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CONTRIBUTIONS TO THE SYNTHESIS AND
STEREOCHEMISTRY OF NEW: 1-THIA-3-OXA; 1,3-DIOXA;
1-OXA-3-AZA CYCLOHEXANE DERIVATIVES

Ph.D. Thesis

Abstract

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PART A: SYNTHESIS, STRUCTURAL ANALYSIS AND REACTIVITY OF PERHYDRO-1,3-OXAZINES DERIVATIVES—literature review

I. General Introduction

II. Synthesis
   II.1. Direct Reaction Between γ-aminoalcohols and Carbonyl Derivatives
   II.2. Reaction between carbonyl derivatives and 1,3,2-oxaazaborinani
   II.3. Reduction of dihydro-1,3-oxazines derivatives
   II.4. Reaction between 1,3-diol and 1,3,5-hexahydro-s-triazine
   II.5. Synthesis by isoxazolidines and isoxazolidinium salts
   II.6. Other synthesis

III. Structure of the main perhydro-1,3-oxazines ring
   III.1. Ring-chain tautomerism of perhydro-1,3-oxazines
      III.1.1. Solution ring-chain tautomerism
      III.1.2. Gas phase ring-chain tautomerism
      III.1.3. Solid phase ring-chain tautomerism
   III.2. Perhydro-1,3-oxazines ring inversion
      III.2.1. 1H-NMR spectral data for perhydro-1,3-oxazines
      III.2.2. 13C-NMR spectral data for perhydro-1,3-oxazines
   III.3. Pyramidal nitrogen inversion in perhydro-1,3-oxazines
      III.3.1. Ab initio data
      III.3.2. Dipol moment
      III.3.3. Infrared spectra
      III.3.4. 1H-RMN spectra

IV. Reactivity
   IV.1. Reaction with ring opening
   IV.2. Reaction without ring opening
   IV.3. Asymmetric Syntheses Based on perhydro-1,3-Oxazines

V. References

PART B: SYNTHESIS AND STRUCTURE OF 1-OXA-3-AZA CYCLOHEXANE DERIVATIVES (PERHYDRO-1,3-OXAZINES)

I. Stereochemistry of dispiro-compounds with six-membered Rings
   I.1. Introduction
   I.2. Contributions to the synthesis and stereochemistry of new dispiro
derivatives containing perhydro-1,3-oxazines units
   I.3. Contributions to the synthesis and stereochemistry of new dispiro
derivatives containing N-tosyl-perhydro-1,3-oxazines units

II. Synthesis, Stereochemistry and ring-chain tautomerism of the bis(perhydro-
1,3-oxazines)
   II.1. Introduction
   II.2. Synthesis, Stereochemistry and ring-chain tautomerism of the new N-
unsubstituted bis(perhydro-1,3-oxazines)
   II.3. Synthesis and Stereochemistry of the new N-substituted bis(perhydro-
1,3-oxazines)

III. Experimental part
IV. Conclusions
V. References
PART C: SYNTHESIS AND STRUCTURE OF 1-THIA-3-OXA CYCLOHEXANE DERIVATIVES (1,3-OXATHIANES)

I. Synthesis and stereochemistry of new mono spiro-1,3-oxathianes
   I.1. Introduction
   I.2. Stereochemistry of mono spiro-1,3-oxathianes
   I.3. Synthesis of new mono spiro-1,3-oxathianes
   I.4. Stereochemistry of new mono spiro-1,3-oxathianes
      I.4.1. Stereochemistry of new mono spiro-1,3-oxathianes with semiflexible structures
      I.4.2. Stereochemistry of new mono spiro-1,3-oxathianes with anancomeric structures

II. Synthesis and stereochemistry of some new 1,3-oxathianes derivatives
   II.1. Introduction
   II.2. Synthesis of some new 2,5-substituted 1,3-oxathiane derivatives
   II.3. Stereochemistry of some new 2,5-substituted 1,3-oxathiane derivatives

III. Experimental part
IV. Conclusions
V. References

PART D: SYNTHESIS AND STRUCTURE OF 1,3-DIOXACYCLOHEXANE DERIVATIVES (1,3-DIOXANE)

I. Stereochemistry of 1,3-dioxane derivatives
   I.1. Stereochemistry of 2-alchyl 1,3-dioxane derivatives
   I.2. Stereochemistry of 2-aryl 1,3-dioxane derivatives
   I.3. Stereochemistry of 1,3-dioxane derivatives of 1,4-diacetylbenzene

II. Synthesis and stereochemistry of some new 1,3-dioxane derivatives of 1,3-diacetylbenzene
   II.1. Synthesis of some new 1,3-dioxane derivatives of 1,3-diacetylbenzene
   II.2. Stereochemistry of some new 1,3-dioxane derivatives of 1,3-diacetylbenzene

