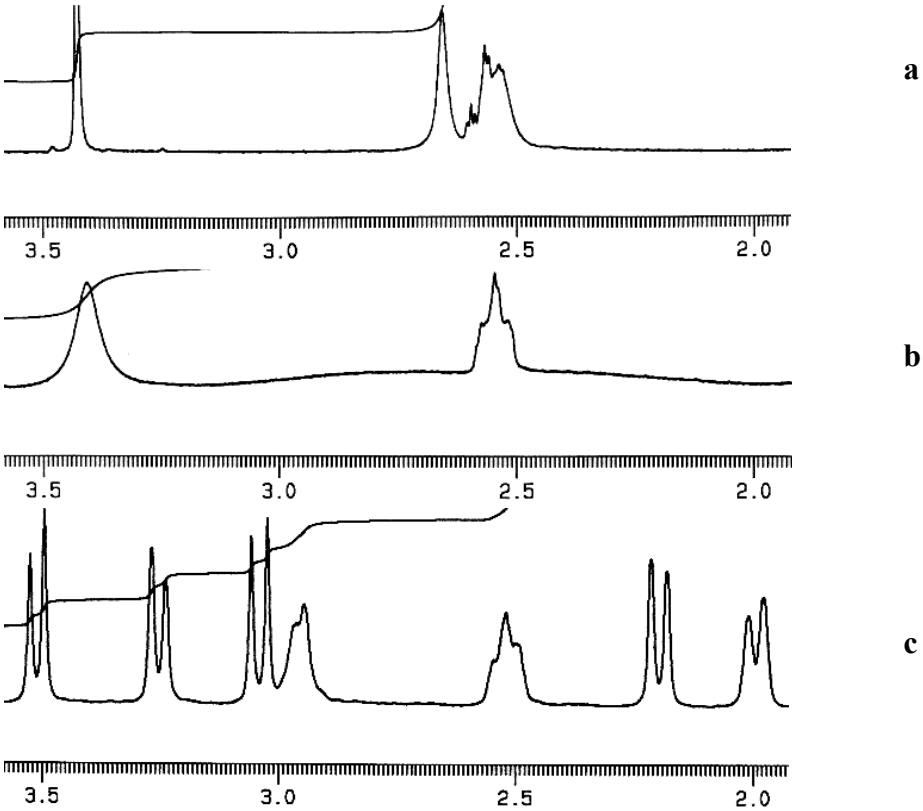


Figure 14. Variable temperature spectra of *trans* isomer of compound **44** (400 MHz, CD_2Cl_2; a: 298 K, b: 263 K, c: 223 K).

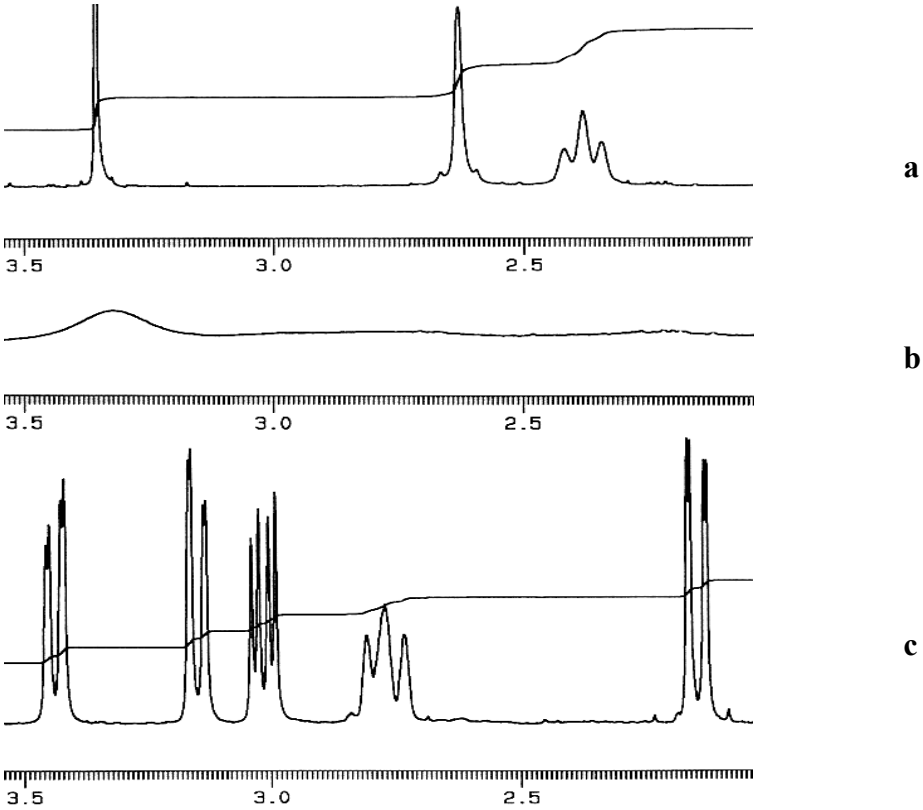


Figure 15. Variable temperature spectra of *cis* isomer of compound **45** (400 MHz, CD_2Cl_2; a: 298 K, b: 263 K, c: 223 K).

The spectrum of *trans* isomer at *rt* exhibits for the protons of the heterocycle two AB systems (Figure 16a). 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 = 2.49; $\delta_{2'}$ = 2.56 ppm; δ_4 = 3.42; $\delta_{4'}$ = 3.46 ppm). The chiral centre 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.

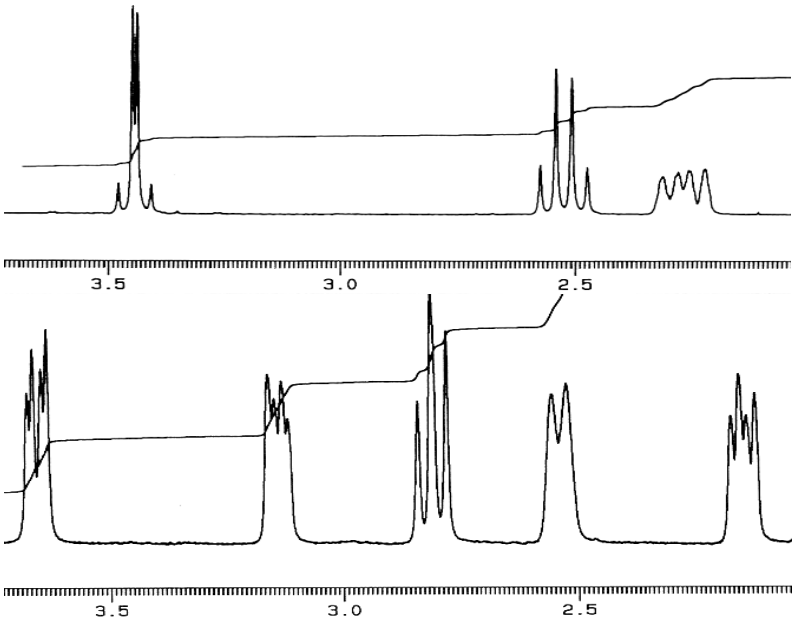
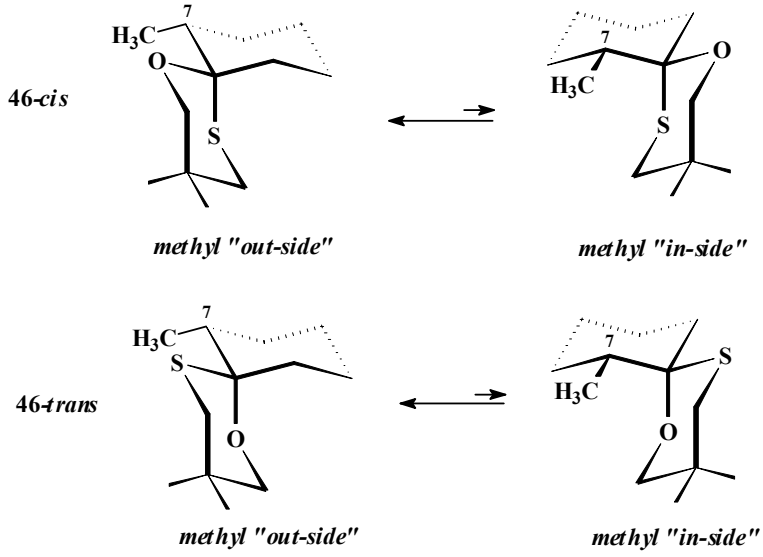


