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Synthesis and Stereochemistry of Some New Chiral Spiro-1,3-Dioxanes

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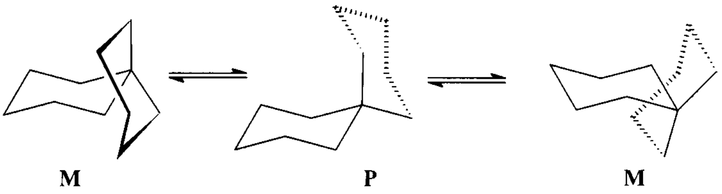
Abstract: The stereoisomerism of some spiro-1,3-dioxanes obtained from chiral 1,3-diols or chiral substituted cyclohexanones is discussed on the basis of the helical chirality of the 1,5-dioxaspiro[5.5]undecane skeleton and of the data of conformational analysis. The influence of the flexibility of the rings on the representative number of isomers and on their NMR spectra is commented. The compositions of the stereoisomers (diastereoisomers and enantiomers) of some representative compounds have been determined by gas chromatography using chiral columns.

INTRODUCTION

In previous papers[1-4] the stereochemistry of spiro compounds with six-membered rings, obtained from achiral substituted cyclohexanones and 1,3-diols has been discussed on the basis of the conformational analysis and of the axial and helical chirality of the spiro skeleton. A polyspiro system with six-membered rings adopts a helical disposition and the helix (with P or M configuration) can turn identical with itself after each fourth six-membered ring. Contrary to the initial opinions,[5-8] that considered the chirality of spiro[5.5]undecane (the parent spiro compound with six-membered rings) due to a chiral carbon atom (the spiro one) of the type $C_{a,a,a,a}$, this spirane exhibits helical chirality (the characteristic helix begins to be built). The flipping of the rings results into an enantiomeric equilibrium (Scheme 1).

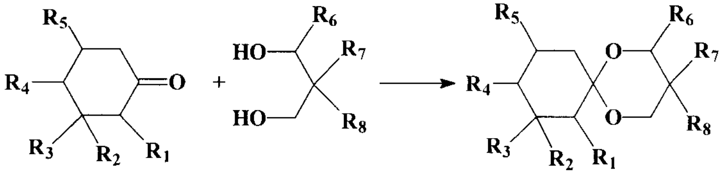


Scheme 1

It was considered of interest to develop a study on the stereochemistry of some new spiro compounds displaying chiral carbon atoms in the 1,5-dioxaspiro[5.5]undecane skeleton and to investigate the influences induced by the helical chirality and the chiral carbon atoms on the stereoisomerism of these compounds.

RESULTS AND DISCUSSION

New spiro-1,3-dioxanes have been obtained by the usual acetalization reaction starting from chiral substituted cyclohexanones or chiral 1,3-diols (Scheme 2).



$R_1=R_2=R_3=R_4=R_5=R_7=R_8=H$, $R_6=CH_3$ **1**

$R_1=R_3=R_4=R_5=R_6=R_7=R_8=H$, $R_2=CH_3$ **2**

$R_1=R_3=R_4=R_5=R_6=H$, $R_2=R_7=R_8=CH_3$ **3**

$R_1=R_3=R_4=R_5=R_6=H$, $R_2=CH_3$, $R_7=R_8=COOC_2H_5$ **4**

$R_2=R_3=R_4=R_5=R_6=H$, $R_1=R_7=R_8=CH_3$ **5**

$R_2=R_3=R_4=R_5=R_6=H$, $R_1=CH_3$, $R_7=R_8=COOC_2H_5$ **6**

$R_1=R_4=R_6=H$, $R_2=R_3=R_5=R_7=R_8=CH_3$ **7**

$R_1=R_4=R_6=H$, $R_2=R_3=R_5=CH_3$, $R_7=R_8=COOC_2H_5$ **8**

$R_1=R_2=R_3=R_5=R_7=R_8=H$, $R_4=R_6=CH_3$ **9**

$R_1=R_2=R_3=R_5=R_7=R_8=H$, $R_4=t\text{-}C_4H_9$, $R_6=CH_3$ **10**

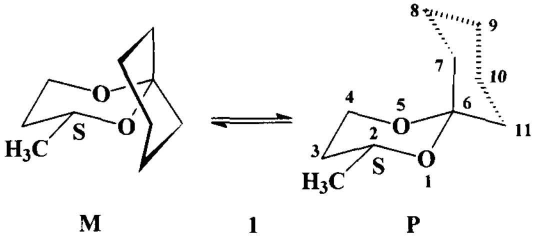
$R_1=R_3=R_4=R_5=R_6=R_8=H$, $R_2=R_7=CH_3$ **11**

$R_2=R_3=R_4=R_5=R_6=R_8=H$, $R_1=R_7=CH_3$ **12**

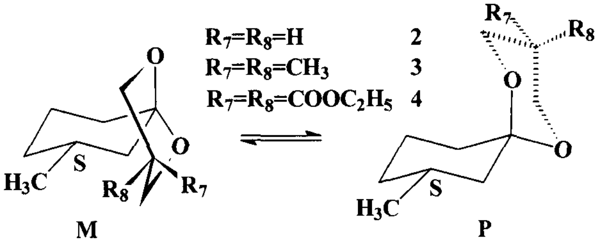
Scheme 2

Compounds with semiflexible structure

Spiranes **1-4** exhibit semiflexible structures, the unsymmetrically substituted rings being anancomeric, while the symmetrically substituted (or unsubstituted) ones are flipping (Schemes 3 and 4).



Scheme 3



Scheme 4

The compounds show four stereoisomers in correlation with the different configurations of the helix and of the chiral carbon atom: M,S; M,R; P,S and P,R. The flipping of the rings changes one diastereoisomer into the other one (M,S $\rightleftharpoons$ P,S; M,R $\rightleftharpoons$ P,R; Schemes 3 and 4 show only one of these possible equilibria).

The conformational behaviour of the molecules was deduced from the NMR investigations of the compounds. The spectra show unique signals (at mean values of the chemical shifts) for the axial and equatorial positions of the protons of the flexible rings and for the protons and carbon atoms of the similar groups located on it, but exhibit distinct signals for the equatorial and axial positions of the protons belonging to the anancomeric cycles.

Compound **1** displays an anancomeric 1,3-dioxane ring and a flipping cyclohexane one. The ^{1}H NMR spectrum of this compound (Figure 1, Table 1) shows for the protons of position 4 two doublets of doublets of doublets. The more deshielded one (with overlapped peaks) exhibiting a large vicinal coupling constant ($J_{4ax\text{-}3eq}$=12.3 Hz) belongs to the axial proton (δ_{4ax}=3.89 ppm) and the other one with small vicinal coupling constants ($J_{4eq\text{-}3eq}$=1.5 and $J_{4eq\text{-}3ax}$=5.5 Hz) is assigned to the equatorial one (δ_{4eq}=3.71 ppm). The axial proton of position 2 exhibits an overlapped doublet of doublets of quartets (resulting into a doublet of sextets, δ_{2eq}=3.95 ppm).

Compounds **2-4** exhibit anancomeric cyclohexane rings and flipping heterocycles. The chirality of the systems induces the diastereotopicity of the positions 2 and 4.

