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Synthesis and Stereochemistry of Some Dispiro-1,3-Dioxanes with Axial and Helical Chirality

Ion Grosu[a]*, Sorin Mager[a], Gerard Plé[b] and Eugen Mesaros[a]

[a]"Babes-Bolyai" University, Organic Chemistry Department, 11 Arany Janos str., RO-3400 Cluj-Napoca, România

[b]Université de Rouen et IRCOF, Laboratoire associé au CNRS DO-464, Faculté des Sciences de Rouen, 76821 Mont Saint-Aignan, Cedex, France

Abstract: The stereoisomerism of some dispiro-1,3-dioxanes is discussed in terms of conformational analysis and axial and helical chirality. The influence of the flexibility of the rings on the representative number of isomers and on their NMR spectra is commented. For the 3,12-disubstituted-1,5,10,14-teraoxadispiro[5.2.5.2]hexadecane derivatives displaying a semiflexible structure two configurational diastereomers named "6,9-dispiro-syn" and "6,9-dispiro-anti" were identified. The ratio between these isomers was determined by the diastereotopicity of protons and carbon atoms.

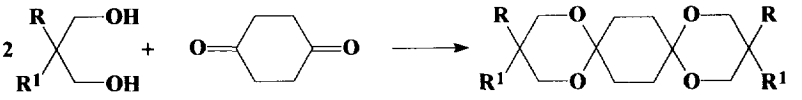
INTRODUCTION

In previous papers[1,2] a new theory concerning the controversial[3-12] problem of the chirality of spiro compounds with six-membered rings was developed. According to the new conception, both axial and helical chirality are assigned to this type of compounds. It was observed that a spiro skeleton displaying six-membered rings can show a helical disposal similar to the helicity reported for helicenes, proteins or spiro compounds with five membered rings.[13] The helix (P or M configuration) can turn identical with it self after each four six-membered ring.

The stereoisomerism of some spiro and trispiro-1,3-dioxanes was explained on the basis of conformational analysis and the helical and axial chirality of the compounds. It was considered of interest to develop the study of the stereochemistry of spiranes with six-membered rings by investigating the stereoisomerism of some dispiro 1,3-dioxanes.

RESULTS AND DISCUSSION

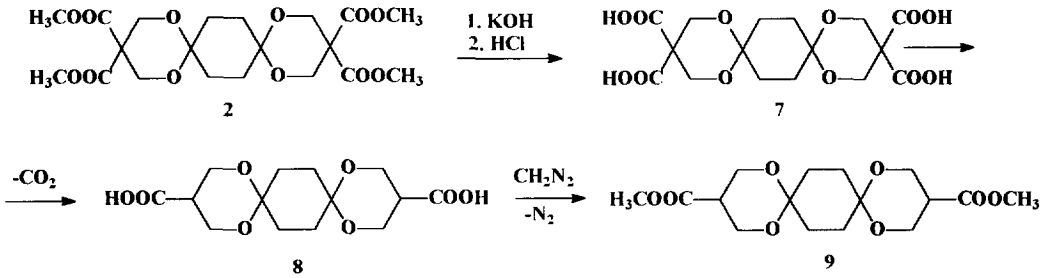
New dispiro-1,3-dioxanes were obtained by the acetalization reaction of 1,4-cyclohexanedione with some 1,3-propanediols (Scheme 2).



$R=R_1=H$	1
$R=R_1=COOCH_3$	2
$R=CH_3$, $R_1=C_2H_5$	3
$R=H$, $R_1=CH_3$	4
$R=H$, $R_1=C_6H_5$	5
$R=H$, $R_1=OCH_2C_6H_5$	6

Scheme 2

The tetraester **2** was subjected to hydrolization up to the tetraacid **7** and afterwards, to decarboxilation resulting into the diacid **8.** The reaction of the diacid **8** (as raw product) with diazomethane led to the diester **9** (Scheme 3).

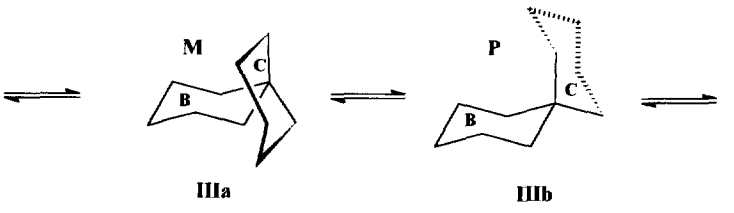


Scheme 3

All the investigated compounds display the 1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane skeleton, that shows a close stereochemistry to the parent dispiro compound with six-membered rings (dispiro[5.2.5.2]hexadecane), which exhibits only cyclohexane rings. The presence of the heterocycles in compounds **1-6** and **9**, besides of the facile synthesis of the system, enables an easier use of NMR methods in the investigations on their stereochemistry.

The parent skeleton of dispiro[5.2.5.2]hexadecane can be formally obtained, by adding a cyclohexane ring to spiro[5.5]undecane. As it was already shown[1,2] this spirane displays helical chirality and the flipping of

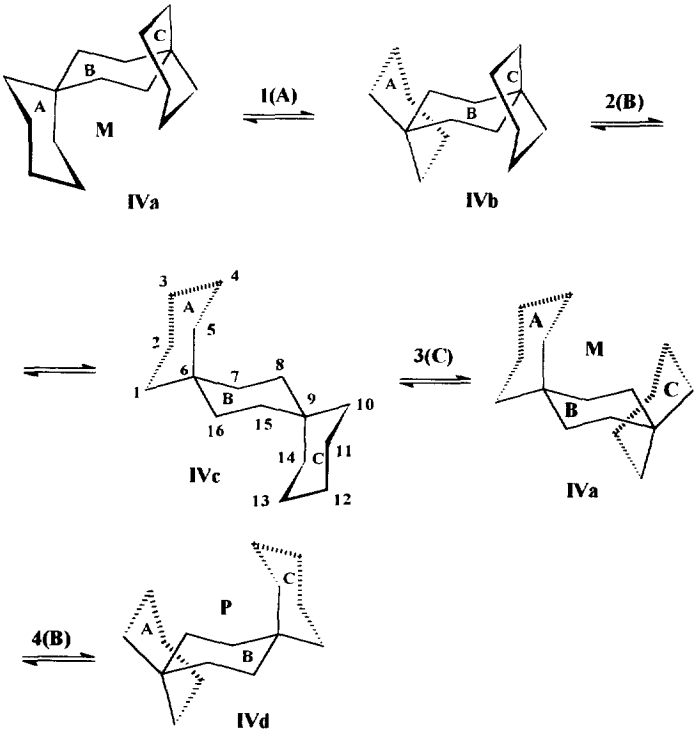
the cyclohexane rings (B and C) brings about an enantiomeric interconversion [Scheme 4: IIIa(M) ⇌ IIIb(P)].