III. Experimental part
IV. Conclusions
V. References
CONCLUSIONS
LIST OF PRODUCTS

Key words: perhydro-1,3-oxazines, 1,3-oxathianes, 1,3-dioxane, ring-chain tautomerism, chirality diastereomers, stereochemistry, NMR spectra, conformational equilibria, heterocycles, anancomeric.
INTRODUCTION

The research work presented in this Ph.D. Thesis is structured in four main parts. The first chapter (Part A) is dedicated to the exhaustive literature investigation of the perhydro-1,3-oxazines 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 perhydro-1,3-oxazines derivatives (Part B), in the field of the synthesis and stereochemistry of 1,3-oxathianes (Part C) and in the field of bis(1,3-dioxane-2-yl) derivatives (Part D).

The studies on spiro compounds were focused on the synthesis and the structural investigations of the first reported dispiro perhydro-1,3-oxazines I and bis(perhydro-1,3-oxazines) II and of investigated mono spiro-1,3-oxathianes III and of the 2,5-substituted 1,3-oxathianes IV derivatives. The aims of the research were also synthesis and the structural investigated 1,3-dioxane derivatives of 1,3-diacetylbenzene V.

The possibility to describe the peculiar structural features of the investigated monospiranes and dispiranes as well as structural features of the investigated bis(perhydro-1,3-oxazines) using the original stereochemistry descriptors proposed in previous works and the versatility of 1,3-dioxane derivatives of 1,3-diacetylbenzene motivated our research in these fields.
PART B: SYNTHESIS AND STRUCTURE OF 1-OXA-3-AZA CYCLOHEXANE DERIVATIVES (PERHYDRO-1,3-OXAZINES)

I. Stereochemistry of dispiro-compounds with six-membered rings

The marginal rings (A and C, Scheme 2) in dispiro[5.2.5.2]hexadecane (or in heterocyclic analogous) show “syn” [on the same side of the plane C₁C₅C₆ (C⁹C¹⁰C¹⁴) 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. The syn or anti disposition of the rings A and C with reference to ring B in dispirane can be deduced from the value of the dihedral angle C₁C₂C₄C₅/C¹⁰C¹¹C¹₃C¹₄. 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° the syn disposition of rings A and C must be taken into account.

\[ \text{Scheme 2} \]

I.2. Synthesis and stereochemistry of new dispiro derivatives containing perhydro-1,3-oxazines units

New dispiro perhydro-1,3-oxazine derivatives 1 and 2 were obtained by the condensation reaction of some cyclohexanones with 3-amino-1-propanols (Scheme 3).

\[ \text{Scheme 3} \]
The two dispiro-1,3-oxathianes 1 and 2 exhibit flexible structure as both 1,3-oxathiane rings and the carbocycle are flipping. A fast equilibrium like the one described in Scheme 4 for trispirane occurs between the 6,9-syn and 6,9-anti structures. The reaction mixture consisted of two diastereomers (cis and trans)

![Scheme 4](image)

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 5) 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 (V ax,ax) enantiomer. The diastereomeric equilibrium 5(A) results into configuration P 6,9-syn (IV eq,eq), the enantiomer of the structure M 6,9-syn (IV eq,eq).

![Scheme 5](image)

Equilibration of cis isomer (Scheme 5) takes place through the same stages as that of isomer trans. The equilibrium 2(B) is a homomeric inversion. In fact, there is one pair of enantiomers (I eq,ax (ax,eq) M and P) that trans form themselves into each other through an enantiomeric equilibration as the result of the inversion of the 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.
The $^1$H NMR spectra of compound 1 consisting of both isomers (mixture cis and trans isomers), show one signal for the protons near the oxygen at $\delta = 3.87-3.74$ ppm, respectively two signals doublets of doublets overlapped for the protons near the nitrogen atom at $\delta = 3.19$ ppm and 2.98 ppm. The protons from the methyl groups at positions 3, 7, 8, 12, 15, 16 exhibit a multiplet at $\delta = 1.4-2$ ppm (overlapped peaks for both isomers).

The ratio between cis and trans isomers is 1:2,8 has been determined from the intensities of the specific signals recorded in $^1$H-NMR spectrum.

### I.3. Synthesis and stereochemistry of new dispiro derivatives containing N-tosyl perhydro-1,3-oxazines units

New dispiro perhydro-1,3-oxazine derivatives 4 and 5 were obtained by the condensation reaction of some cyclohexanones with N-tosyl-3-amino-1-propanols (Scheme 9).
The reaction between 3-amino-1-propanols and tosylchloride led to the corresponding N-tosyl-3-amino-1-propanols (Scheme 8):

\[
\begin{align*}
\text{OH} & \quad \text{NH}_2 \\
\text{Cl} & \quad \text{SO}_2 \quad \text{CH}_3 \\
\text{Et}_3\text{N} & \quad -50 \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

The stereochemistry of dispiro-N-tosyl-perhydro-1,3-oxazine derivatives is similar to those of dispiro N-unsubstituted perhydro-1,3-oxazines.

