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SYNTHESIS, STRUCTURAL ANALYSIS AND PROPERTIES OF SOME NEW COMPOUNDS WITH SATURATED SIX-MEMBERED RINGS

Ph. D. Thesis Abstract

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INTRODUCTION

The study of saturated heterocyclics compounds is a research field which has been known a continuous development in the last years, the compounds from this class having practical applications in chemical industry, medicine, materials science, pharmaceutical industry, and nanotechnology or food industry.

Between the heterocyclic compounds, an important place is taken by 1,3-dioxanes and perhydro-diazines, due to their relatively simple synthesis and to the existence of uncountable methods of preparation. In the NMR spectra of these compounds, the signals are separated clearly due to the deshielding effect of oxygen or nitrogen atoms, and due to the heteroatoms position in the molecule.

The results of the research activity presented in the Ph. D. thesis are structured into four main parts. In the first part, the literature information regarding perhydro-diazines, also named diazacyclohexanes are included, grouped by the following themes: the synthesis, stereochemistry, reactivity and uses. The second part contains original contributions from the field of the synthesis and structural analysis of 1,3-dioxane derivatives of terephthalic aldehyde, of 5-methyl-2,2-disubstituted and 5,5-Bis(bromomethyl)-2-substituted 1,3-dioxanes. The third part describes the synthesis, structural analysis and properties of new spiranic compounds of 1,3-dioxane. The fourth part includes the synthesis, stereochemistry and properties of some intermediates for the synthesis of spiranic compounds with different heterocycles or with different heteroatoms.

PART II. SYNTHESIS, STRUCTURAL ANALYSIS AND PROPERTIES OF SOME NEW 1,3-DIOXANE DERIVATIVES SUBSTITUTED IN POSITIONS 2, 5

II.1. General informations

Conformational analysis [1] targets the establishment of relative stability of conformers and the establishment of the functional relation between conformations and the physical and chemical properties. In the balance research between two conformations of the same compound, the value of the balance constant K is used to calculate the properties of the majority conformer.

$C_1 \leftrightarrows C_2$, $\left(K = \frac{C_2}{C_1} \right)$, and using the relationship:

$$\Delta G^o = -RT\ln K$$

is computed **the free conformational enthalpy**, which represents the free enthalpy difference between a certain conformation in regard to the minimum enthalpy conformation (minimum energy conformer). [1,2]

The NMR spectroscopy is used for the study [3] of conformational equilibria. A conformer must exist (without transforming itself into another conformer) a period of time longer than 0.1 seconds in order to provide distinct signals in NMR spectra. If the endurance time is less than 0.1 seconds, the signals obtained correspond to an average value of the chemical shifts for the conformers which quickly shift one in the other.

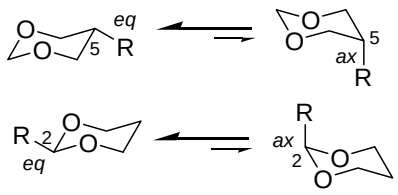
In the case of a vicinals protons (bounded to neighboring carbon atoms in the molecule frame) the coupling constant depends by the dihedral angle formed between the bonds. The Karplus equation [2,4] allows the computing of this constant *J* starting from the dihedral angle θ from CH-CH the fragment: $J = A \cdot \cos^2 \theta$

The A constant has the 8,5 Hz value for the angles less then 90º and the value 9,5 Hz if the angle is greater than 90º. In consequence, a vicinal coupling constant in *trans* orientation has a

[1] Mager, S. ; Grosu, I.; David, L.; *Stereochimia compuşilor organici*; Editura Dacia: Cluj-Napoca, 2006; pp 12-42, 284-291, 434-447.
[2] Mager, S.; *Analiză structurală organică*; Editura Ştiinţifică şi Enciclopedică: Bucureşti, 1979; pp 69-71, 148-151.
[3] Grosu, I.; Mager, S.; Plé, G.; Dărăbanţu, M.; *Aplicaţii ale NMR în analiza structurală organică*; Editura Cluj University Press: Cluj-Napoca, 1996; pp. 22-23, 67-68; 74-80.
[4] Riddell, F. G.; *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: New York, 1980; pp 34-35.

greater value than in the case of a vicinal coupling in *gauche*, since θ = 180 º in regard to θ = 60 º, and because of this, the *axial-axial* vicinal couplings have 8-15 Hz coupling constants, and the *equatorial-equatorial* or the *equatorial-axial* vicinal couplings have values between 0-6 Hz.

1,3-Dioxane is the heterocycle which can be easily obtained by synthesis, and the NMR spectra can be easily interpreted as a consequence of the oxygen atoms effect, which separates the carbon atoms and generates an significant deshielding. [1]



Scheme 4

Free conformational enthalpies [5] of some substituents are positive if the *equatorial* conformer is more stable, respectively negative if the *axial* conformer is favoured.

II.2. 1,3-Dioxane derivatives of terephthalic aldehyde

II.2.1. Introduction

Numerous works [6,7,8,9,10,11,12,13,14,15,16] have as subject the study of 1,3-dioxanes stereochemistry, accomplished by different physical methods, between which the most important are the NMR spectroscopy and X-ray diffraction. In this way was determined that the free conformational enthalpies of aryl groups from the position 2 are greater than 3 kcal/mol, which determines the preference of these groups for the *equatorial* orientation in the frame of the 1,3-dioxanic cycle. As a consequence, these substituents can be used as anancomeric groups, which

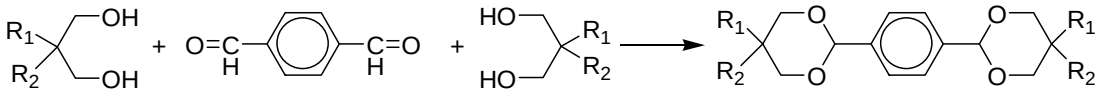
[5] Eliel, E. L.; Willen, S. H.; *Stereochemistry of Organic Compounds*; John Wiley & Sons, Ltd.: New York, 1994; pp 740-754
[6] Anteunis, M. J. O., Tavernier, D.; Borremans, F.; *Heterocycles*, **1976**, *4*, 293-371.
[7] Nader, F. W.; Eliel, E. L.; *J. Am. Chem. Soc.* **1970**, *92*, 3050-3055.
[8] Bailey, W. F.; Eliel, E. L.; *J. Am. Chem. Soc.* **1974**, *96*, 1798-1806.
[9] Mager, S.; Grosu, I.; Horn, M.; Hopârtean, I.; Dărăbanţu, M.; Puşcaş, C.; Kovacs, D.; Plé, G.; *Roumanian Chemical Quarterly Reviews,* **1995**, *3*, 201-228.
[10] Grosu, I.; Camacho, B.; Toscano, A.; Plé, G.; Mager, S.; Martinez, R.; Gavino, R. R.; *J. Chem. Soc. Perkin Trans. 1*, **1997**, 775-781.
[11] Socaci, C.; Grosu, I.; Plé, G.; Zwanziger, H. W.; Mesaroş, E.; Mărginean, D.; Mager, S.; *Heterocyclic Commun.* **2000**, *6*, 219-224.
[12] Pop, M.; Grosu, I.; Plé, G.; Mager, S.; Muntean, L.; Mărginean, D.; Dincă, N.; *Heterocyclic Commun.* **2002**, *8*, 35-38.
[13] Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Pop, M.; Balog, M.; Mager, S.; Bogdan, E.; *Monatsh. Chem.* **2002**, *133*, 631-641.
[14] Liu, J.; Hu, X. M.; Xu, H. S.; *Chinese Chem. Lett*. **1999**, *10*, 199–200.
[15] Florian, M. C.; Circu, M.; Toupet, L.; Terec, A.; Grosu, I.; Ramondenc, Y.; Dinca, N.; Plé, G.; *Cent. Eur. J. Chem.* **2006**, *4*, 808-821.
[16] Balog, M.; Grosu, I.; Plé, G.; Ramondenc, Y.; Condamine, E.; Varga, R. A.; *J. Org. Chem.* **2004**, *69*, 1337-1345.

shift the conformational equilibrium towards the diastereoizomer with the corresponding *equatorial* group. [6 - 9, 17,18]

II.2.2. Synthesis

By the reaction between 1,4-Benzenedicarbaldehyde (**15**), also named *para*-Phthaldialdehyde or Terephthaldialdehyde, and substituted 1,3-propandiols, the new 1,3-dioxane derivatives **16** – **22** (Scheme 9) were obtained. [19]

The compounds **16 – 19** are unique diastereoisomers, [19] while the compounds **20** – **22** can present several conformational isomers.



15

$R_1=R_2=H$	**16**
$R_1=R_2=COOCH_2CH_3$	**17**
$R_1=R_2=CH_3$	**18**
$R_1=R_2=CH_2Br$	**19**
$R_1=H,\ R_2=CH_3$	**20**
$R_1=H,\ R_2=C_6H_5$	**21**
$R_1=CH_3,\ R_2=C_2H_5$	**22**

Scheme 9

II.2.3. Structural analysis and stereochemistry

The compounds **16-19** presents anancomeric structures, the preferential conformation being the one with the *para*-phenylene group in *equatorial* orientation, this being an „holding group", fact confirmed by the molecular structure of the compound **17**, determinated by X-ray diffraction on monocrystal, and by the NMR investigation done for the compounds **16-22**.

The ORTEP diagram of the compound **17** (Figure 1) shows the *equatorial* orientation of the aromatic group in regard to the both heterocycles and the preference of the benzene core for an geometry close to the ideal orthogonal rotamer.

[17] Grosu, I.; Mager, S.; Plé, G.; Plé, N.; Toscano, A.; Mesaroş, E.; Martinez, R.; *Liebigs Ann./Recueil* **1997**, 2371-2377.
[18] Grosu, I.; Mager, S.; Mesaroş, E.; Plé, G.; *Heterocyclic Commun.*, **1998**, *4*, 53-58.
[19] Grosu, I.; Mager, S.; Toupet, L; Plé, G.; Mesaroş, E.; **Mihiş, A**.; *Acta Chem. Scand.* **1998***, 52*, 366-371.

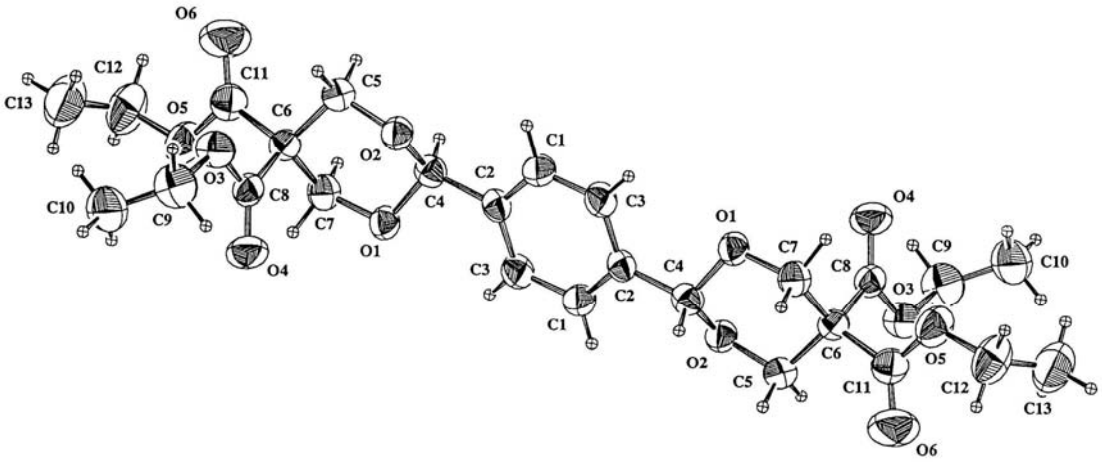


Figure 1. The ORTEP diagram of the compound **17**

There is a slight deflection of the aromatic cycle plane from the ideal orthogonal orientation, the angles between the reference planes of the 1,3-dioxane rings (P_1: $C^4C^6C^8C^{11}$; P_2: $C^{4a}C^{6a}C^{8a}C^{11a}$) and the plane of the aromatic ring (P: $C^{1-3}C^{1a-3a}$) has been calculated, so P/P_1=99,3°; P_2/P_1=0°. From the structural parameters (Table 3), it could be observed that the structure of the heterocycles were close to the ideal *chair* conformation. The two 1,3-dioxane rings assume, in the solid state, an „*anti*" orientation caused by the dispositions of the *axial* protons in positions 2 and 2′, which are located on the opposite faces of the aromatic ring considered, as the reference plane.

The NMR spectra of the compounds **16-22** (Table 4) presents different signals for *axials* and *equatorials* protons from the positions 4(4′) and 6(6′), as for the protons and the carbon atoms of the identical groups placed in the positions 5 and 5′ (for the compounds **17**-**19**).

Table 4. The significant NMR data (δ) for the compounds **16-22**.

		Positions 4(4′), 6(6′)		
Compound	Positions 2(2′)	*Equatorial*	*Axial*	Δ(*ec-ax*)
16	5,30	3,87	3,43	0,44
17	5,18	5,04	3,95	1,09
18	5,25	3,52	3,25	0,27
19	5,41	4,24	3,84	0,4
20 (diastereoisomer **I**)	5,27	3,89	3,08	0,81
21 (diastereoisomer **I**)	5,41	4,15	3,68	0,47
22 (cycles A)	(5,259, 5,268)	3,610, 3,614	3,280	0,33
22 (cycles B)	(5,283, 5,292)	3,702, 3,698	3,22	0,47-0,48

The ^{1}H NMR spectrum of the compound **17**, at 400 MHz, in deuterated benzene (Figure 2, Table 4) shows unique signals, undifferentiated for the protons of the two heterocycles. The signal assignment has been done using the bi-dimensional COSY spectrum of the compound **17**.

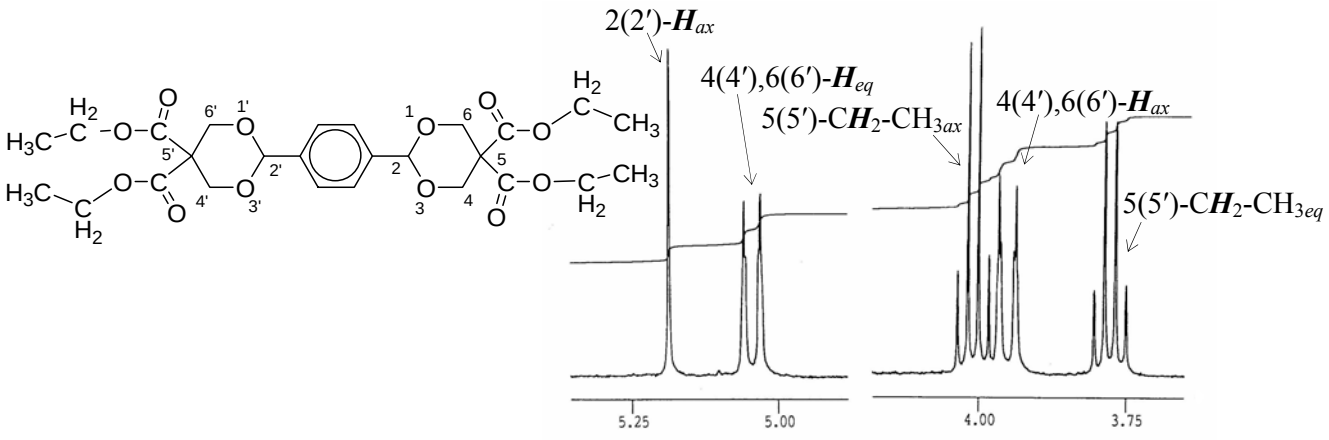


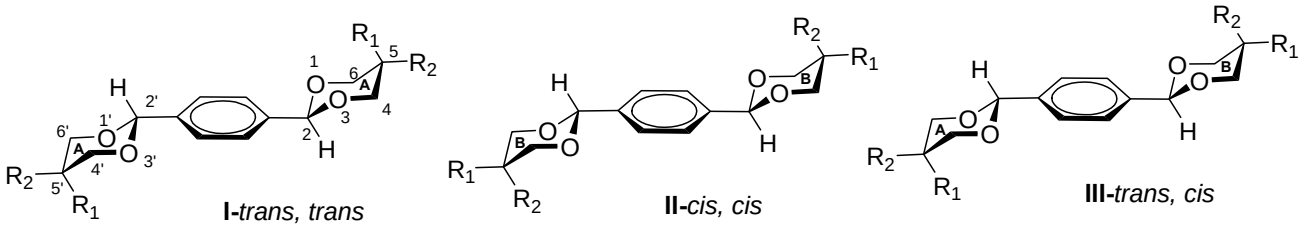
Figure 2. The ^{1}H NMR spectrum (C_6D_6, 400 MHz) (fragment) of the compound **17**

The *axial* protons in positions 2 and 2′ generate a singlet (δ=5,18 ppm), the *equatorial* protons from the positions 4(4′) and 6(6′) presents a deshielded doublet $\delta_{4(4'),\ 6(6')eq}$=5,04 ppm, while the *axial* protons from the same positions have as signal another doublet $\delta_{4(4'),\ 6(6')ax}$=3,95 ppm. The difference in the chemical shifts between between the signals of the protons from the *axial* and *equatorial* ethyloxycarbonyl groups consist with the literature reported data [20,21,22] for the 1,3-dioxanic anancomeric compounds with *axial* and *equatorial* ester groups in the position 5 of the 1,3-dioxane cycle. Thus, for the methylene protons from the ethyloxycarbonyl groups in the ^{1}H NMR spectrum are recorded two quartets $\delta_{\text{-CH2-}ax}$=4,01 ppm, $\delta_{\text{-CH2-}eq}$= 3,77 ppm, so $\Delta\delta_{ax\text{-}eq}$=0,24 ppm, according to the Figure 2.

The compounds **20-22** also have anancomeric structures, the benzene group having *equatorial* orientation in regard to the both 1,3-dioxane cycles. But the substituents from the positions 5 and 5′ can have *axial* or *equatorial* orientation, being feasible three diastereoisomers (Scheme 10). These diasteroisomers are determinated by the *trans* or *cis* dispositions of the substituents from the positions 5(5)′ and of the aromatic ring from the position 2(2′). Thus, the diastereoisomer in which the reference groups in position 5(5′) (denoted by R_2) and the aromatic substituent from the position 2(2′) are *trans* with respect to both 1,3-dioxane cycles is denoted with **I**. The diastereoisomer in which R_2 and the phenylene group are in *cis* in regard to the both heterocycles is denoted with **II**, and the one with *cis* configuration for the substituents belonging

[20] Grosu, I.; Plé, G.; Mager, S.; *Tetrahedron* **1995**, *51*, 2659-2672.
[21] Grosu, I.; Mager, S.; Plé, G.; Martinez, R.; Muntean, L.; Mesaroş, E.; *Heterocycles* **1995**, *41*, 2233-2244.
[22] Grosu, I.; Mager, S.; Plé, G.; Muntean, L.; Schirger, I.; *Heterocyclic Commun.* **1996**, *2*, 423-430.

to one of the 1,3-dioxane ring and *trans* for the other 1,3-dioxane ring is denoted by **III**. The reference group is methyl for the compound **20**, phenyl for the compound **21** and ethyl for the compound **22**.



Scheme 10

At the synthesis of the derivatives **20** and **21** a mixture of the diastereoisomers **I** and **III** was obtained, and their molecular ratio was calculated from the integrals of the specific signals for the each diastereoisomer. For the compound **20**, 85 % of the diastereoisomer **I** was obtained, and for the compound **21**, almost 70 %, according to the preference for the *equatorial* orientation determinated by the free conformational enthalpies („A" values) which are ΔG^0_{Me}=0,80-0,89 kcal/mol, and ΔG^0_{Ph}=1,03 kcal/mol.

From the values of the coupling constants [6] of the proton from the position 5(5′) was determinated the *axial* or *equatorial* orientation of the substituents from this position. If the proton from the position 5 (5′) has an *equatorial* orientation, it can present a small coupling with the neighboring vicinal *equatorial* and *axial* protons from the positions 4(4′) and 6(6′), and if is *axial*, the coupling constant with the *axial* vicinal proton has higher values.

For the compound **22** (named 1,4-Bis(5-ethyl-5-methyl-1,3-dioxane-2-yl)benzene) the difference between the free conformational enthalpies of the methyl and ethyl groups located in the positions 5(5′) of the 1,3-dioxane cycle is insignificant, respective ΔG^0_{Me}=0,80-0,89 kcal/mol, ΔG^0_{Et}=0,75-0,81 kcal/mol, which by synthesis implies all the three diastereoisomers possible. Their ratio is in accordance with the statistical rule: **I** : **II** : **III** = 1:1:2, since the probability to obtain the diastereoisomer **III** is double over the other diastereoisomers.[6,19]

The ^{1}H NMR spectra of the compound **22** in C_6D_6 at 400 MHz, (Figure 4 and Table 5) reveals for the protons in positions 2 and 2′ the existence of four singlets with fairly similar intensities. The proton in position 2 is magnetically equivalent to the proton in the position 2′ in the case of diastereoisomers **I** and **II**, but is different in diastereoisomer **III**. Similar intensities for the four signals can only be obtained if the diastereoisomer **III** has twice the population of diastereoisomer **I**, and the last has similar population with diastereoisomer **II**, in agreement with their similar conformational energies. Unfortunately, for all distereoisomers, the signals in the ^{1}H

NMR are overlapped, and their complete characterisation was not possible. However, two important groups of signals of similar intensities could be observed, the first set of signals belonging to the rings (denoted "A"), bearing *equatorial* ethyl groups. The rings "A" are those two heterocycles of the diastereoisomer **I** and one 1,3-dioxane ring of diastereoisomer **III**. The protons of the rings denoted "B" gives the second set of signals, and these rings bear *axial* ethyl groups and they are the 1,3-dioxanic rings of diastereoisomer **II** and the other heterocycle belongs to diastereoisomer **III** (Scheme 10, Table 5).