Scheme 4

Starting from one of these structures (*e.g.* IIIa), a new six-membered ring (A) is added in order to obtain the dispiro[5.2.5.2]hexadecane; this new ring can develop the helix (structure IVa, Scheme 5) or can adopt an arrangement in which the helicity of the system is canceled (structure IVb).

The inversion of the rings in dispiro[5.2.5.2]hexadecane (Scheme 5) shows that the disymmetric structure IVa (M configuration of the helix), passes by the flipping of ring A into the structure IVb having a

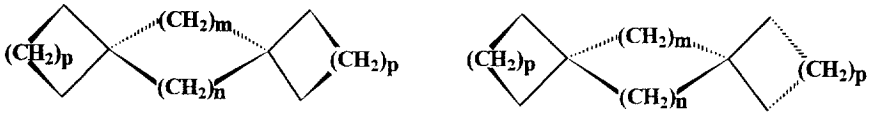


Scheme 5

center of symmetry. The inversion of ring B leads to structure IVc (identical to IVb) permitting in the end, by the inversion of ring C, to regain the initial structure IVa. The flipping of ring B in structure IVa inverts the helicity and leads to another disymmetric structure IVd [opposite configuration (P) of the helix].

Structures IVa and IVd (considered as frozen) are chiral (different configurations of the helix) and structure IVb (identical with IVc) is achiral displaying a center of symmetry. If the bisection plane of ring B ($C^1C^5C^6C^9C^{10}C^{14}$) is taken as reference, the rings A and C, in conformer IVb, are one in the front and the other one behind this best plane. It is proposed to name this structure as "6,9-dispiro-anti". The disymmetric conformations IVa and IVd displaying the rings A and C on the same part of the best plane represent the "6,9-dispiro-syn" structure.

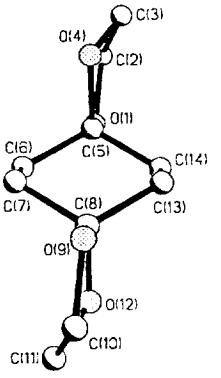
Generally, as in this peculiar case, in a dispiro skeleton the marginal rings can be oriented on the same side of the plane taken as reference in the middle ring generating the "dispiro-syn" isomer, or can be oriented in the opposite sides describing the "dispiro-anti" structure (Scheme 6).



"dispiro-syn" "dispiro-anti"

Scheme 6

A conclusive example is given by the analysis of the structure (Scheme 7) of 1,4,9,12-tetraoxadispiro[4.2.4.2]tetradecane (10) determined by X-ray diffractometry[14], that points out the "anti" orientation of the 1,3-dioxolane rings related to the best $O^1O^4C^5C^8O^9O^{12}$ plane (deviations calculated from the atomic coordinates: C^2 0.129, C^3 0.542, C^{10} -0.129 and C^{11} -0.542 Å). The investigated crystal corresponds to the "5,8-dispiro-anti" frozen structure.



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Scheme 7

The unsubstituted skeleton (R=H) shows a conformational equilibrium between the "syn" and "anti" structures (Va $\rightleftharpoons$ Vb), while if R is a bulky group (*e.g.* R=*tert*-C_4H_9) two separable diastereomers ("syn" and "anti") are possible.

Dispiro[5.2.5.2]hexadecane and its heterocycle analog 1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane, as well as their derivatives bearing identical geminal substituents in both extremities of the spiro skeleton, show two disymmetric structures (corresponding to "6,9-dispiro-syn" isomer and to P and M configurations of the helix) and an achiral structure (corresponding to the "6,9-dispiro-anti" isomer).

The new synthesized dispiro compounds **3-6** and **9**, exhibiting different substituents at the extremities of the dispiro skeleton, besides the helical chirality (in "syn" isomer) also show axial chirality (axes of chirality C^3-C^6 and C^9-C^{12}). The "6,9-dispiro-syn" isomer, in correlation with three chiral elements of the molecules, exhibits 8 possible stereoisomers (Table 1).

Table 1. Possible stereoisomers of "6,9-dispiro-syn" structures of compounds **3-6** and **9**.

Isomer	Configurations of chiral elements			Orientation of bulky groups*	
	Helix	Axis C^3-C^6	Axis C^9-C^{12}	C^3	C^{12}
C_1	P	aR	aR	eq.	eq.
C_2	P	aS	aR	ax.	eq.
C_3	P	aR	aS	eq.	ax.
C_4	P	aS	aS	ax.	ax.
C_5	M	aS	aS	eq.	eq.
C_6	M	aR	aS	ax.	eq.
C_7	M	aS	aR	eq.	ax.
C_8	M	aR	aR	ax.	ax.

*In the use of CIP convention for the specification of axial chirality the higher precedence is considered for these groups

The isomers C_1 and C_5 (enantiomers) are the main ones, bearing both bulky substituents in equatorial orientations.

The "6,9-dispiro-anti" isomer shows two axes of chirality, making possible four isomers (Table 2) two achiral ones (C_9 and C_{10}, displaying a center of symmetry) and a pair of enantiomers (C_{11} and C_{12}).

Table 2. Possible stereoisomers of "6,9-dispiro-anti" structures of compounds **3-6** and **9**.

Isomer	Configuration of axes		Orientation of substituents*	
	C^3-C^6	C^9-C^{12}	C^3	C^{12}
C_9	aR	aS	eq.	eq.
C_{10}	aS	aR	ax.	ax.
C_{11}	aR	aR	eq.	ax.
C_{12}	aS	aS	ax.	eq.