Figure 16. Variable temperature spectra of *trans* isomer of compound **45** (400 MHz, CD_2Cl_2; a: 298 K, b: 223 K).

The spectra of **45**-*cis* and **45**-*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 28) and *trans* (D_5, D_6, Scheme 28) 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* showing the significant modifications of the conformational behaviour of the molecules.

The *cis* and *trans* isomers of **46** exhibit anancomeric structures (Scheme 29), 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 were already reported for analogous 1,3-dioxane derivatives).[13] The NMR spectra of the *cis* and *trans* isomers of **46** (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

axial-equatorial inversion of the signals for the protons at positions 2 and 4 is clearly visible as the equatorial ones are dublets of dublets). The pattern of these spectra (at *rt*) is close to that of the spectra of **42-44** run at low temperature.

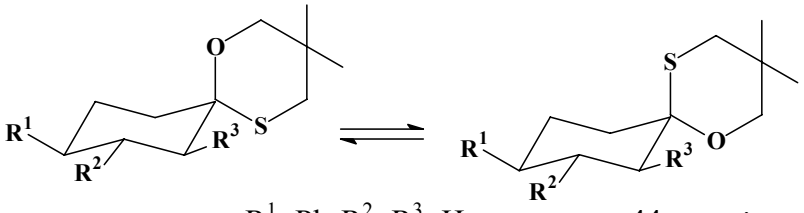


Scheme 29

In order to confirm the assignment of the signals belonging to the protons of position 2 and 4 NOE experiments were performed with the *cis* isomer of **46**. 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 same influence appeared for the protons at position 4. The results of these experiments show the higher deshielding for the axial protons at positions 2 and 4 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 **44**, **45** and **46**, using the data of *trans-cis* isomers equilibrations (Scheme 30). 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 and by measuring the ratio between the isomers using the intensities of specific signals.



trans	R^1=Ph; R^2=R^3=H,		**44**	*cis*
cis	R^2=Me;	R^1=R^3=H,	**45**	*trans*
trans	R^3=Me;	R^1=R^2=H,	**46**	*cis*

Scheme 30

The collecting of data 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 10.

$$\ln \frac{x_e}{x_e - x} = (k_1 + k_{-1}).t \quad (1) \qquad \frac{k_1}{k_{-1}} = K \quad (2)$$

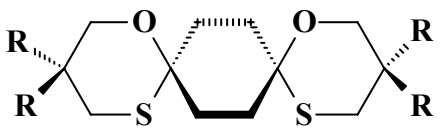
In equations (1) and (2) k_1 and k_{-1} are the forward and reverse reaction rate constants, K is the equilibrium constant, x_e is the concentration of the *cis* isomer for **44** and **45** and of *trans* isomer for **46** at equilibrium and *x* is the concentration of the same isomer at the "*t*" time. The k values (Table 10) are similar, the rate of the isomerization reaction is not strongly influenced by the position of the substituents.

Table 10. Kinetic parameters (k_1, k_{-1}; min^{-1}) for isomerizations of **44-46**.

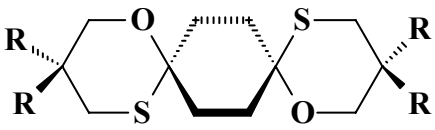
Compound	starting isomer	initial concentration (mol/l)	K	$k_1 \cdot 10^3$	$k_{-1} \cdot 10^3$
44	*trans*	$3.4\ 10^{-2}$	1.43	4.24	2.96
45	*trans*	$4.3\ 10^{-2}$	0.625	7.37	11.8
46	*cis*	$4.8\ 10^{-2}$	0.69	2.63	3.81

The two dispiro-1,3-oxathianes **48** and **49** exhibit flexible structure as both 1,3-oxathiane rings and the carbocycle are flipping. A fast equilibrium like the one described in scheme 18 for trispirane **33** occurs between the 6,9-*syn* and 6,9-*anti* stuctures.

The reaction mixture consisted of two diastereomers (*cis* and *trans*) that were separated by flash chromatography.