The assignment of the signals belonging to the substituents at positions 5(5′) took into account the significantly higher deshielding of the protons in the *axial* groups in regard to those *equatorial* groups: for the ethyl group $\Delta\delta(\text{-}CH_2\text{-})_{ax\text{-}eq}$=1,01 ppm and $\Delta\delta(\text{-}CH_3)_{ax\text{-}eq}$=0,23 ppm; for the methyl group $\Delta\delta(\text{-}CH_3)_{ax\text{-}eq}$=0,89 ppm. [19]

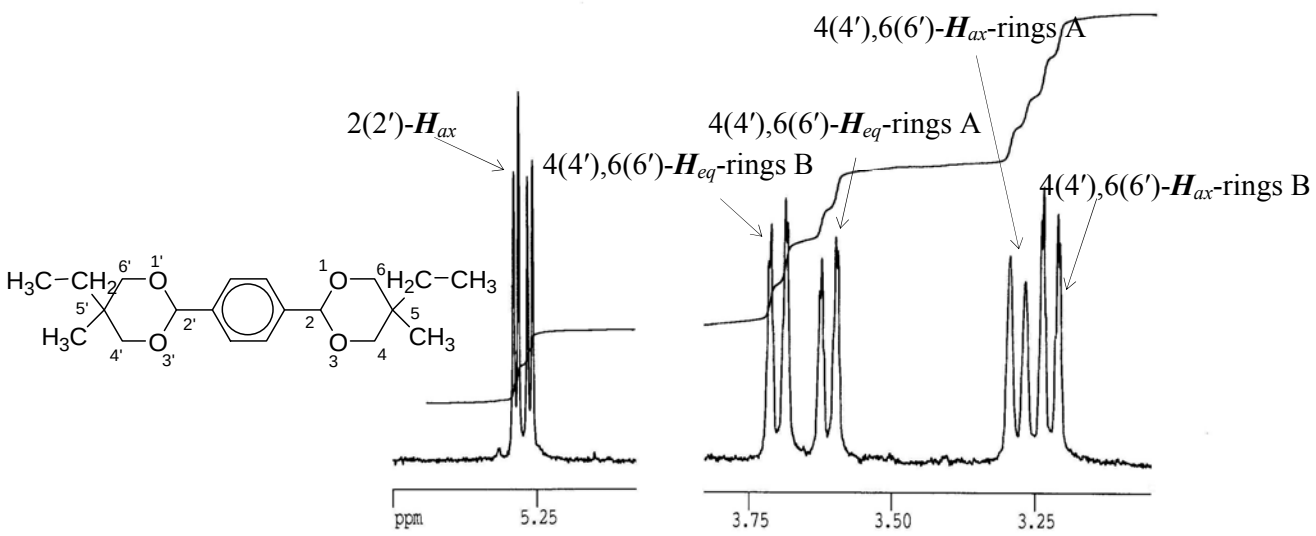


Figure 4. ^{1}H NMR spectrum (fragment) in C_6D_6 at 400 MHz of the compound **22**

Table 5. Chemical shifts δ (ppm) for the substituents located at position 5(5′) of the 1,3-dioxane rings in compound **22**

Rings	Ethyl				Methyl	
	-CH_2-(*eq*)	-CH_2-(*ax*)	-CH_3(*eq*)	-CH_3(*ax*)	*equatorial*	*axial*
A	0,71	-	0,529, 0,532	-	-	1,17
B	-	1,72	-	0,757, 0,762	0,276, 0,280	-

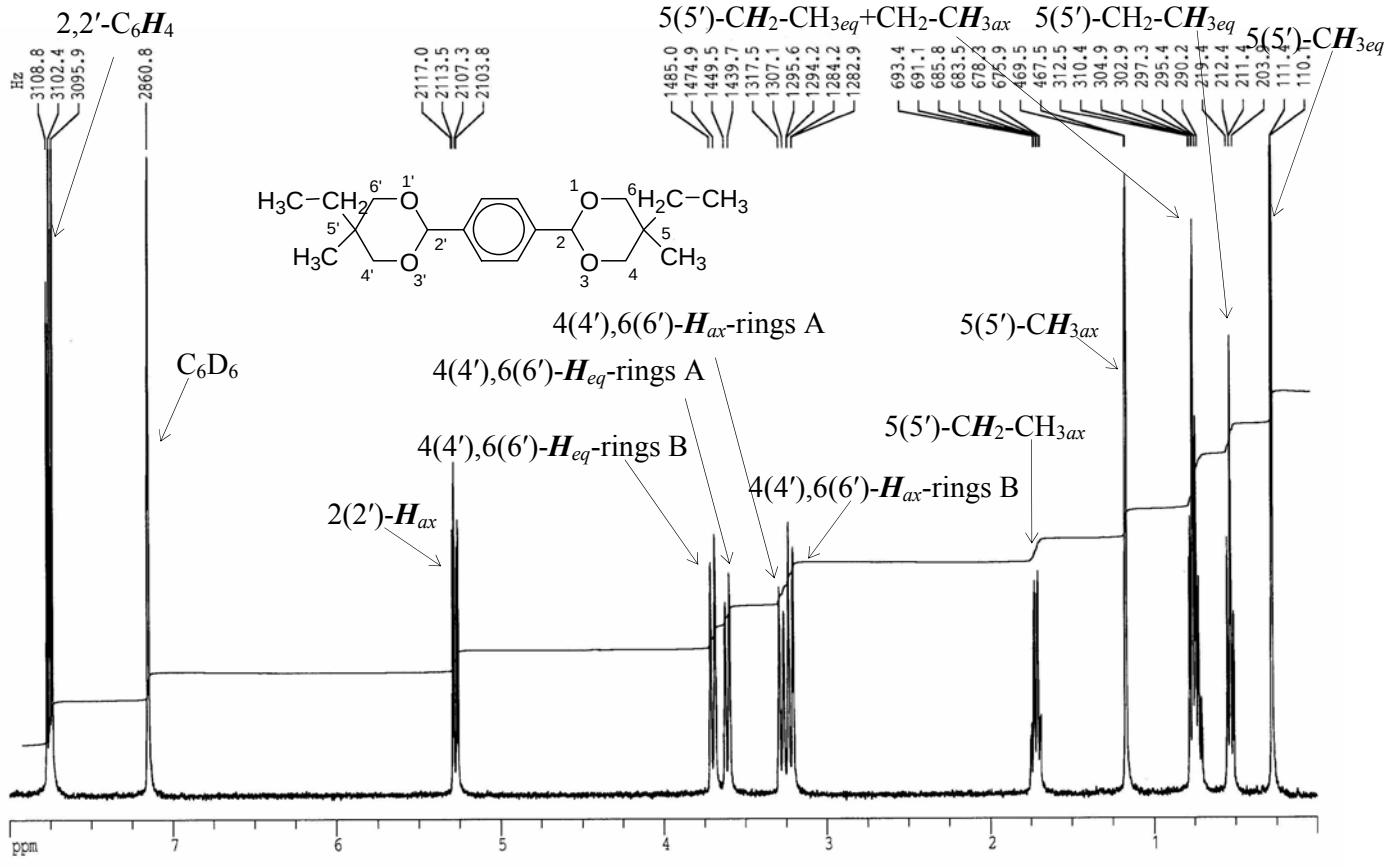


Figure 5. NMR spectum in C_6D_6 at 400 MHz of the compound **22**

The assignment of the signals due to the protons in positions 4(4′) and 6(6′) for the two types of rings (rings A and B) was made using Nuclear Overhauser Effect experiments. Irradiation of the singlet due to the protons of the *axial* methyl group (δ=1,17 ppm) showed in the Nuclear Overhauser Effect difference (NOEDiff.) spectrum a large influence on the doublet at δ=3,61 ppm (*equatorial* protons in positions 4(4′) and 6(6′) of rings A), while irradiation of the singlet due to the protons of the *equatorial* methyl groups (δ=0,28 ppm) showed, in the NOE difference spectrum an influence on the doublets belonging to the *equatorial* and *axial* protons in positions 4(4′) and 6(6′) of rings B (δ_{eq}=3,70 ppm, δ_{ax} =3,22 ppm) (Table 5). The higher influence of the Nuclear Overhauser Effect on the more shielded doublet confirmed the *axial* position of the protons associated with this signal. The *equatorial* position of the protons giving the more deshielded doublet, belonging to the B rings (δ=3,70 ppm) was confirmed by irradiation of the quartet due to the methylene protons (δ=1,72 ppm) of the *axial* ethyl group (rings B). When the NOE difference spectrum was recorded, a large enhancement was observed only on this doublet (δ=3,70 ppm) of *equatorial* protons in positions 4(4′) and 6(6′) of the B rings.

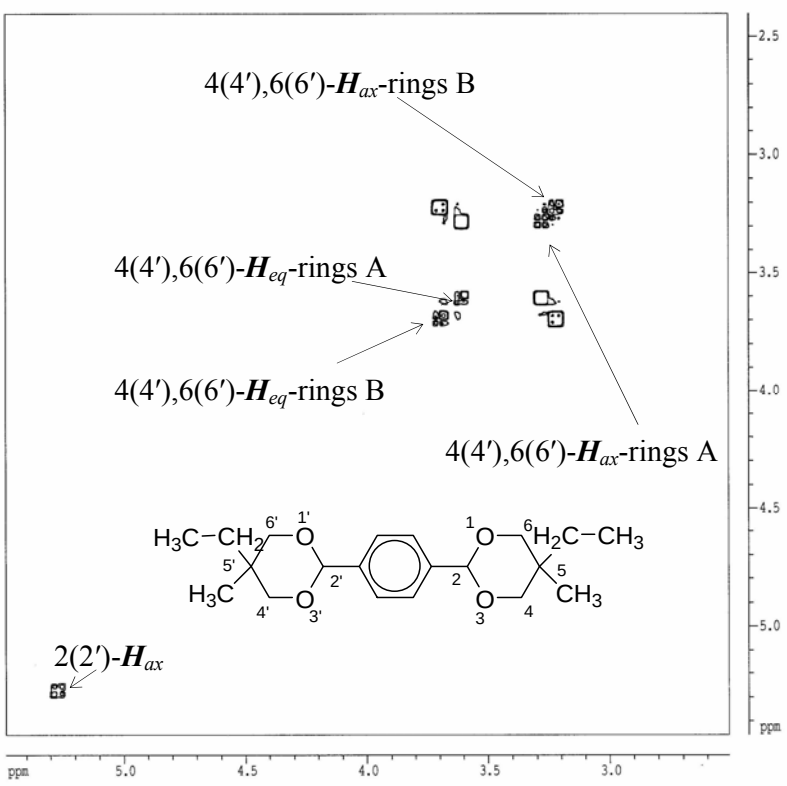
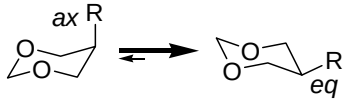


Figure 8. COSY spectrum of the compound **22** in C_6D_6 at 400 MHz, detail for the *axial* and *equatorial* protons in positions 4(4′), 6(6′)

II.3. 5-Methyl-2,2-disubstituted 1,3-dioxane derivatives

II.3.1. Introduction

The 5-alkyl-1,3-dioxane compounds (monosubstituted in position 5) display anancomeric structures, despite the fact that the value of the conformational free enthalpy for the group in position 5 is quite small in comparison with the case in which the substituent is in position 2, for instance for methyl group $\Delta G^0_{Me(position\ 2)}$ =3,98 kcal/mol, and $\Delta G^0_{Me(position\ 5)}$=0,83 kcal/mol. Even so, the conformational equilibria are shifted towards the conformer having the substituent in position 5 *equatorial* placed (Scheme 11). [23]

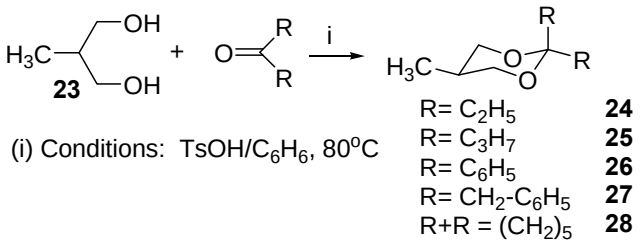


Scheme 11

[23] Muntean, L.; Turos, G.; Socaci, C.; Grosu, I.; Mager, S.; **Mihiş, A.**; *Stud. Univ. "Babeş-Bolyai", Chemia* **2000**, *45*, 55-60.

II.3.2. Synthesis

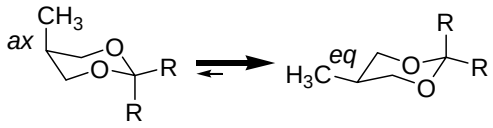
A new compound 1,3-dioxanic (**24**) belonging to the 1,3-dioxane series **25-28** had been obtained by the ketalisation (condensation) between 2-methyl-1,3-propandiol (**23**) and symmetric ketones (Schema 12). [23]



Scheme 12

II.3.3. Structural analysis and stereochemistry

The investigated compounds exhibit anancomeric structures, conformational equilibria being shifted towards the conformations that display the 5-methyl group in *equatorial* orientation (Scheme 13).



Scheme 13

The spectra of these compounds (**24-28**) exhibit different signals for the *axial* and *equatorial* orientation of the protons in positions 4 and 6, and for the alkyl groups in position 2, identically constitutive , but non-equivalent magnetically (Table 6).

Table 6. Chemical significant shifts δ (ppm) from ^{1}H NMR and ^{13}C NMR spectra of the compounds **24-28**.

Compound	^{1}H NMR			^{13}C NMR			
	4,6-H(*ax*)	**4,6-H(*eq*)**	**5-CH_3**	**C2**	**C4,6**	**C5**	**5-CH_3**
24	3,42	3,77	0,31	-	67,72	29,57	13,01
25	3,22	3,59	0,44	100,59	65,56	23,18	13,28
26	3,28	3,60	0,47	100,16	65,61	29,43	13,35
27	3,69	3,95	0,78	100,17	66,01	28,94	13,27
28	3,59	3,25	0,44	97,12	64,96	29,32	12,88

In the ^{1}H NMR spectrum in C_6D_6 at 300 MHz of 2,2-diphenyl-5-methyl-1,3-dioxane (**24**) exists a doublet at δ=0,31 ppm for the *equatorial* methyl group in position 5, having the vicinal

coupling constant $^{3}J_{(5CH3eq\text{-}5Hax)}$=6,6 Hz (Figure 10). The *axial* proton in position 5 has as signal a multiplet at δ=1,81 ppm, and the protons in positions 4 and 6 give a pseudo-triplet (overlapped doublet of doublets) at $\delta_{4(6)ax}$ = 3,42 ppm, with equal geminal and vicinal coupling constants, $^{2}J_{4(6)ax\text{-}4(6)eq}$ = $^{3}J_{4(6)ax\text{-}5Hax}$ = 11,3 Hz for the *axial* proton, respective a doublet of doublets at $\delta_{4(6)eq}$ = 3,77 ppm for the *equatorial* protons, with the coupling constants $^{2}J_{4(6)eq\text{-}4(6)ax}$ = 11,3 Hz and $^{3}J_{4(6)eq\text{-}5Hax}$ = 4,2 Hz..

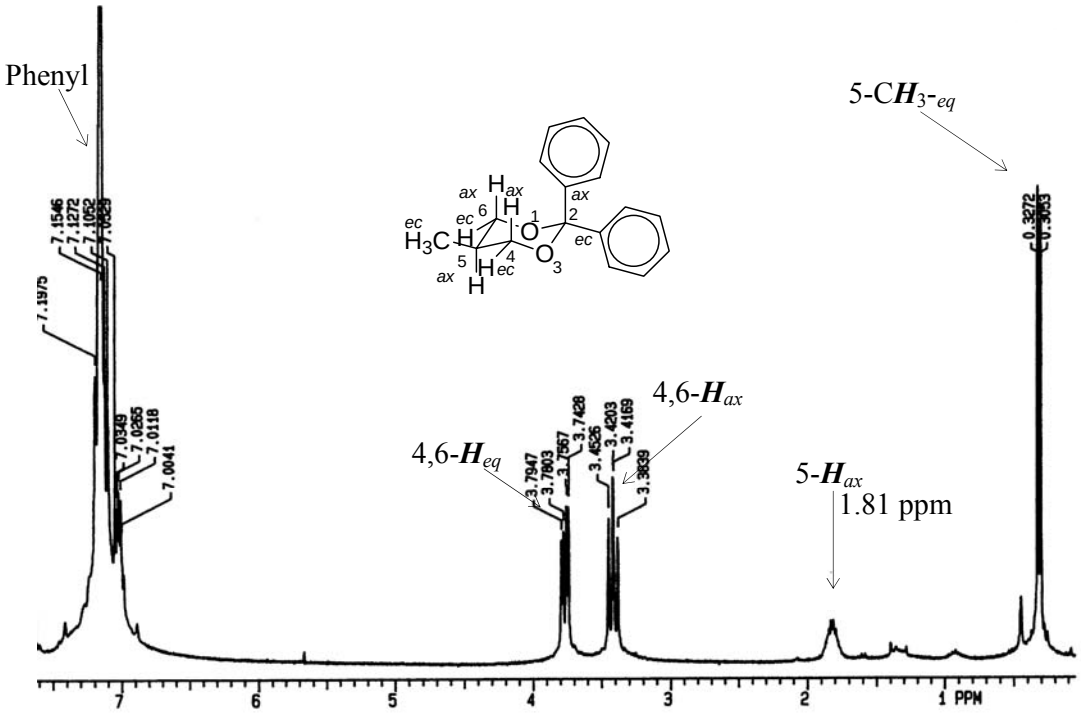


Figure 10. NMR spectrum of compound **24** in C_6D_6 at 300 MHz

II.4. Derivatives of 5,5-Bis(bromomethyl)-2-substituted 1,3-dioxane

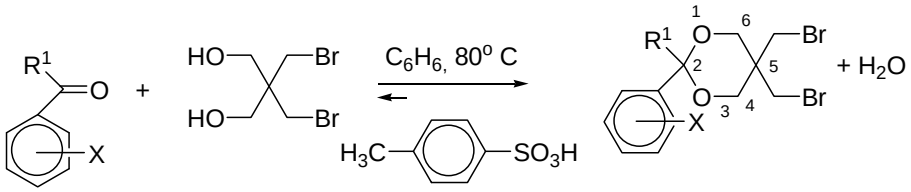
II.4.1. Introduction

The 1,3-dioxane compounds with bromomethyl groups are used at the synthesis of cyclic sulphides which have applications in nanotechnologies as absorbents on gold or colloidal gold surfaces [24,25]. The 5,5-Bis(bromomethyl) 2-substituted derivatives of 1,3-dioxane are synthesized by the acetalization reaction (cetalization) between the carbonyl compounds and 2,2-bis(bromomethyl)-1,3-propandiol catalyzed by the *para*-toluensulfonic acid. [26]

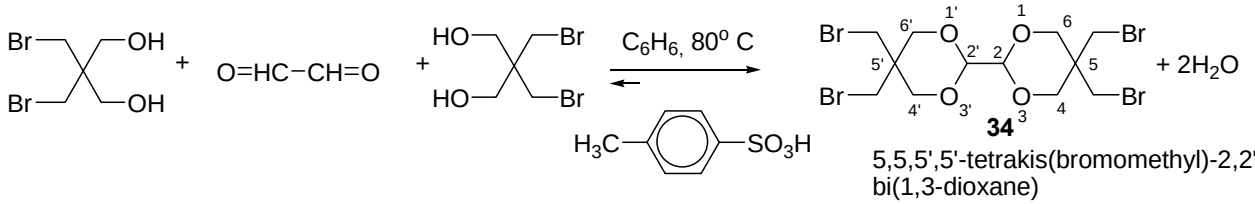
[24] Nuzzo, R. G.; Allara, D. L.; *J. Am. Chem. Soc.* **1983**, *105*, 4481-4483.
[25] Herranz, M. A.; Yu, L.; Martin, N.; Echegoyen, L.; *J. Org. Chem.*, **2001**, *68*, 8379-8385.
[26] Gropeanu, R.; Woiczechowski-Pop, A.; Ţînţaş, M.; Turdean, R.; Grosu, I. *Stud. Univ. Babeş-Bolyai, Chem.* **2005**, *50*, 247-252.

II.4.2. Synthesis

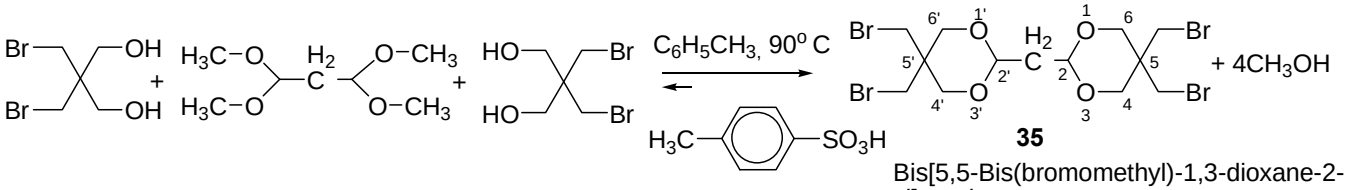
New 1,3-dioxane with bromomethyl groups substituted compounds were synthesized (**30**-**35**) by the reaction between the carbonyl compounds and 2,2-bis(bromomethyl)-1,3-propandiol (Schema 15), which were refined through crystallization from methanol or ethanol.



R^1=CH_3, X=*meta*-NO_2 **30**
R^1=CH_3, X=*para*-NO_2 **31**
R^1=H, X=*meta*-NO_2 **32**
R^1=H, X=*para*-NO_2 **33**



34 5,5,5',5'-tetrakis(bromomethyl)-2,2'-bi(1,3-dioxane)

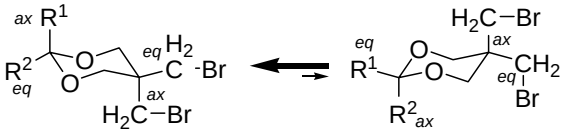


35 Bis[5,5-Bis(bromomethyl)-1,3-dioxane-2-yl]-methane

Schema 15

II.4.3. Structural analysis and stereochemistry

The analyzed compounds **30** – **35** are anancomeric, the conformational equilibra being shifted towards the conformer in which the bulky substituent R^2 is in *equatorial* position, one of the two bromomethyl groups has *equatorial* orientation and the other *axial*. (Scheme 16).