*In the use of CIP convention for the specification of axial chirality the higher precedence is considered for these groups

The "6,9-dispiro-anti" isomer prefers to exist as the achiral conformer C_9 bearing both bulky substituents in equatorial orientation.

Compounds **1** and **2** show flexible molecules, with flipping structures for both 1,3-dioxane and cyclohexane rings. The flipping of the rings induces a rapid conversion between the "6,9-dispiro-anti" and "6,9-dispiro-syn" structures and between the P and M configurations of the helix. The data of the literature show that in spiro 1,3-dioxanes the activation parameters ($\Delta G^{\#}$=8.9-9.0 kcal./mol)[15] for the heterocycle inversion are somewhat lower than for the unsubstituted 1,3-dioxane ($\Delta G^{\#}$=10.0 kcal./mol)[16], but are close to the value found for 2,2,5,5-tetramethyl-1,3-dioxane ($\Delta G^{\#}$=9.0 kcal./mol).[15] The lower values of $\Delta G^{\#}$ observed for spiro 1,3-dioxanes are explained by the ground state strain from non-bonded interactions between the two rings and by a stabilization of the transition state corresponding to the concerted inversion of the rings. In spiro compound showing a cyclohexane and a 1,3-dioxane ring the dynamic NMR experiments reported in the literature[9,11] putted in evidence a two steps freezing of the rings flipping. Thus, lowering the temperature first the inversion of the carbocycle is ceasing (higher value of $\Delta G^{\#}$) and only at lower temperature the flipping of the 1,3-dioxane ring is frozen too. The value of $\Delta G^{\#}$ found for flexible dispiro 1,3-dioxanes is smaller as the values found for flexible monospiro derivatives in agreement with the increasing of the specific interactions due to the presence of more spiranic unites ($\Delta G^{\#}$=8.7 kcal./mol). The NMR spectra (recorded at room temperature) of compounds **1** and **2** are quite simple (as it was observed for other similar compounds)[17] displaying unique signals (Table 3) for the axial and equatorial positions of the protons belonging to the rings or for the protons and carbon atoms belonging to the identical groups located at the extremities of the spiro skeleton [*e.g.* the ^{1}H-NMR spectrum of compound **2** (C_6D_6) displays only three singlets: $\delta_{2,4,11,13}$=4.35 ppm; $\delta_{7,8,15,16}$=1.84 ppm; δ_{COOMe}=3.25 ppm]. The flipping of the cycles renders equivalent the protons of the 1,3-dioxane rings and the protons of the cyclohexane ring, respectively. The spectrum (Table 3) of compound **1** shows a doublet of doublets ($\delta_{2,4,11,13}$=3.46 ppm) and an unsolved multiplet ($\delta_{3,12}$=1.15-1.20 ppm) for the protons of the heterocycles and only one singlet ($\delta_{7,8,15,16}$=1.90 ppm) for the protons of the cyclohexane ring. The protons of positions 3 and 12 (exhibiting different axial prochiralities) are different in NMR.

Unfortunately, no data concerning variable NMR experiments have been obtained for these two compounds. The experiments could not be carried out because of the very small solubility at low temperature of the compounds in the usual solvents used for this type of studies.

Compound **3** displays different substituents at the extremities of the dispiro skeleton. However, the compound exhibits flexible structure (both cyclohexane and 1,3-dioxane rings are flipping), the differences between the conformational free energies of the two groups (methyl and ethyl)[16] in the aliphatic part of the heterocycle being too small to induce the anancomericity of the cycles. The NMR spectra show unique signals (mean values of the chemical shifts) for the axial and equatorial positions of the protons belonging to the rings and for the protons and carbon atoms belonging to the groups located on it. The geminal protons are diastereotopic for both cyclohexane and 1,3-dioxane rings. As a consequence the ^{1}H-NMR spectrum (diethyl ether-d_{10}) shows an AB splitting pattern (Figure 1a, $\delta_{2,4,11,13}$=3.42 and 3.49 ppm) for the protons of positions

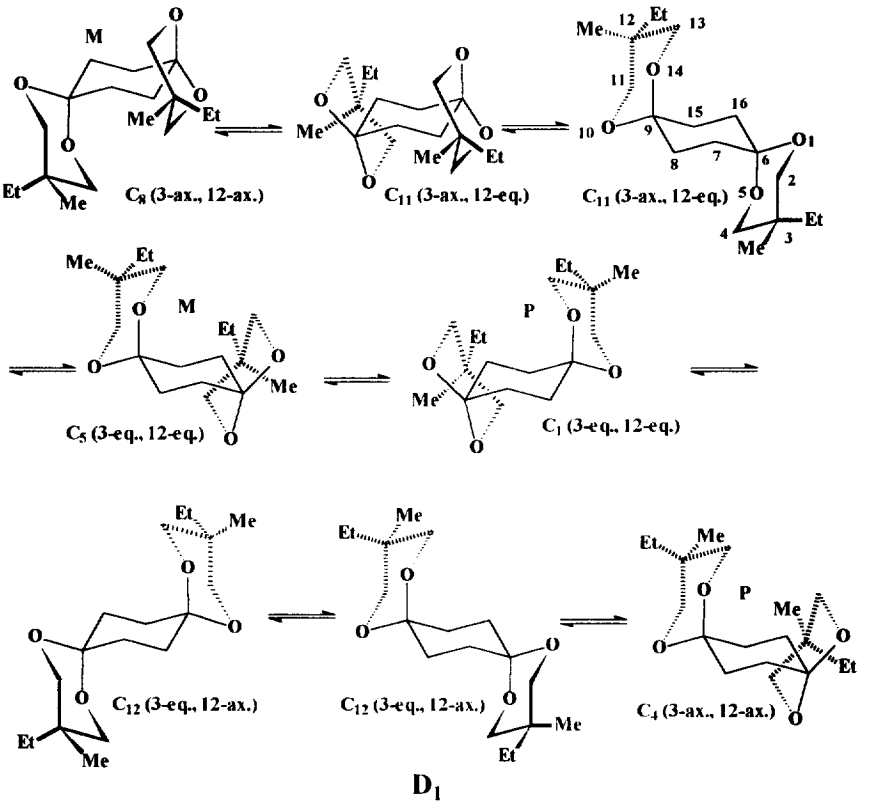
Table 3. ^{1}H NMR parameters (C_6D_6, δ, ppm) for compounds **1-6 and 9**