II. Synthesis, Stereochemistry and ring-chain tautomerism of the bis(perhydro-1,3-oxazines)

II.2. Synthesis, stereochemistry and ring-chain tautomerism of the new N-unsubstituted bis(perhydro-1,3-oxazines)

This work is the first to report synthesis, stereochemistry and ring-chain tautomerism of N-unsubstituted bis(perhydro-1,3-oxazines).

New N-unsubstituted bis(perhydro-1,3-oxazines (6, 7 and 8) were obtained by the condensation reaction of 3-amino-1-propanols with several aromatic dicarbonyl compounds (Scheme 10).

The structures of numerous saturated N-unsubstituted perhydro-1,3-oxazines can be characterized by the ring-chain tautomeric equilibria of the ring perhydro-1,3-oxazines and the corresponding Schiff bases; this is often exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry.
The ring-chain tautomeric equilibria establishment can be detected by corresponding signals in the $^1$H-NMR\textsuperscript{11-14} and $^{13}$C-NMR\textsuperscript{15} spectra from both tautomeric forms: protons and carbon atoms from C(2) of the ring form respective atoms of the chain form.

For compound 6 due to the two heterocycles the tautomeric forms I, II and III can occur (Scheme 11).

The proportions of chain and ring forms of the tautomeric equilibria are usually determined by integration of the well-separated O-CH-N (ring) and CH-Ar (chain) proton singlets in the $^1$H-NMR spectra. In order to achieve, the samples are dissolved in an appropriate deuterated solvent and the solutions are allowed to stand at ambient temperature for some period before the $^1$H-NMR spectra are run.

As an example, the $^1$H-NMR spectrum of compound 6 in CDCl$_3$ (Figure 4) exhibits distinct signals for every structure. Aromatic protons display a singlet for structure I at $\delta = 7.45$ ppm and the signal corresponding to the protons at positions 2, 2’ appear as singlet at the chemical shift $\delta = 5.17$ ppm. For the structure II aromatic protons display a singlet at $\delta = 7.72$ ppm 2, 2’-protons appear as singlet at $\delta = 8.27$ ppm. Whereas the aromatic protons of structure III which is unsymmetrical appear as doublets of doublets at $\delta = 7.66$ ppm and $\delta = 7.52$ ppm, respectively with a coupling constant $J=8.02$ Hz, the proton belonging to the position 2 is found as singlet at $\delta = 5.14$ ppm and the imine proton at 2’ position appears as singlet at the chemical shift $\delta = 8.23$ ppm.
All the investigated compounds show ananomeric structures. The conformational equilibria for compounds 6 and 7 (Scheme 14) are shifted towards the conformers having the substituents at positions 2(2’)-the aromatic ring Z is in equatorial orientation in both heterocycles.

![Diagram showing conformational equilibria of compounds 6 and 7](image)

R=H, Z= -C₆H₄-meta or para

Scheme 14

II.3. Synthesis and stereochemistry of the new N-substituted bis(perhydro-1,3-oxazines)

New N-substituted bis(perhydro-1,3-oxazines) were obtained by the condensation reaction of several corresponding aromatic dicarbonyl compounds with N-tosyl-3-amino-1-propanols²⁰ (Scheme 16).
In this compounds ring-chain tautomeric equilibria is not possible because of the substitution of the nitrogen atoms. In these cases the NMR spectra will be more simple (Figure 7). As an example, the $^1$H-NMR spectrum of compound 9 in CDCl$_3$ (figure 7), the aromatic protons at the tosyl groups appear as doublets of doublets at $\delta = 7.89$ ppm and $\delta = 7.37$ ppm and the aromatic protons from the benzene ring appear as singlet at $\delta = 7.50$ ppm.

For the protons belonging to the positions 2(2') of the heterocycle a singlet is observed at $\delta = 6.68$ ppm. The signals corresponding to the protons at positions 6(6') appear as doublets of doublets overlapped at $\delta = 3.86$ ppm and the signal of the protons at positions 4(4') is found as doublets of doublets overlapped at $\delta = 3.58-3.75$ ppm. The axial protons at positions 5 and 5' appear as doublets of doublets overlapped at $\delta = 3.30$ ppm. It is more deshielded than the signal of the equatorial protons at the same positions that appear as doublets of doublets overlapped at $\delta = 1.43$ ppm.
PART C: SYNTHESIS AND STRUCTURE OF 1-THIA-3-OXA CYCLOHEXANE DERIVATIVES (1,3-OXATHIANES)

This work is the first to report the synthesis of the 1-oxa-5-thiaspiro[5.5]undecane, a new class of organic compounds.