Scheme 16

^{1}H NMR spectrum in $CDCl_3$ at 300 MHz of the compound **30** at room temperature contains the following signals: at δ=1,58 ppm the methyl group singlet in position 2, with *equatorial* orientation; at δ=3,12 ppm the methyl protons singlet of the *equatorial* bromomethyl

group in position 5. At δ=3,52 ppm are the *axial* protons in positions 4(6) which gives a doublet, with geminal coupling constant $^2J_{4(6)ax\text{-}4(6)eq}$ = 11,8 Hz, and at δ=3,93 ppm the *equatorial* protons doublet (more deshielded) overlapped on the *axial* bromomethyl group singlet in position 5 at δ=3,95 ppm (Figure 12). The aromatic protons give signals between δ=7,58-8,27 ppm, and the signal assignation have being done by the COSY spectrum recorded (Figure 13).

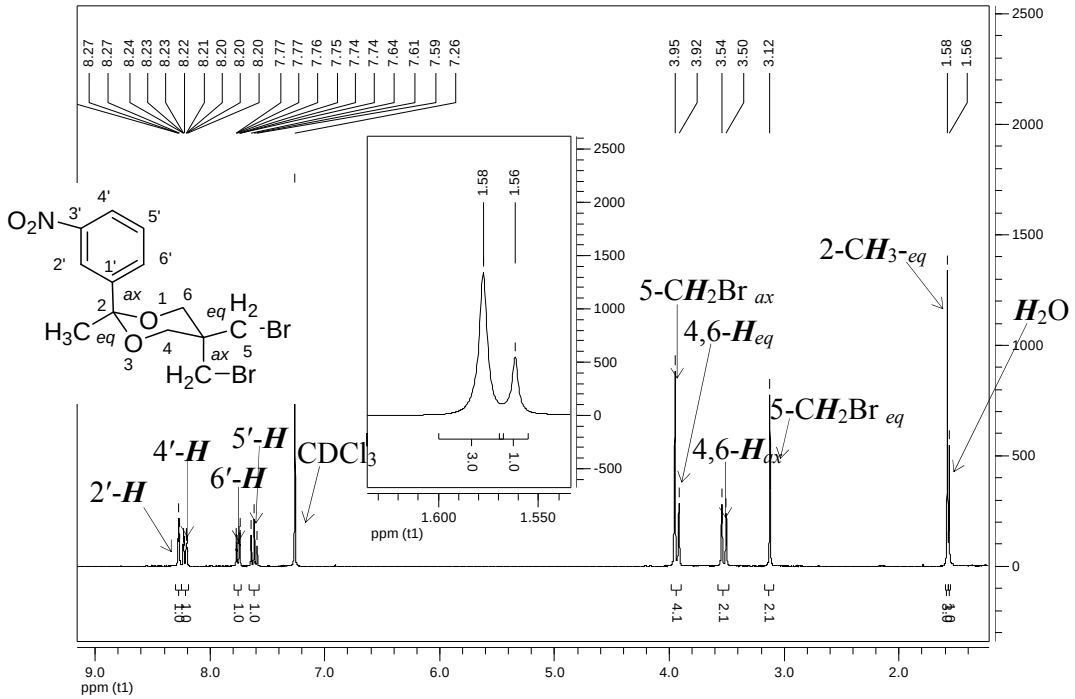


Figure 12. NMR spectrum in $CDCl_3$ at 300 MHz of compound **30**

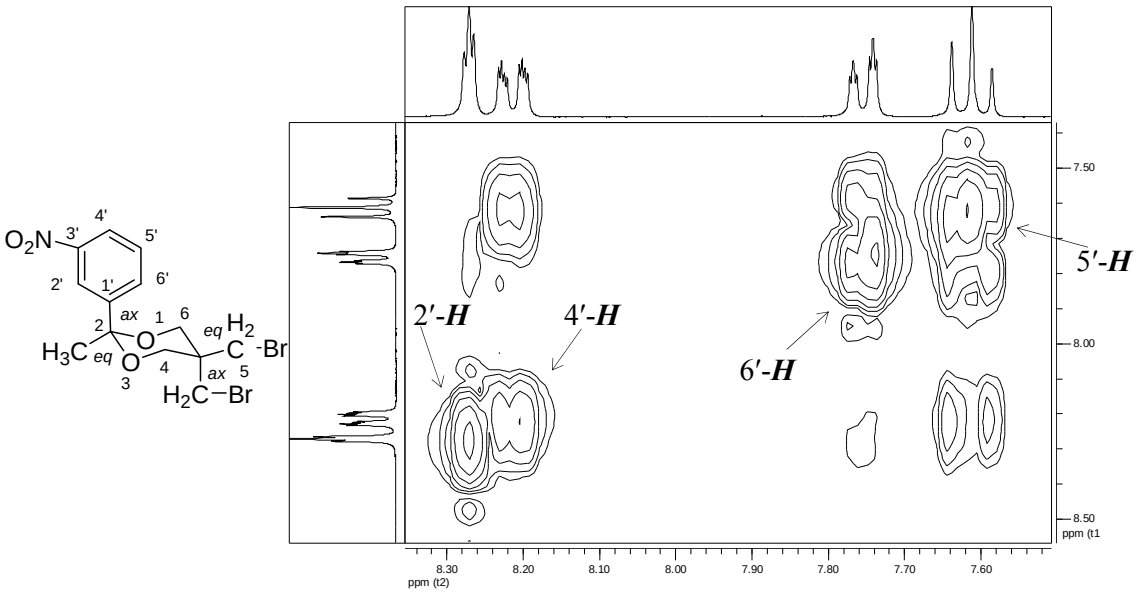


Figure 13. COSY spectrum in $CDCl_3$ at 300 MHz of compound **30** – detail for aromatic protons

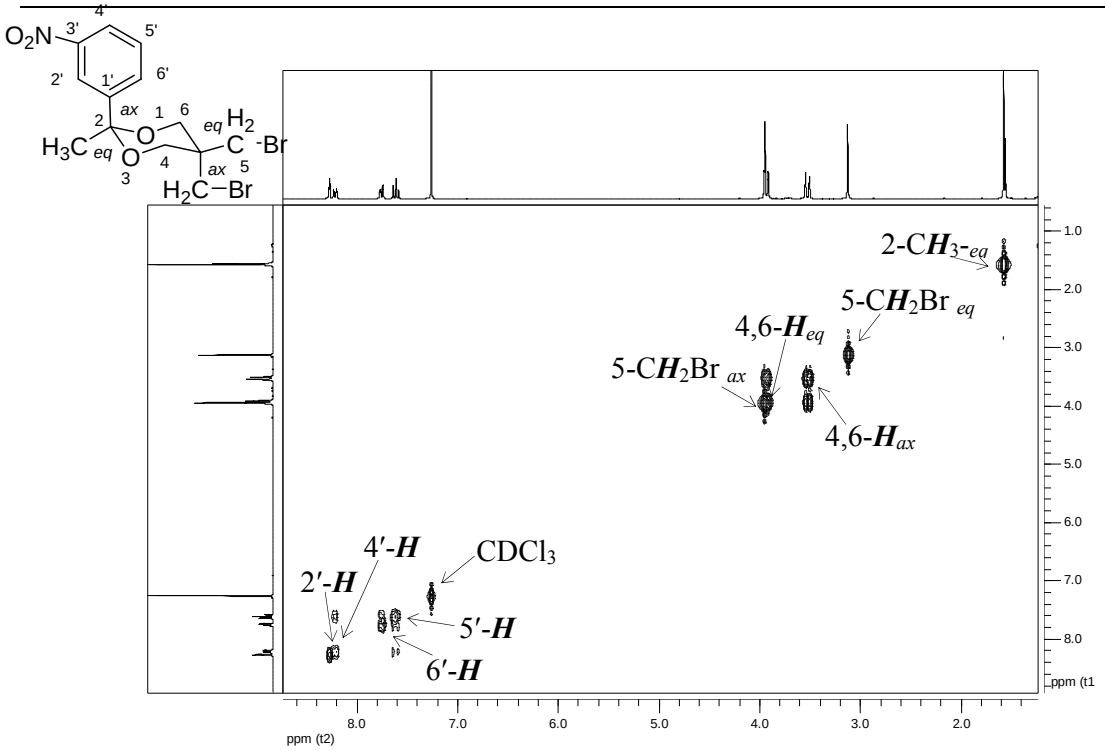


Figure 14. COSY spectrum in $CDCl_3$ at 300 MHz of compound **30**

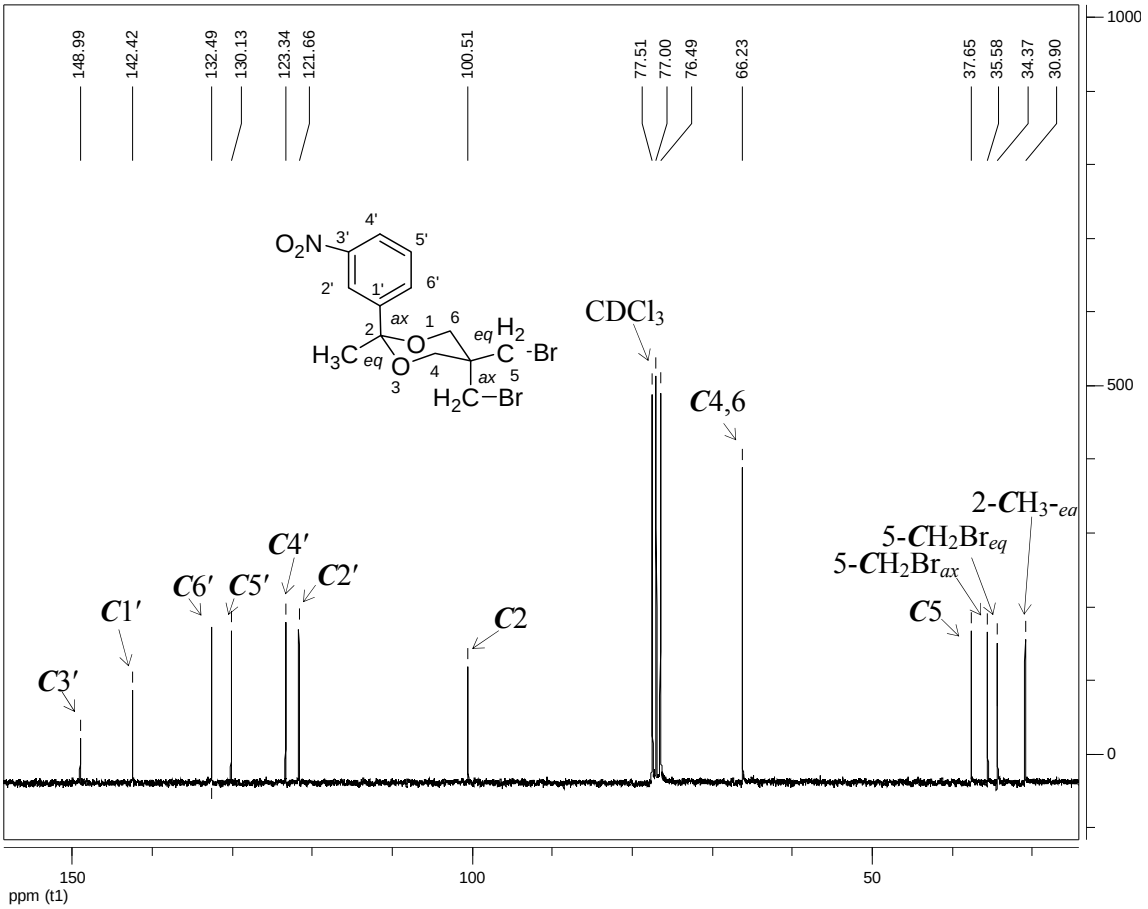


Figure 15. ^{13}C NMR spectrum in $CDCl_3$ at 62,9 MHz of compound **30**

HMQC spectrum (also named HETCOR, based on the proton detection) (Figure 16) confirms the assignments previous done, thus is noticed that the bromomethyl group protons in position 2 at δ=1,58 ppm are bounded to the primary carbon from δ=30,90 ppm, and the bromomethyl group protons in position 5 *equatorial*, at δ=3,13 ppm, respective *axial* at δ=3,96 ppm are bounded at the carbon atoms from δ=34,37 ppm, respective δ=35,58 ppm. Also, the carbon atoms C4 and C6 from δ=66,23 ppm are bounded to the protons in positions 4,6 *axial* (δ=3,52 ppm), respective *equatorial* (δ=3,93 ppm).

For the aromatic protons [27] is noticed that the proton in position 5′ at δ=7,51 ppm is bounded to the C5′ atom from δ=130,13 ppm; the proton in position 6′ at δ=7,75 ppm corresponds to the C6′ atom from δ=132,49 ppm; the proton in position 4′ at δ=8,20 ppm is bounded to the C4′ atom from δ=123,34 ppm; and the proton in position 2′ at δ=8,27 ppm corresponds to the C2′ atom from δ=121,66 ppm (Figure 17).

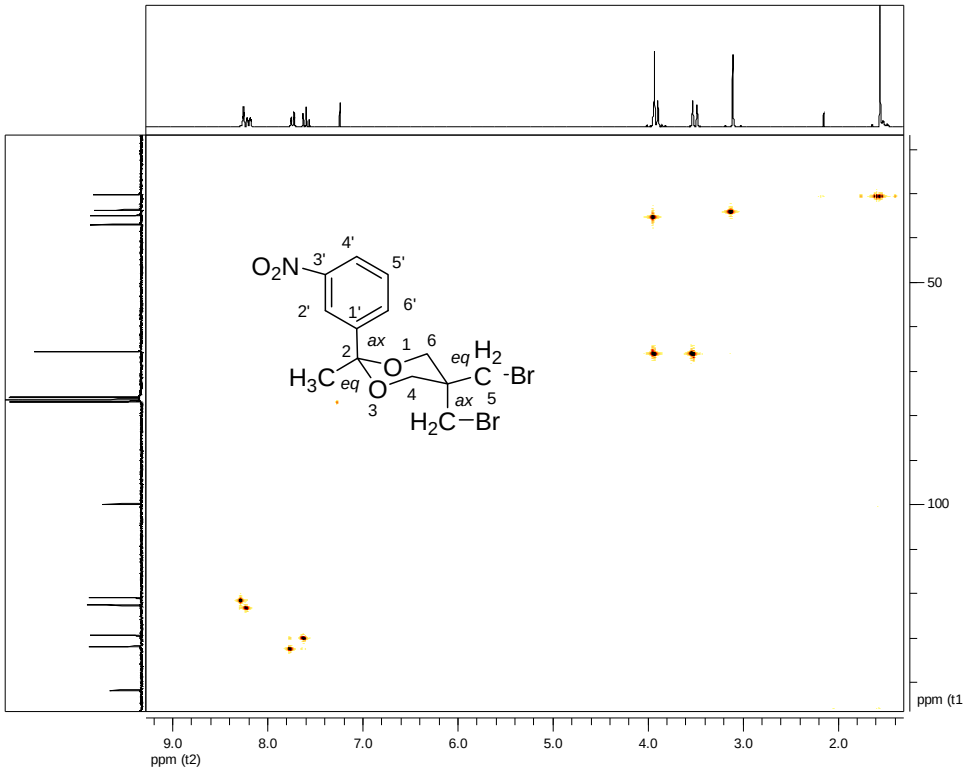


Figure 16. HMQC spectrum in $CDCl_3$ at 125 MHz-C and at 500 MHz-H of compound **30**

[27] Lambert, J. B.; Mazzola, E. P.; *Nuclear Magnetic Resonance Spectroscopy- An Introduction to Principles, Applications, and Experimental Methods*, Prentice Hall, 2003; pp. 74-75, 87-88.

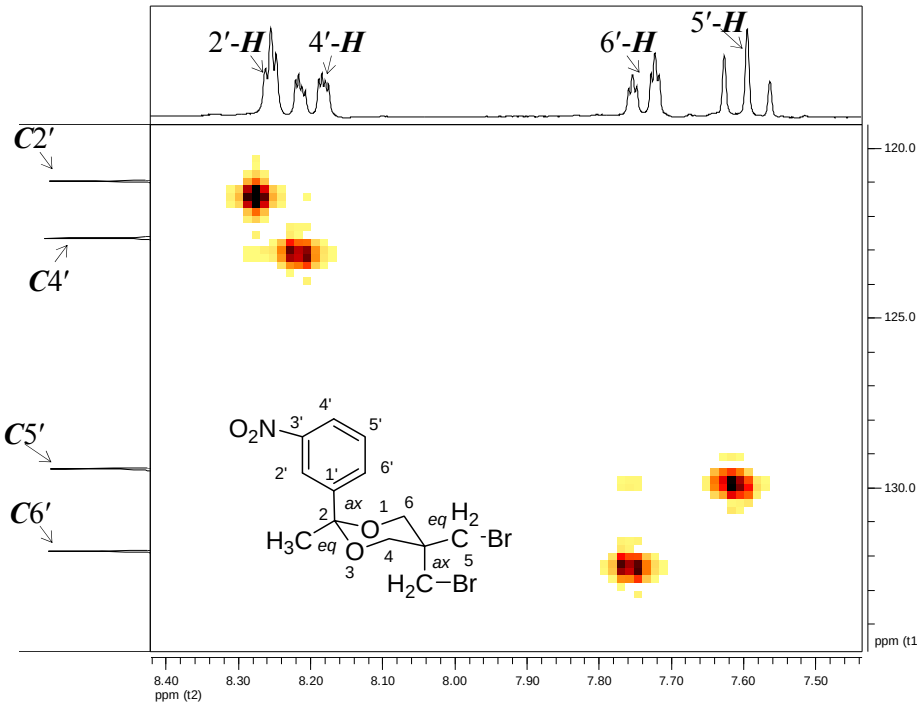


Figure 17. HMQC spectrum of compound **30**-detail for the aromatic area

Table 7. ^{1}H NMR comparative data for compounds **30-35**

Chemical shift/group	CH_2-4,6 *axial* (ppm)	CH_2-4,6 *equatorial* (ppm)	CH_2Br *axial* pos. 5 (ppm)	CH_2Br *equatorial* pos. 5 (ppm)	R^1 –pos. 2 (ppm)
Compound **30**	3,52	3,93	3,95	3,12	1,58
Compound **31**	3,52	3,92	3,95	3,11	1,56
Compound **32**	3,90	4,29	3,94	3,33	5,49
Compound **33**	3,90	4,29	3,94	3,32	5,49
Compound **34**	3,70	4,20	3,88	3,25	4,53
Compound **35**	3,62	4,08	3,88	3,23	CH_{2eq}-2,03 H_{ax}-4,59

The compound **35** has the ^{1}H NMR spectrum in $CDCl_3$ at 300 MHz different from the other spectra, appears the signal for the methylene bridge in position 2 and 2' with couplings between the protons from the bridge, but even other coupling between the protons from the positions 4(4′), 6(6′) are noticed. A triplet is present at δ=2,03 ppm for the methylenic bridge between the two 1,3-dioxanic rings, with *equatorial* orientation in regards to the both heterocyclic rings. In the spectrum is a singlet at δ=3,23 ppm corresponding to the bromomethyl

group protons in positions 5(5′) with *equatorial* orientation and a singlet at δ=3,88 ppm for the *axial* bromomethyl group protons in positions 5(5′).

The *axial* protons from the positions 4(4′), 6(6′) give a doublet of triplets (in fact a doublet of doublets of overlapped doublets) at δ=3,62 ppm due to the geminal coupling 4(6)-*axial*-4(6)-*equatorial* with the coupling constant $^{2}J_{4(6)ax\text{-}4(6)eq}$ =11,8 Hz and the long range coupling of *axial* protons in position 4(6), 4′(6)′ with the *axial* proton in position 6(4), 6′(4′) and with the *equatorial* proton in 6(4), 6′(4′), both coupling constants having closed values. The *equatorial* protons from the positions 4(4′), 6(6′) have as signal another doublet of triplets at δ=4,08 ppm, due to the geminal coupling with the *axial* proton in 4(6), 4′(6)′ and the long range coupling with the *axial* and *equatorial* proton in 6(4), 6′(4′). The coupling constant is $^{2}J_{4(6)ax\text{-}4(6)eq}$ =11,8 Hz, and the coupling constants are $^{4}J_{4(6)ec\text{-}6(4)ax}$ =$^{4}J_{4(6)ec\text{-}6(4)eq}$=1,5 Hz and $^{4}J_{4(6)ax\text{-}6(4)ax}$ =$^{4}J_{4(6)ax\text{-}6(4)eq}$= 1,6 Hz.

In the spectrum appears another triplet corresponding to the *axial* protons in positions 2(2′) at δ=4,59 ppm. The coupling constant between the methylene bridge protons and the *axial* protons from the positions 2(2′) is ^{3}J=5,4 Hz (Figure 24).