Compound	Isomer	Position of the protons		
		2,4, 11, 13		7,8,15,16
		eq.	ax.	
1	-	3.46		1.90
2	-	4.35		1.84
3	D_1 and D_2	3.54, 3.46		1.83, 1.81
4	syn	3.49	3.12	1.93, 1.88
4	anti	3.50	3.12	1.94, 1.87
5*	anti	3.84	3.91	2.06, 1.69
6*	syn	3.800	3.624	1.65, 1.77
6*	anti	3.805	3.628	1.65, 1.77
9	syn	3.88	3.77	1.84, 1.69
9**	anti	-	-	1.78, 1.71

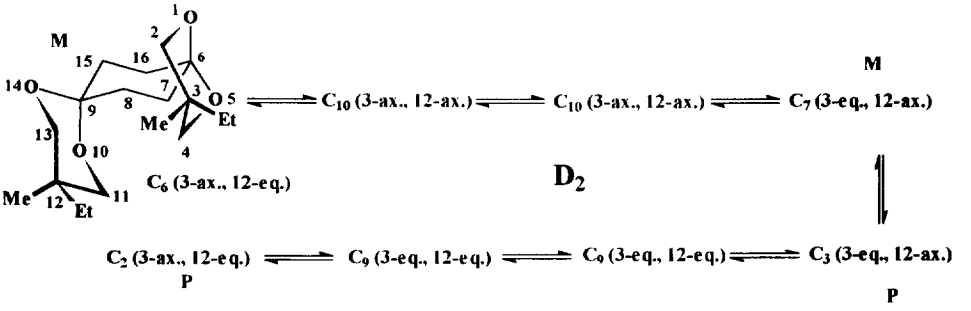
* Data of the spectrum run in $CDCl_3$

**The signals belonging to the protons of the heterocycle are overlapped with those of the major isomer and the chemical shifts could not be measured

2,4,11,13 and a triplet (overlapped doublets; $\delta_{7,8,15,16}$=1.74 and 1.77 ppm) for the protons of the positions 7,8,15,16. The compound shows two diastereomers D_1 and D_2 represented by the conformers: C_1, C_4, C_5, C_8, C_{11}, C_{12} and C_2, C_3, C_6, C_7, C_9, C_{10}, respectively (Tables 1 and 2, Scheme 8 and 9). The structures of the two diastereomers can not be associated with the classic configurational formulas (F_1 and F_2, Scheme 10) that also suggest the existance of two diastereomers with a "cis" and "trans" disposal of the methyl and ethyl groups. The use of this type of configurational formula for spiro compounds with six-membered rings is not recommended. Owing to the very close average magnetic environments of the protons and carbon atoms in these two diastereomers, the NMR spectra ($CDCl_3$, diethylether-d_{10}) display only one set of signals for the two structures. Only in the spectrum run in C_6D_6 two sets of signals for the protons of the groups located on the dispiro skeleton were observed (for the methylene protons of the ethyl group two quartets at 1.300 and 1.306 ppm and two singlets for the methyl groups connected to positions 3 and 12 at 0.773 and 0.768 ppm). The variable NMR experiment for compound **3** shows the transformation in the low temperature spectrum (-90° C) of the doublets and of the triplet recorded at room temperature for the protons of the heterocycles and of the cyclohexane ring into dispersed groups of signals (unfortunately unsolved) in the ranges 3.3-3.7 ppm (Figure 1b) and 1.2-1.8 ppm, respectively. These signals correspond to the structures C_1-C_{12} (Table 1 and 2) resulted from the freezing of both cyclohexane and 1,3-dioxane rings and representing the equatorial and axial positions of the protons in these structures.

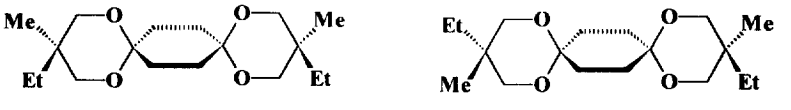


Scheme 8



Scheme 9

Note: in schemes 8 and 9 between paranthesis is shown the orientations of the ethyl groups.



Scheme 10

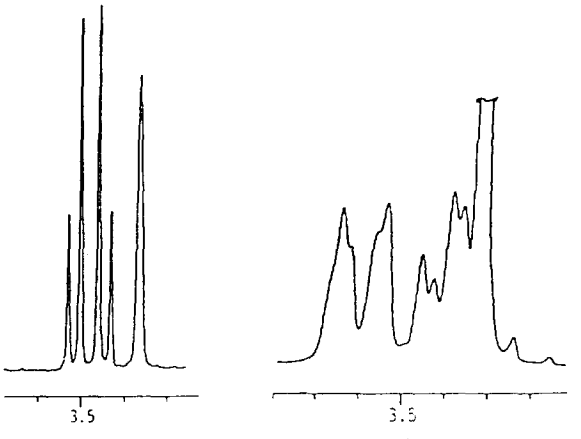
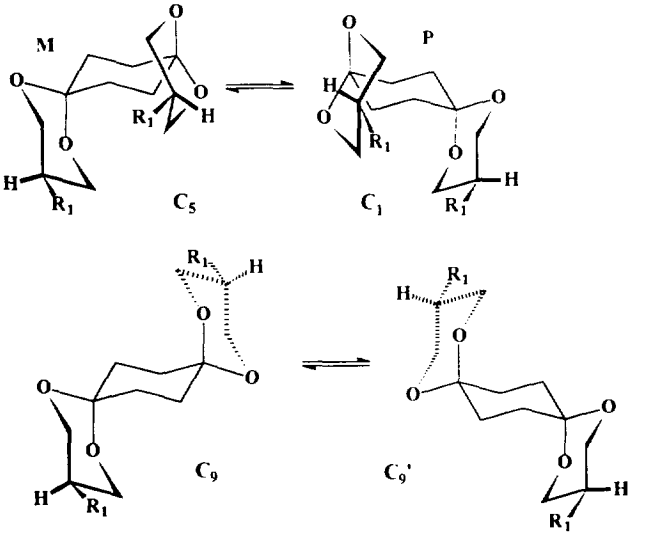


Figure 1. ^{1}H NMR spectra (diethylether-d_{10}) of compound 3 (a at room temperature and b at -90°C)
Note: the signal of 3.26 ppm is a solvent line [$(C_2D_5)_2O$].