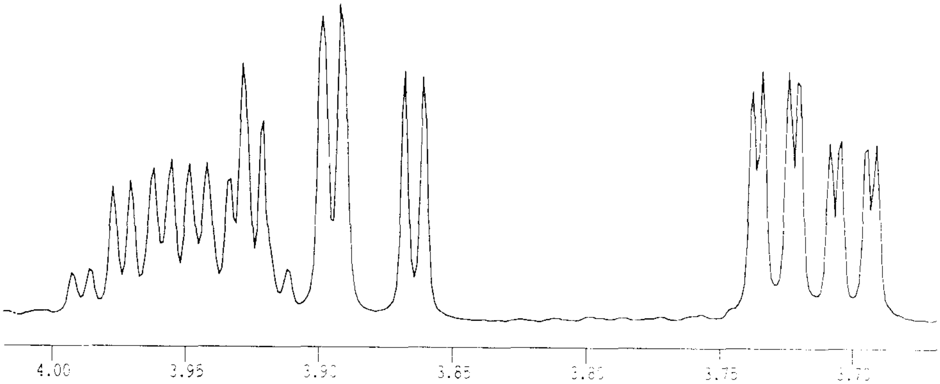


Figure 1. ^{1}H NMR spectrum (fragment) of compound **1**.

Table 1. NMR data (C_6D_6, δ ppm) for compounds **1-12**.

Compound	^{1}H				^{13}C	
	2eq	2ax	4eq	4ax	2	4
1	-	3.95	3.71	3.89	59.36	54.45
2	3.65		3.53		58.65	58.58
3	3.39		3.29		69.85	69.85
4*	4.35		4.31		62.26	62.14
5	3.22	3.52	3.20	3.35	69.63	69.50
6	4.67	4.31	4.64	4.18	62.06	62.03
7	3.32	3.44	3.23	3.34	69.77	69.63
8	4.63	4.50	4.59	4.42	62.10	61.89
9 (D_1, D_2)	-	3.68, 3.90	3.729, 3.738	3.66, 3.84	59.42, 59.59	54.43, 54.69
10 (D_1, D_2)	-	3.721, 3.941	3.757, 3.759	3.700, 3.882	59.70, 59.85	54.49, 54.79
11(D_1, D_2)	3.630, 3.632	3.35, 3.39	3.584, 3.599	3.17, 3.22	65.01, 65.14	
12(D_1)	3.61	3.38	3.59	3.21	65.18	65.08
12(D_2)	3.32	3.83	3.28	3.67	64.08	63.92

* ^{1}H NMR spectrum run in DMF-d_6

The ^{1}H NMR spectrum of compound **2** (Table 1) shows for the protons of the positions 2 and 4 (rendered diastereotopic by the chirality of the molecule) two triplets (δ_2=3.65 and δ_4=3.53 ppm), recorded at mean values of the chemical shifts, corresponding to the average magnetic environment of the equatorial and axial positions of these protons.

The spectrum of compound **4** (Figure 2a, Table 1) recorded at room temperature in DMF-d_6 exhibits for the protons belonging to the diastereotopic positions 2 and 4 (of the flipping heterocycle) two singlets (δ_2=4.35, δ_4=4.31 ppm) one of them being overlapped with the quartets recorded for the methylene protons of the diastereotopic ester groups located in the position 3 (δ_q=4.274 and δ_q'=4.268 ppm). The shape of the spectrum run in benzene-d_6 exhibits significant modifications (ASIS effect) being observed besides the good separation of the previously overlapped signals the recording of different signals for the geminal protons (showing different prochiralities) of each of the diastereotopic positions 2 and 4 (the differences of magnetic environments of the geminal protons in DMF-d_6 were too small to be observed). The previously recorded two singlets (Figure 2a) are replaced in the spectrum run in C_6D_6 (Figure 2b) by two well resolved AB systems (δ_2=4.56, δ_2'=4.51, δ_4=4.48 and δ_4'=4.42 ppm) belonging to the proR and proS protons of each of the diastereotopic positions 2 and 4.

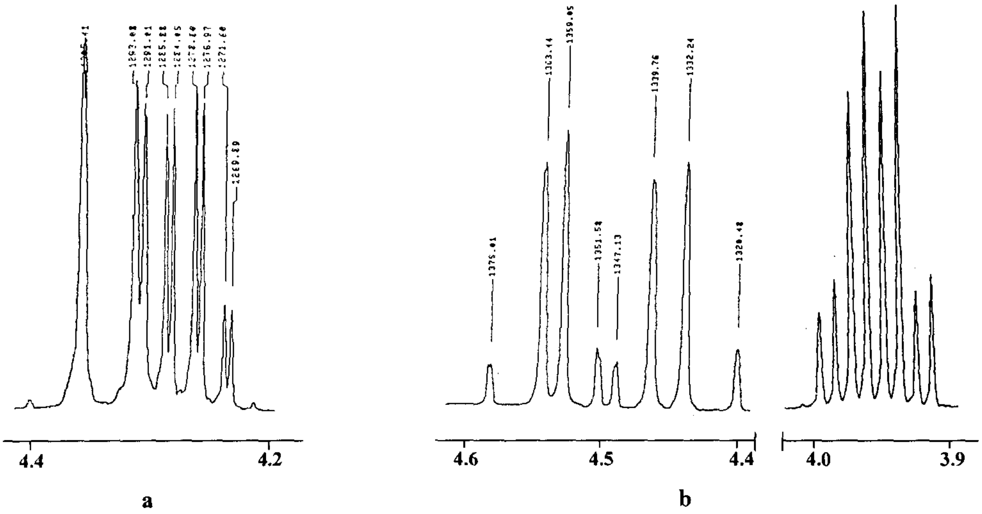


Figure 2. ^{1}H NMR spectra (fragments) of compound **4** run in DMF-d_6 (a) and C_6D_6 (b).

The ^{1}H NMR spectra of compound **3** run at room temperature, in CD_2Cl_2 or in aromatic solvents (no ASIS effect), show for the protons located in the diastereotopic positions 2 and 4 two singlets (Figure 3a, δ_2=3.48 and δ_4=3.42 ppm) recorded at mean values of the chemical shifts corresponding to the equatorial and axial positions of the protons. A variable temperature ^{1}H NMR experiment carried out with this compound shows in the spectrum recorded at low temperature (-90°C) the changing of the two singlets (recorded at room temperature) into four groups of signals (dispersed from 3.00 to 4.20 ppm) corresponding to the axial and equatorial orientations of the protons of the diastereotopic positions 2 and 4 belonging to the two diastereisomers of the frozen structure of compound **3** (Figure 3b). In order to observe the diastereotopicity of the geminal protons (proR and proS) attached to C^2 and C^4, the spectra of compound **3** in the presence of chemical shift regents have been recorded. The spectrum run with $Pr(FOD)_3$, besides the significant shielding of all the signals (Figure 3c) shows for the protons of the heterocycle two well resolved AB systems assigned to the diastereotopic geminal protons of the diastereotopic positions 2 and 4 (δ_2=2.60, δ_2'=2.54, δ_4=1.77 and δ_4'=1.68 ppm).