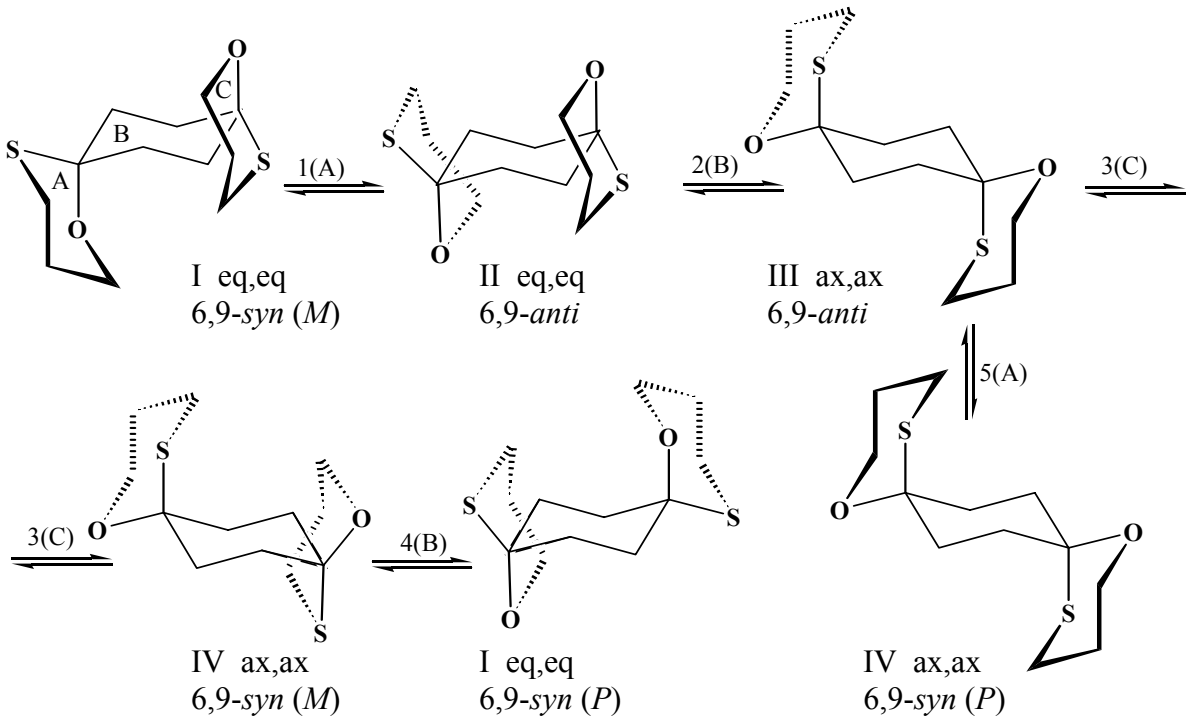
cis



trans

There are three structures that appear for the dispiro[5.2.5.2]hexadecane – two disymmetric structures for the 6,9-dispiro-*syn* isomer with *M* or *P* configurations of the helix and an achiral structure for the 6,9-dispiro-*anti* isomer. Beside the helical chirality in the *syn* isomer, in the dispiro-1,3-oxathiane derivatives two virtual chiral centres appear.

Equilibration of *trans* isomer (Scheme 31) with *M* 6,9-*syn* (I eq,eq) configuration through equilibria 1(A), 2(B), 3(C) and 4(B) – all four of them are diastereomeric inversions - leads to the *P* 6,9-*syn* (I eq,eq) enantiomer. The diastereomeric equilibrium 5(A) results into configuration *P* 6,9-*syn* (IV ax,ax), the enantiomer of the structure *M* 6,9-*syn* (IV ax,ax).

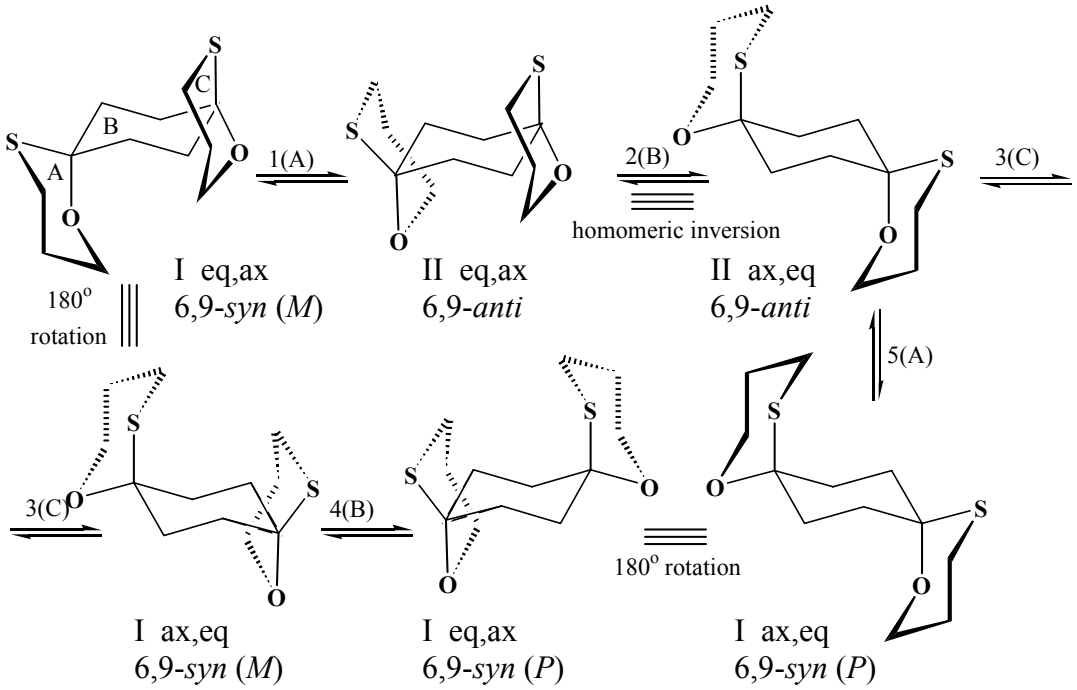


(axial or equatorial orientation of sulphur atoms is shown)

Scheme 31 *trans* isomer

Equilibration of *cis* isomer (Scheme 32) takes place through the same stages as that of isomer *trans*. The equilibrium 2(B) is a homomeric inversion. In fact, there is one enantiomer pair (I eq,ax (ax,eq) *M* and *P*) that transform themselves into each other through an enantiomeric equilibration as the result of the inversion of cyclohexane ring.

Due to the flexibility of the rings, the ^{1}H NMR spectra of the two isomers are quite simple and there are only slight differences in the cyclohexane part.



(axial or equatorial orientation of sulphur atoms is shown)

Scheme 32 *cis* isomer

So, for the *trans* isomer of **49** there are two singlets for the protons near the oxygen and sulphur, respectively at δ=3.40 and 2.61 ppm and for the protons from the middle ring there are two dublets (^2J=10 Hz) at δ=2.13 and 1.94 ppm for the diastereotopic protons at positions 7, 8, 15 and 16. For the *cis* isomer the protons near the oxygen give a signal at δ=3.42 ppm, those near the sulphur atoms a singlet at δ=2.59 ppm and the protons from the cyclohexane ring exhibit a multiplet at 1.92-2.14 ppm. In both isomers, the methyl groups at positions 3 and 12 appear as singlets at δ=1.05 ppm.

The molecular structure of the *trans* isomer of **49** was also investigated by X-ray diffractometry. The ORTEP diagram (Figure 20) shows chair conformations for both heterocycle and saturated carbocycle and also the preference in the solid state for the 6,9-*anti* structure.

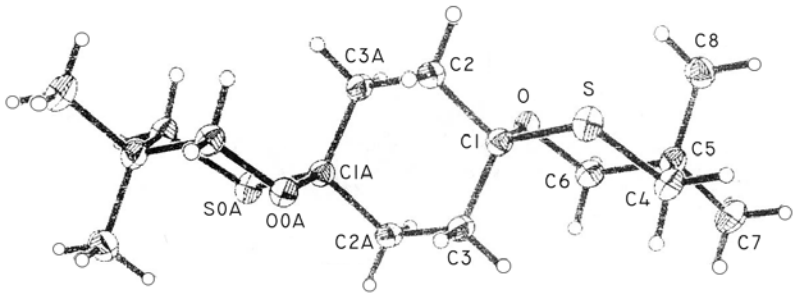


Figure 20. ORTEP diagram of *trans* isomer of compound **49**.

The synthesised trispirane **50** exhibit flexible structure. The stereochemistry of unsubstituted trispirane compounds has already been discussed in terms of helical chirality. The introduction of the virtual chirality due to the 1,3-dioxane rings leads to the existence of two separable enantiomers in this case.

There are many possible structures for these compound. We have to consider that in each of the six possible structure presented for a trispirane (VIII-XIII, Table 1) the two sulphur atoms may have several orientations: eq,eq; ax,eq and ax,ax in each of them.