Compounds **4-6** and **9** display semiflexible structures, the marginal 1,3-dioxane rings being anancomeric (holding groups at positions 3 and 12) whereas the middle cyclohexane ring is flipping.



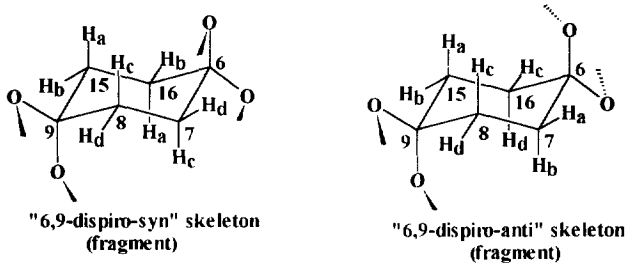
Scheme 11

The compounds exist as "6,9-dispiro-syn" and "6,9-dispiro-anti" diastereomers. The flipping of the cyclohexane ring induces a conversion between the two enantiomers (C_1 and C_5) of "6,9-dispiro-syn" isomer and between the two identical conformers of the achiral "6,9-dispiro-anti" isomer (C_9 and C_9'. Tables 1 and 2.

Scheme 11), but cannot transform the "6,9-dispiro-syn" into the "6,9-dispiro-anti" isomer. For passing from one of these isomers to the other one the whole dispiro skeleton has to be rebuild.

The diastereomers ("6,9-dispiro-syn" and "6,9-dispiro-anti") were identified using the different diastereotopicities of the protons and carbon atoms in the two diastereomers.

The ratio of the two isomers was calculated from ^{1}H-NMR spectra, choosing the signals for the protons of the cyclohexane part of the molecules. The analysis of the steric relation among these protons (Scheme 12), made using Dreiding models, points out the equivalence, from the NMR point of view, of the geminal and vicinal protons in the case of the "6,9-dispiro-syn" isomer and of the geminal protons belonging to the "6,9-dispiro-anti" structure. The ^{1}H-NMR pattern displays for the protons belonging to the cyclohexane ring two singlets for the "6,9-dispiro-syn" structure and two doublets of doublets (corresponding to an AA'XX' splitting system; sometimes overlapped giving triplets), for the "6,9-dispiro-anti" isomer.



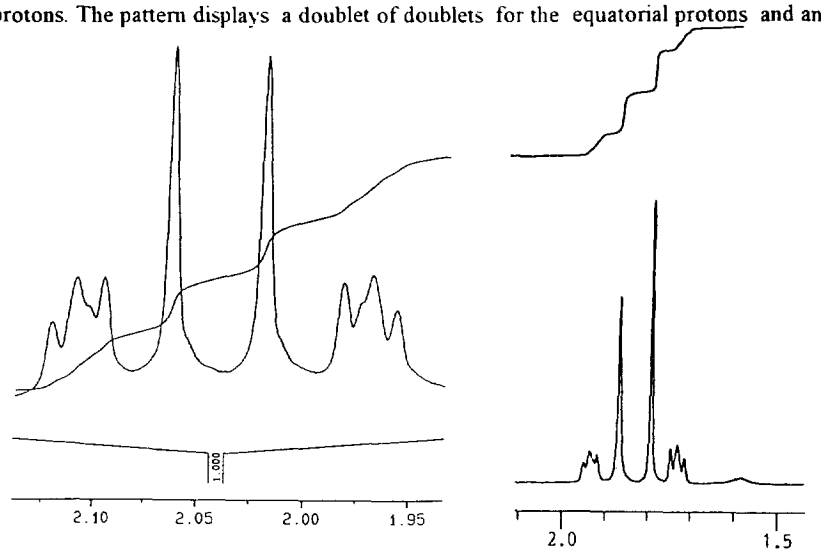
Scheme 12

Note: The protons designed with the same letter are equivalent (or are render equivalent by the flipping of the cyclohexane ring), the protons a with b and c with d are enantiotopic and the other situations represent diastereotopic protons.

In the acetalization reactions of 1,4-cyclohexanedione (Scheme 2) mixtures of the two diastereomers have been obtained. The isomers were identified and their ratio was calculated from the specific signals for the protons of the cyclohexane ring. For example, the spectrum of compound 6 (Figure 2a) obtained with a 500 MHz apparatus shows for the protons of the cyclohexane ring two overlapped doublets of doublets ($\delta_{7,15}$=1.97 and $\delta_{8,16}$=2.12 ppm) for the "6,9-dispiro-anti" isomer and two singlets ($\delta_{7,8}$=2.02 and $\delta_{15,16}$=2.07 ppm) for the similar protons of the "6,9-dispiro-syn" isomer. The observed data (Table 4) show a preference in the synthesis for the "6,9-dispiro-anti" isomer (about 100% for R=C_6H_5, 80% for R=CH_3 and 58% for R=O-CH_2-C_6H_5). In the decarboxilation reaction of the tetraacid 7 (Scheme 3) a bigger amount of "6,9-dispiro-syn" isomer (Figure 2b, Table 4) is formed.

In each isomer ("dispiro-syn" or "dispiro-anti") the flipping of the cyclohexane ring renders equivalent from the NMR point of view the positions 2,4,11,13. The ^{1}H and ^{13}C-NMR spectra (Table 3 and Table 5) show unique signals for the protons and carbon atoms of these positions. However, because the 1,3-dioxane rings areanancomeric the ^{1}H-NMR spectra show different signals for the equatorial and axial orientations of the

corresponding protons. The pattern displays a doublet of doublets for the equatorial protons and another one



a b

Figure 2. ^{1}H NMR spectra (domains used for the identification of the diastereomers) of compounds **6** (a) and **9** (b)

Table 4. The ratios of "6,9-dispiro-syn" and 6.9-dispiro-anti" isomers of compounds **4-6** and **9**

Compound	Substituents in 3 and 12	Ratio of isomers (%)	
		"syn"	"anti"
4	CH_3-	20	80
5	C_6H_5-	-	100
6	$C_6H_5CH_2O$-	42	58
9	-$COOCH_3$	70	30

for the axial ones. The signals corresponding to the axial and equatorial protons were identified using the values of the coupling constants with the vicinal axial protons of positions 3 and 12.