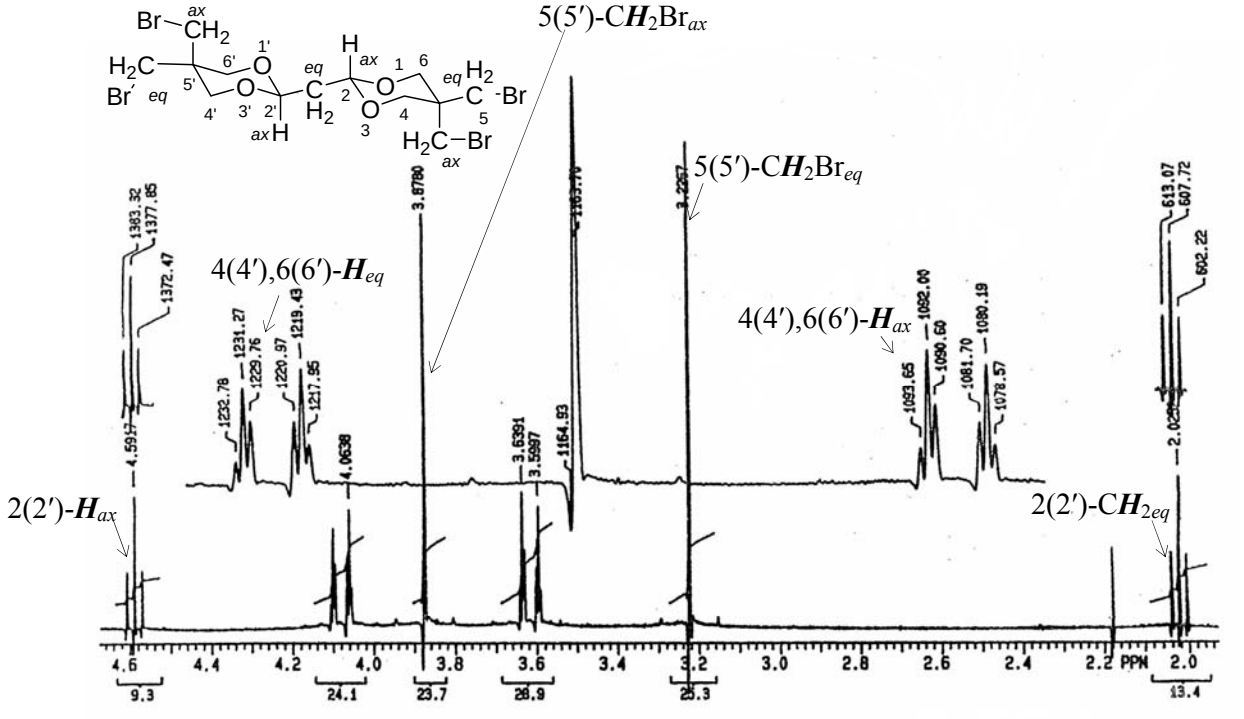
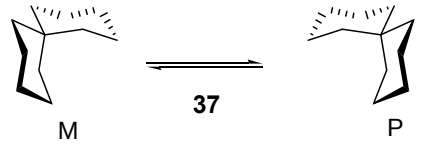


Figure 24. Spectrul ^{1}H NMR în $CDCl_3$ la 300 MHz al compusului **35**

PART III. SPIRANIC COMPOUNDS OF 1,3-DIOXANE

III.1. Introduction

The stereochemistry of the spiranes with six-membered rings has been studied extensively [28], and many of the investigated compounds contained 1,3-dioxane units [29,30,31,32,33]. It has been determined that spiro-1,3-dioxanes have helical chirality [1,**Error! Bookmark not defined.**], because the polyspiranes with hexaatomic cycles presents a helical arrangement similar to the protein helix or with the organic compounds named helicenes. The helix can be configure P or M (being orientated in this way by synthesis) and continues identical to itself, having a structure of four by four six-membered rings which repeats continuously (Scheme 17).

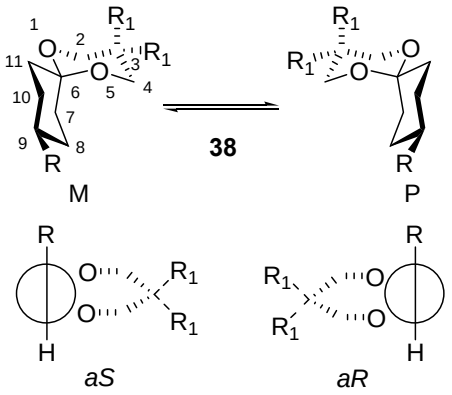


Scheme 17

Spiranic compounds can have in the same time or separately beside the helical chirality, central or axial chirality. For instance, for the semi-flexible derivates of 1,5-dioxaspiro[5.5]undecane (**38**) (Schema 18) with helical chirality (as a result of the specific arrangement of the spirane skeleton of the molecule), exhibit axial chirality too, despite the identical substituents located in position 3 of the spirane system [30,31,34].

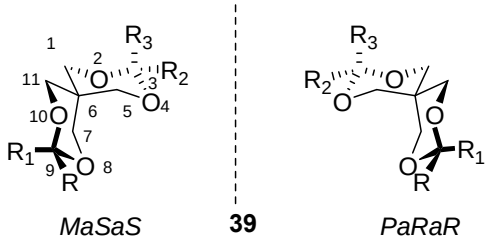
The C^6-C^9 axis is a chiral element and the different groups at the ends of this symmetry axis are R and H at carbon atom C^9 and the 1,3-dioxane ring on one side and the missing ligand on the other side at C^6. In these compounds (**38**) the carbocycle is anancomeric and the heterocycle is flipping. This conformational equilibrium (flipping of the heterocycle) is an enantiomeric inversion (Scheme 18)

[28] Cismaş, C.; Terec, A.; Mager, S.; Grosu, I. *Curr. Org. Chem.* **2005**, *9*, 1287-1314.
[29] Mursakulov, I.G.; Ramazanov, E. A.; Guseinov, M. M.; Zefirov, N. S.; Samoshin, V. V.; Eliel, E. L. *Tetrahedron* **1980**, *36*, 1885-1890.
[30] Grosu, I.; Mager, S.; Plé, G.; Horn. M *J. Chem. Soc. Chem. Commun.* **1995**, 167-168.
[31] Grosu, I.; Mager, S.; Plé, G. *J. Chem. Soc. Perkin Trans. 2* **1995**, 1351-1357.
[32] Terec, A.; Grosu, I.; Condamine, E.; Breau, L.; Plé, G.; Ramondenc, Y.; Rochon, F. D.; Peulon-Agasse, V.; Opriş, D. *Tetrahedron* **2004**, *60*, 3173-3189.
[33] Grosu, I.; Plé, G.; Mager, S.; Martinez, R.; Mesaroş, C.; Camacho, B. C.; *Tetrahedron* **1997**, *53*, 6215-6232.
[34] **Mihiş, A**.; Condamine, E.; Bogdan, E.; Terec, A.; Kurtán, T.; Grosu, I. *Molecules* **2008**, *13*, 2848-2858.



Scheme 18

Compounds with 2,4,8,10-tetraoxaspiro[5.5]undecane skeleton (**39**, Schema 19) bearing different substituents at both ends of the spirane system were also investigated. In these compounds, besides the helical chirality, other two chiral axis (C^3-C^6 and C^6-C^9) can be considered and six stereoisomers are possible (Table 8) [31,34,35, 36].



Scheme 19

Table 8. Possible stereoisomers for the monospirane with two chiral axes and helical chirality

Isomer	**Configuration**			**Orientation of the reference substituents at**	
	Axis C^3-C^6	Axis C^6-C^9	Type helix	C^3 (**R**)	C^9 (**R_2**)
I	*aS*	*aS*	*M*	***ec***	***ec***
II	*aR*	*aS*	*P*	*ax*	*ec*
II′ *	*aS*	*aR*	*P*	*ec*	*ax*
III	*aR*	*aR*	*M*	*ax*	*ax*
IV	*aR*	*aR*	*P*	***ec***	***ec***
V	*aS*	*aR*	*M*	*ax*	*ec*
V′*	*aR*	*aS*	*M*	*ec*	*ax*
VI	*aS*	*aS*	*P*	*ax*	*ax*

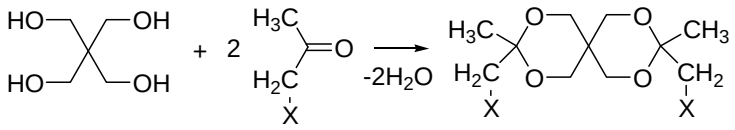
[35] Grosu, I.; Mager, S.; Plé, G.; Martinez, R.; Horn, M.; Gavino, R. R. *Monatsh. Chem.* **1995**, *126*, 1021-1030.
[36] Mager, S.; Horn, M.; Grosu, I.; Bogdan, M. *Monatsh. Chem.* **1989**, *120*, 735-742.

* because similar substitutions at C^3 and C^9, structures II and II′; V and V′ are equivalent

In all studied compounds **39** there are large conformational energy differences between the substituents located at the same positions and the compounds exhibit anancomeric structures. If substituents R and R_2 have a considerably higher free energy than other substituents located at the same positions (R_1 and R_3), the preferred structures (majority) I and IV exhibit those groups in *equatorial* orientations. Those structures I and IV are considered representative for compounds **39**, they cannot be transformed into one other by conformational processes and thus represent separable enantiomers.

III.2. Synthesis

New spiranic compounds with 2,4,8,10-tetraoxaspiro[5.5]undecane skeleton **42-46** were obtained by the condensation of pentaerythritol with non-symmetrical ketones in acid catalysis (*para*-toluensulfonic acid) at reflux in benzene or toluene (Scheme 21). [34]

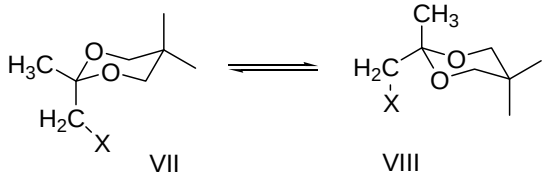


X = $COOCH_3$ **42**
X = $COOCH_2CH_3$ **43**
X = OCH_3 **44**
X = Cl **45**
X = C_6H_5 **46**

Scheme 21

III.3. Structural analysis and stereochemistry

It was demonstrated that CH_3 and CH_2X groups located in the ketal part of the 1,3-dioxane ring (position 2) have very close conformational enthalpies and 1,3-dioxane derivates which contains in position 2 the groups CH_3 and CH_2X are flexible compounds (Scheme 22) [6,37]. Conformers VII and VIII have similar contributions to the average structure of the compound.



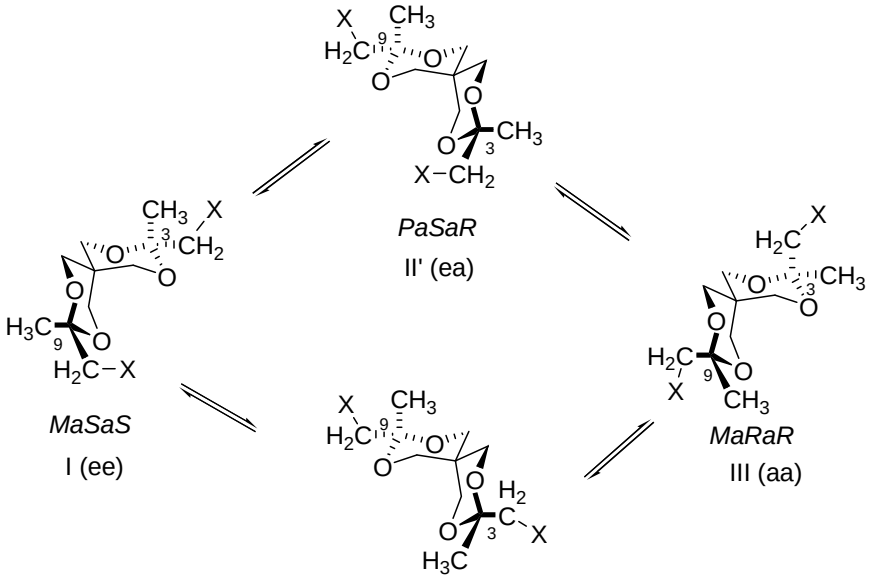
VII VIII

Scheme 22

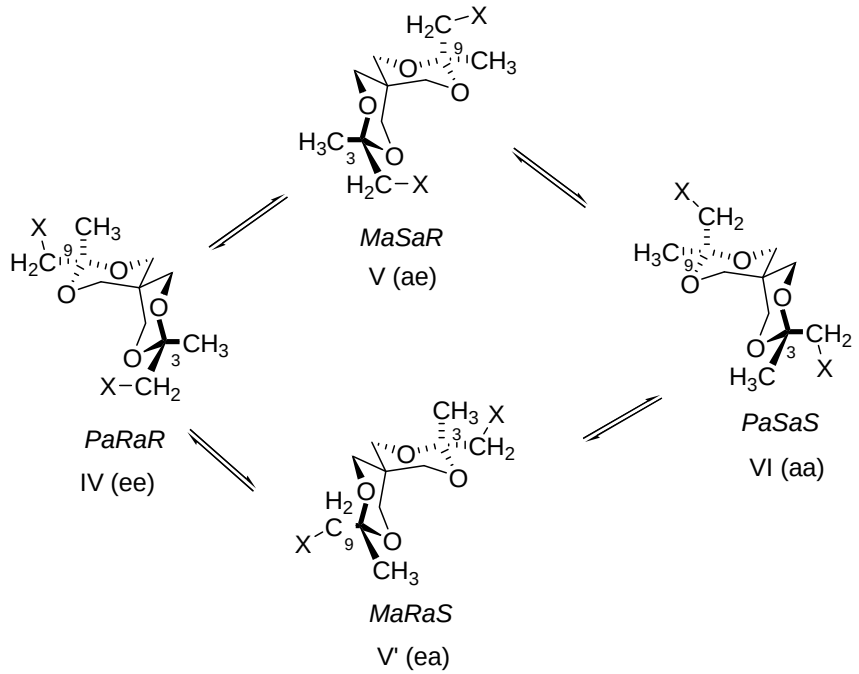
Taking into account these data compounds **42-46** were considered flexible. Like compounds **39** they exhibit six conformers (Table 8). These conformers form two groups [I, II

[37] Mesaroş, E.; Grosu, I.; Mager, S.; Plé, G.; Farcas, I.; *Monatsh. Chem.* **1998**, *129*, 723-733.

(II′), III and IV, V (V′), VI] involved in the equilibria I⇄II(II′)⇄III and IV⇄V(V′)⇄VI (Schemes 23 and 24). [34]



Scheme 23



Scheme 24

The conformers of each group are diastereoisomers [ee, ae(ea), aa; CH_2X is taken as reference] and they have an enantiomer (optical antipode) in the other group. To transform a structure of one group into a structure of the other group it is necessary to break bonds and to

remake bonds. Compounds **42-46** despite their flexible structure, exhibit separable enantiomers. In order to discriminate the enantiomers, chiral HPLC experiments, using CHIRALCEL OD column and normal and chiral (OR) detections, were run with compounds **43** and **46**. The peaks of the enantiomers are baseline separated (t_τ for compound **43** : 27,34 min, respective 33,05 min, and for **46**: 11,6 min, 13,9 min; Figure 29), but the signal in CD detection are weak probably because these ones are average of similar contributions belonging to diastereoisomers (Schemes 23 and 24) with opposite optical activity.

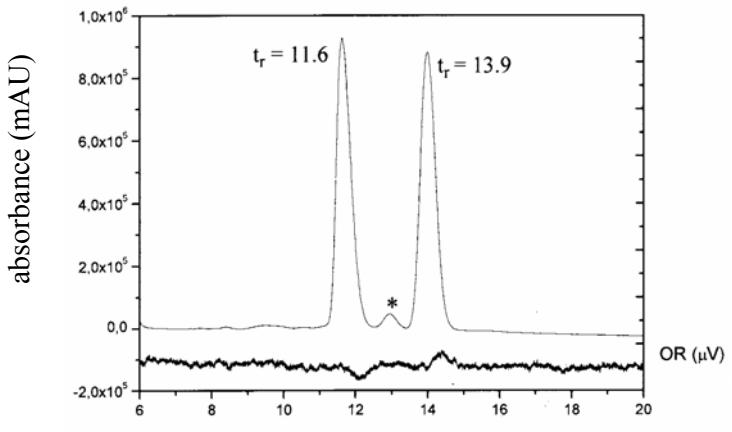


Figure 29. HPLC chromatograms of derivative **43** on Chiralcel OD using UV (211 nm) and OR detection.

The flexible structure of the compounds was revealed y dynamic ^{1}H NMR and ^{13}C NMR experiments. The room temperature ^{1}H NMR spectrum exhibits for the three diastereoisomers of the compounds **42-46** only one set of signals at mean values of the chemical shifts due to the rapid conformational equilibrium.

For instance for the compound 3,9-dimethyl-3,9-Bis(methyloxycarbonylmethyl)-2,4,8,10-tetraoxaspiro[5.5]undecane (**42**) the ^{1}H NMR spectrum recorded at 283 K in $(C_2D_5)_2O$ (Figure 30) shows the existence of a flexible structure, due to the fact that the substituents located at positions 3 and 9 have free conformational enthalpies with closed values. Through the helical and axial chirality positions 1(11) and 5(7) are diastereotopic, giving different signals for the heterocyclic protons. At δ=1,49 ppm is the singlet belonging to the methyl group protons located at the positions 3(9) directly bounded to the 1,3-dioxane cycle; at δ=2,72 ppm is the singlet belonging to the methylenic protons of the methyloxycarbonylmethyl group located at the positions 3(9), and at δ=3,59 ppm is the singlet of the methoxy ester group from the positions 3(9). At δ=3,68 ppm appears a singlet with the pattern of a "AB" splitting system for the

heterocycle protons from the positions 1(11); and at δ=3,75 ppm is the signal of the 1,3-dioxane cycle protons located at the positions 5(7) (Figure 30). At δ=3,33 ppm is the signal of the residual deuterated diethyl ether, and the signal at 2,30 ppm are the traces of water from the diethyl ether.

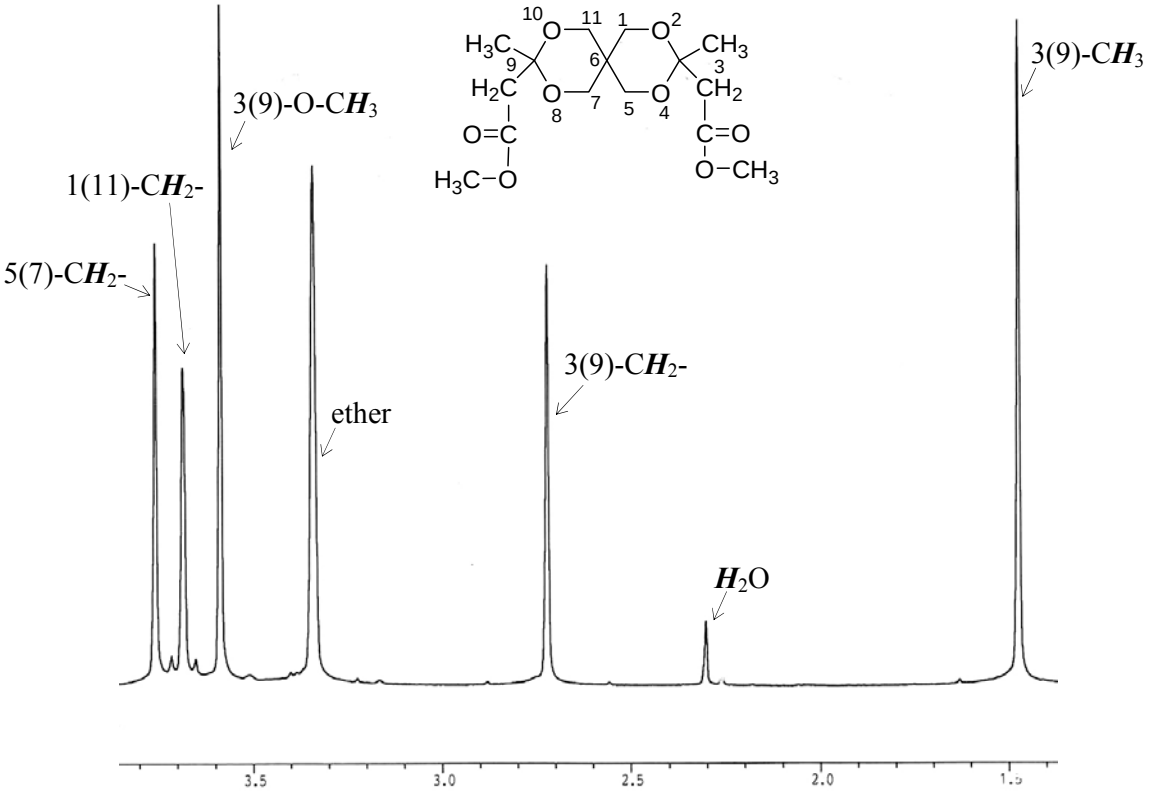


Figure 30. ^{1}H NMR spectrum of compound **42** at 283 K, 400 MHz in $(C_2D_5)_2O$

The room temperature spectra in C_6D_6 reveals the diastereotopicity of protons located at the same position (one is *procis*, and the other one is *protrans* referred to the substituent with higher precedence located at the closer extremity of the spirane skeleton).a The pattern of the spectrum for the protons of the spirane skeleton consists of two AB systems (Figure 31).

The variable temperature ^{1}H NMR spectre reveals the coalescence of signals at the 203 K temperature and at lower temperature separated groups of signals which correspond to the three frozen diastereoisomers and to the *axial* and *equatorial* positions of the protons of the spirane and of the groups located at positions 3(9) (Figures 32 and 33). The complete assignment of the signals in the low temperature spectrum was not possible, but the evolution of the pattern of the spectra observed by diminishing the temperature clearly shows the freezing of conformational equilibria. Then the signals obtained at low temperature correspond to the three frozen diastereoisomers in agreement with the structures shown in schemes 23 and 24.