The spectrum of **50** run at *rt* (Figure 21a) exhibits unique signals for the axial and equatorial protons near oxygen ($\delta_{4,16}$=3.39 ppm) or sulphur ($\delta_{2,14}$=2.57 ppm) of the heterocycles and for the protons of the similar groups ($\delta_{3,15\text{-Me}}$=1.02 ppm) at positions 3 and 15.

But in the low temperature spectrum (180 K, Figure 21c; coalescence at 243 K, Figure 21b) the axial and equatorial protons or groups at the mentioned positions exhibit different signals. Furthermore, there are two sets of signals for the protons of the heterocycle rings corresponding to at least four frozen diastereomers (D_1, D_2, D_3 and D_4) (the overlapped signals at δ=2.86 and 3.50 ppm indicate this) in a D_1+D_2 : D_3+D_4 = 60 : 40 ratio that are in fast equilibrium at *rt* – most probably isomers that exhibit at least one of the sulphur atoms in equatorial position and they have different conformations of the cycles and different configuration of the spirane skeleton. For the methyl groups ($\delta_{3,15\text{-Me(eq)}}$= 0.86 ppm and $\delta_{3,15\text{-Me(ax)}}$= 1.61, 1.75 ppm) there are also overlapped signals of the different frozen structures.

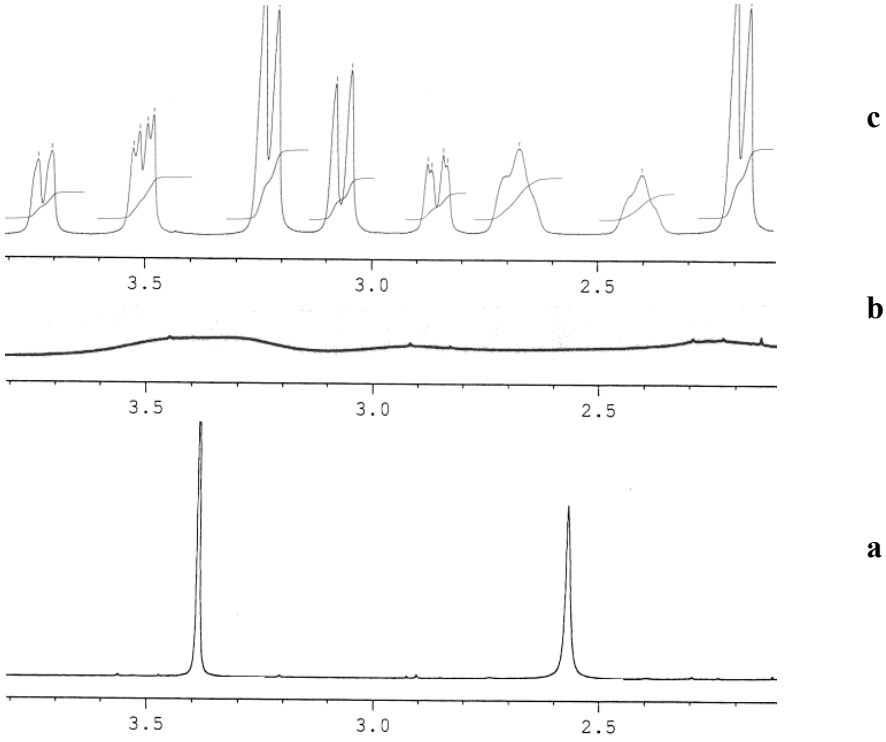


Figure 21. Variable temperature NMR spectra of compound **50** (400 MHz, CD_2Cl_2; a: 299 K, b: 243 K, c: 180 K).

As we move forward to the tetra-, penta- and hexaspiro-1,3-oxathianes the number of possible structures increase rapidly while the NMR spectra at *rt* do not differ esentially. When odd number (1 or 3) of cyclohexane cycles separate the 1,3-oxathiane rings (**51, 52, 53** and **55**) two separable diastereomers are obtained, while for compounds with even number (2) of cyclohexane cycles that separate the 1,3-oxathiane rings (**54**) a pair of enantiomers is obtained.

The differences between the ^{1}H NMR spectra at *rt* of the separated diastereomers are only in the signals of the middle part. For example it is compound **51** whose behaviour in the ^{1}H NMR is similar to that of compound **49**, *i.e.* for the protons of the interior cyclohexane ring in the *trans* and *cis* isomer there are two dublets and a multiplet, respectively. But notable differences appear in the low temperature spectra of these two isomers, the spectra of the *cis* isomer are more complex, there are more (or more different) frozen stuctures in the *cis* isomer than in the *trans* isomer.

As the number of spirane units - and especially the number of cyclohexane units that separate the two heterocyclic rings - increases, the differences in the low temperature NMR spectra of the diastereomers [compounds **52**, **53, 55**] are not significant. The number of different frozen structures at low temperature is higher for the compounds derived from 1-hydroxymethyl-1-mercaptomethyl-cyclohexane **14** [**51, 54, 55**] and overlapped with the signals from the cyclohexane rings.

The structure of the *trans* isomer of compound **52** was assumed by the molecular structure determined by X-ray diffractometry and from NMR spectra. The ORTEP diagram (Figure 27) and the calculated reference angles (C18O1S1C17 / C2C11C6C13 = 99.6°; C5C9C14C15 / C7C12C10C16 = 17.9°; C2C11C13C6 / C20O2S2C19 = 96.9°) show the 6,9-*syn*-9,12-*anti*-12,15-*syn* structure in solid state of the isolated isomer.

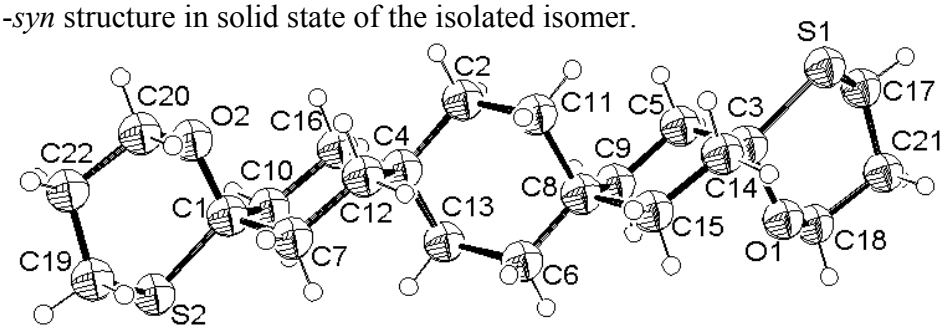


Figure 27. ORTEP diagram for the *trans* isomer of **52**.

PART C: BROMINATION REACTION OF DERIVATIVES EXHIBITING TWO 1,3-DIOXANE RINGS CONNECTED BY ALIPHATIC CHAINS

1. Bromination of Cyclic Acetals

Studying the stereochemistry of 1,3-dioxane derivatives, an important place is taken by compounds that have chiral substituents on the ring. The consequence of introducing a chirality centre in the molecule is the appearance of interesting aspects in the NMR spectra of these compounds. So, the stereochemical status of hydrogen or carbon atoms of the heterocycle or of groups attached to it is changed.