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\(^\text{15}\) 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 allenes (b), are considered as a classical example of axial chirality; as far as different geminal groups are found at both ends of the system (X≠Y).

![Scheme 2](image)

The spiro junction\(^\text{16-19}\) of the rings forces the disposal of the substituents in orthogonal plans and this provokes the dissymmetry of the structure. Other spiro derivatives of type (c) were also put into this category of compounds with axial chirality by the assumption that the rapid inversion of the rings leads to an average planarity and a proper substitution pattern 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 3](image)

Studying Dreiding\(^\text{20-22}\) models and by means of NMR spectra at low temperature, H. Dodziuk 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 \( C_1 \) and \( C_3 \) and \( C_2 \) and \( C_4 \), respectively are identical, but \( C_1 \) is enantiomeric with \( C_2 \) (and \( C_3 \) with \( C_4 \)). 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 \( C_{a,a,a,a} \) (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. The chirality of the chair conformation of 1,3-oxathiane has been reported, the flipping of the heterocycle results into an enantiomeric interconversion.

Specification of the configurations (R or S) of 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 page); the order of priority of the ligands is established according to the rules of Cahn, Ingold and Prelog.

Scheme 7

I. Synthesis and stereochemistry of new mono spiro-1,3-oxathianes

New spiro-1,3-oxathiane derivatives 1-3 were obtained by the condensation reaction of some cyclohexanones with 3-mercapto-1-propanols (Scheme 9).

Scheme 9

9-R = CH\(_3\) (1)
8-R = CH\(_3\) (2)
7-R = CH\(_3\) (3)
I.4.1. Stereochemistry of new mono spiro-1,3-oxathianes with semiflexible structures

The present work is also the first to report the existence of the cis-trans isomerism of spiro-1,3-oxathiane derivatives with semiflexible structure (bearing substituents in the cyclohexane part of the molecule).