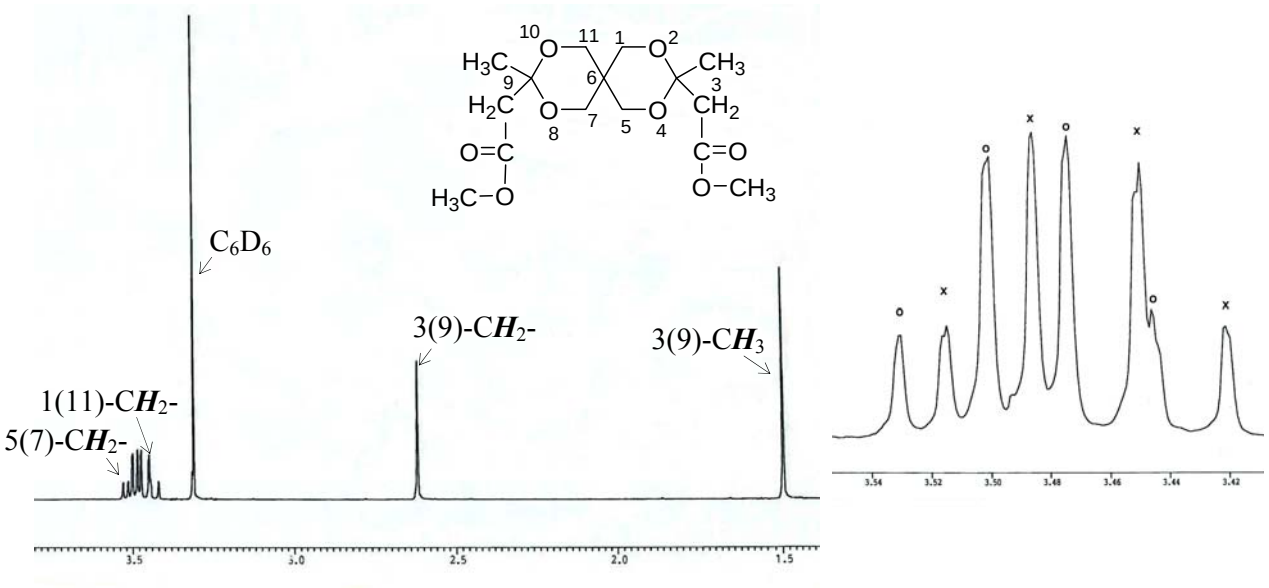


Figure 31. NMR spectrum of compound **42** at room temperature in C_6D_6 at 400 MHz

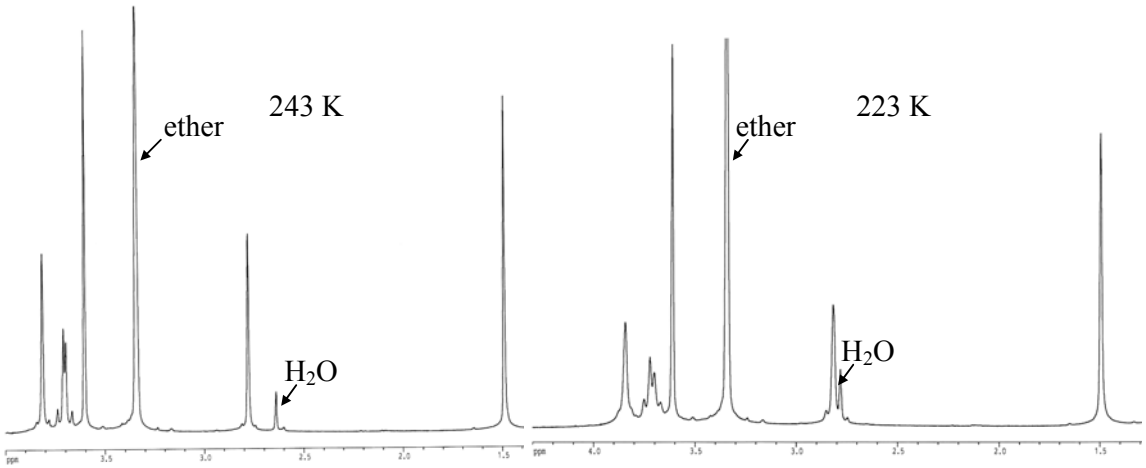


Figure 32. NMR spectra of compound **42** at variable temperature at 400 MHz in $(C_2D_5)_2O$

Due to the temperature dropping the water signal from the deuterated ether is migrating to higher values of the chemical shift. The results obtained in the variable temperature ^{1}H NMR experiments run with the other compounds **43-46** are similar with those shown for **42**.

Variable temperature ^{13}C NMR experiments in the domain 300 K – 164 K were run with compounds **42**, **44** and **46** in THF-*d8* (Table 9, Figures 34, 35, 36, 37 and 38). The coalescence of the signals for **44** was observed at lower temperature (T_C=170 K) in comparison with the results in the ^{1}H NMR variable temperature experiment run with the compound **44**, in THF-*d8*. The THF-*d8* signal appears as quintets at δ=67,4 and 25,2 ppm, according to the literature data.[38]

[38] Silverstein, R. M.; Webster, F. X.; *Spectrometric Identification of Organic Compounds*; 6th Edition, John Wiley & Sons, Inc.: Canada, 1997; pp. 214, 245.

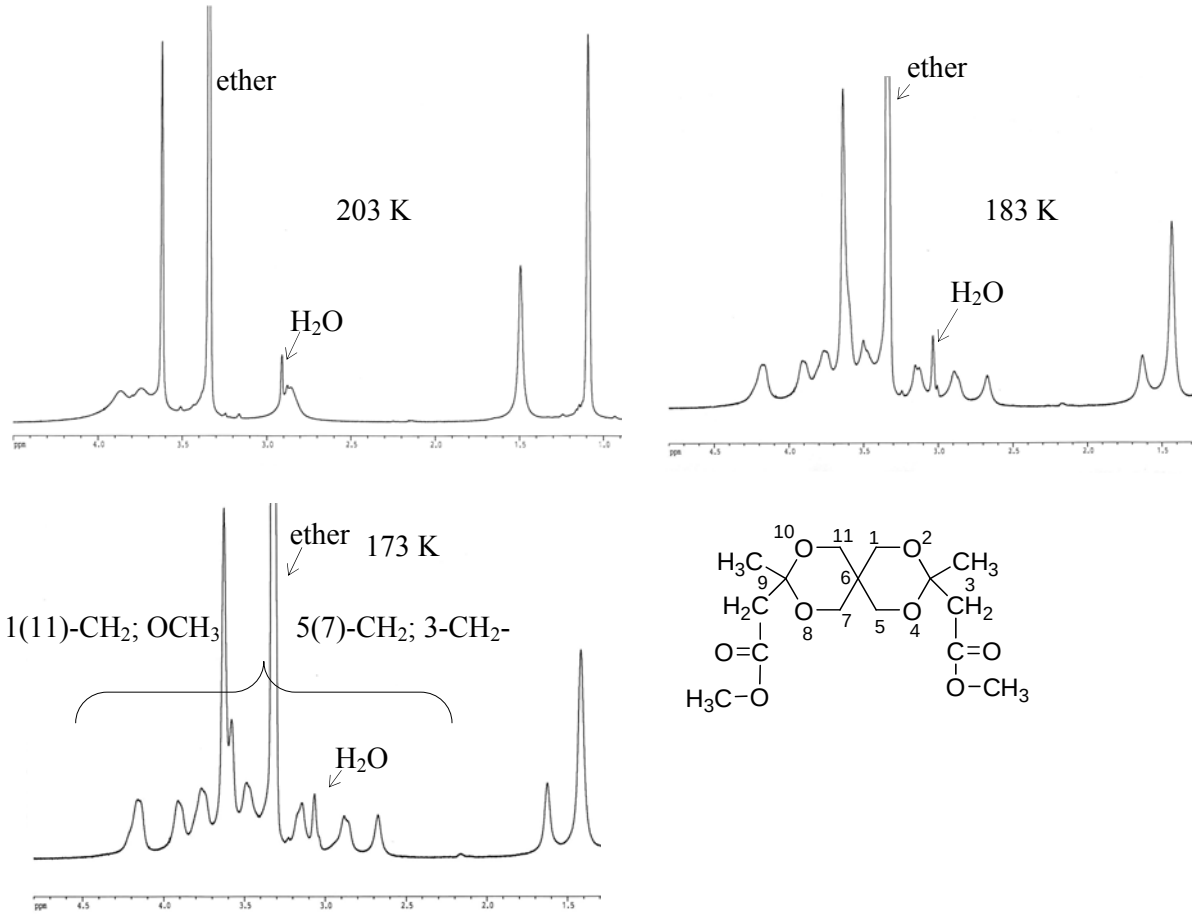


Figure 33. ^{1}H NMR spectra of compound **42** at variable temperature at 400 MHz in $(C_2D_5)_2O$

Table 9. Results (δ, ppm) of the variable temperature ^{13}C RMN experiments run with compounds **42** and **46**

Compound	**C^3, C^9**		**C^1, C^{11}, C^5, C^7**		**C^6**		**C=O/$C_{aromatic}$**	
Temp.	**298 K**	**164 K**	**298 K**	**164 K ***	**298 K**	**164 K**	**298 K**	**164 K**
42	98,92	99,15	64,47	63,22	32,93	31,99	170,03	170,43
		98,59	64,42	63,60		32,20		170,72
				63,87				
46	100,39	100,09	64,49	63,55	33,28	-	a) 128,40	a) 128,51
		100,37	64,54	63,81			b) 138,13	a) 128,87
								b) 137,70
								b) 138,89

***** These signals belong to C^1, C^{11} the other group of signals belonging to C^5, C^7 are overlapped at 164 K with the signals of the solvent. Some of the signals are still in coalescence at 164 K

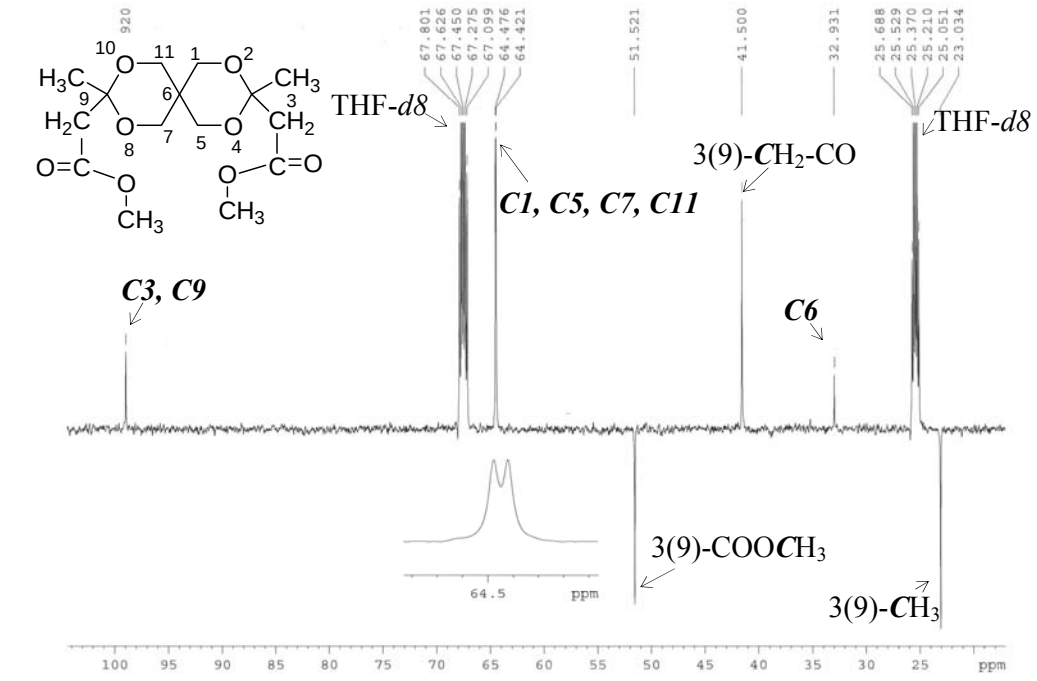


Figure 34. NMR spectrum of compound **42** at 298 K and 500 MHz in THF-*d8*

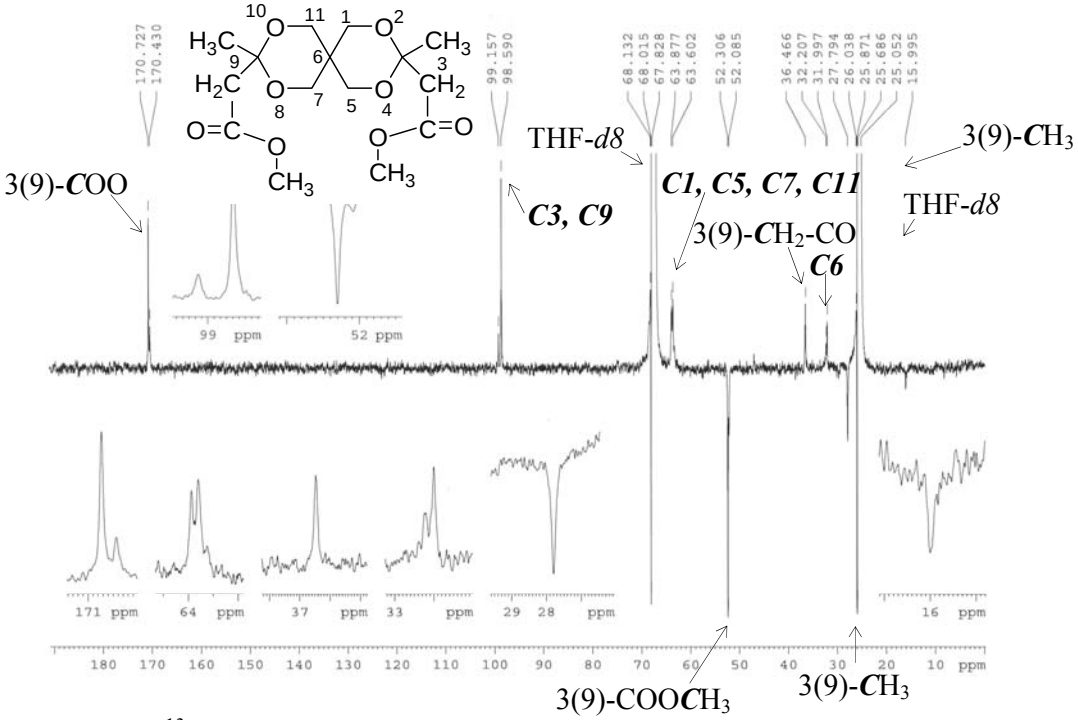


Figure 35. ^{13}C RMN spectrum of compound **42** at 164 K and 500 MHz in THF-*d8*

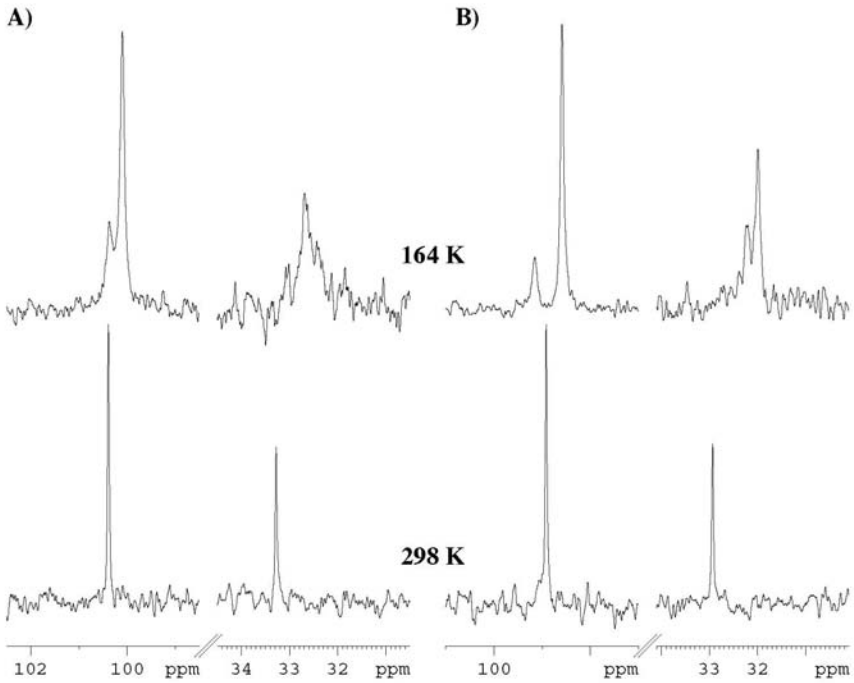


Figure 38. Fragments for the C3, C9, respective C6 of the ^{13}C NMR spectra of compound **46** (**A**) and **42** (**B**) recorded at 298 K and 164 K at 500 MHz in THF-*d8*

The coalescences in the ^{13}C NMR for the other compounds takes place at similar or higher temperatures then in ^{1}H NMR. At the temperature of 164 K the ^{13}C NMR spectra are more complicated and exhibit many signals suggesting the freezing of the conformational equilibria. Thus, instead of each signal recorded at room temperature two or more signals (with different intensities) belonging to the frozen diastereoisomers appear.

Despite these, the assignment of the signals to each of the frozen diastereoisomers both for the compound **42**, and for **46**, was not possible, but the recorded results prove the existence of the conformational equilibrium between the diastereoisomers, according to the Schemes 23 and 24.

The determination of the X-ray crystal structures was attempted for the compounds **45** and **46**, failed, due to the fact that in solid state the compounds are mixtures of all diastereoisomers, whose resolution was not possible. The X-ray crystal structures obtained for similar compounds [39] reveal the preference of the six-membered rings for the *chair* conformation.

[39] Khusainov, M. A.; Makarevich, S. S.; Odovskaya, A.E.; Starikova, Z. A.; Musavirov, R. S. *Zh. Strukt. Khim.*, **1988**, *29*, 154-161.

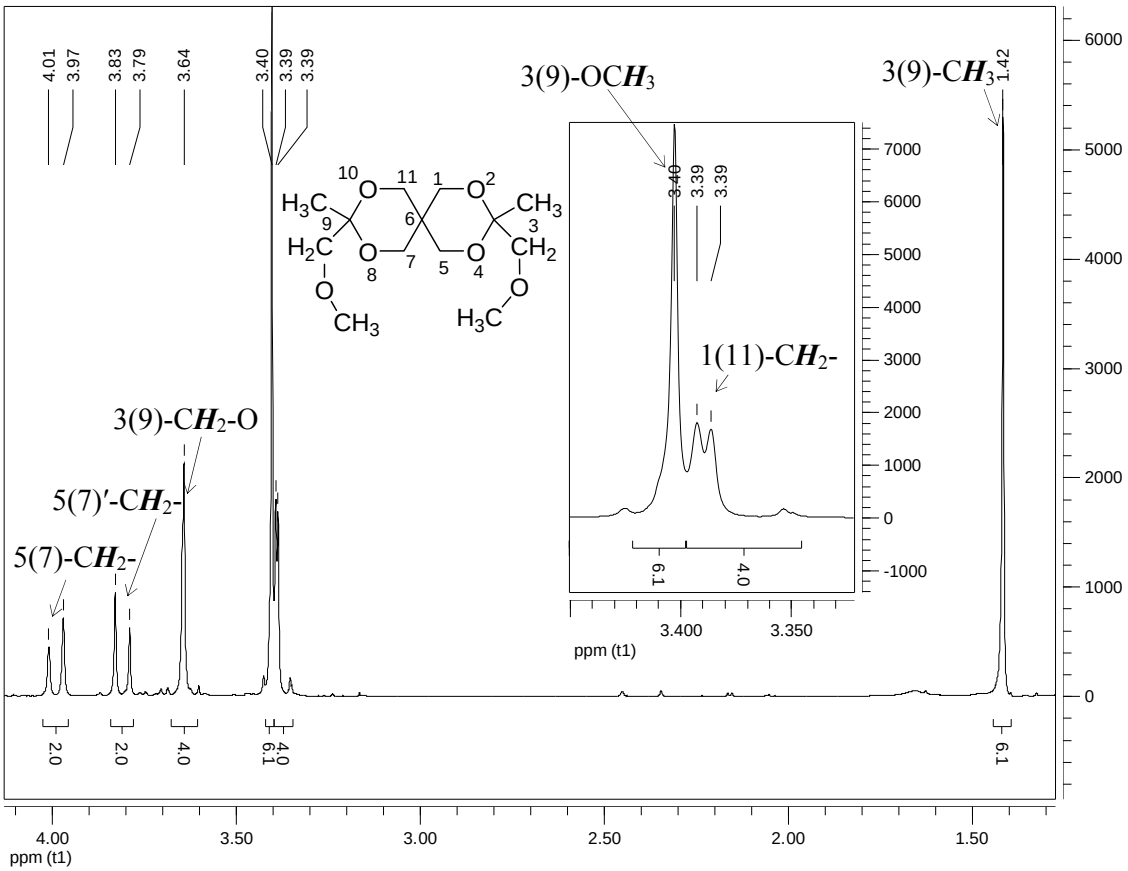


Figure 43. The ^{1}H NMR spectrum of the compound **44** at 300 MHz in $CDCl_3$

The compound 3,9-bis(Methoxymethyl)-3,9-dimethyl-2,4,8,10-tetraoxaspiro[5.5]undecane (**44**) show in ^{1}H NMR spectrum recorded at 300 MHz in $CDCl_3$ a singlet by δ=1,42 ppm for the methyl group in position 3(9), overlapped peaks between 3,37-3,39 ppm for the protons from positons 1(11) which have type „AB" splitting pattern (observing the partial splitting in two doublets), at δ=3,40 ppm is the singlet of methyl protons of methoxy ether group, at δ=3,64 ppm the singlet of methylene protons from methoxymethyl group in positions 3(9), at δ=3,80 ppm the doublet of pro-*cis* protons from positions 5(7) with coupling constant ^2J=11,8 Hz, at δ=3,99 ppm the doublet of pro-*trans* protons from positions 5(7) with coupling constant ^2J=11,8 Hz (Figure 43).