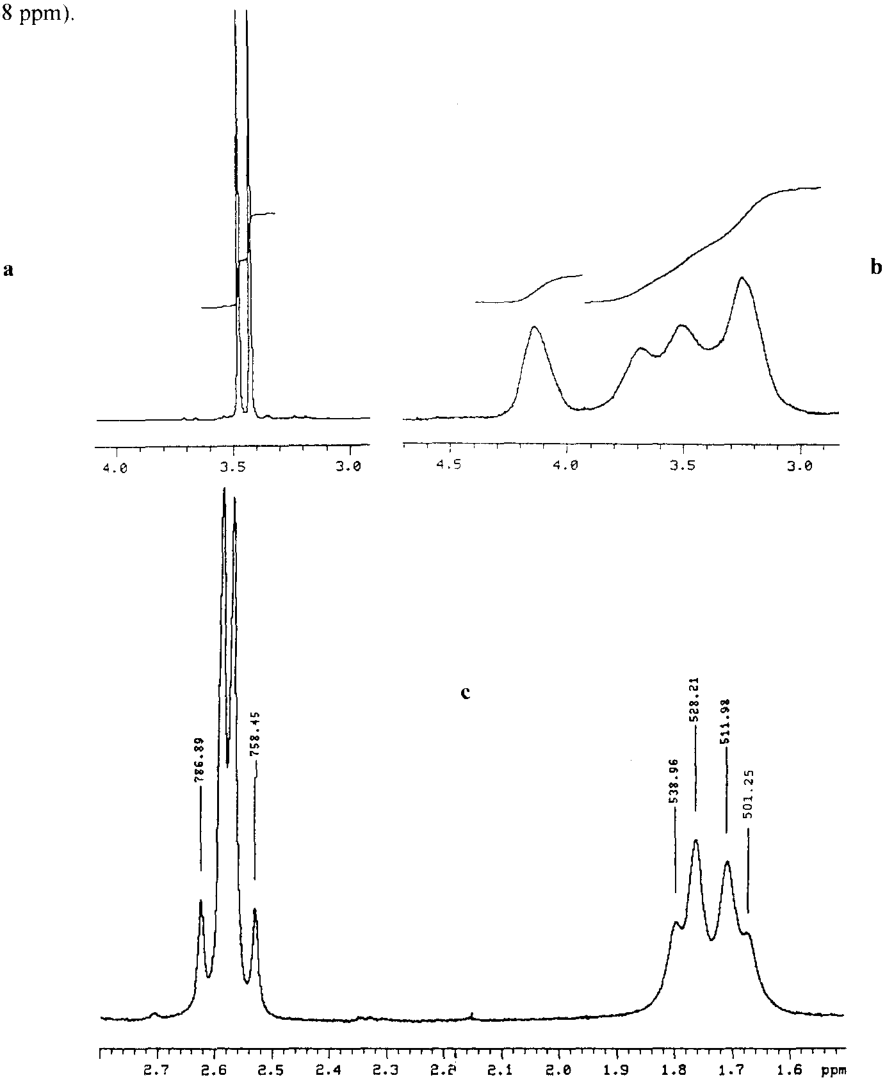
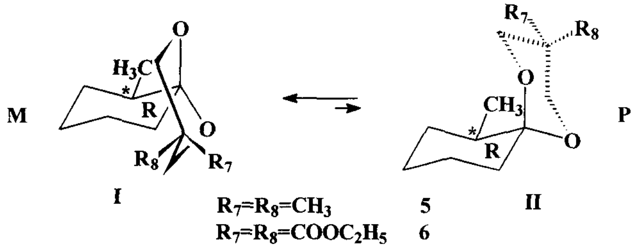


Figure 3. ^1H NMR spectra (CD_2Cl_2) of compound **3** run at room temperature (a), at -90 °C (b) and with $Pr(FOD)_3$ (c)

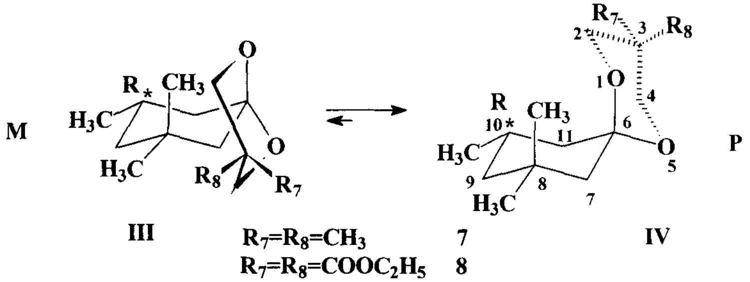
Compounds with anancomeric structures

Spiranes **5-8** exhibit anancomeric structures, the conformational equilibria (Schemes 5 and 6) for the flipping of the apparently symmetrical substituted heterocycles being shifted towards the conformations I and IV that display the heterocycle in the opposite side with the equatorial methyl group located in position 7 (I) or with the axial methyl group located at C^8 (IV). Compounds **5-8** can show four stereoisomers in agreement with the different configurations of the two chiral elements of the molecule: M,S; M,R; P,S and P,R. The conformational equilibria (P,R $\rightleftarrows$ M,R; M,S $\rightleftarrows$ P,S; Schemes 5 and 6 show only one of these possible equilibria) are shifted towards the conformations displaying M,R and P,S configurations of the chiral elements. The representative stereoisomers of each of these compounds are a pair of enantiomers. These results were deduced by the NMR spectra of the compounds and by the gas chromatographic investigation of compound **7** performed on a chiral column. The chromatogram shows two separated peaks displaying the same intensity and belonging to the two enantiomers of the compound (R_F=27.10 and R_F'=27.71 min.).



R_7=R_8=CH_3 **5**
R_7=R_8=$COOC_2H_5$ **6**

Scheme 5



R_7=R_8=CH_3 **7**
R_7=R_8=$COOC_2H_5$ **8**

Scheme 6

The ^{1}H NMR spectra of compounds **5-8** (Table 1) exhibit different signals for the equatorial and axial protons of the rings and of the groups located on it. As an example the spectrum of compound **8** (Figure 4) shows two doublets of doublets for the equatorial, as well as for the axial protons of the diastereotopic positions 2 and 4 (δ_{2eq}=4.63, δ_{2ax}=4.50, δ_{4eq}=4.59 and δ_{4ax}=4.42 ppm). The signals of the equatorial protons exhibit a further splitting due to the long range coupling between these protons, render possible by the W (M) disposition of the bonds H_{eq}-C^2-C^3-C^4-H_{eq} (^4J=1.3 Hz).

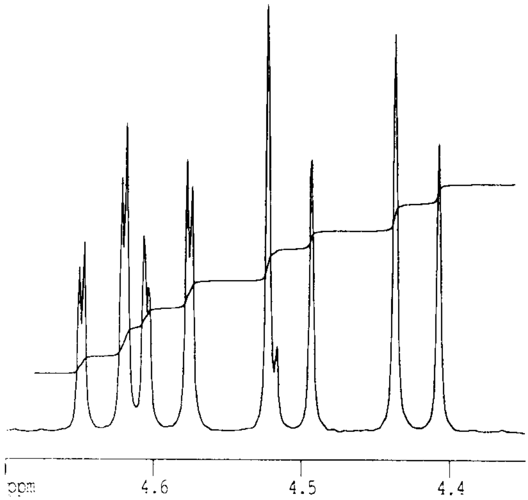
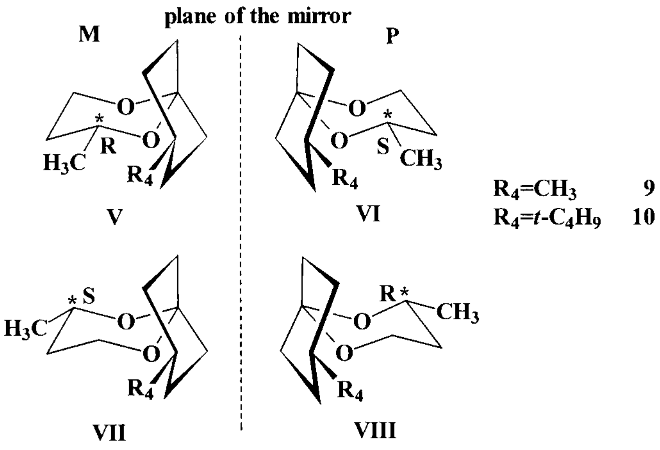


Figure 4. ^{1}H NMR spectrum (fragment) of compound **8**.