Atoms or even groups that were homotopic or enantiotopic in the achiral molecule and thus displaying unique signals in NMR spectra may become diastereotopic in the chiral derivatives. Nuclei that are diastereotopic will differ – in principle – in chemical shift, they will be "anisochronous".[1]

The introduction of a chiral centre on 1,3-dioxanes can be accomplished by bromination and the reaction proceeds in conditions similar to those used by Giusti in the bromination reaction of 1,3-dioxolane derivatives.[2]

Until now, studies concerning the bromination of variously substituted 1,3-dioxane derivatives were carried out and the conclusion was that the reaction presents high regio- and diastereoselectivity.[3-8]

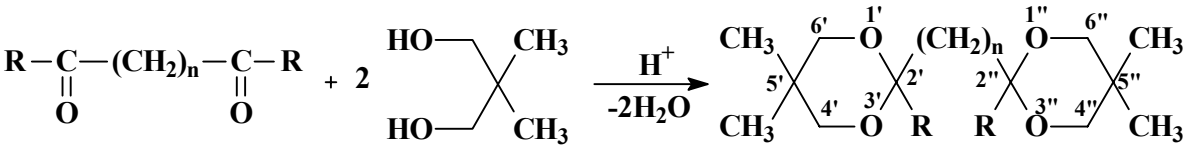
An interesting situation appears when two chiral centres are formed in the same molecule.

The configuration of the first created chiral centre (or of the pre-existent chiral centre where possible) influences the configuration of the next chiral centres introduced in the molecule by bromination. The chirality of the molecule induces the diastereotopicity of protons and carbon atoms, as noticed in the NMR spectra.

On this background, it was considered of interest to study a case when the newly formed chiral centres in the molecule do not share the same atom from the heterocycle (the carbon atom at position 2 on the 1,3-dioxane ring in the previous studies) and how do they influence each other. For this purpose compounds derived from α,ω-dicarbonylhydrocarbons with straight chain were chosen which were then brominated.

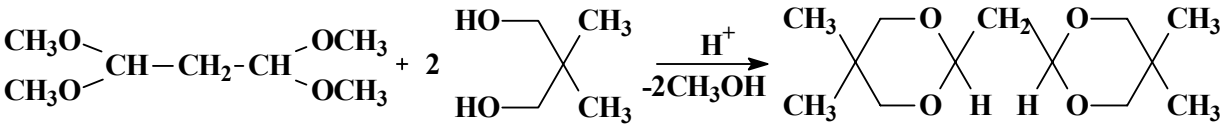
2. Synthesis and Stereochemistry of the 1,3-Dioxane Intermediates

The derivatives **4-12** [among them, six are new compounds and three of them have already been described in the literature (**4**[9], **7**[10], **11**[11])] were obtained after the reaction between the appropriate dicarbonyl derivative and 2,2-dimethyl-1,3-propanediol in acidic conditions (PTSA) in toluene; the equilibrium was shifted towards the product by azeotropic removal of the formed water.



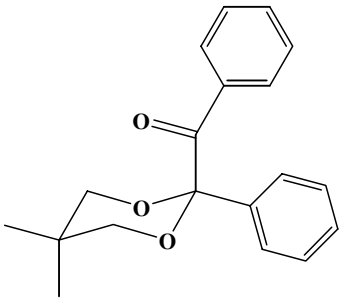
R = H, n=0 **4**
R = H, n=2 **5**
R = H, n=3 **6**
R = Ph, n=0 **7**
R = Ph, n=2 **8**
R = Ph, n=3 **9**
R = Ph, n=4 **10**

Compound **11** was obtained by transacetalisation of the corresponding tetraacetal [malonaldehyde-bis(dimethylacetal)].



11

In the attempt to prepare **7**, a significant amount of the mono-1,3-dioxane derivative **12** was obtained [in a 4:1 (**7**:**12**) ratio] and it was separated by repeated crystallisations from ethanol and acetone. The structure was confirmed by NMR and X-ray analysis.



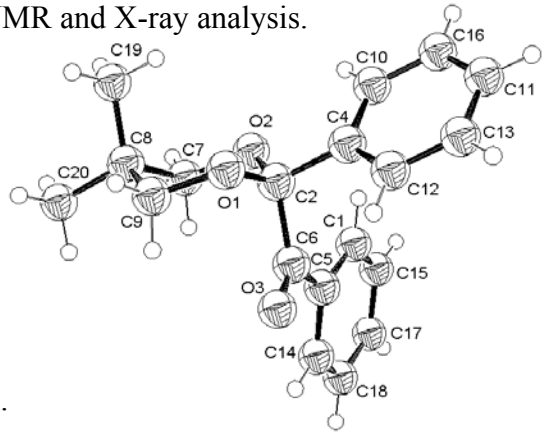


Figure 1. ORTEP diagram of **12**.

Studies[12-17] on the stereochemistry of 2-alkyl-1,3-dioxanes and of 2-alkyl-2-aryl-1,3-dioxane derivatives showed a high conformational free enthalpy for the methyl group – or substituted methyl groups - (ΔG_{Me}=3.8-3.9 kcal·mol^{-1}).[15,18-20] Compared to a methyl group, the phenyl substituent displays lower value of conformational free enthalpy (ΔG_{Ph}=3.12 kcal·mol^{-1})[19]. In 2-methyl (or substituted methyl)-2-phenyl-1,3-dioxanes, the phenyl group shows a higher preference for the axial orientation ($\Delta G°_{Me\text{-}Ph}$ = 2.42 kcal·mol^{-1})[20] than calculated by simple addition of the conformational free enthalpies measured for the two groups in monosubstituted compounds ($\Delta G°_{Me}$ - $\Delta G°_{Ph}$ = 0.8 kcal·mol^{-1})[15].

The result is that the conformational equilibrium for the investigated type of compounds is shifted toward the conformer that displays the hydrogen or the phenyl group in axial position and all the derivatives exhibit anancomeric structures.

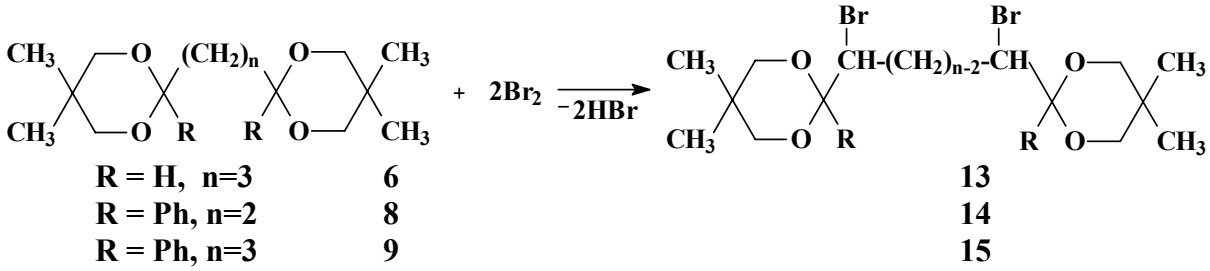
The rigid structure of the compounds is illustrated in ^{1}H NMR spectra by the appearance of different sets of signals for axial and equatorial methyl groups at positions 5'(5") as well as for the axial and equatorial protons at positions 4 and 6 of the heterocycles.