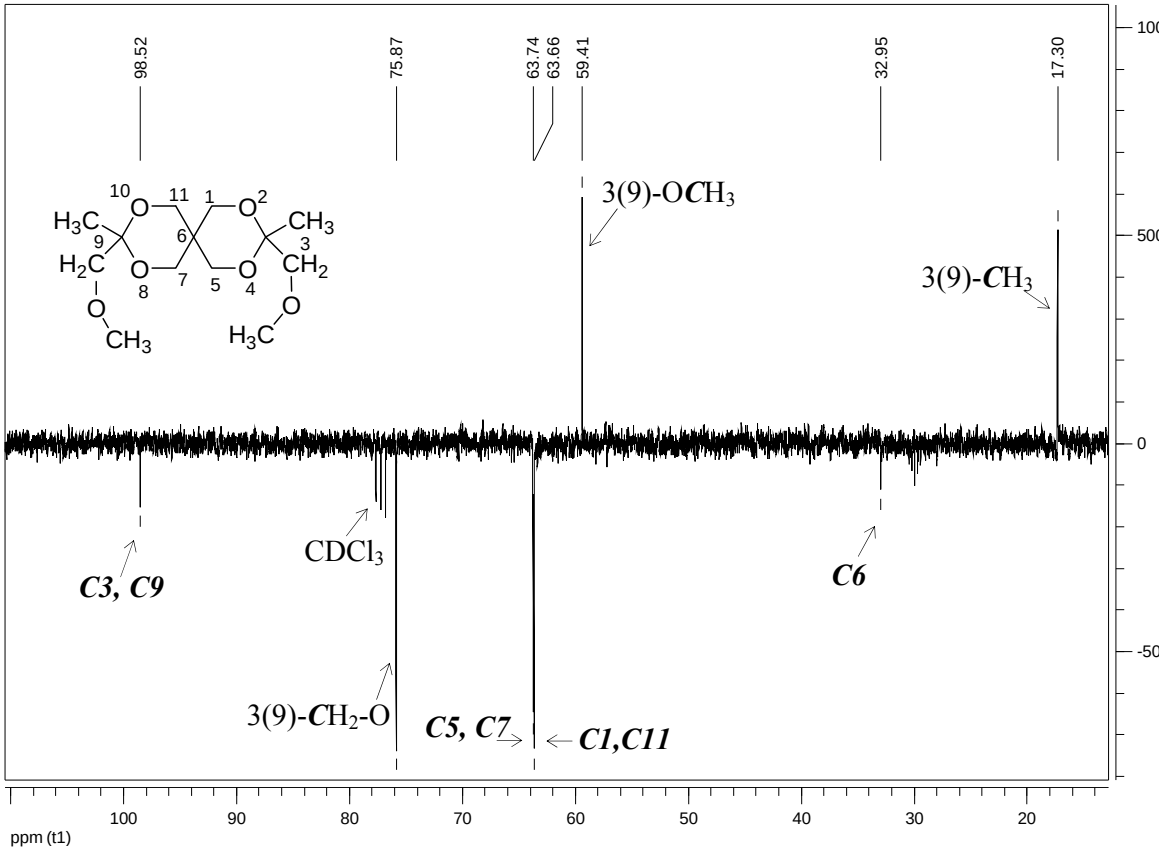


Figure 44. ^{13}C NMR APT spectra of compound **44** at 75 MHz in $CDCl_3$

The compound 3,9-dibenzyl-3,9-dimethyl-2,4,8,10-tetraoxaspiro[5.5]undecane (**46**) also has a flexible structure as can be remarked from the ^{1}H NMR spectrum of the compound **46** recorded at 300 MHz in $CDCl_3$. At δ=1,29 ppm is a singlet for the methyl group protons in positions 3(9); at δ=1,58 ppm is the water signal from the deuterated solvent; at δ=2,98 ppm is the singlet for the methylene protons from the benzyl group in the positions 3(9); at δ=3,63 ppm is the doublet of one of the protons from the positions 1(11) with the coupling constant ^{2}J=11,7 Hz; at δ=3,72 ppm is the doublet of the second proton from the positions 1(11) overlapped to the first proton doublet located at the positions 5(7) from δ=3,73 ppm. At δ=3,86 ppm is the second proton doublet from the positions 5(7) with the coupling constant ^{2}J=11,7 Hz, and between δ=7,23-7,31 ppm are the overlapped signals of aromatic protons belonging to the benzyl groups from the positions 3(9) (Figure 47).

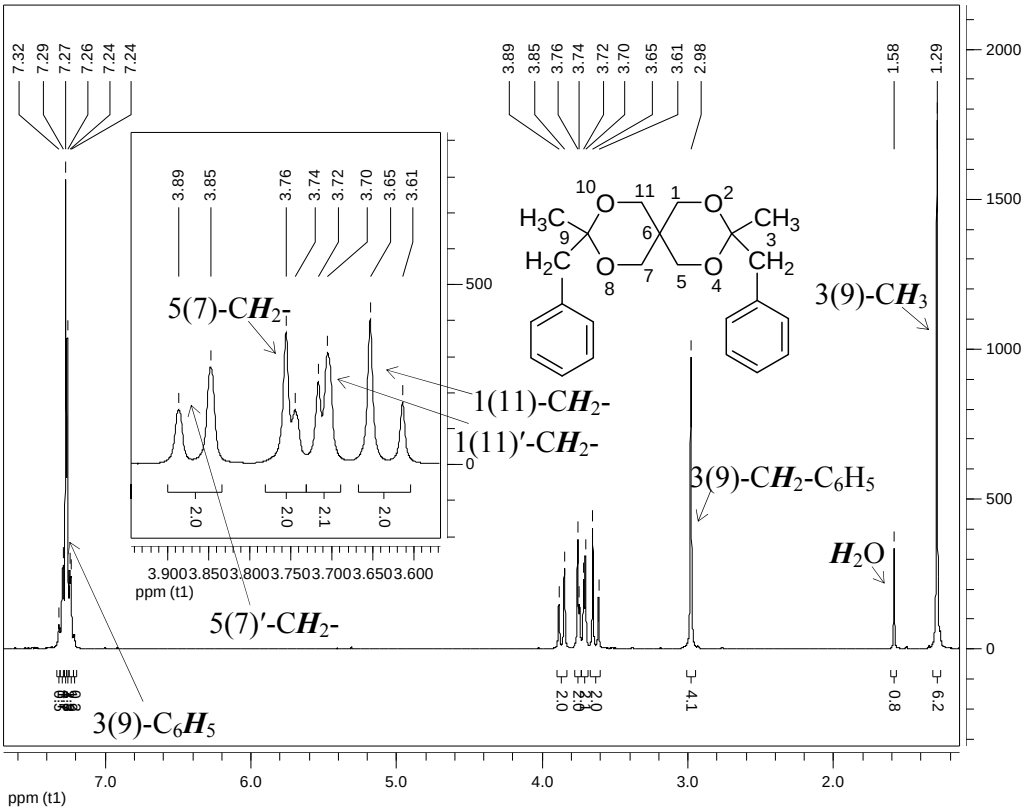


Figure 47. ^{1}H NMR spectrum of compound **46** at 300 MHz in $CDCl_3$

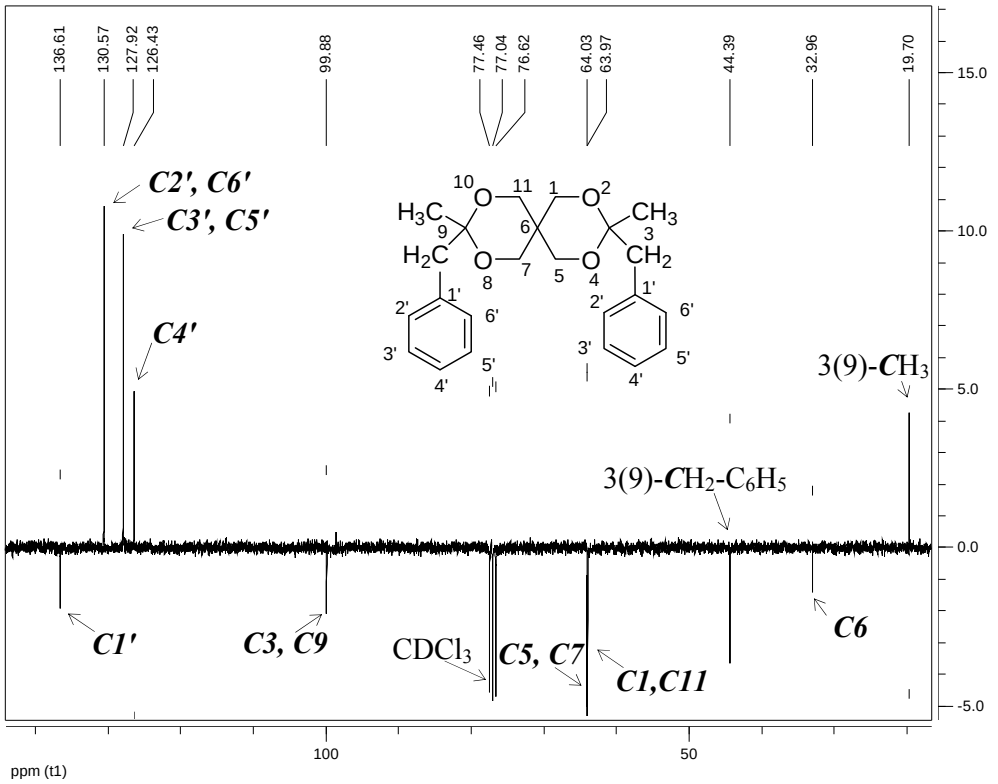


Figure 48. ^{13}C NMR APT spectrum of compound **46** at 75 MHz in $CDCl_3$

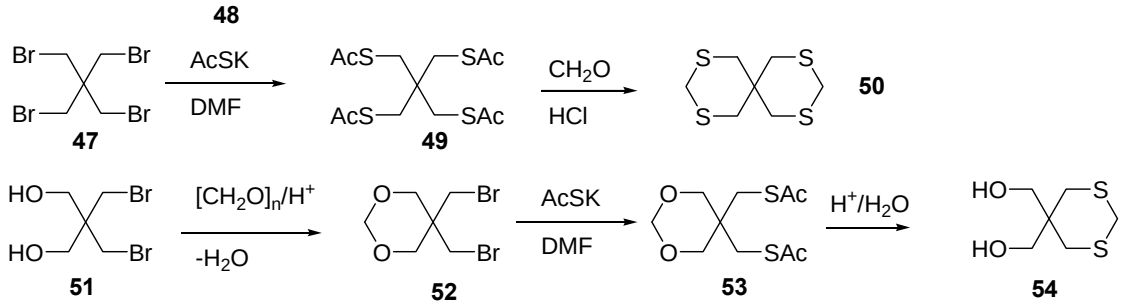
PART IV. SPIRANIC COMPOUNDS WITH DIFFERENT HETEROCYCLES

IV.1. Data from literature

The synthesis of spiranic compounds with sulfur-containing heterocycles is a research theme which was boarded in the literature, existing many strategies of obtaining these types of compounds.

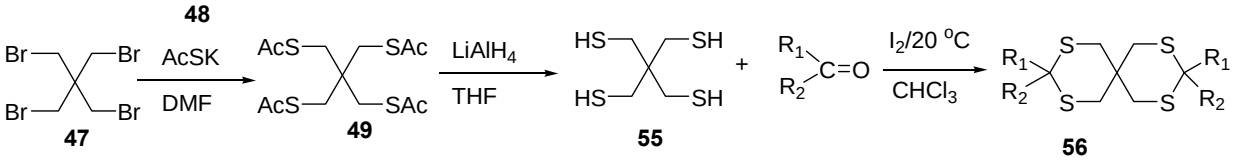
One method constitutes [40] the reaction of pentaerythrityl tetrabromide (**47**) with potassium thioacetate (**48**) followed by the acid hydrolysis of thioester group and thioacetalization (both reactions in a single step) with formaldehyde under acid conditions (Scheme 25).

Another method is [40] the acetalization of 2,2-bis(bromomethyl)-1,3-propandiol (**51**) with formaldehzde, giving 5,5-bis(bromomethyl)-1,3-dioxane (**52**) which reacts with the potassium thioacetate in anhydrous *N,N*-dimethylformamide, followed by the transthioacetalization in acid medium resulting 5,5-bis(hydroxymethyl)-1,3-dithiane (**54**) (Scheme 25).



Scheme 25

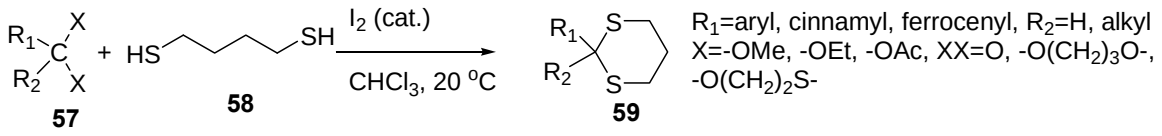
Tetrathianic spirane were synthesized [41] by a sequence of reactions which started from pentaerythrityl tetrabromide [42] (Scheme 26).



Scheme 26

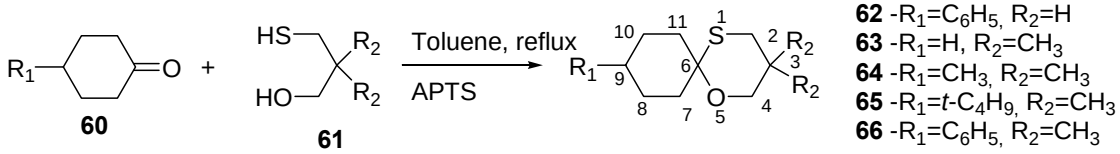
[40] Mitkin, H.; Wan, Y.; Kurchan, A. N.; Kutateladze, A. G. *Synthesis* **2001**, 1133-1142.
[41] Gâz, Ş. A.; Condamine, E.; Bogdan, N.; Terec, A.; Bogdan, E.; Ramondenc, Y.; Grosu, I. *Tetrahedron* **2008**, *64,* 7295-7300.
[42] Wan, Y.; Mitkin, O. D.; Barnhurst, L.; Kurchan, A. N.; Kutateladze, A. G *Org. Lett.* **2000**, *2*, 3817-3819.

The thioacetalization reaction [43] was used to obtain dithianes by the reaction between aldehydes and aromatic or aliphatic cetones, *O,O*-acetals, *O,O*-cetals, *O,S*-cetals and dithiols in the presence of iod at room temperature (Scheme 27).



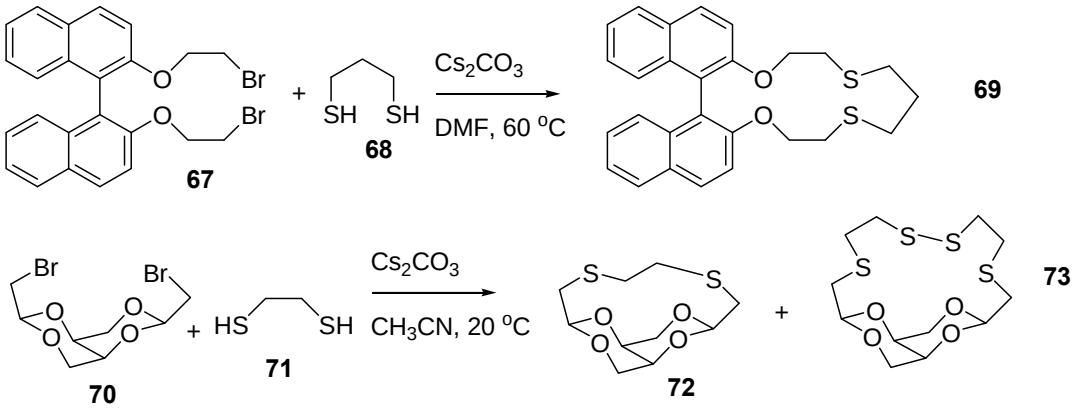
Scheme 27

Spiranic compounds were synthesized [44] by the reaction between substituted cyclohexanones (**60**) with substituted 3-mercapto-1-propanols (**61**) in toluen in the presence of *para*-toluenesulfonic acid at reflux (Scheme 28).



Scheme 28

An reaction approach for the sulfur-containing macrocyclic compounds [45] is the reaction between the dibromurate derivative (**67**) and 1,3-propandithiol (**68**) in the presence of cesium carbonate, *N,N*-dimethylformamide at 60 °C (Scheme 29). Another method [46] is the reaction of the bromurate compound (**70**) with 1,2-ethanedithiol (**71**) in the presence of cesium carbonate and anhydrous acetonitrile at room temperature, when the **72** and **73** sulfur-containing macrocycles are obtained (Scheme 29).

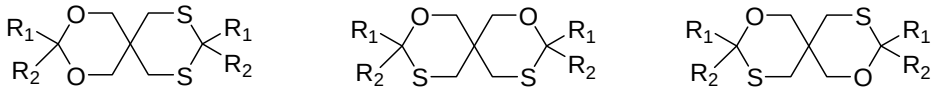


Scheme 29

[43] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527-7529.
[44] Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Socaci, C.; Mager, S. *Tetrahedron* **2001**, *57,* 8751-8758.
[45] Stock, H. T.; Kellog, R. M. *J. Org. Chem.* **1996**, *61*, 3093-3105.
[46] Grabarnik, M.; Goldberg, I.; Fuchs, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3123-3125.

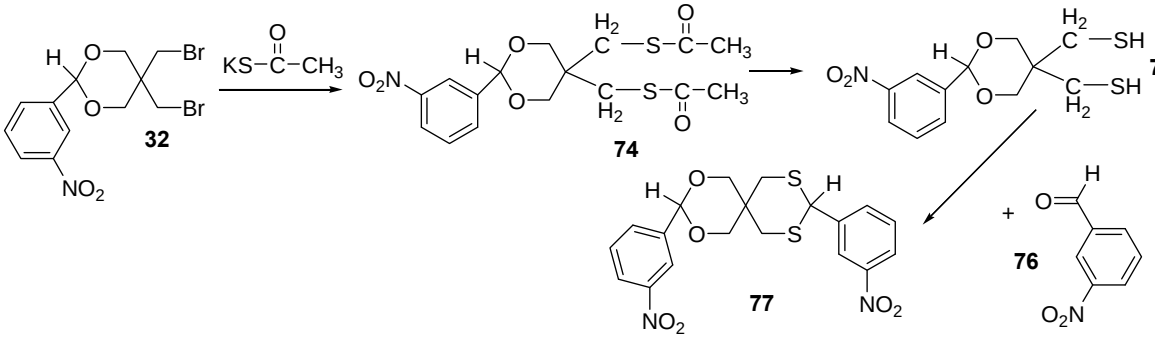
IV.2. Target compounds - obtaining strategies

The research theme is the obtaining by synthesis of some new spiranic compounds with different heterocycles or with different heteroatoms into the cycle (Scheme 30).



Scheme 30

b) **The second strategy** consists in the synthesis of the spiranic derivatives with dioxane and dithiane cycles. For this, in the first stage, the scope was to transform the bromurate derivate **32**(5,5-bis(bromomethyl)-2-(3′-nitrophenyl)-1,3-dioxane) into 2-(3′-nitro-phenyl)-5,5-bis(acetylthiomethyl)-1,3-dioxane (**74**) by the reaction with potassium thioacetate, followed in the second stage by the basic hydrolysis of the thioacetate **74** to dithiole **75** (2-(3′-nitro-phenyl)-5,5-bis(mercaptomethyl)-1,3-dioxane), then the thioacetalization with 3-nitrobenzaldehyde (**76**).



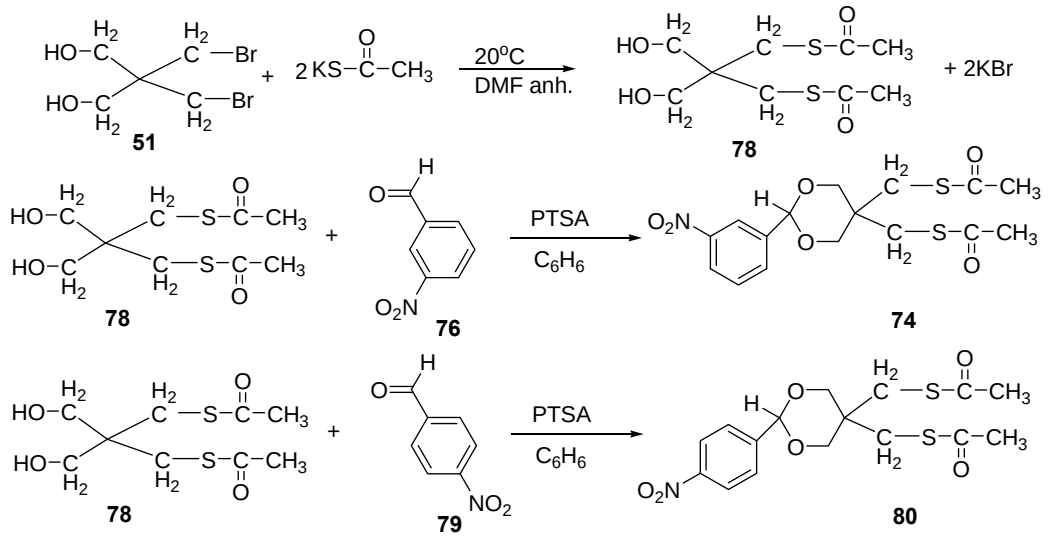
Scheme 32

In the first stage was realised [47] the reaction of the compound **32** with the potasium thioacetate in a mixture of acetonitrile:dichloromethane=1:1, but the expected results didn't followed. Because of these, was proposed the synthesis of 2,2-bis(acetyltiomethyl)-1,3-propandiol (**78**) from 2,2-Bis(bromomethyl)-1,3-propandiol (**51**), followed by the acetalization with 3-nitrobenzaldehyde (**76**) in order to obtain 2-(3′-nitro-phenyl)-5,5-bis(acetylthiomethyl)-1,3-dioxane (**74**) (Scheme 33).

The reaction of the potassium thioacetate with 2,2-bis(bromomethyl)-1,3-propandiol (**51**) in anhydrous *N,N*-dimethylformamide, at the room temperature lead to a mixture of three main compounds (Scheme 33) which were separated by the column cromotography, using as eluent *n*-hexane:AcOEt=2:1. The fraction with R_f =0,58 is the useful compound from this stage, but it was used in the reaction without being completely refined, the ^{1}H NMR spectrum indicating a

[47] Turdean, R.; Bogdan, E.; Terec, A.; Petran, A.; Vlase, L.; Turcu, I.; Grosu, I. *Cent. Eur. J. Chem.* **2009**, *7*, 111-117.

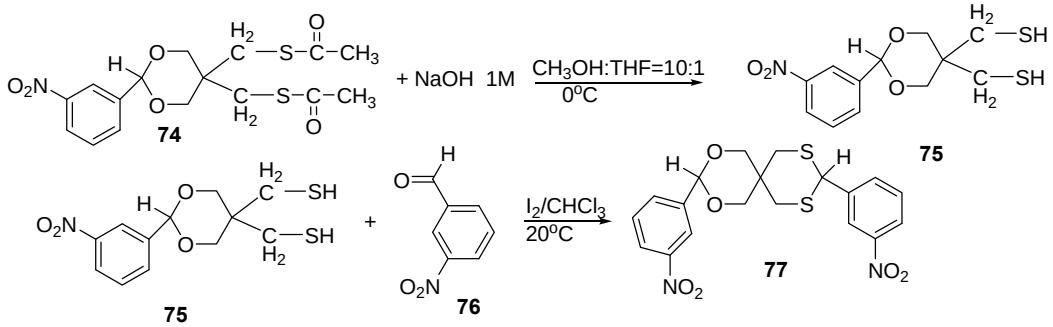
mixture of compounds. This reacted with 3-nitrobenzaldehyde (**76**) in the presence of PTSA (*para*-toluenesulfonic acid) and benzene resulting **74**, identified by ^{1}H NMR. If 4-nitrobenzaldehyde (**79**) is used for the acetalization reaction of the compound **78**, 2-(4′-nitro-phenyl)-5,5-bis(acetylthiomethyl)-1,3-dioxane (**80**) is obtained.