Compounds 1 and 2 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 10 and 11). The flipping of the heterocycle in the cis and trans isomers of 1 represents an enantiomeric inversion (Scheme 10)

```
Scheme 10
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while in the cis and trans isomers of 2 it results in diastereoisomeric equilibria (Scheme 11):

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Scheme 11
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The conformational behaviour of these compounds was deduced from the data of NMR spectra recorded at room temperature.

I.4.2. Stereochemistry of new mono spiro-1,3-oxathianes with anancomeric structures

The cis and trans isomers of 3 exhibit anancomeric structures (Scheme 12), 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. Due to the flipping of the heterocycle the conformational equilibria 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).

\[ \text{Scheme 12} \]

The anancomeric structure of these derivatives in solution is confirmed by the \(^1\)H-NMR spectra (at \( r.t. \)) which exhibit different signals for the axial and equatorial protons at positions 2 and 4 corresponding to the two diastereoisomers of cis and trans isomers (Scheme 12). 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.

It is interesting to consider the region of the spectrum where appear of protons the heterocycles appear. The signals (Figure 2) corresponding to the axial protons at position 4 for both diastereoisomers appear as doublets at \( \delta \) 3.96 ppm and \( \delta \) 3.92 ppm, respectively. The signals of the equatorial protons at the same positions exhibit doublets of doublets overlap at \( \delta \) 3.82 ppm and \( \delta \) 3.79 ppm. The shape of the signal is determined by coupling with the geminal axial proton and the W coupling with the equatorial proton at position 2.

\[ \text{Figure 2 (}^1\text{H-NMR spectrum –fragment- of compound 3 (a)-one isomer, (b)-other isomer)} \]

The signals (Figure 3) corresponding to the axial protons at position 2 for both diastereoisomers (cis and trans) appear as doublets at \( \delta \) 2.91 ppm and \( \delta \) 3.35 ppm,
respectively. The signals of the equatorial protons at the same positions are well-resolved as doublets of doublets at δ 2.95 ppm and δ 3 ppm. The shape of the signal is determined by coupling with the geminal axial proton and the W coupling with the equatorial proton from position 4.

![Figure 3](image-url)  
*Figure 3* (1H-NMR spectrum—fragment-of compound 3 (a)-one isomer, (b)-other isomer)

### II. Synthesis and stereochemistry of some new 1,3-oxathianes derivatives

The stereochemistry of 1,3-oxathiane derivatives\(^{1-5}\) is less studied than the stereochemistry of 1,3-dioxanes\(^{6-8}\) or 1,3-dithianes\(^{2,9}\), mainly due to the relatively difficult access to 3-mercapto-1-propanol synthones and to the complex stereochemistry of the heterocycles bearing different heteroatoms in the ring.

#### II.2. Synthesis of some new 2,5-substituted 1,3-oxathiane derivatives

2,5-Substituted 1,3-oxathiane derivatives 21-36 were obtained by condensation of mercaptopropanol 20 with several aldehydes and ketones\(^{39}\) (Scheme 21).

![Scheme 21](image-url)

**Scheme 21**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>Compounds</th>
<th>R(_1)</th>
<th>R(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>29</td>
<td>H</td>
<td>1-C(_{10})H(_7)</td>
</tr>
<tr>
<td>22</td>
<td>CH(_2)CH(_3)</td>
<td>CH(_2)CH(_3)</td>
<td>30</td>
<td>H</td>
<td>2- C(_{10})H(_7)</td>
</tr>
<tr>
<td>23</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>31</td>
<td>CH(_3)</td>
<td>C(_6)H(_5)</td>
</tr>
<tr>
<td>24</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>32</td>
<td>CH(_3)</td>
<td>CH(_2)C(_6)H(_5)</td>
</tr>
<tr>
<td>25</td>
<td>H</td>
<td>CH(_3)</td>
<td>33</td>
<td>CH(_3)</td>
<td>p-NO(_2)-C(_6)H(_4)</td>
</tr>
<tr>
<td>26</td>
<td>H</td>
<td>CH(CH(_3))(_2)</td>
<td>34</td>
<td>CH(_3)</td>
<td>1- C(_{10})H(_7)</td>
</tr>
<tr>
<td>27</td>
<td>CH(_3)</td>
<td>C(CH(_3))(_3)</td>
<td>35</td>
<td>CH(_3)</td>
<td>2- C(_{10})H(_7)</td>
</tr>
<tr>
<td>28</td>
<td>H</td>
<td>C(_6)H(_5)</td>
<td>36</td>
<td>CH(_2)CH(_3)</td>
<td>C(_6)H(_5)</td>
</tr>
</tbody>
</table>
II.3. Stereochemistry of some new 2,5-substituted 1,3-oxathiane derivatives

Compounds 21-24 exhibit flexible structures, due to a fast flipping of the 1,3-oxathiane ring (Scheme 24).

The NMR spectra exhibit unique signals for the axial and equatorial orientations of the protons of the heterocycles or of the similar groups located on it. The flipping of the 1,3-oxathiane ring is an enantiomeric inversion.

The recording of different signals of the methylene protons of the –CH2-R (R= CH3, C6H5) groups at position 2 is an interesting feature in the NMR spectra of compounds 21 and 24. These protons exhibit different signals despite the flipping of the 1,3-oxathiane ring and despite missing a conformationally constant chiral element. The careful inspection of structures I-IV obtained using the substitution test (Scheme 25) shows that the replacement of a hydrogen atom at the prochiral centers α and α’ determines besides the transformation of these centers in chiral carbon atoms, the simultaneous transformation of the carbon atom at position 2 in another chiral center. Structures I-IV exhibit two chiral elements and they form two pairs of enantiomers representing two diastereoisomers (like: I, III and unlike: II, IV). In conclusion protons A and C (B and D) are enantiotopic (isochronous in NMR) and A or C and B or D are diastereotopic (exhibit different signals in NMR).