Compounds **9** and **10** show anancomeric structures, both cyclohexane and 1,3-dioxane rings being unsymmetically substituted. The characteristic conformational equilibria are shifted towards the conformations that exhibit both groups in equatorial orientations. Four isomers displaying both groups in equatorial orientations (Scheme 7, structures V-VIII) are possible: diastereoisomer D_1: structures V, VI and diastereoisomer D_2: structures VII, VIII. Their are no significantly energetical differences between these two diastereoisomers, so in the acetalization reaction, they have been obtained close to an equimolecular ratio (Table 2), as it could be determined using the intensity of their separated signals recorded in ^{1}H NMR spectra.



Scheme 7

Table 2. The ratio (%) of diastereoisomers of compounds **9-12**.

Compound	D_1	D_2	Method used
9	53	47	NMR
10	54	46	NMR
11	49.0	51.0	gas-chromatography
12	73.2	26.8	gas-chromatography

The NMR spectra of these compounds show two sets of signals corresponding to the two diastereoisomers, their chemical shifts close, in agreement with the small structural differences between the stereoisomers. As un example the ^1H NMR spectrum of compound **9** run in C_6D_6 with a 600 MHz apparatus (Figure 5) exhibits for the proton of position 2 of each diastereisomer [$\delta(D_1)=3.90$ and $\delta(D_2)=3.68$ ppm] overlapped doublet of doublet of quartets (resulting into doublets of sextets). The axial proton of position 4 displays a doublet of doublets of doublets with two close and large coupling constants ($^2J_{4ax\text{-}4eq}\approx{}^3J_{3ax\text{-}4ax}=11.7$ Hz) the peaks being overlapped in doublets of triplets. The signal [$\delta_{4ax}(D_1)=3.84$ ppm] corresponding to one of the diastereoisomers (D_1) is more deshielded than the doublets of triplets (overlapped doublet of doublets of doublets) belonging to the equatorial proton of the same position [$\delta_{4eq}(D_1)=3.729$ ppm], whereas for the other diastereoisomer (D_2) the signal (overlapped doublet of doublet of doublets) corresponding to the equatorial proton [$\delta_{4eq}(D_2)=3.738$ ppm] of position 4 is more deshielded as the signal belonging to the axial proton of the same position [$\delta_{ax}(D_2)=3.66$ ppm]. The signals pertaining to the equatorial protons of position 4 exhibit three coupling constants with different values. The geminal coupling constant shows a high value ($^2J_{4ax\text{-}4eq}=11.7$

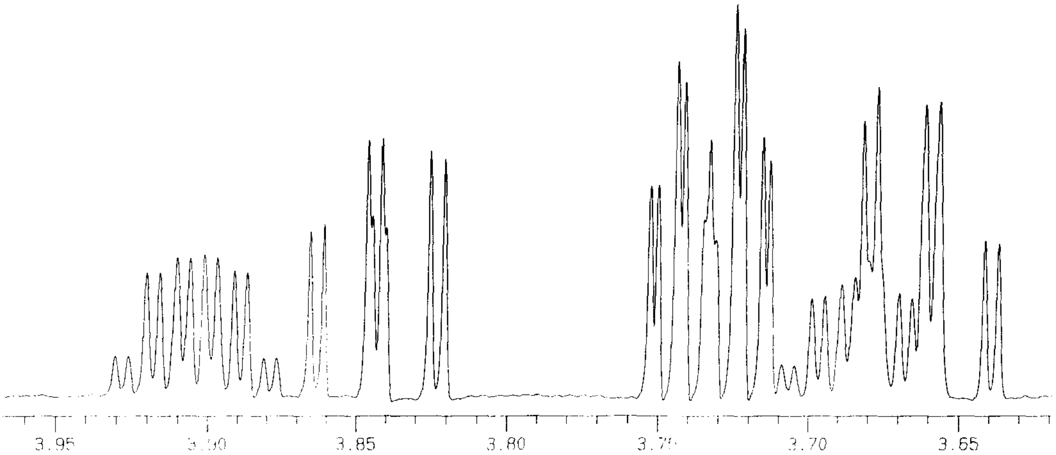
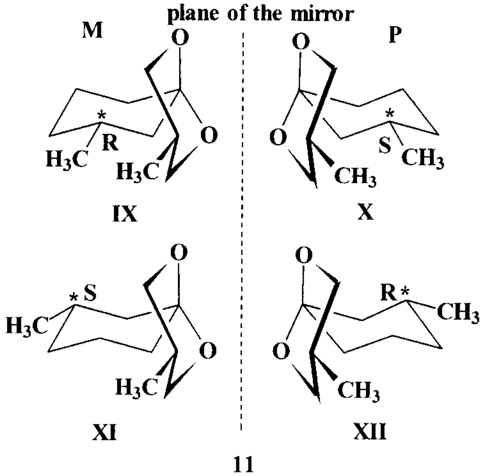


Figure 5. ^1H NMR spectrum (fragment, 600 MHz) of compound **9**.

Hz), while the vicinal coupling constants are considerably smaller ($^3J_{3ax\text{-}4eq}$=5.2 Hz and $^3J_{3eq\text{-}4eq}$=1.5 Hz). The signals of the equatorial protons of position 4 of the two diastereoisomers are overlapped the resulted pattern is looking (without being in fact) as triplets of doublets [$\delta_{2eq}(D_1)$=3.729 and $\delta_{2eq}(D_2)$=3.738 ppm].

The stereochemistry of compound **11** is close to that observed for compounds **9** and **10**. Both rings are anancomeric and the structures displaying both substituents in equatorial orientations are preferred (Scheme 8).

The two representative diastereoisomers D_1 (structures IX, X) and D_2 (XI, XII) have been obtained very close to an equimolecular ratio (Table 2) as it was measured in the NMR spectrum and determined by gas chromatography on a chiral column. The peaks of the enantiomers of one of the diastereoisomers are well separated (Figure 6, R_F1=25.43 and R_F1'=26.30 min) while for the other diastereoisomer only one peak is recorded (R_F2=27.05 min).



11

Scheme 8

The ^1H and ^{13}C NMR spectra of compound **11** show two sets of signals with close values of the chemical shifts pertaining to the two diastereoisomers of the compound. Different signals for the equatorial and axial positions of the protons and for the diastereotopic positions 2 and 4 have been recorded (Table 1).