Scheme 33

The next stage after the synthesis of 1,3-dioxane dithioacetate is the saponification (basic hydrolysis) of them. It was tried the basic hydrolysis with sodium methoxide in anhydrous methanol according to the literature data [48,49,50], but the result was the compounds degradation.

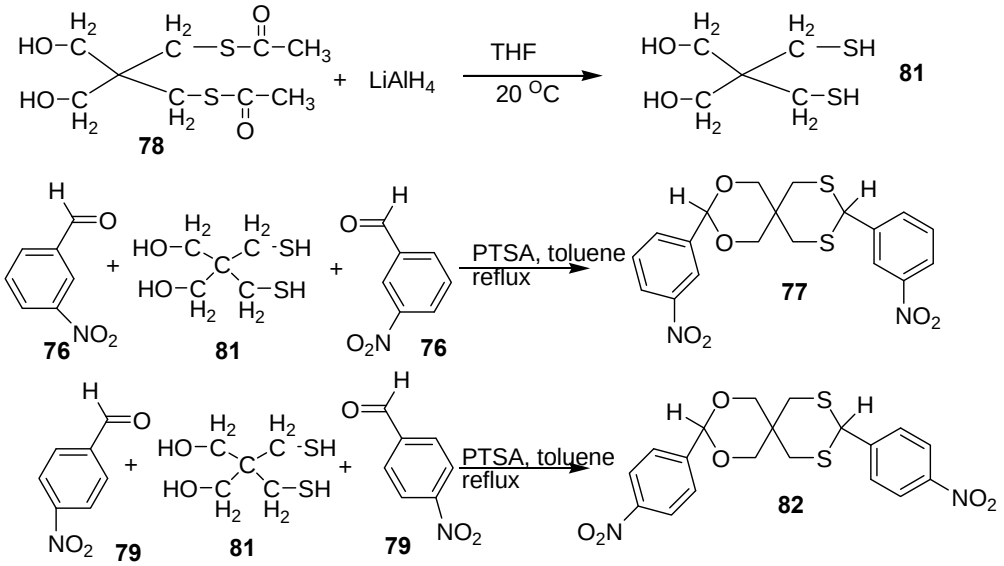
The saponification of the dithioacetate **74** with NaOH 1 M in methanol [51] lead, after the excess base neutralization by bringing the solution on pH=7, to the obtaining of the compound **75** (2-(3′-nitro-phenyl)-5,5-bis(mercaptomethyl)-1,3-dioxane) (Scheme 35).



Scheme 35

[48] Furuike, T.; Aiba, S.; Nishimura, S-I. *Tetrahedron* **2000**, *56*, 9909-9915.
[49] Capelle, S. L.; Vogels, I. A.; Govaerts, T. C.; Toppet, S. M.; Compernolle, F.; Hoornaert, G. J.; *Tetrahedron* **2002**, *58*, 3655-3666.
[50] Govaerts, T. C.; Vogels, I. A.; Compernolle, F.; Hoornaert, G. J.; *Tetrahedron Lett.* **2002**, *43*, 799-802.
[51] Sato, H.; Sakoh, H.; Hashihayata, T.; Imamura, H.; Ohtake, N.; Shimizu, A.; Sugimoto, Y.; Sakuraba, S.; Bamba-Nagano, R.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem.* **2002**, *10*, 1595-1610.

c) **The third strategy** consist in the obtaining of 2,2-bis(mercaptomethyl)-1,3-propandiol (**81**) by the reduction with $LiAlH_4$ of 2,2-bis(acetylthiomethyl)-1,3-propandiol (**78**). The next stage consists in the acetalization and simultaneous thioacetalization reaction with 3-nitrobenzaldehyde (**76**), respective 4-nitrobenzaldehyde (**79**) without the previous refinement of the 2,2-bis(mercaptomethyl)-1,3-propandiol (**81**) (Scheme 36). This was identified by the ^1H NMR, and the melting point measurement, according to the literature data [52,53]. The synthesis of the 3,9-bis(3′-nitrophenyl)-8,10-dioxa-2,4-dithia-spiro[5.5]undecane (**77**), respective of 3,9-bis(4′-nitrophenyl)-8,10-dioxa-2,4-dithia-spiro[5.5]undecane (**82**) was accomplished by the reaction between 2,2-bis(mercaptomethyl)-1,3-propandiol (**81**) with 3-nitrobenzaldehyde (**76**), respective 4-nitrobenzaldehyde (**79**) in toluen at reflux [44] in the presence of *para*-toluen sulfonic acid.



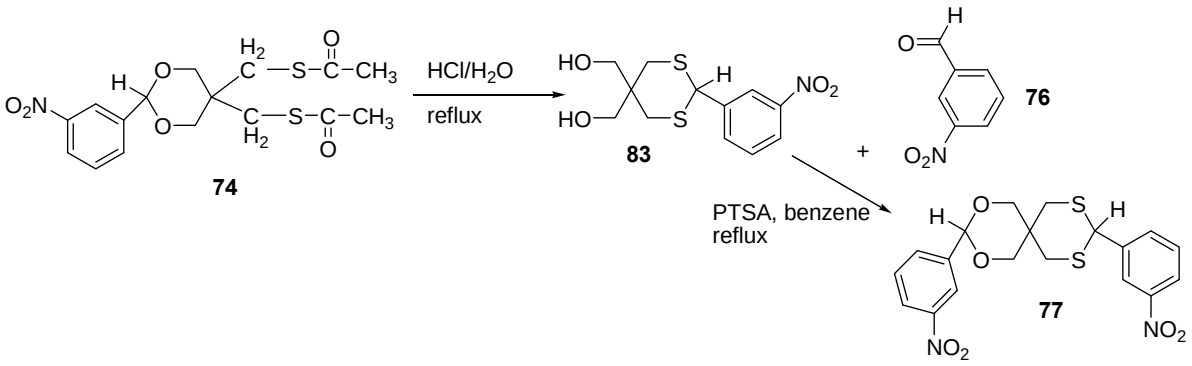
Scheme 36

d) **The fourth strategy** is the same as the second strategy, until the synthesis of the 2-(3′-nitro-phenyl)-5,5-bis(acetylthiomethyl)-1,3-dioxane (**74**) and 2-(4′-nitro-phenyl)-5,5-bis(acetylthiomethyl)-1,3-dioxane (**80**).

In the following, in a single step [40] the acid hydrolysis of the thioacetic group and the transacetalization of 1,3-dioxane with thioacetate group (**74**) was accomplished and the result was 2-(3′-nitro-phenyl)-5,5-bis(hydroxymethyl)-1,3-dithiane (**83**) in aqueous solution of HCl 2N at reflux. The next stage is the acetalization with 3-nitrobenzaldehyde (**76**) in benzene solution

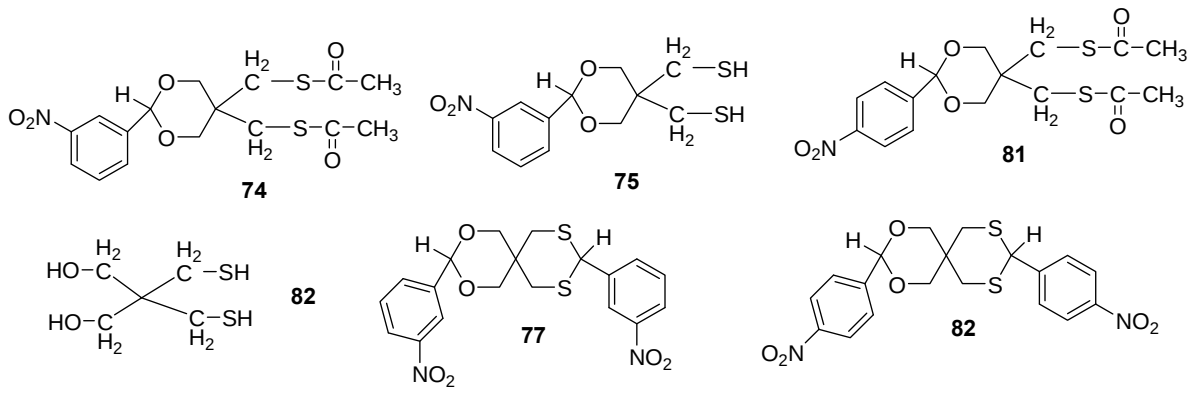
[52] Backer, H. J.; Tamsma, A. F. *Recl. Trav. Ch. Pays-Ba.* **1938**, *57*, 1183-1210.
[53] Bladon, P.; Owen, L. N. *J. Chem. Soc.* **1950**, 585-90.

with the catalyst of *para*-toluenesulfonic acid at reflux, when it should be obtained 3,9-bis(3′-nitrophenyl)-8,10-dioxa-2,4-dithia-spiro[5.5]undecane (**77**) (Scheme 37).



Scheme 37

IV.3. Intermediates



Scheme 38

IV.4. Structural analysis and stereochemistry

The compound 2-(3′-nitro-phenyl)-5,5-bis(acetylthiomethyl)-1,3-dioxane (**74**) has an anancomeric structure, having in ^{1}H NMR spectrum the following signals: at δ=2,09 ppm a singlet for the *equatorial* methyl group located at the position 5 (from the thioacetate group); at δ=2,11 ppm a singlet for the *axial* methyl group located at the position 5 (from the thioacetate group); at δ=2,85 ppm a doublet for the *axial* protons from the positions 4(6) with the geminal coupling constant $^2J_{4(6)ax\text{-}4(6)eq}$=14,5 Hz; another doublet at δ=3,04 ppm for the *equatorial* protons from the positions 4(6) with the geminal coupling constant $^2J_{4(6)eq\text{-}4(6)ax}$=14,5 Hz. At δ=4,05 ppm is a singlet for the methylene protons from the thioester *equatorial* group located at the position 5; at δ=4,64 ppm is the methylene protons singlet from the *axial* -CH_2-S- group from the position 5 and at δ=5,17 ppm is the singlet of the *axial* proton from the position 2. The signal assignment of the protons from the aromatic area was done by the COSY spectrum. Thus, at δ=7,55 ppm is the signal of the aromatic proton from the position 5′ which is splitted into a triplet, since it is

involved into two *orto* coupling – the first coupling is with the proton located at the position 6′ (which also has a splitted signal in a doublet at δ=7,87 ppm) and the second coupling with the proton from the position 4′ (with a splitted signal into a doublet at δ=8,19 ppm). The aromatic proton from the position 2′ has the signal at δ=8,36 ppm (Figure 51).

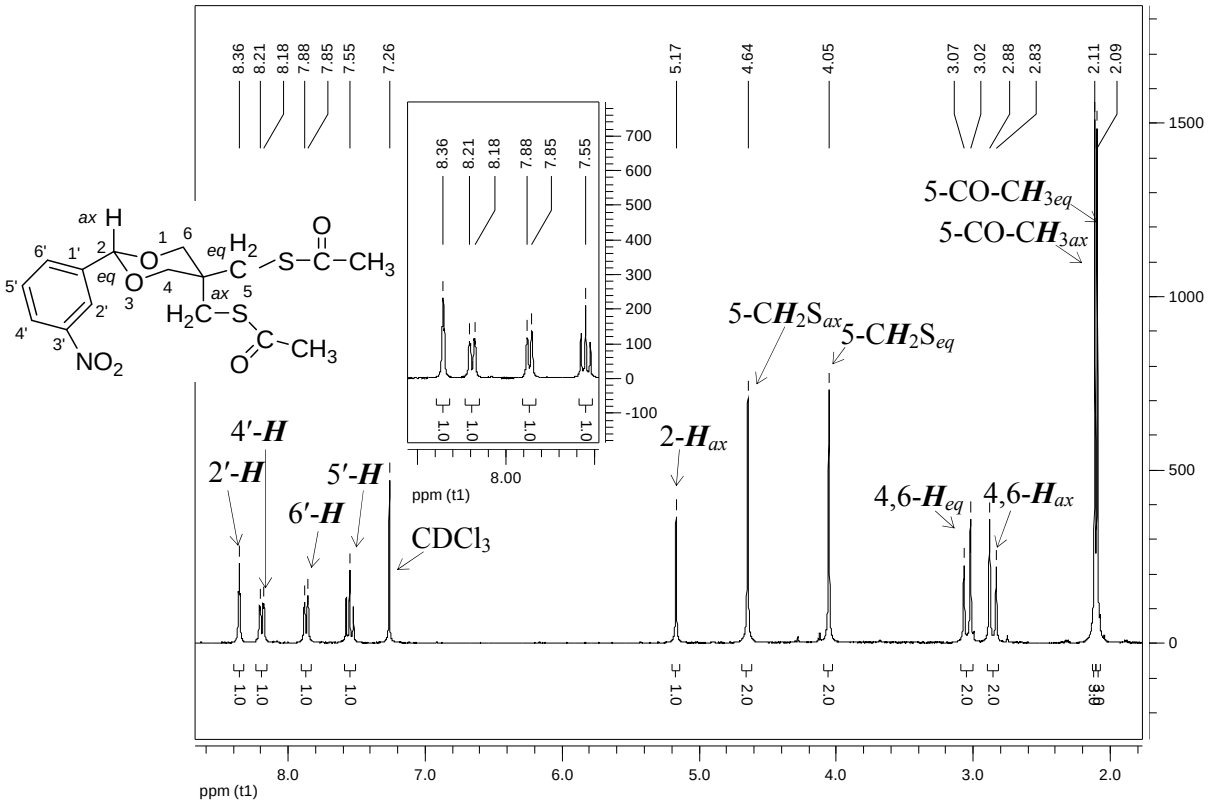


Figure 51. ^{1}H NMR spectrum of compound **74** at 300 MHz in $CDCl_3$

With the help of COSY and HETCOR spectra, was done the signal assignment from the ^{13}C NMR spectra recorded in $CDCl_3$ at 90 MHz. At δ=20,73 ppm is the signal for the carbon atom of the *equatorial* methyl group located at the position 5 (from the thioacetate group); at δ=20,80 ppm is the signal of the carbon atom of the *axial* methyl group located at the position 5; at δ=30,87 ppm is the acetone signal; at δ=32,03 ppm is the C5 signal; at δ=35,08 ppm is the signal for the C4 and C6; at δ=50,19 ppm is the signal of the tertiary carbon C2. The methyl carbon atom from the *equatorial* thioester group CH_2-S-CO from the position 5 resonate at δ=62,72 ppm, and the *axial* resonate at δ=67,52 ppm. At δ=123,04 ppm resonate the tertiary carbon C2′ from the aromatic group located at the position 2 ; at δ=123,64 ppm resonate carbon C4′; at δ=129,85 ppm is the C5′ carbon; at δ=133,95 ppm is C6′ carbon; at δ=140,02 ppm is the quaternary carbon C1′, and at δ=148,35 ppm is the quaternary carbon C3′. The carbonyl group carbon atom from the *equatorial* thioester group has signal at δ=170,52 ppm, and the carbon from the *axial* thioester group is at δ=170,54 ppm (Figure 52).

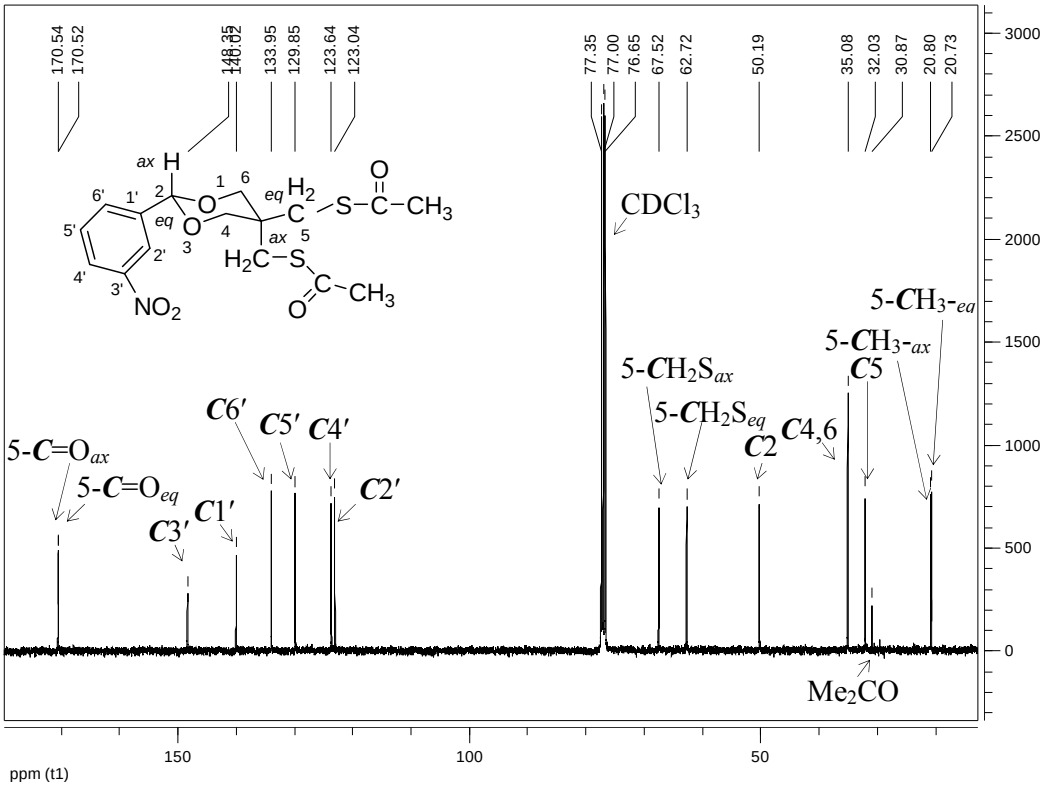


Figure 52. ^{13}C NMR spectrum of compound **74** at 90 MHz in $CDCl_3$

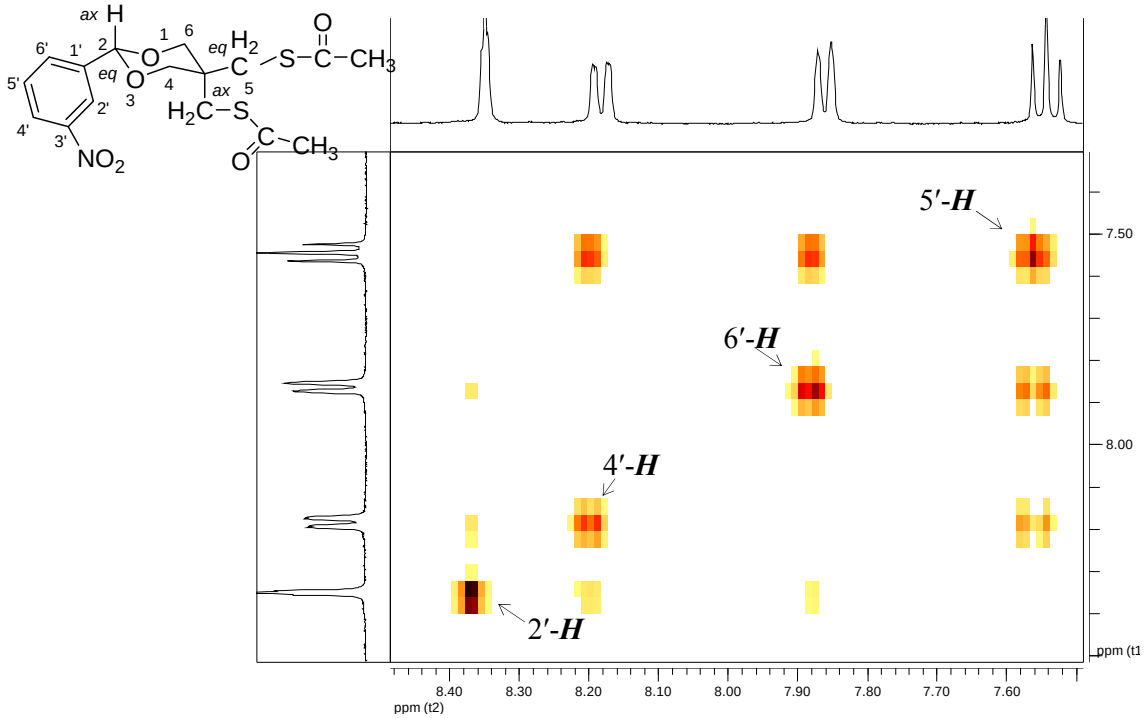


Figure 54. COSY spectrum of compound **74** at 500 MHz in $CDCl_3$-detail for aromatic protons

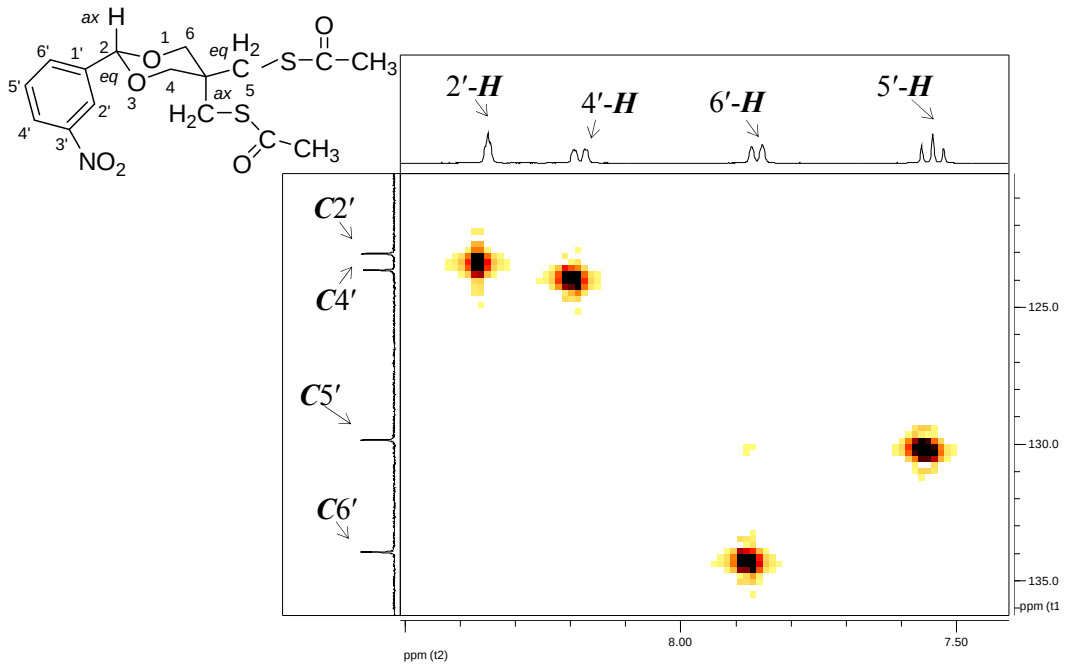


Figure 56. HETCOR spectrum of compound **74** at 500 MHz-H and 125 MHz-C in $CDCl_3$-detail for the aromatic area

For the compound 3,9-bis(3′-nitrophenyl)-8,10-dioxa-2,4-dithia-spiro[5.5]undecane (**77**) the positions 1 and 5 are diastereotopic, due to the *axial* and helical chirality of the molecule. Positions 7 and 11 are also diastereotopic. In every case, there is an *axial* and an *equatorial* proton. In the ^1H NMR spectrum recorded at 250 MHz in $CDCl_3$ (Figure 64) are the corresponding signals for the proposed anancomeric structure: a doublet of doublets at δ=2,54 ppm for the *equatorial* proton from the position 1 with $^2J_{1eq\text{-}1ax}$=14,3 Hz and $^4J_{1eq\text{-}5eq}$= 1,8 Hz (coupling in W); a doublet at δ=2,90 ppm for the *axial* proton located at the position 1 with $^2J_{1ax\text{-}1eq}$=14,3 Hz (geminal coupling is confirmed by the „roof effect"); a doublet of doublets at δ=3,05 ppm for the *axial* proton located at position 5 with $^2J_{5ax\text{-}5eq}$=14,3 Hz and $^4J_{5ax\text{-}1eq}$= 1,9 Hz; another doublet of doublets δ=3,59 ppm for the *equatorial* proton from position 5 with $^2J_{5eq\text{-}5ax}$=14,2 Hz and $^4J_{5eq\text{-}1eq}$= 2,1 Hz; a doublet of doublets at δ=3,71 ppm for the *axial* proton at position 7 with $^2J_{7ax\text{-}7eq}$=11,6 Hz and $^4J_{7ax\text{-}11eq}$= 1,9 Hz; a doublet at δ=3,88 ppm for the *axial* proton from the position 11 with $^2J_{11ax\text{-}11eq}$=11,5 Hz; another doublet of doublets at δ=3,99 ppm for the *equatorial* proton located at position 11 with $^2J_{11eq\text{-}11ax}$=11,4 Hz and $^4J_{11eq\text{-}7eq}$= 2,7 Hz; another doublet of doublets at δ=5,30 ppm for the *equatorial* proton in position 7 with $^2J_{7eq\text{-}7ax}$=11,6 Hz and $^4J_{7eq\text{-}11eq}$= 2,9 Hz. There is a singlet at δ=5,19 ppm for the *axial* proton located at position 3, and at δ=5,55 ppm a singlet for the *axial* proton located at position 9 (more deshielded due to the deshielded effect of oxygen atoms through space) (Figure 65).