The $^1$H NMR spectrum of compound 24 (Figure 4) due to the flexibility of the heterocycle exhibits a singlet for the methyl groups at position 5 ($\delta=0.93$ ppm) and split singlets (doublets, due to the long range coupling with the protons of the benzyl groups; $^5J=1.7$ Hz) for the protons at positions 4 ($\delta=2.44$ ppm) and 6 ($\delta=3.62$ ppm). The methylene protons of the benzyl groups exhibit two well separated doublets of doublets ($\delta_{A,C}=3.03$; $\delta_{B,D}=3.25$ ppm) with large geminal ($J=14.3$ Hz) and small long range ($^5J=1.7$ Hz) coupling constants. The diastereotopicity ($\Delta\delta_{A,C-B,D}$) for the 2-CH$_2$-protons for compound 24 ($\Delta\delta(24)=0.22$ ppm) is somewhat larger than the same difference for 21 ($\Delta\delta(21)=0.13$ ppm).

The flexible structure of the compound 22 is demonstrated by $^1$H-NMR spectra which due to the flexibility of the heterocycle exhibits a singlet for the methyl groups at position 5 ($\delta=1.03$ ppm). Only singlet signal are observed proving the equivalence of the both methylic groups at positions 4 and 6 at $\delta=2.58$ and $\delta=3.37$ ppm, respectively. The methylene protons of ethyl groups at position 2 have a signal that looks like a triplet ($J=9.0$ Hz) because of the coupling with the vicinal protons. The methylene protons of the ethylic groups have a diastereotopic character. One is disposed in the neighbourhood of the oxygen atom and the other one in the neighbourhood of the sulfur atom. In the NMR spectrum these two protons give different signal (Figure 6) one at a chemical shift $\delta=1.76$ ppm and one at the $\delta=1.93$ ppm. The feature of this signal is a multiplet because of the coupling: first with the geminal proton and in addition with the methyl protons at the vicinal position.
Compounds 25-36 exhibit an ananomeric structures. The conformational equilibria for compounds 25, 26, 28, 29 and 30 are shifted towards the conformer exhibiting the substituent at position 2 in equatorial orientation (V, Scheme 26).

![Scheme 26](image)

The conformational equilibria in compounds 31-36 are shifted towards the conformer bearing the aromatic group in axial orientation (Scheme 27). As in similar 2-alkyl-2-aryl-1,3-dioxane derivatives the aromatic group in compounds 31-36 strongly prefers the axial orientation.

![Scheme 27](image)

The NMR spectra of these compounds (Table 1) exhibit different signals for the axial and equatorial protons of the heterocycle and for the axial and equatorial methyl groups at position 5. As an example the spectrum of compound 28 (figure 7) exhibits more deshielded signals for the axial groups or protons at positions 5 (δ_{5Me(ax)} = 1.40; δ_{5Me(eq)} = 0.97).

![Figure 7](image)

The signals corresponding to the axial protons at positions 4 and 6 of the ring appear as doublets at δ=3.1 and δ=3.49 ppm, respectively. The signals of the equatorial protons at the same positions give rise to doublets of doublets at δ=2.47 ppm and δ=3.78 ppm with a corresponding large coupling constant with the axial proton (^{3}J=13.4 and 11.5 Hz) and a small coupling constant through 4 bonds (^{1}J=2.3 Hz) due to the W(M) disposal of the equatorial
protons at position 4 and 6. For the proton belonging to the position 2 is registered a singlet at \( \delta = 5.66 \) ppm is observed.

The spectrum of compound 26 (Figure 9) is typical for an anancomeric structure. Thus at the chemical shift \( \delta = 0.84 \) ppm a singlet for the protons of the equatorial methyl group in position 5 is observed. The proton of the axial methyl group in position 5 also give rise to a signal at \( \delta = 1.20 \) ppm. The two doublets (\( \delta = 0.98 \) ppm and \( \delta = 1.05 \) ppm) with a coupling constant (\( 3J_{H-H} = 3.0 \) Hz) corresponding to the methyl protons of the i-propylic group at position 2 appear very closed next to each other. These two groups give two different signals because of their diastereotopicity, the splitting is caused by the coupling with methyl protons. The methyllic proton of the i-propylic group appears in the NMR spectra as a multiplet at \( \delta = 1.93 \) ppm because of the coupling with the protons of the methyl groups.

![Figure 9 (\(^1\)H-NMR spectrum of compound 26)](image)

It is interesting to consider the region of the spectrum between 2.2 ppm and 4.5 ppm where the protons of the ring appear (Figure 10). In this area at \( \delta = 2.39 \) ppm, as a doublet of doublets is observed for the signal of the equatorial proton in position 4. The shape of the signal is determined by coupling with the geminal axial proton (\( \tilde{2}J = 13.4 \) Hz) and the W(M) coupling with the equatorial proton at position 6 (\( \tilde{4}J = 2.2 \) Hz). The signal of the axial proton at position 4 at \( \delta = 2.84 \) ppm appears as doublet, this splitting is caused by the coupling with the geminal proton. The signal of the axial proton at position 6 appears a bit dishielded at \( \delta = 3.25 \) ppm. The signal of the equatorial proton at position 6 appears as a doublet of doublets at the chemical shift \( \delta = 3.59 \) ppm. The signal of the proton in position 2 is found as a doublet at 4.42 ppm in the NMR-spectrum. The splitting is due to the coupling with the methine proton of the i-propyl group.