Compound **12** shows a different stereochemistry to that observed for compounds **9-11**, despite of apparently small structural changes operated in the substitution of the cycles. In this case the configuration of the chiral center induces the configuration of the spiro skeleton. Only two structures (with the heterocycle pushed in the opposite side of the methyl substituent located in C_7) of the spirane with equatorial substituents are possible, one of them displaying M configuration of the helix and R configuration for the chiral carbon atom and the other one showing P and S configurations for the chiral elements (Scheme 9).

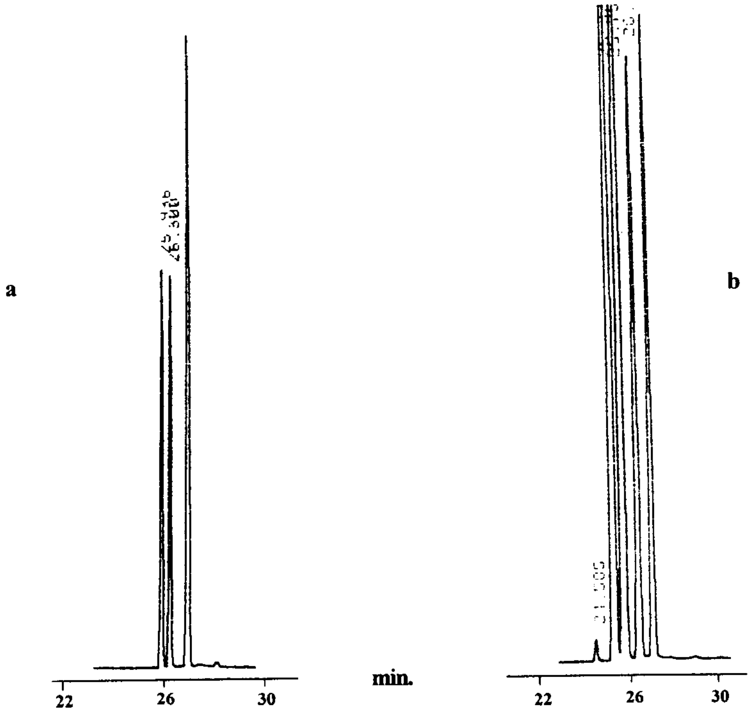
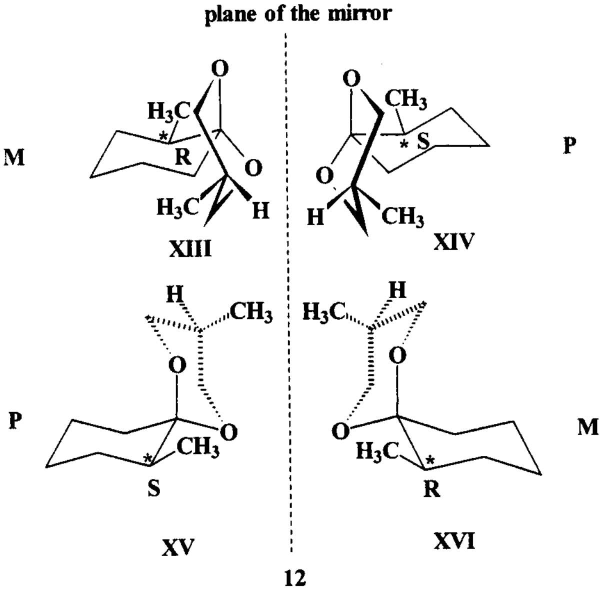


Figure 6. The gas-chromatograms (on chiral column) for compounds **11** (a) and **12** (b).



Scheme 9

The NMR and chiral gas-chromatographic investigations of the compound render evident the presence of two diastereoisomers (each of them as racemic mixture). In both diastereoisomers the methyl group located on the cyclohexane ring prefers the equatorial orientation but the methyl group located on the heterocycle exhibits an equatorial orientation in the major diastereoisomer (D_1: structures XIII, XIV) and an axial orientation on the minor one (D_2: structures XV, XVI), in agreement with the considerably higher values reported for the conformational free enthalpy of the methyl groups located on a cyclohexane ring[8,9] than in the position 5 (position 3 of this spiro compound) of the 1,3-dioxane system.[10] The ratio of the two diastereoisomers (D_1: 73.2% and D_2: 26.8%) was determined from the results of the gas chromatographic investigation of compound **12** on a chiral column. The chromatogram (Figure 6b) shows two well-separated peaks for the enantiomers of each diastereoisomer [D_1: $R_F(1)$=25.32 and $R_F(1)'$=25.75; D_2: $R_F(2)$=26.13 and $R_F(2)'$=27.07 min). These data have been used for calculate the conformational free enthalpy of the methyl group located in the position 3 of the spiro compound (position 5 of the 1,3-dioxane ring). It has been considered that the two diastereoisomers are in equilibrium during the acetalization reaction. This equilibrium was frozen at the end of the reaction by the neutralisation of the catalyst. The ratio of the two diastereoisomers found by gas-chromatography corresponds to the composition of equilibrium at the boiling point of benzene. The value found ΔG^{353}=0.71 kcal/mol ($K=\%(D_2)/\%(D_1)$, $\Delta G= -RT\ln K$) is somewhat smaller then the values reported in standard conditions for the free conformational enthalpy of the methyl group located in the position 5 of the 1,3-dioxane ring (ΔG^{o}=0.80-0.83 kcal./mol).[10,11]

The axial or equatorial orientation of the methyl group located on the heterocycle can be assumed by the ^{1}H NMR spectrum of the mixture of isomers (Figure 7).

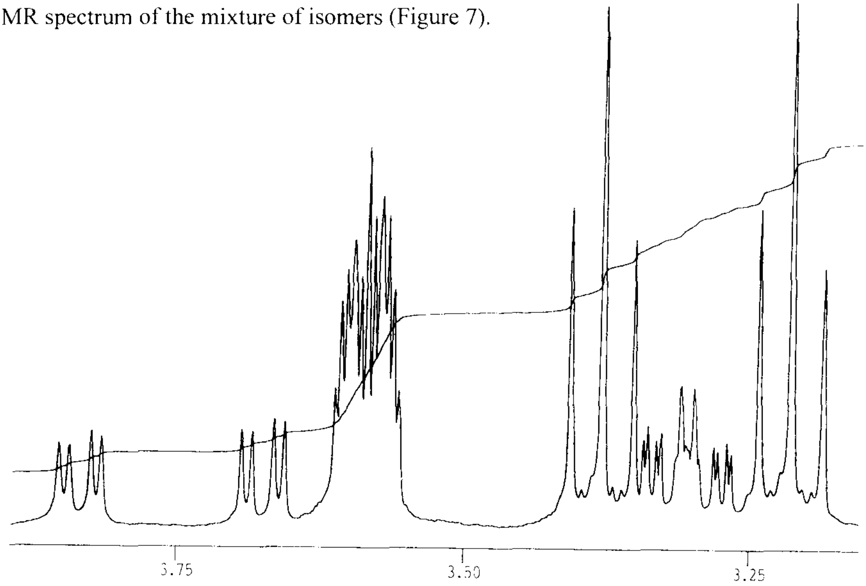


Figure 7. ^{1}H NMR spectrum (C_6D_6, fragment) of compound **12**.