Compounds **7-10** exhibit axial phenyl group. The rotation of the phenyl substituent around its bond with the heterocycle is hindered by the interactions between the aromatic substituent and the axial hydrogen atoms at positions 4 and 6 of the 1,3-dioxane ring[9,21] and thus the preferred rotamer corresponds to the orthogonal arrangement, that minimises the syn-axial interactions.

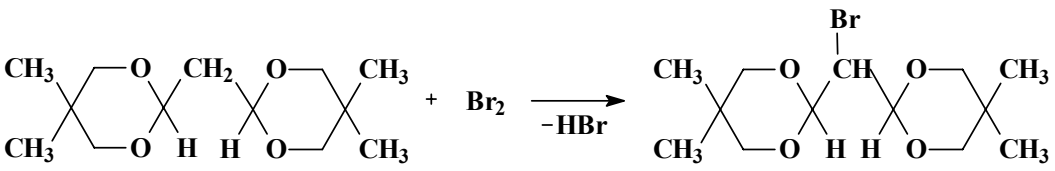
In compound **12**, the aromatic group prefers the equatorial position as the volume of the other substituent at position 2 (COPh) is smaller (Figure 1).

3. Synthesis and Structural Analysis of New Brominated Derivatives

Bromination of the 1,3-dioxanes prepared previously was performed with bromine in conditions similar to those used by Giusti in the bromination of 1,3-dioxolane compounds[2]. The aim of the project was to obtain the dibrominated derivatives where dibromination could take place. The reaction schemes are presented below.

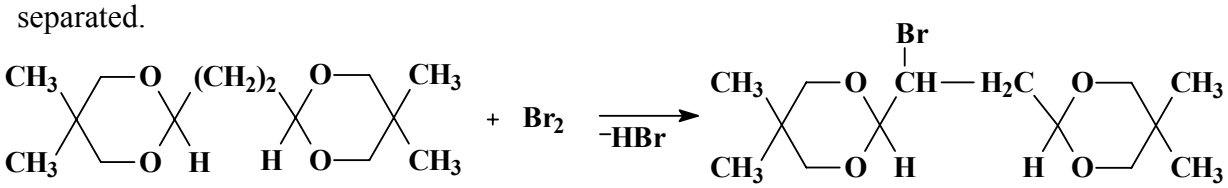


R = H, n=3 **6** **13**
R = Ph, n=2 **8** **14**
R = Ph, n=3 **9** **15**



11 **16**

When the 1,3-dioxane **5** was brominated, only the monobrominated derivative **17** was separated.



As in the case of the non-brominated 1,3-dioxanes, the molecules are rigid, anacomeric as the conformational equilibrium is shifted toward the conformer that bears the aliphatic (or the brominated aliphatic) part in equatorial position. This behaviour is illustrated by more complex NMR spectra.

In order to explain the ^{1}H NMR spectrum of compound **16** (Figure 2), some considerations must be made. Positions 4'(4") and 6'(6") are diastereotopic even if there are no chiral centres in the molecule; a similar example has been reported for citric acid.[22] This is because the carbon atom that bears the bromine atom (C^{α}) is a prochiral centre.

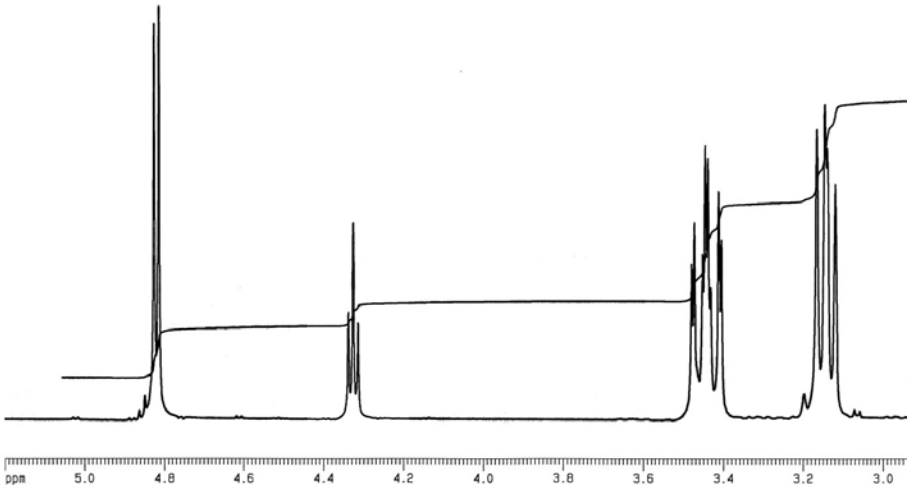
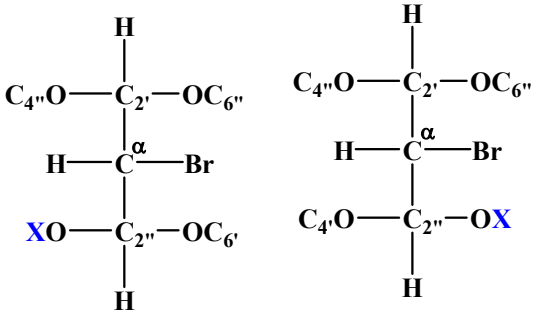


Figure 2. ^{1}H NMR spectrum of **16** (400 MHz, C_6D_6, detail)

Substituting one of the equivalent groups at $C_{2"}$, $OC_{4'}$ for example, with another group OX (priority $OX>OC_{4"}$), C^{α} becomes chiral as well as $C_{2"}$ and, due to the presence of two chiral centres, *like* and *unlike* isomers are possible. Substitution of the second group at $C_{2"}$ produce the opposite configuration at $C_{2"}$ while at C^{α} the same configuration is preserved. The scheme below summarise the above discussion for one chosen configuration at C^{α} (S, for example): the structure on the left has SS configurations (*like* isomer) and the one on the right has SR configurations (*unlike* isomer). So, positions 4 and 6 are diastereotopic.

like
(SS configurations)



unlike
(SR configurations)