The synthesis and the stereochemistry of an important number of 2,5-substituted-1,3-oxathiane derivatives is reported. The NMR investigations reveal flexible and anancomeric structures. The aromatic group in 2-aryl-1,3-oxathianes prefers the equatorial orientation, while in 2-aryl-2-alkyl derivatives the aromatic group exhibits an axial orientation. The protons of the prochiral center of the substituents located at the position 2 in flipping compounds are diastereotopic and show different signals in NMR spectra.

PART D: SYNTHESIS AND STRUCTURE OF 1,3-DIOXANE CYCLOHEXANE DERIVATIVES (1,3-DIOXANE)

I. Stereochemistry of 1,3-dioxane derivatives

I.2. Stereochemistry of 2-aryl-1,3-dioxane derivatives

The studies on the stereochemistry of 2-aryl-1,3-dioxanes showed the shifting of the characteristic conformational equilibrium of the flipping of the heterocycle (Scheme 2) towards the conformation exhibiting the aromatic group in equatorial orientation.
The studies\textsuperscript{11,13} on the stereochemistry of 2-methyl-2-aryl-1,3-dioxanes showed the shifting of the characteristic conformational equilibrium of the flipping of the heterocycle (scheme 3) towards the conformation exhibiting the aromatic group in axial orientation.

\begin{center}
\textbf{Scheme 3}
\end{center}

The investigations performed by X-ray diffractometry\textsuperscript{13-16} and by room temperature and low temperature NMR spectra\textsuperscript{17-20} showed the high preference of the axial aromatic group for the orthogonal rotamer, either in solid state or in solution (scheme 5).

\begin{center}
\textbf{Scheme 5}
\end{center}

The preference for the orthogonal rotamer in solution was proved by the influence of the magnetic anisotropy of the aromatic ring on the chemical shifts of the protons of the 1,3-dioxane ring and of the equatorial groups at the position 5 of the heterocycle. Indeed the orthogonal disposition of the aromatic substituent determines a significant modification of the magnetic environment in different areas of the molecule resulting in a strong shielding of the protons belonging to the equatorial group at position 5 and of the equatorial protons at positions 4 and 6 of the heterocycle\textsuperscript{22}.

Despite the preference of the axial aromatic group for the orthogonal orientation (this rotamer is more stable than the bisectional one) this group exhibits at \textit{r.t.} a free rotation (the sterical hindrance is not high enough to freeze the rotation of the aromatic substituent). Interesting data about the rotation of the axial aryl group were obtained by dynamic NMR investigations carried out with compounds bearing dissymmetric aromatic\textsuperscript{23} substituents. As an example the o-nitrophenyl derivative exhibits a chiral axis (C\textsuperscript{1'} – C\textsuperscript{2}, the reference groups are the hydrogen atom at position 6' and the NO\textsubscript{2} group at one of the ends and the methyl group and the whole heterocycle at the other end of the chiral axis) (Scheme 6).
Positions 4 and 6 of the 1,3-dioxane ring are diastereotopic in this case but the free rotation of the aromatic ring at \( r.t. \) (enantiomeric inversion) renders equivalent in NMR spectrum of the protons at these positions. The spectra recorded at \( r.t. \) show unique signals corresponding to the average of the magnetic environments of the diastereotopic positions.

At low temperature the rotation of the aromatic ring is frozen and the NMR spectra exhibit different signals for the protons at positions 4 and 6. The values of diastereotopicites are relatively high \([\Delta \delta_{4ax-6ax} = 0.08-0.16 \text{ ppm}}); \ (\Delta \delta_{4eq-6eq} = 0.16-0.27 \text{ ppm})\]25.

Investigations carried out with 1,3-dioxane derivatives obtained from benzenedicarboxaldehydes showed anancomeric structures with the equatorial orientation of the aromatic group in both heterocycles.

II. Synthesis and stereochemistry of some new 1,3-dioxane derivatives of 1,3-diacyetylbenzene

In this work, the results of the investigations concerning the synthesis and the stereochemistry of some new 1,3-dioxane derivatives obtained from 1,3-diacyetylbenzene are reported. The investigated structural aspects are considered of interest due to the complex configurational and conformational behaviour of the target compounds.

II.1. Synthesis of some new 1,3-dioxane derivatives of 1,3-diacyetylbenzene

Two new compounds exhibiting two 1,3-dioxane rings were obtained by the condensation reaction of 1,3-diacyetylbenzene with several 1,3-propanediols (scheme 10).
II.2. Stereochemistry of some new 1,3-dioxane derivatives of 1,3-diacetylbenzene

All the investigated exhibit anancomeric structures, the conformational equilibrium (A $\rightleftharpoons$ B $\rightleftharpoons$ C $\rightleftharpoons$ D) for each 1,3-dioxane ring (Scheme 11) being shifted towards the conformer with axial aromatic substituent. So the 1,3-phenylene group is axial connected to both 1,3-dioxane rings (structure D, Scheme 11).

The dissymmetry of the aromatic substituent introduces the axial chirality of the investigated compounds. The bond between the aromatic group and the saturated heterocycles ($C^2 - C^{1''}$ and $C^2' - C^{3''}$) are chiral axes, the reference groups being the second 1,3-dioxane ring at position 3”” and the H at position 5”” at one of the ends of the considered chiral axis and the methyl group at position 2 and the whole 1,3-dioxane ring at the other end of the chiral axis (Scheme 12).