The major isomer D_1 (structures XIII and XIV) exhibits for the axial and equatorial protons of the diastereotopic positions 2 and 4 two doublets of doublets. The axial protons show two large coupling constants with close values $[{}^2J_{2(4)ax-2(4)eq} \approx {}^3J_{2(4)ax-3ax} = 11.3$ Hz], the doublet of doublets being overlapped into triplets $[\delta_{2ax}(D_1) = 3.38$ and $\delta_{4ax}(D_1) = 3.21$ ppm]. The equatorial protons of this isomer are more deshielded and exhibit a vicinal coupling constant (with the axial proton of position 3) of only J=3.5 Hz. The signals of the equatorial protons are overlapped and show a further splitting due to the characteristic long range coupling between the diastereotopic equatorial protons $[\delta_{2eq}(D_1) = 3.59$ and $\delta_{4eq}(D_1) = 3.57$ ppm].

The minor diastereoisomer D_2 (structures XV and XVI) exhibits for the axial protons of the diastereotopic positions 2 and 4 two doublets of doublets $[\delta_{2ax}(D_2) = 3.83$ and $\delta_{4ax}(D_2) = 3.67$ ppm] with smaller vicinal coupling constants $[{}^3J_{2(4)ax-3eq} = 3.7$ Hz] in the usual range of values for the coupling between vicinal equatorial and axial protons located in a 1,3-dioxane ring[11]. The signals (doublets of doublets) of the equatorial protons are more shielded as those of the corresponding axial protons $[\delta_{2eq}(D_2) = 3.32$ and $\delta_{4eq}(D_2) = 3.28$ ppm] and show the characteristic further splitting due to the long range coupling between the equatorial protons of the diastereotopic positions 2 and 4 (W disposal of the bonds H_{eq}-C^2-C^3-C^4-H_{eq}, ${}^4J = 1.6$ Hz).

CONCLUSIONS

The investigated substituted 1,5-dioxaspiro[5.5]undecane derivatives exhibit anancomeric or semiflexible structures in correlation with the number of substituents and with their positions on the rings. The numbers of stereoisomers observed in the NMR spectra and in the chiral gas-chromatography of these compounds are in agreement with the results of the conformational analysis, with the helical chirality of the spiro skeleton and with the presence of the chiral carbon atoms located in it. The conformational free enthalpy of the methyl group attached in the position 3 of the spiro skeleton (position 5 of the 1,3-dioxane ring) has been calculated from the ratio of diastereoisomers of compound **12**.

ACKNOWLEDGEMENTS

The work was supported by a grant of the Romanian Council for University Scientific Research (CNCSU), also the financial support provided by OLTCHIM S. A. for the service of the Varian NMR equipment (Babes-Bolyai University) is greatly acknowledged.

EXPERIMENTAL

General. - NMR spectra have been run on a Bruker AM 400 (Varian*) spectrometer operating at 400 (300*) MHz for protons and 100 (75*) MHz for carbon atoms. No Me_4Si was added; the chemical shifts were

measured against the solvent line. The gas-chromatographic determinations were performed on a Kontron Instruments apparatus on a silice capillary chiral column of 15 m (Supelco β-Dex-120), filled up with a film of β-cyclodextrine, using a temperature program from 60 to 140°C with a temperature gradient of 2°/min.
M.ps were measured with Electrothermal melting point apparatus and are uncorrected.

*New compounds **1-12**, general procedure.* - Equimolecular amounts of 1,3-diol and carbonyl compound (0.1 mol) with catalytic amounts of p-toluenesulphonic acid (0.1 g) were solved in 200 ml benzene. The mixture was refluxed and the water resulted in the reaction was removed using a Dean-Stark trap. When 80-90 % of the theoretical water was separated, after cooling at room temperature, the catalyst was neutralized (under stirring 0.5 h) with CH_3-COONa 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 spiranes were purified by crystallization from ethanol or by vacuum distillation.

2-Methyl-1,5-dioxaspiro[5.5]undecane 1. Liquid. bp=70-71°C (1mm col.Hg), 6.90 g (0.0405 mol) yield 81 % (Found: C, 70.35; H, 10.80. $C_{10}H_{18}O_2$ requires C, 70.53; H, 10.66); δ_H (C_6D_6) 1.09(3H, d, J=6.1 Hz, 2-CH_3), 1.30-1.39(4H, overlapped peaks, 9-H, 10-H), 1.47-1.55(6H, overlapped peaks, 7-H, 8-H, 11-H), 1.78(1H, m, 3-H_{ax}), 1.87(1H, m, 3-H_{eq}), 3.71(1H, ddd, J=11.7, J'=5.5, J"=1.5 Hz, 4-H_{eq}), 3.89[1H, ddd (overlapped peaks giving dt), J≈J'≈12.0, J"=2.8 Hz, 4-H_{ax}] and 3.95[1H, ddq (overlapped peaks giving a doublet of sextets), J=12.1, J'=6.1, J"=3.4 Hz, 2-H_{ax}], δ_C (C_6D_6) 18.03 (2-CH_3), 18.35(C^3), 21.69(C^9), 23.73($C^{8,10}$), 28.91(C^{11}), 34.83(C^7), 54.45(C^4), 59.36(C^2) and 93.54(C^6).

8-Methyl-1,5-dioxaspiro[5.5]undecane 2. Liquid. bp=76-77°C (1mm col.Hg), 6.29 g (0.037 mol) yield 74 % (Found: C, 70.39; H, 10.75. $C_{10}H_{18}O_2$ requires C, 70.53; H, 10.66); δ_H (C_6D_6) 0.74(1H, m, 7-H_{ax}), 0.84(3H, d, J=6.6 Hz, 8-CH_3), 0.99[1H, t (overlapped dd), J≈J'≈12.7 Hz, 11-H_{ax}], 1.20(1H, m, 10-H_{ax}), 1.26-1.32(2H, overlapped peaks, 3-H), 1.45-1.60(3H, overlapped peaks, 9-H_{ax}, 9-H_{eq}, 10-H_{eq}), 1.72(1H, m, 8-H_{ax}), 2.25-2.34(2H, overlapped peaks, 7-H_{eq}, 11-H_{eq}), 3.53(2H, t, J=5.7 Hz, 4-H) and 3.65(2H, t, J=5.5 Hz, 2-H), δ_C (C_6D_6) 21.61(C^3), 22.07(8-CH_3), 25.78(C^9), 28.73($C^{8,}$), 32.53(C^{10}), 34.62(C^{11}), 41.63(C^7), 58.58(C^4), 58.65(C^2) and 97.94(C^6).

3,3,8-Trimethyl-1,5-dioxaspiro[5.5]undecane 3. Liquid. bp=84-85°C (1mm col.Hg), 6.64 g (0.0335 mol) yield 67 % (Found: C, 72.49; H, 11.15. $C_{12}H_{22}O_2$ requires C, 72.67; H, 11.19); δ_H (C_6D_6) 0.73(3H, s, 3-CH_3), 0.80-0.90(1H, m, 9-H_{ax}), 0.82(3H, s, 3-CH_3)', 0.86(3H, d, J=6.6 Hz, 8-CH_3), 1.02(1H, t, J≈J'=11.5 Hz, 7-H_{ax}), 1.21(1H, dt, J=11.5, J'=4.8 Hz, 11-H_{ax}), 1.46-1.62(3H, overlapped peaks, 9-H_{eq}, 10-H_{ax}, 10-H_{eq}), 1.75(1H, m, 8-H_{ax}), 2.26-2.36(2H, overlapped peaks, 7-H_{eq}, 11-H_{eq}), 3.29(2H, s, 4-H) and 3.39(2H, s, 2-H). δ_C (C_6D_6)

22.47(3-CH$_3$), 22.50(C^9), 22.72(3-CH$_3$)', 22-78(8-CH$_3$), 29.18(C^8), 30.14(C^3), 32.21 (C^{10}), 34.96(C^{11}), 41.75(C^7), 69.85(C^{2,4}) and 98.21(C^6).