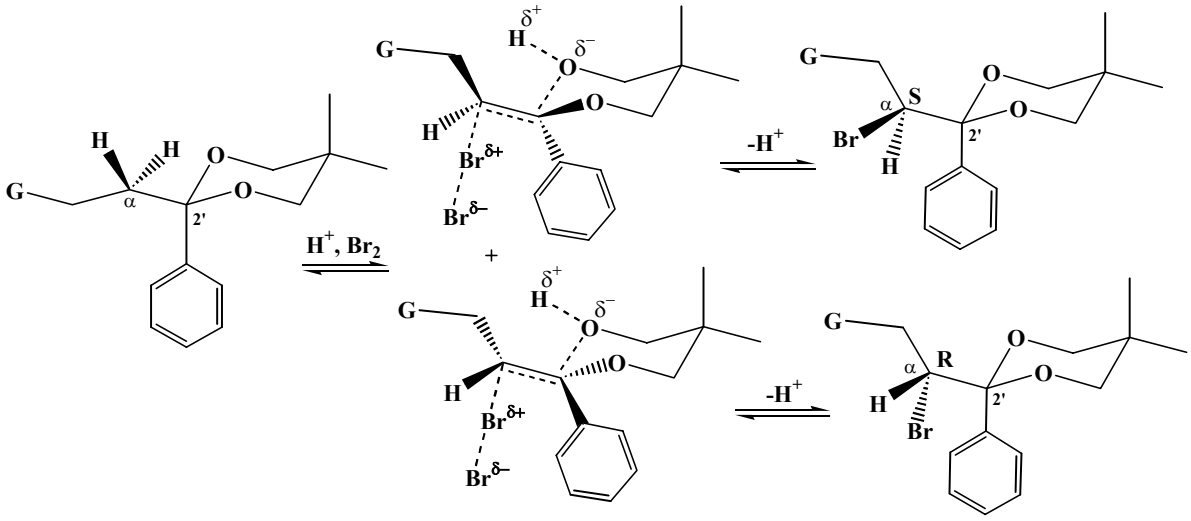
When the dibromination takes place, two new chiral centres are formed and therefore two diastereoisomers are possible: a *meso* isomer (RS or SR configurations for the chiral carbon atoms) and a racemic *d,l* isomer (RR or SS configurations). In some cases, the two isomers can be differentiated in NMR spectra as some of the carbon atoms or protons are diastereotopic (*i.e.* distinguishable in NMR spectrum) in one isomer and enantiotopic or homotopic (*i.e.* not distinguishable in NMR spectrum) in the other.

One of the situations that do not fit to the above recognition algorithm is compound **14**. Both possible isomers will have the same pattern in NMR spectra.

When we build Fischer projections for the two isomers and perform the substitution test for the protons on the carbon atoms bearing the bromine atoms, the result is that the two protons would be isochronous (they would give only one signal in the ^{1}H NMR spectrum) in both cases, as they are enantiotopic in the *meso* isomer and homotopic in the *d,l*, isomer.

Trying to decide which isomer was obtained, we have studied with the aid of Dreiding models the bromination mechanism on this compound. Studies on the bromination of acetals were made and it was demonstrated that the enol ether Z prevails over the E isomer.[24]

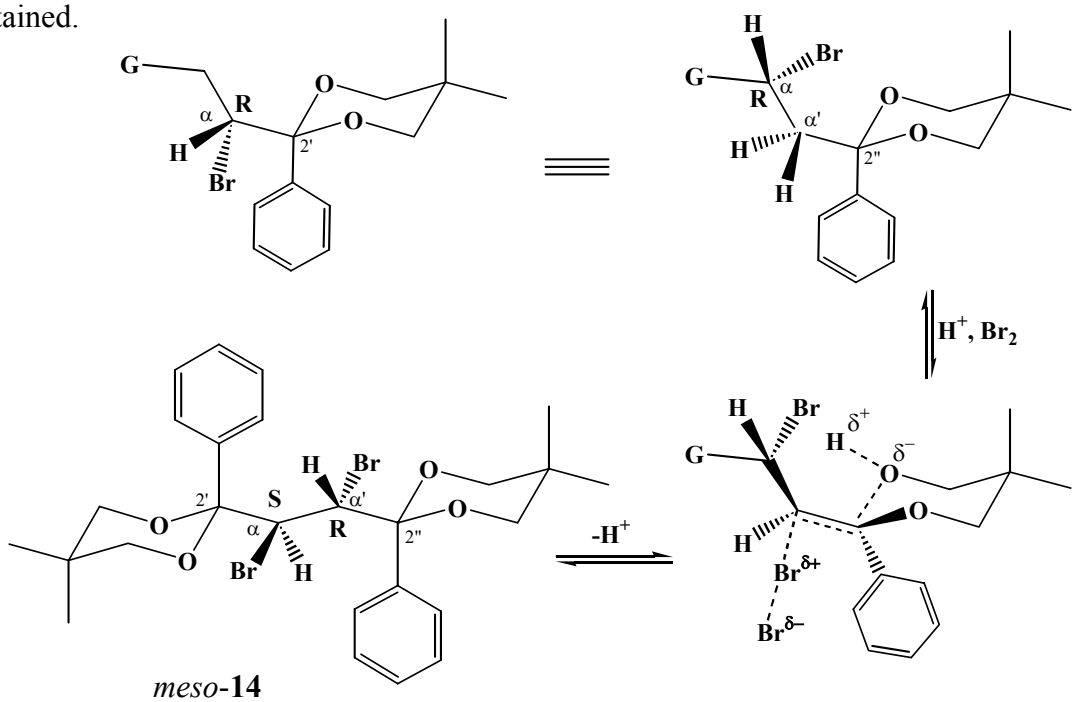
The monobrominated derivative may have R or S configuration at C^{α} because each of the C2'-O bonds may brake and the bromine will attack from the opposite side.



(**G** is the substituted 1,3-dioxanyl moiety)

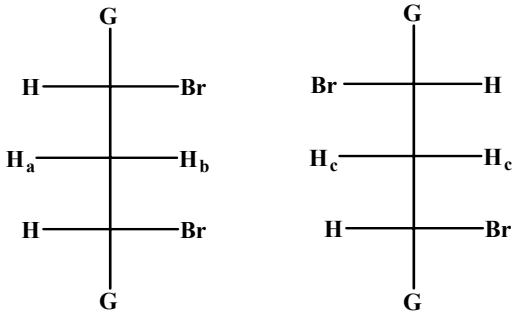
But the configuration of the second chiral atom is imposed by the configuration of the first chiral atom, already in the molecule. The bulky bromine atom will restrict the attack of the second bromine from only one of the *si* or *re* faces. Therefore, only one of the C2"-O bonds will brake, namely the one on the same side with the first bromine atom so that the bromine molecule may enter only in *anti* to the existing bromine and also in *anti* to the C2"-O bond that is then re-formed. So, if we draw the mechanism for the R isomer of C^{α} for example, the attack will take place on the *re* face only and the configuration of the new chiral carbon atom $C^{\alpha'}$ will be R (because the priority of the substituents changed and the configuration of the C^{α} will also be changed – S) and therefore from the R monobromoderivative, the SR isomer will

be obtained. In conclusion, in the dibromination reaction of **8** only the *meso* isomer of **14** is obtained.



meso-**14**

As the aliphatic chain becomes longer, the differences in the NMR spectra of the two possible isomers should be more obvious. This is the case of the dibrominated compound **13** for which chiral (*d,l*) and *meso* stereoisomers may be distinguished.[25]



meso *d,l*

The methylene protons H_c are homotopic and isochronous in the *d,l* isomer because of a C_2 axis while protons H_a and H_b in the *meso* form are diastereotopic and therefore anisochronous.

So, for the *d,l* isomer (RR or SS configurations for the chiral carbon atoms formed by bromination), the ^{1}H NMR spectra would display an AA'XX' system for the methylene protons between the two newly formed chiral centres and for the two protons attached to the chiral carbon atoms [these last protons exhibit a supplemental splitting due to the protons at positions 2' (2")]. For the hydrogens at positions 2',2" of the 1,3-dioxane rings (the substitution test reveals they are homotopic) one doublet should appear in the ^{1}H NMR spectrum. The 1,3-dioxane protons at positions 4'(4") and 6' (6") are diastereotopic and hence for the axial protons two doublets will appear, while for the equatorial protons two doublets of doublets [for positions 4'$(4")_{eq}$ and 6'$(6")_{eq}$] will be displayed.