For the equatorial protons the values of the coupling constants are in the range J=4.7-4.8 Hz (characteristic values for coupling constants between vicinal axial and equatorial protons)[16]. For the axial protons the values of the coupling constants are in the range J=7.2-10.5 Hz (characteristic for coupling constants between vicinal axial protons)[16]. The ^{1}H NMR spectrum (Figure 3a) of compound **5** (only "6,9-dispiro-anti" isomer) displays a doublet of doublets (δ=3.84 ppm, J=5.3, J'=12.0 Hz), for the equatorial protons and another one (two peaks are overlapped) for the axial ones (δ=3.91 ppm, J=10.5, J'=12.0 Hz). The spectra of compounds **4** (Figure 3b) and **9** (Figure 3c) exhibit, for the protons of the heterocycles, signals similar to those

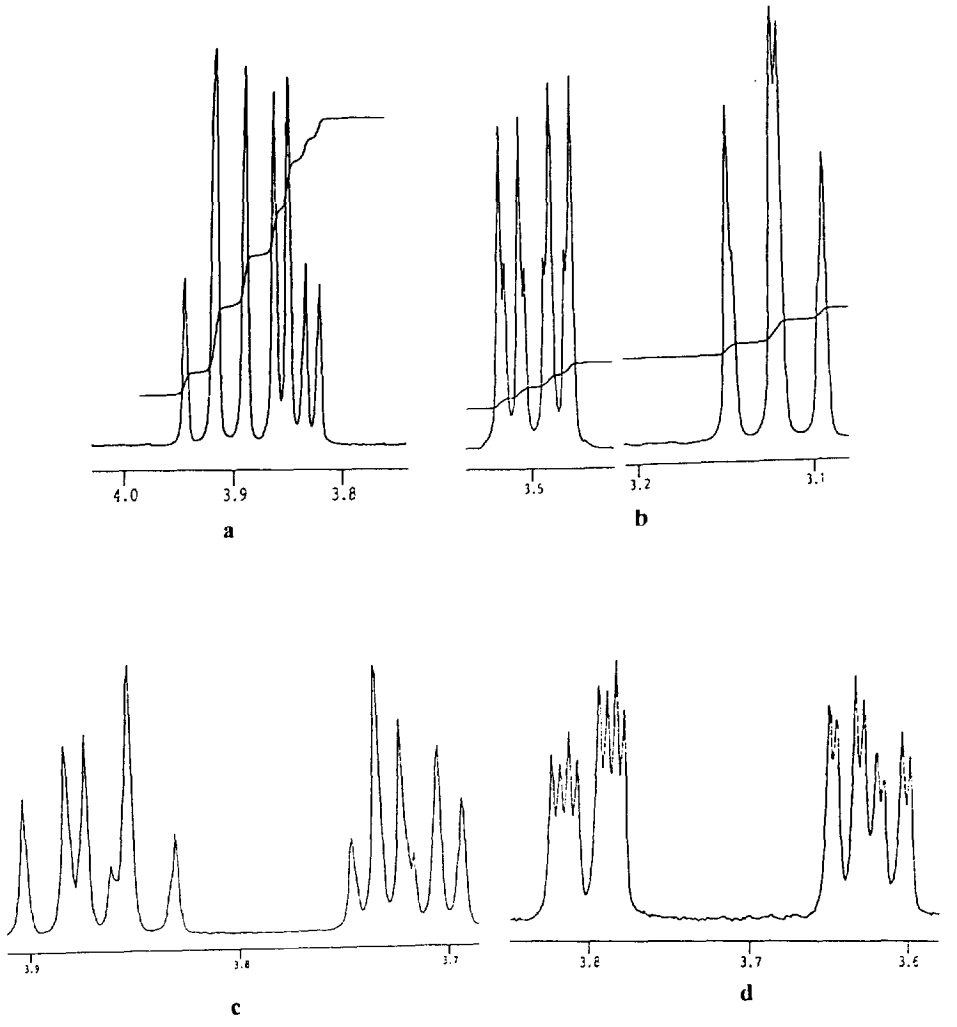


Figure 3. Fragments of the ^{1}H NMR spectra ($CDCl_3$ a and d; C_6D_6 b and c) corresponding to the protons of the positions 2, 4, 11, 13 of compounds 4(b), 5(a), 6(d) and 9(c).

recorded for compound **5** (Table 3), despite the fact that the main isomers are different (for **4**: 6,9-dispiro-anti; for **9**: 6,9-dispiro-syn). In both cases the signals of the minor isomer can be also observed. The ^{1}H-NMR spectrum (Figure 3d, Table 3) of compound **6** (with close amounts of 6,9-dispiro-syn and 6,9-dispiro-anti isomers) shows two well resolved sets of signals corresponding to both isomers. The ^{13}C NMR spectra show usual values[1] of the chemical shifts for 1,3-dioxane spiro compounds (Table 5). The magnetic environments of the carbon atoms of the "6,9-dispiro-syn" and "6,9-dispiro-anti" structures are quite similar while different signals for these isomers were obtained only for the carbon atoms of the cyclohexane ring.