3,3-Bis(ethyloxycarbonyl)-8-methyl-1,5-dioxaspiro[5.5]undecane 4. Liquid. bp=155-156°C(1mm col.Hg), 10.06 g (0.032 mol) yield 64 % (Found: C, 61.33; H, 8.48. $C_{16}H_{26}O_6$ requires C, 61.13; H, 8.34); δ_H (DMF-d$_6$) 0.93[3H, d, J=6.4 Hz, 8-CH$_3$(eq)], 0.95-1.68(7H, overlapped peaks, 7-H$_{ax}$, 8-H$_{ax}$, 9-H$_{ax}$, 9-H$_{eq}$, 10-H$_{ax}$, 10-H$_{eq}$, 11-H$_{ax}$), 1.288(3H, t, J=7.1 Hz, 3-COOCH$_2$C$\underline{H}_3$), 1.291(3H, t, J=7.1 Hz, 3-COOCH$_2$C$\underline{H}_3$)', 2.18-2.28(2H, overlapped peaks, 7-H$_{eq}$, 11-H$_{eq}$), 4.268(2H, q, J=7.1 Hz, 3-COOC$\underline{H}_2$CH$_3$), 4.274(2H, q, J=7.1 Hz, 3-COOC$\underline{H}_2$CH$_3$)', 4.31(2H, s, 4-H) and 4.35(2H, s, 2-H). δ_C (C$_6$D$_6$) 13.93(8-CH$_3$), 22.25(3-COOCH$_2$-$\underline{C}$H$_3$), 22.41(C^9), 29.19(C^8), 32.06(C^{10}), 34.71(C^{11}), 41.40(C^7), 61.59(3-COO$\underline{C}$H$_2$-CH$_3$), 62.14(C^4), 62.26(C^2), 99.20(C^6) and 168.18, 168.21(3-$\underline{C}$OOCH$_2$-CH$_3$).

3,3,7-Trimethyl-1,5-dioxaspiro[5.5]undecane 5. Liquid. bp=82-83°C (1mm col.Hg), 5.94 g (0.030 mol) yield 60 % (Found: C, 72.81; H, 11.29. $C_{12}H_{22}O_2$ requires C, 72.67; H, 11.19); δ_H (C$_6$D$_6$) 0.46[3H, s, 3-CH$_3$(eq)], 1.10[3H, s, 3-CH$_3$(ax)], 1.24(3H, d, J=6.9 Hz, 7-CH$_3$), 1.15-1.60[5H, overlapped peaks 7-H$_{ax}$, 8-H$_{ax}$, 9-H$_{ax}$, 10-H$_{ax}$, 11-H$_{ax}$], 1.76-1.84(2H, overlapped peaks, 9-Heq, 10-H$_{eq}$), 2.37-2.44(2H, overlapped peaks, 8-H$_{eq}$, 11-H$_{eq}$), 3.20(1H, dd, J=11.3, J'=2.4 Hz, 4-H$_{eq}$), 3.22(1H, dd, J=11.3, J'=2.4 Hz, 2-H$_{eq}$), 3.35(1H, d, J=11.3 Hz, 4-H$_{ax}$) and 3.52(1H, d, J=11.3 Hz, 2-H$_{ax}$), δ_C (C$_6$D$_6$) 14.34(7-CH$_3$), 22.19[3-CH$_3$(eq)], 23.05(C^9) 23.28[3-CH$_3$(ax)], 25.26(C^{10}), 27.49(C^8), 29.89(C^3), 31.16(C^{11}), 40.36(C^7), 69.50(C^4), 69.63(C^2) and 98.82(C^6).

3,3-Bis(ethyloxycarbonyl)-7-methyl-1,5-dioxaspiro[5.5]undecane 6. Liquid. bp=152-153°C(1mm col.Hg), 8.17 g (0.026 mol) yield 52 % (Found: C, 61.28; H, 8.37. $C_{16}H_{26}O_6$ requires C, 61.13; H, 8.34); δ_H (C$_6$D$_6$) 0.84[3H, t, J=7.2 Hz, 3-COOCH$_2$C$\underline{H}_3$(eq)], 1.00[3H, t, J=7.2 Hz, 3-COOCH$_2$C$\underline{H}_3$(ax)], 1.10[3H, d, J=6.6 Hz, 7-CH$_3$), 1.05-1.52[5H, overlapped peaks 7-H$_{ax}$, 8-H$_{ax}$, 9-H$_{ax}$, 10-H$_{ax}$, 11-H$_{ax}$], 1.71-1.80(2H, overlapped peaks, 9-Heq, 10-H$_{eq}$), 2.29-2.40(2H, overlapped peaks, 8-H$_{eq}$, 11-H$_{eq}$), 3.84[2H, q, J=7.2 Hz, 3-COOC$\underline{H}_2$CH$_3$(eq)], 4.08[2H, q, J=7.2 Hz, 3-COOC$\underline{H}_2$CH$_3$(ax)], 4.18(1H, d, J=11.7 Hz, 4-H$_{ax}$), 4.31(1H, d, J=11.7 Hz, 2-H$_{ax}$), 4.64(1H, dd, J=11.7, J'=2.2 Hz, 4-H$_{eq}$) and 4.67(1H, dd, J=11.7, J'=2.2 Hz, 2-H$_{eq}$), δ_C (C$_6$D$_6$) 13.84[3-COOCH$_2$$\underline{C}H_3$ (ax. and eq.)], 14.07(7-CH$_3$), 23.02(C^9), 24.98(C^{10}), 27.52(C^8), 30.94(C^{11}), 40.03(C^7), 54.04(C^3), 61.52 and 61.57[3-COO$\underline{C}$H$_2$CH$_3$ (ax. and eq.)], 62.03(C^4), 62.06(C^2), 99.43(C^6), 167.69[3-$\underline{C}$OOCH$_2$CH$_3$ (eq)] and 168.16[3-$\underline{C}$OOCH$_2$CH$_3$ (ax)].