In the *meso* isomer, the methylene protons in the aliphatic chain are diastereotopic and the protons from the carbon atoms that bear the bromine atoms are enantiotopic (and thus isochronous) and therefore an A_2MX system will appear for them in the ^{1}H NMR spectrum

(and again the –CHBr exhibit a supplemental splitting). The two protons at positions 2'(2") are enantiotopic and they will appear as a doublet. The 1,3-dioxane protons have the same pattern as in the *d,l* isomer.

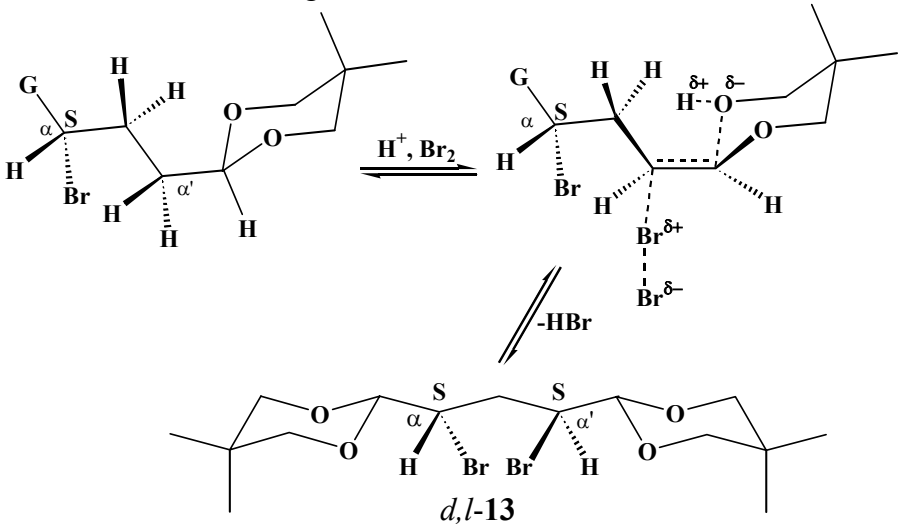
In the ^{1}H NMR spectrum of **13** there is an AA'XX' system for the methylene protons ($\delta_{A(A')}$=2.45 ppm) and for the –CHBr protons ($\delta_{X(X')}$=4.30 ppm) as for the *d,l* isomer.

If we presume that, in the *d,l* isomer, the two methylene protons are magnetically equivalent but each of them couple differently with the two protons –CHBr- because of the different torsional angle between them, the result would be indeed an AA'XX' system for the methylene protons.

The conclusion might then be that in the bromination of **9** the *d,l* isomer of **13** is obtained.

This assumption is further confirmed when we study the bromination mechanism for this compound. As mentioned before for compound **14**, the chiral centre in the monobrominated derivative may have R or S configuration, but the configuration of the second chiral carbon atom is induced by the first one. Again, the bromine may attack selectively in *anti* to the first bromine atom and in *anti* to the broken C2"-O bond (attack on the *si* face) and the resulted isomer is in this case the *d,l* isomer of **13**.

For example, if the monobrominated derivative has an S configuration at C^{α} and the most stable conformer is taken into consideration (the one with both 1,3-dioxanyl rings in *anti*), the resulted isomer will have SS configurations, *i.e.* the *d,l* isomer.



d,l-**13**

When at position 2'(2") of the 1,3-dioxane rings phenyl groups appear instead of the hydrogen atoms as in the case of compound **15**, the ^{1}H-NMR spectrum is similar, again the *d,l* isomer is obtained.

CONCLUSIONS

1. The complete review of 1,3-oxathiane derivatives, structured on 8 chapters dedicated to the synthesis, structural aspects in solid state and in solution, to the data of NMR and mass spectrometry investigations and to the reactivity of the most important compounds exhibiting this heterocycle was elaborated on the basis of more than 130 literature references. Despite the four previously published reviews (before 1985) on specific and limited topics, this work is motivated by the increased number of works in this field published in the last ten years and by the demand of a complete overview on this field.

2. The synthesis of 5 new tetraspiro-, of two pentaspiro- and of two hexaspiro-1,3-dioxanes is reported, these compounds being the largest six-membered spiranes reported in the literature. The dynamic NMR investigations revealed the semiflexible or the flexible structure of the reported compounds. The stereochemistry of these derivatives is discussed on the basis of specific original stereochemical descriptors proposed in our works.

3. The molecular structures of three tetraspiro-1,3-dioxanes are reported and, beside the symmetric *syn-anti-syn* and *anti-anti-anti* structures of the spirane skeleton, an asymmetric form *anti-anti-syn* was also observed.

4. The synthesis and the structural analysis of 7 flexible, semiflexible and anancomeric spiro-1,3-oxathiane derivatives are reported. The configurational (*cis* and *trans*) isomers of these compounds were separated and analysed as single compounds. The configurational aspects of the stereochemistry of these derivatives were discussed considering beside the axial and helical chirality of the spirane skeleton the influence of the virtual tricoordinated chiral center as specific chiral element of the 1,3-oxathiane ring. The flexible behaviour of the whole spirane or only of the heterocycle was demonstrated by variable temperature NMR experiments.

5. The synthesis and the stereochemistry of the first reported di-, tri-, tetra-, penta- and hexaspiro-1,3-oxathiane are discussed using the specific stereochemical descriptors for spiro compounds with six-membered rings (axial and helical chirality) and for the saturated six-membered ring heterocycles with two different heteroatoms (virtual tricoordinated chiral center). Similarly with substituted cumullenes (that show different type configurational isomers in correlation with the number of joined double bonds), *cis, trans* or optic isomerism of polyspiro-1,3-oxathianes, in correlation with the odd or even number of carbocycles which are separating the two 1,3-oxathiane rings of the polyspirane was observed. If this number is odd, separable *cis – trans* isomers are possible and, if this number is even, the polyspirane exhibits separable enantiomers. In all cases the *cis* and *trans* isomers were separated and investigated as single compounds, whereas the optically active spiro-1,3-oxatianes were investigated as racemic mixture.

6. Three molecular structures in solid state (obtained by X-ray diffractometry), the first ones reported for spiro- and polyspiro-1,3-oxathianes, reveal the peculiar chair conformation of the heterocycle.

7. Important improvements of the procedures for the synthesis of starting diols, mercapto-alcohols and diketones are reported. The original solutions made possible the synthesis in good yields of three new diols and mercaptoalcohols.

8. The high diastereoselectivity of the bromination reaction of derivatives bearing two 1,3-dioxane rings connected by a (poly)methylene chain was revealed and explained on the basis of the mechanism of the bromination reaction of cyclic acetals. In correlation with the length of the chains *meso* or *d,l* dibrominated compounds are obtained.

9. In this Ph. D. Thesis 37 new compounds are reported and characterized (10 polyspiro-1,3-dioxanes, 14 spiro and polyspiro-1,3-oxathianes, 6 bis(1,3-dioxane-2-yl) derivatives, 4 brominated 1,3-dioxanes and 3 starting materials). For 7 of these compounds the molecular structure in solid state obtained by X-ray diffractometry is reported.

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