Table 5. ^{13}C NMR parameters (C_6D_6, δ, ppm) for compounds **1-6** and **9**

Compound	Position of carbon atoms	
	2,4,11,13	7,8,15,16
1	54.68	24.66
2	62.04	28.23
3	68.36	28.96, 28.90, 28.50, 28.44
4	61.16	29.10, 20.02
5*	64.59	33.33, 23.92
6	70.60	30.77, 30.50, 26.69, 26.42
9	60.01	31.01, 30.75, 25.61, 25.36

*Data obtained from the spectrum run in $CDCl_3$

CONCLUSIONS

The stereoisomerism of dispiro compounds with six-membered rings was explained in detail considering the axial and helical chirality of this type of spiranes and the data of conformational analysis. The proposed names of "6,9-dispiro-syn" and "6,9-dispiro-anti" are useful not only for giving an identity to the diastereomers of 3,12-disubstituted derivatives of dispiro[5.2.5.2]hexadecane skeleton (or heterocyclic analogs) but also for correlating the stereochemistry of dispiro compounds and of cycloalkylidenecycloalkane derivatives.[18,19] This type of nomenclature can be easily extended to designate the stereoisomers of polyspiro compounds. So, the three diastereomers observed[1,2] for 3,15-disubstituted-7,11,18,21-tetraoxatri-spiro[5.2.2.5.2.2]henicosane (involved in a conformational equilibrium by the flipping of the 1,3-dioxane rings) can be identified as "6,9,12-trispiro-syn, syn"; "6,9,12-trispiro-syn, anti" and "6,9,12-trispiro-anti, anti". For each diastereomer two structures corresponding to the M or P configurations of the helix are possible. A NMR method, based on the diastereotopicities of protons and carbon atoms, was developed for the identification and the calculation of the ratio of the diastereomers belonging to the dispiranes **4-6** and **9**.

EXPERIMENTAL

General. - NMR spectra were obtained on a Bruker AM 400 spectrometer (with an Aspect 3000 computer) operating at 400 MHz for protons and 100 MHz for carbon atoms. No Me_4Si was added; the chemical shifts were measured against the solvent line.

M.ps were determinated with an Electrothermal apparatus and are uncorrected.

*Compounds **1-6**, general procedure.* - Stoichiometric amounts of 1,3-diol (0.1 mol) and 1,4-cyclohexanedione (0.05 mol) with catalytic quantities of p-toluenesulphonic acid (0.1 g) were solved in 200 ml benzene. The mixture was refluxed and the water was removed using a Dean-Stark trap. When 80 % of the theoretical water was separated, after cooling at room temperature, the catalyst was neutralized (under stirring 0.5 h) with CH_3-CO_2Na powder in excess (0.2 g). The reaction mixture was washed twice with 100 ml water. After drying (with Na_2SO_4) the benzene was removed and the 1,3-dioxane compound was purified by crystallization from ethanol.

*Diester **9**, general procedure.* - The tetraester **2** was saponified by heating to reflux (2h) the mixture of the tetraaester with an ethanolic solution (10 %) of KOH (100 % excess). The resulted potassium salt was filtered, then washed with dry ethanol and acetone. The salt was solved in a small amount of water and a volume twenty times larger of diethyl ether was added. A concentrated HCl solution was then added dropwise at 0-5°C, under stirring up to pH=2. After separation, the organic phase was dried and the ether was removed (in vacuum ; t<30°C). The obtained tetraacid **7** was decarboxylated without purification, by heating (1 h at 90-95°C) its pyridinic solution (50 ml pyridine for 1 g diacid). The pyridine was then removed in vacuum and the raw product was solved in an 10 % KOH aqueous solution (20 % excess) and washed twice with 50 ml diethyl ether. To the potassium salt solution a ten times larger volume of diethyl ether was added. After cooling (at 0-5°C) a concentrated HCl solution was slowly added, under stirring, up to pH=2. The etheric solution was separated and washed with a small amount of cold water. After drying, the ether was removed in vacuum. The diacid **8** was subject to the reaction with CH_2N_2 under usual conditions. The diester **9** was crystallized from ethanol.

1,5,10,14-Tetraoxadispiro[5.2.5.2]hexadecane. White plates, mp 184-185 °C, 8.21 g (0.036 mol), yield 72 % (Found: C, 63.02; H, 8.92. $C_{12}H_{20}O_4$ requires C, 63.14; H, 8.83 %); δ_H (C_6D_6) 1.15-1.20(4H,m,$H^{3,12}$), 1.90(8H, s,$H^{7,8,15,16}$) and 3.46(8H,dd,J=J'=5.6 Hz, $H^{2,4,11,13}$); δ_C (C_6D_6) 21.43($C^{3,12}$), 24.66 ($C^{7,8,15,16}$), 54.68($C^{2,4,11,13}$) and 93.24($C^{6,9}$)

3,3,12,12-Tetrakis(methyloxycarbonyl)-1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane 2. White plates, mp 81-82 °C, 17.48 g (0.038 mol), yield 76% (Found: C, 52.43; H, 5.98. $C_{20}H_{28}O_{12}$ requires C, 52.17; H, 6.13 %). δ_H (C_6D_6) 1.84(8H, s, $H^{7,8,15,16}$), 3.25(12H, s, 3,12-$COOCH_3$) and 4.35(8H, s, $H^{2,4,11,13}$). δ_C (C_6D_6) 28.23($C^{7,8,15,16}$), 52.06(3,12-$COO\underline{C}H_3$), 53.82($C^{3,12}$), 62.04($C^{2,4,11,13}$), 98.07($C^{6,9}$) and 167.97(3,12-$\underline{C}OOCH_3$).

3,12-Diethyl-3,12-dimethyl-1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane 3. White plates, mp 127-128 °C, 5.62 g (0.018 mol), yield 72% (Found: C, 69.39; H, 10.21. $C_{18}H_{32}O_4$ requires C, 69.19; H, 10.32 %). δ_H (C_6D_6) 0.72(6H, t, J=7.1 Hz, 3,12-CH_2-$C\underline{H}_3$), 0.768(3H, s, 3,12-CH_3), 0.773(3H, s, 3,12-CH_3), 1.300(2H, c,

J=7.1Hz, 3,12-CH_2-CH_3), 1.307(2H, c, J=7.1Hz, 3,12-CH_2-CH_3), 2.05(4H, d, J=3Hz, $H^{7,8,15,16}$), 2.06(4H, d, J=3Hz, $H^{7,8,15,16}$), 3.34(4H, d, J=11.4 Hz, $H^{2,4,11,13}$) and 3.42(4H, d, J=11.4 Hz, $H^{2,4,11,13}$). δ_C (C_6D_6) 7.20(3,12-CH_2-$\underline{C}H_3$), 18.80(3,12-CH_3), 27.73(3,12-$\underline{C}H_2$-CH_3), 28.44, 28.50. 28.90, 28.96($C^{7,8,15,16}$), 32.42($C^{3,12}$), 68.36($C^{2,4,11,13}$) and 97.59(C6,9).