The compounds can show like (aRaR, aSaS) or unlike (aRaS) isomers. Due to the chirality of the molecule, in the frozen structures, positions 4(4’) and 6(6’) become diastereotopic ones. Due to the fast rotation at rt of the aromatic ring around its bonds with the heterocycles the spectra show a unique set of signals (at mean values of the chemical shifts) and the presence of like and unlike structures and the diastereotopicity of 4(4’) and 6(6’) positions can not be observed.

The anancomeric structure of the compounds leads to the recording, in the rt. NMR spectra, of different signals for the equatorial and axial protons of the 1,3-dioxane rings (position 4(4’) and 6(6’)) and for the axial and equatorial protons of the similar groups located at positions 5(5’).

The anancomeric structure of these derivatives in solution is confirmed by the ¹H-NMR spectra at r.t. As an example, the ¹H-NMR spectrum of compound 7 in CDCl₃ (Figure 1) exhibits signals for the methyl protons of the equatorial ester groups at positions 5(5’) as triplet at δ=0.79 ppm. The signals corresponding to the axial protons of the methyl ester groups appear as triplet at δ=0.91. The signals corresponding to the axial protons at positions 4(4’) and 6(6’) of the heterocycles appear as doublets of doublets δ 3.95 ppm, the signals of the equatorial protons at the same positions as doublet at δ 5.05 ppm

Figure 1 (¹H-NMR spectrum of compound 7)
CONCLUSIONS

1. The complete review (Part A) of perhydro-1,3-oxazine derivatives, structured in 3 chapters dedicated to the synthesis, structural aspects in solid state and in solution, to NMR data and mass spectrometry investigations and to the reactivity of the most important compounds exhibiting this heterocycle was elaborated on the basis of 86 literature references.

2. The synthesis of 4 new dispiro perhydro-1,3-oxazines is reported. The NMR investigations revealed the flexible structure of the reported compounds (Part B). The stereochemistry of these derivatives is discussed on the basis of specific original stereochemical descriptors proposed in our works.

3. The synthesis of 6 new N-unsubstituted bis(perhydro-1,3-oxazine) and N-substituted bis(perhydro-1,3-oxazine) compounds is reported (Part B). The structures of the saturated N-unsubstituted bis(perhydro-1,3-oxazines) can be characterized by the ring-chain tautomeric equilibria of the perhydro-1,3-oxazines ring and the corresponding Schiff bases. The proportions of chain and ring forms of the tautomeric equilibria were determined by integration of the well-separated singlets belonging to O-CH-N (ring) and CH-Ar (chain) protons in the $^1$H-NMR spectra. For the N-substituted bis(perhydro-1,3-oxazines) compounds ring-chain tautomeric equilibria are not possible. All the investigated compounds show anancomeric structures.

4. The synthesis and the structural analysis of 3 semiflexible and anancomeric new spiro-1,3-oxathiane derivatives are reported (Part C). 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 centre 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 NMR experiments.

5. The synthesis and the structural analysis of 16 flexible and anancomeric new 2,5-substituted 1,3-oxathiane derivatives are reported (Part C). An interesting feature in the NMR spectra of the compounds with flexible structure is the recording of different signals for the methylene protons of the –CH$_2$-R (R= CH$_3$, C$_6$H$_5$) groups at position 2. These protons exhibit different signals despite the flipping of the 1,3-oxathiane ring and despite missing a conformationally constant chiral element. The NMR spectra (table 2) exhibit unique signals for the axial and equatorial orientations of the protons of the heterocycles or of the similar groups located on it.
6. The synthesis and the stereochemistry study of 2 new 1,3-dioxane derivatives obtained from 1,3-diacetylbenzene are reported (Part D). The NMR investigations of new 1,3-dioxane derivatives obtained from 1,3-diacetylbenzene revealed the anancomeric structure. The axial position of the aromatic ring for both heterocycles was deduced by the equivalence in NMR spectra of the two heterocycles and by the important shielding of the equatorial protons at positions 4(4') and 6(6') and of the protons belonging to the equatorial groups at the positions 5(5').

7. In this Ph. D. Thesis 31 new compounds are reported and characterized: 4 dispiroperhydro-1,3-oxazines, 6 bis(perhydro-1,3-oxazines), 3 monospiro-1,3-oxathianes, 16 2,5-substituted 1,3-oxathiane derivatives, and 2 1,3-dioxane derivatives obtained from 1,3-diacylbenzene.
Selected References for the original parts B, C and D:

PART B:
20. Synthesis and stereochemistry of some new perhydro-1,3-oxazines and aza-oxa crown ethers starting from aromatic dicarbonyl compounds

**Nan A.**, Ioana Georgeta Grosu, Dora Demeter, Luminița David, Sorin Mager.

PART C:
18. Mursakulov I.G., Ramazanov E.A., Guseinov M.M., Zefirov N.S., Samoshin V.V., Eliel E.L., 
*Tetrahedron*, 1980, **15**, 1885

19. Mursakulov I.G., Ramazanov E.A., Samoshin V.V., Zefirov N.S., Eliel E.L., 
*Zh.Org.Khim.*, 1979, **15**, 2415


22. Dodziuk H., Sitkowski J., Stefanian I., Mursakulov I.G., Guseinov M.M., Kurbanova 

*Monatsh.Chem.*, 2004, **135**, 89

PART D:


Trans. 1*, 1974, 1895


Ann.Chem.*, 1997, 2371


2002, 47, 327