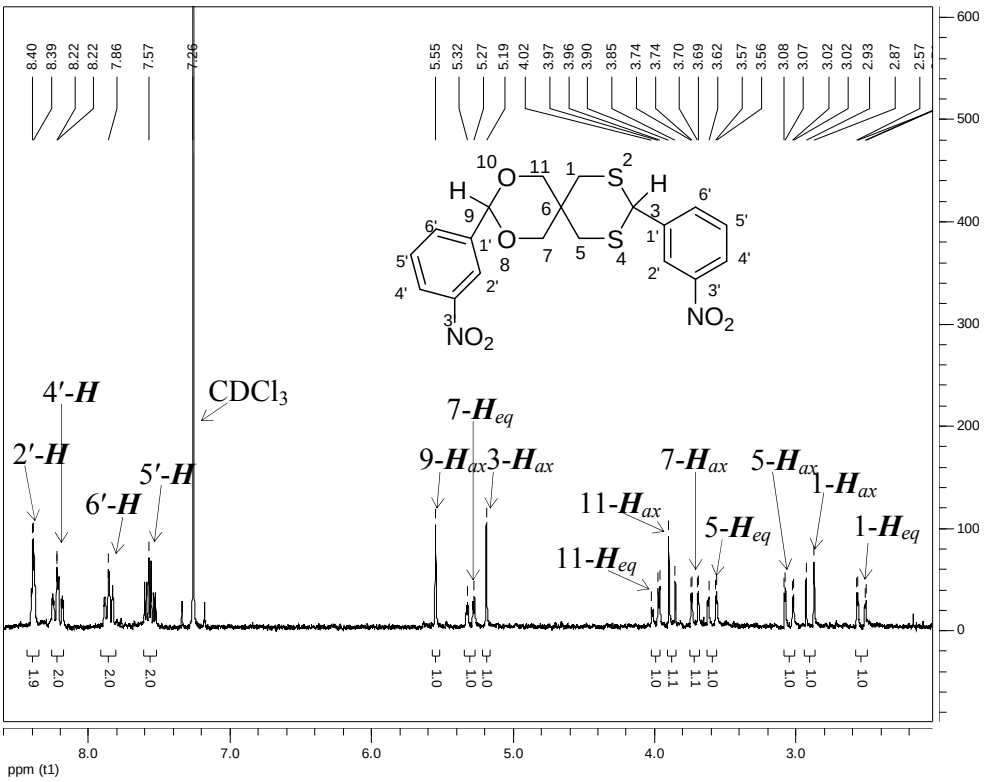


Figure 64. ^{1}H NMR spectrum of compound **77** at 250 MHz in $CDCl_3$

In the aromatic area [54] appears the specific model of *meta*-nitro-phenyl group, with the mention that every signal corresponding to the proton belonging to the *meta*-nitro-phenyl group located at the position 3 is overlapped over one signal of the similar group from the position 9. Thus at δ=7,56-7,57 ppm exist the two signals for the proton from position 5′ of the *meta*-nitro-phenyl group located in positions 3 and 9 (J=J'=8,0 Hz); at δ=7,84-7,87 ppm (J=7,7 Hz) the doublet of the proton in position 6′ for the groups from the positions 3 and 9 (overlapped in a pseudo-triplet); at δ=8,21-8,22 ppm (J=8,2 Hz, J'=1,0 Hz) the triplet of the proton located at position 4′ for the groups in positions 3, respective 9 (overlapped in a splitted pseudo-triplet),and at δ=8,39-8,40 ppm is the signal for the proton at the position 2′ for the *meta*-nitro-phenyl groups located at positions 3, respective 9 (Figure 66).

[54] **Mihiş, A.**; Golban, M. L.; Cismaş, C.; Terec, A; Bogdan, E.; and Grosu, I., in preparation.

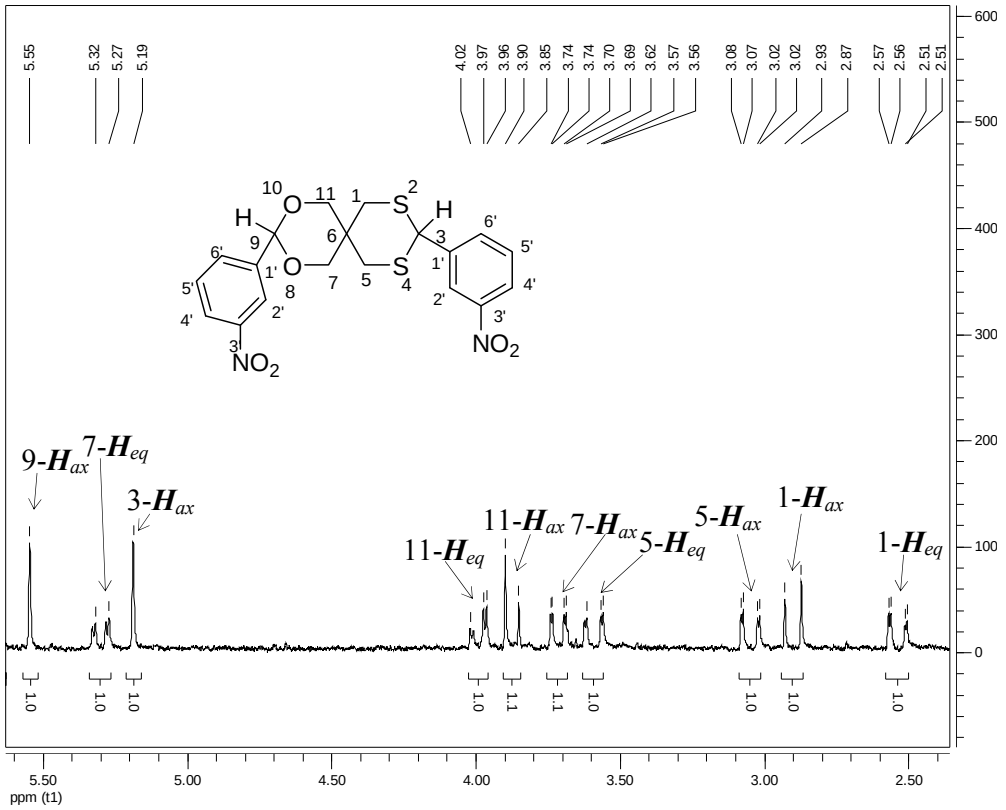


Figure 65. ^{1}H NMR spectrum of compound **77** at 250 MHz in $CDCl_3$-detail for heterocyclic area

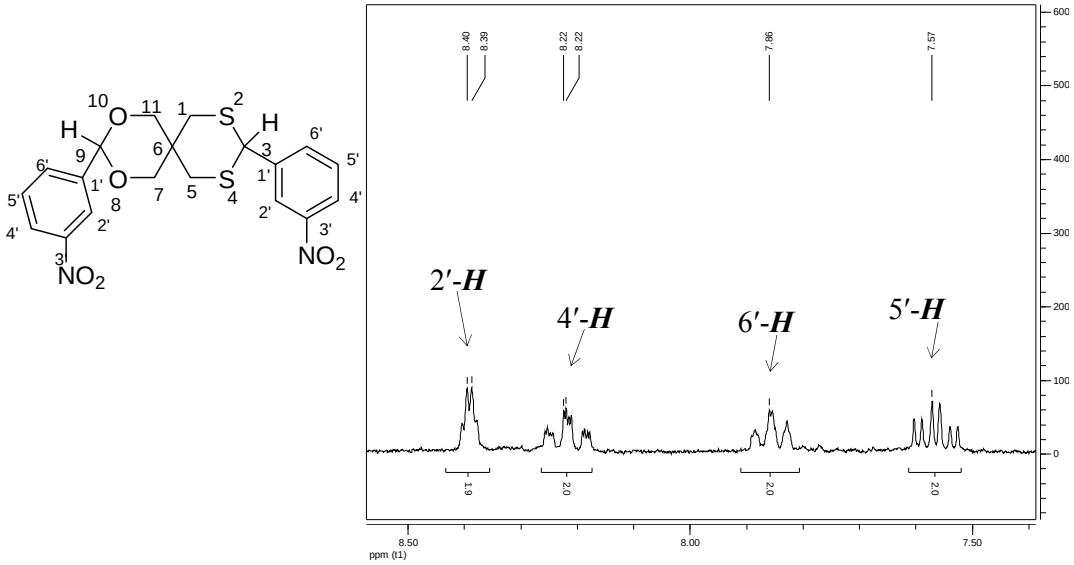


Figure 66. ^{1}H NMR spectrum of compound **77** at 250 MHz in $CDCl_3$ – detail for the aromatic area

PART VI. CONCLUSIONS

The theoretical part of the thesis contains the description of the synthesis, stereochemistry, structural analysis and uses of perhydro-diazines. The perhydro-diazine cycles enters in the structure of many natural compounds, of some drugs used in the treatment of many diseases, or in some derivatives with applications in the analytical chemistry.

The practical part enclose the synthesis and the structural analysis for:

- seven new compounds of 1,3-dioxane derived of terephthalic aldehyde, a new compound 1,3-dioxane 5-methyl-2,2-disubstituted, six new compounds 5,5-Bis(bromomethyl)-2-substituted 1,3-dioxane, five new spiranic compounds with dioxane cycles

- two new intermediates dithioacetic and a new intermediate 1,3-dioxane dithiol which can be used for the synthesis of the spiranic compounds with different heterocycles or with different heteroatoms, two new dioxadithiane spiranes

The structural analysis was accomplished by the X-ray diffraction (for a compound), ^{1}H and ^{13}C NMR spectra at room temperature, COSY spectra, HMQC spectra, a HETCOR spectrum, and even the mass spectrometry (EI-MS, ESI-MS).

The 1,3-dioxane compounds obtained by terephthaldialdehyde present anancomeric structures, with phenylene group in the *equatorial* position, the dioxane cycles having a *chair* conformation. In the case of the presence of different substituents located at the positions 5(5′) are possible three diastereoisomers: *trans*, *trans*, *cis*, *cis* and *trans*, *cis* (according to the relative positions in regard to the 1,3-dioxane cycles of the bulky substituent and to the aromatic group).

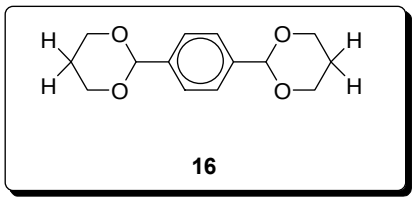
2,2-diphenyl-5-methyl-1,3-dioxane has an anancomeric structure, in which the methyl group in position 5 has an *equatorial* orientation. Also, 5,5-Bis(bromomethyl) 2-substituted 1,3-dioxanes has anancomeric structures, the bulky group taking the *equatorial* position.

The studied spiranic compounds have flexible structure, presenting *axial* and *helical* chirality, and they can be found as two separable enantiomers which cannot transform one into another due to conformational processes, fact proven by HPLC chromatography done on chiral cromatographic column. The flexible structure of the spiranic compounds was confirmed by the ^{1}H and ^{13}C NMR spectra done at variable temperature (in the 293 K-164 K range).

The dithioacetic 1,3-dioxane compounds and the dithiolic 1,3-dioxane intermediate present anancomeric structure, the aromatic group having *equatorial* orientation, and they are precursors for the synthesis of dioxa-dithianic and dioxathianic spiranes. The dioxa-dithianic spiranic compounds present anancomeric structure, the positions 1 and 5, respective 7 and 11 being diastereotopic due to the molecule chirality.

ANNEXE II

List of new synthesized compounds



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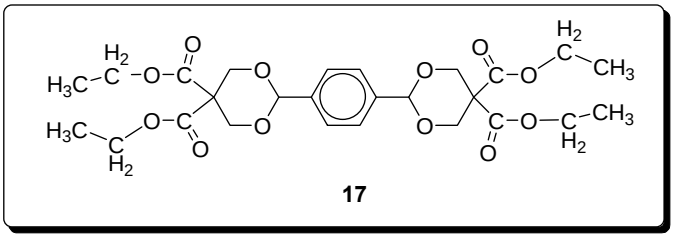

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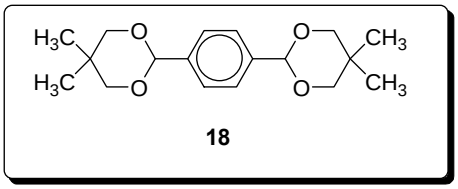

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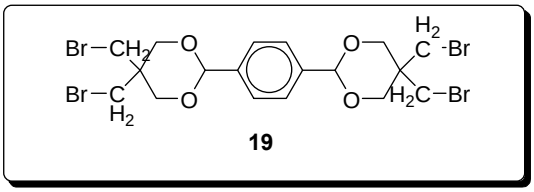

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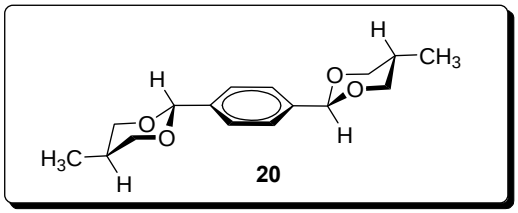

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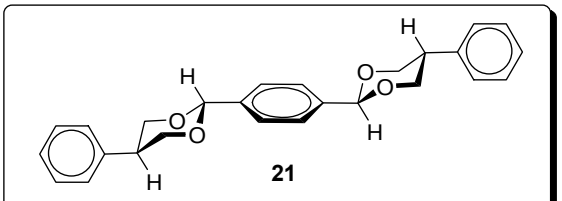

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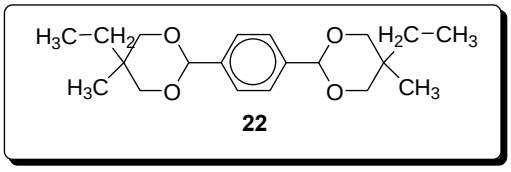

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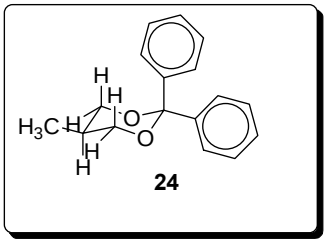

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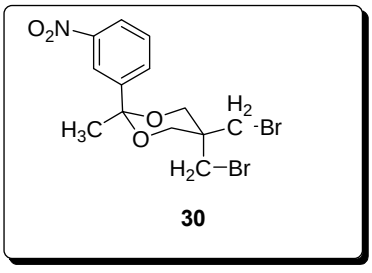

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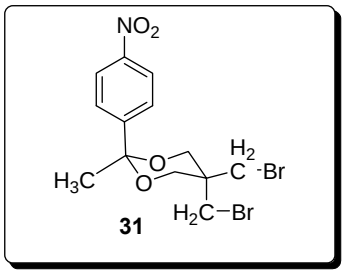

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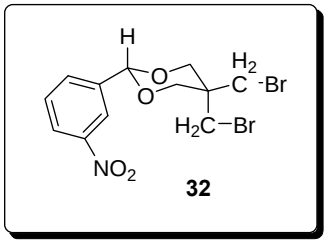

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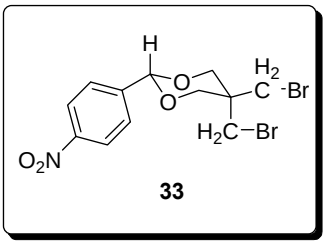

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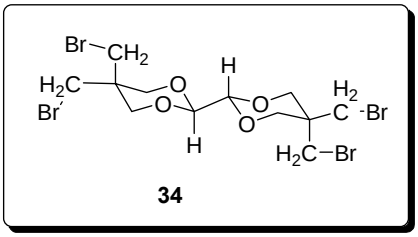

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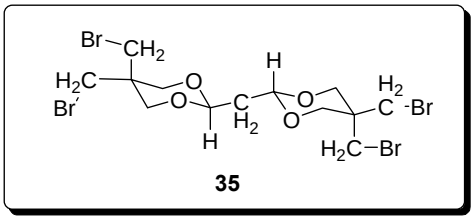

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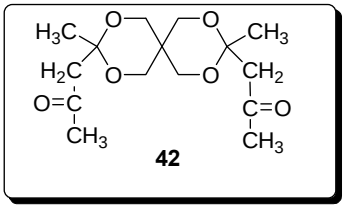

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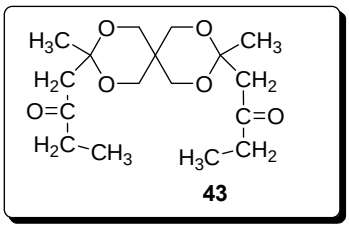

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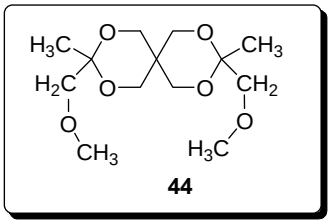

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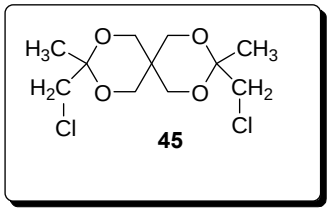

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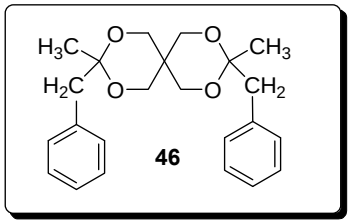

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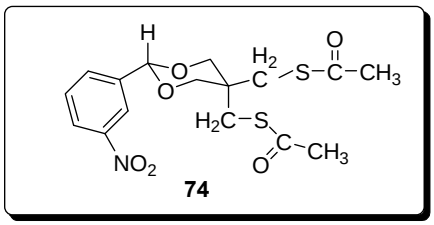

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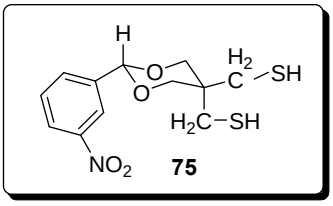

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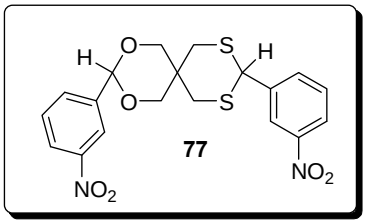

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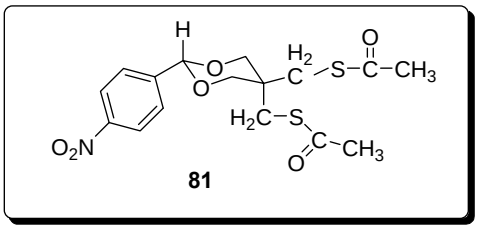

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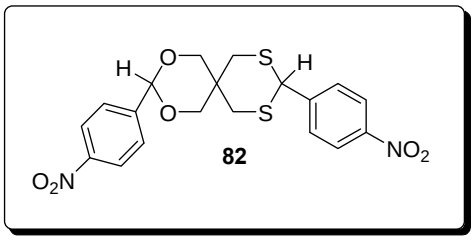

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