3,3-Dimethyl-1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane 4. White plates, mp 172-173 °C, 8.70 g (0.034 mol), yield 68 % (Found: C, 65.39; H, 9.55. $C_{14}H_{24}O_4$ requires C, 65.60; H, 9.44%); δ_H (C_6D_6) 0.28(6H, d, J=6.8 Hz, 3,12-CH_3), 1.63-1.75(2H, m, $H^{3,12}$), 1.88(4H, dd, J=J'=4.5 Hz, $H^{7,8}$)*, 1.89(4H, s, $H^{7,15}$)**, 1.92(4H, s, $H^{15,16}$)**, 1.93(4H, dd, J=J'=4.5 Hz, $H^{8,16}$)*, 3.12[4H, t(overlapped doublet of doublets), J=J'=12.0 Hz, 2,4,11,13-H_{ax}) and 3.50(4H, dd, J=12.0, J'=4.9 Hz, 2,4,11,13-H_{eq}); δ_C (C_6D_6) 8.34(3,12-CH_3), 20.02($C^{7,15}$), 25.10($C^{3,12}$), 29.10($C^{8,16}$), 61.16($C^{2,4,11,13}$) and 92.99 ($C^{6,9}$).

* and ** separated signals for "6,9-dispiro-anti" (80%) and "6,9-dispiro-syn" (20%) isomers, respectively.

3,12-Diphenyl-1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane 5. White plates, mp 227-228 °C, 6.18 g (0.016 mol), yield 65% (Found: C, 75.59; H, 7.60. $C_{24}H_{28}O_4$ requires C, 75.76; H, 7.42 %); δ_H ($CDCl_3$) 1.69(4H, dd, J=J'=6.0 Hz, $H^{7,15}$), 2.06(4H, dd, J=J'=6.0 Hz, $H^{8,16}$), 3.84(4H, dd, J=12.0, J'=5.3 Hz, 2,4,11,13-H_{eq}), 3.91 (4H, dd, J=12.0, J'=10.5 Hz, 2,4,11,13-H_{ax}) and 7.08-7.22(10H, m, aromatic protons); δ_C ($CDCl_3$) 23.92 ($C^{7,15}$), 33.33($C^{8,16}$), 41.20($C^{3,12}$), 64.59($C^{2,4,11,13}$), 97.34($C^{6,9}$), 127.21, 127.65,128.66 (tertiary aromatic carbon atoms) and 138.62 (quaternary aromatic carbon atom).

3,12-Di(benzyloxy)-1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane 6. White plates, mp 105-106°C, 0.83 g (0.0018 mol), yield 63 % (Found: C, 71.01; H, 7.20. $C_{26}H_{32}O_6$ requires C, 70.89; H, 7.32 %); δ_H (C_6D_6) 1.97(4H, dd, J=J'=6.5 Hz, $H^{7,15}$)*, 2.02(4H, s, $H^{7,8}$)**, 2.07(4H, s, $H^{15,16}$)**, 2.11(4H, dd, J=J'=6.5 Hz, $H^{8,16}$)*, 3.19-3.25(2H, m, $H^{3,12}$), 3.556(4H, dd, J=11.7, J'=7.3 Hz, 2,4,11,13-H_{ax})**, 3.563(4H, dd, J=11.8, J'=7.2 Hz, 2,4,11,13-H_{ax})*, 3.664(4H, dd, J=11.8, J'=4.7 Hz, 2,4,11,13-H_{eq})*, 3.671(4H, dd, J=11.7, J'=4.8 Hz, 2,4,11,13-H_{eq})**, 4.09(4H, s, 3,12-O-CH_2-C_6H_5) and 6.95-7.15(10H, overlapped peaks, aromatic protons); δ_C (C_6D_6) 26.42($C^{7,8}$)**, 26.69($C^{7,15}$)*, 30.50($C^{15,16}$)**, 30.77($C^{8,16}$)*, 62.17(3,12-O-CH_2-C_6H_5), 70.06($C^{3,12}$), 70.60 ($C^{2,4,11,13}$), 97.80($C^{6,9}$), 126.95, 127.46, 127,70, 127.94, 128.36 (tertiary aromatic carbon atoms) and 138.68 (quaternary aromatic carbon atom).

* and ** separated signals for "6,9-dispiro-anti" (58%) and "6,9-dispiro-syn" (42%) isomers, respectively.

3,12-Bis(methyloxycarbonyl)-1,5,10,14-tetraoxadispiro[5.2.5.2]hexadecane 9. White plates, mp 146-148 °C, 2.27 g (0.0066 mol), yield (calculated beside the tetraester 2) 33% (Found: C, 55.93; H, 7.19. $C_{16}H_{24}O_8$ requires C, 55.81; H, 7.02%) δ_H (C_6D_6) 1.69(4H, s, $H^{7,8}$)**, 1.71(4H, dd, J=J'=6.3 Hz, $H^{7,15}$)*, 1.78(4H, dd, J=J'=6.3 Hz, $H^{8,16}$)*, 1.84(4H, s, $H^{15,16}$)**, 2.32-2.38(2H, m, $H^{3,12}$), 3.21(3H, s, 3,12-$COOCH_3$)**, 3.23(3H, s,

3,12-$COOCH_3$)* 3.71(4H, dd, J=12.0, J'=4.8 Hz, 2,4,11,13-H_{eq}) and 3.88(4H, dd, J=12.0, J'=7.2 Hz, 2,4,11,13-H_{ax}); δ_C ($CDCl_3$) 25.36($C^{7,15}$)*, 25.61($C^{7,8}$)**, 30.75($C^{15,16}$)**, 31.01($C^{8,16}$)*, 40.03($C^{3,12}$), 60.01($C^{2,4,11,13}$) and 97.59($C^{6,9}$),

* and ** separated signals for "6,9-dispiro-anti" (30%) and "6,9-dispiro-syn" (70%) isomers, respectively.

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