3,3,8,8,10-Pentamethyl-1,5-dioxaspiro[5.5]undecane 7. Liquid. bp=109-110°C (1mm col.Hg), 8.48 g (0.0375 mol) yield 75 % (Found: C, 74.42; H, 11.49. $C_{14}H_{26}O_2$ requires C, 74.27; H, 11.58); δ_H (C$_6$D$_6$) 0.70(1H, m, 9-H$_{eq}$), 0.67[3H, s, 3-CH$_3$(eq)], 0.84(3H, d, J=6.6 Hz, 10-CH$_3$), 0.89[3H, s, 8-CH$_3$(eq)], 0.91[3H, s, 8-CH$_3$(ax)], 1.01[1H, dd (overlapped giving a triplet), J≈J'=12.6 Hz, 9-H$_{ax}$], 1.08(1H, d, J=10.2 Hz, 7-H$_{ax}$), 1.11[3H, s, 3-CH$_3$(ax)], 1.30(1H, m, 11-H$_{ax}$), 1.92(1H, m, 10-H$_{ax}$), 2.17-2.27(2H, overlapped peaks, 7-H$_{eq}$, 11-H$_{eq}$), 3.23(1H, dd, J=11.2, J'=1.6 Hz, 4-H$_{eq}$), 3.32(1H, dd, J=11.2, J'=1.6 Hz, 2-H$_{eq}$), 3.34(1H, d, J=11.2 Hz, 4-H$_{ax}$) and 3.44(1H, d, J=11.2 Hz, 2-H$_{ax}$), δ_C (C$_6$D$_6$) 22.11[3-CH$_3$(eq)], 22.21[3-CH$_3$(ax)], 22.66[10-CH$_3$(eq)], 25.17[8-CH$_3$(eq)], 25.92[8-CH$_3$(ax)], 31.51(C^3), 31.64(C^8), 33.84(C^{10}), 41.75(C^9), 43.14(C^{11}), 48.58(C^7), 69.63(C^4), 69.77(C^2) and 98.67(C^6).

3,3-Bis(ethyloxycarbonyl)-8,8,10-trimethyl-1,5-dioxaspiro[5.5]undecane 8. Liquid. bp=170-172°C(1mm col.Hg), 13.11 g (0.0385 mol) yield 77 % (Found: C, 63.28; H, 8.77. C$_{18}$H$_{30}$O$_6$ requires C, 63.12; H, 8.84); δ_H (C$_6$D$_6$) 0.64[1H, t (overlapped dd), J≈J'=12.8 Hz, 9-H$_{ax}$], 0.75[3H, d, J=6.6 Hz, 10-CH$_3$ (eq)], 0.80[3H, s, 8-CH$_3$(eq)], 0.84[3H, t, J=6.9 Hz, 3-COOCH$_2$C$\underline{\mathrm{H}}_3$(eq)], 0.89[3H, t, J=6.9 Hz, 3-COOCH$_2$C$\underline{\mathrm{H}}_3$(ax)], 0.96(1H, t, J≈J'=12.8 Hz 11-H$_{ax}$), 1.01[3H, s, 8-CH$_3$(ax)], 1.04(1H, d, J=14.0 Hz, 7-H$_{ax}$), 1.21(1H, m, 9-H$_{eq}$), 1.83(1H, m, 10-H$_{ax}$), 2.16-2.21(2H, overlapped peaks, 11-H$_{eq}$, 7-H$_{eq}$), 3.88[2H, q, J=6.9 Hz, 3-COOC$\underline{\mathrm{H}}_2$CH$_3$(eq)], 3.97[2H, q, J=6.9 Hz, 3-COOC$\underline{\mathrm{H}}_2$CH$_3$(ax)], 4.42(1H, d, J=11.6 Hz, 4-H$_{ax}$), 4.50(1H, d, J=11.6 Hz, 2-H$_{ax}$), 4.59(1H, dd, J=11.6, J'=1.3 Hz, 4-H$_{eq}$) and 4.63(1H, dd, J=11.6, J'=1.3 Hz, 2-H$_{eq}$), δ_C (C$_6$D$_6$) 13.55[3-COOCH$_2\underline{\mathrm{C}}$H$_3$ (eq)], 13.60[3-COOCH$_2\underline{\mathrm{C}}$H$_3$ (ax)], 21.88(10-CH$_3$), 25.05[8-CH$_3$(eq)], 25.68[8-CH$_3$(ax)], 31.43(C^8), 33.54(C^{10}), 41.44(C^9), 42.76(C^{11}), 48.75(C^7), 54.16(C^3), 61.28[3-COO$\underline{\mathrm{C}}$H$_2$CH$_3$ (ax. and eq.)], 61.89(C^4), 62.10 (C^2), 99.65(C^6), 167.81[3-$\underline{\mathrm{C}}$OOCH$_2$CH$_3$ (eq)] and 167.94[3-$\underline{\mathrm{C}}$OOCH$_2$CH$_3$ (ax)].

2,9-Dimethyl-1,5-dioxaspiro[5.5]undecane 9. Liquid. bp=82-83°C(1mm col.Hg), 6.62 g (0.036 mol) yield 72 % (Found: C, 71.82; H, 11.09. C$_{11}$H$_{20}$O$_2$ requires C, 71.68; H, 10.95), mixture of diastereoisomers (D$_1$/D$_2$=53/47). δ_H (C$_6$D$_6$) 0.85, 0.86(3H, d, J=6.5 Hz, 9-CH$_3$), 1.05, 1.06(3H, d, J=5.9 Hz, 2-CH$_3$), 0.90-1.70(7H, overlapped peaks, 3-H$_{ax}$, 3-H$_{eq}$, 7-H$_{ax}$, 8-H$_{ax}$, 9-H$_{ax}$, 10-H$_{ax}$, 11-H$_{ax}$), 2.07-2.14(2H, overlapped peaks, 8-H$_{eq}$, 10-H$_{eq}$,), 2.40-2.50(2H, overlapped peaks, 7-H$_{eq}$, 11-H$_{eq}$), 3.66[1H, dt(overlapped ddd), J≈J'=11.7, J"=2.7 Hz, 4-H$_{ax}$], 3.68[1H, doublet of sextets(overlapped ddt), J=11.7, J'=6.2, J"=2.5 Hz, 2-H$_{ax}$], 3.729[1H, ddd, J=11.7, J'=5.2, J"=1.5 Hz, 4-H$_{eq}$], 3.738[1H, ddd, J=11.7, J'=5.2, J"=1.5 Hz, 4-H$_{eq}$], 3.84[1H, dt(overlapped ddd), J≈J'=11.7Hz, J"=2.7 Hz, 4-H$_{ax}$] and 3.90[1H, doublet of sextets(overlapped ddq), J=12.0, J'=6.0, J"=2.5 Hz, 2-H$_{ax}$]. δ_C (C$_6$D$_6$) 17.35, 17.44(9-CH$_3$), 18.00, 18.07(2-CH$_3$), 23.08(C^3), 26.58(C^{10}), 26.70(C^8), 27.80, 27.87(C^9), 28.92(C^{11}), 34.28, 34.41(C^7), 54.43, 54.69(C^4), 59.42, 59.59(C^2) and 93.53(C^6).

2-Methyl-9-t-butyl-1,5-dioxaspiro[5.5]undecane 10. Solid. mp=38-39°C, 7.91 g (0.035 mol), yield 70 % (Found: C, 74.42; H, 11.69. C$_{14}$H$_{26}$O$_2$ requires C, 74.27; H, 11.58), mixture of diastereoisomers (D$_1$/D$_2$=54/46) δ_H (C$_6$D$_6$) 0.83, 0.84[9H, s, 9-C(CH$_3$)$_3$], 0.91-1.70[7H, overlapped peaks, 3-H$_{ax}$, 3-H$_{eq}$, 7-H$_{ax}$, 8-H$_{ax}$, 9-H$_{ax}$, 10-H$_{ax}$, 11-H$_{ax}$), 2.13-2.20(2H, overlapped peaks, 8-H$_{eq}$, 10-H$_{eq}$), 2.54-2.62(2H, overlapped peaks, 7-H$_{eq}$, 11-H$_{eq}$), 3.700[1H, dt(overlapped ddd), J≈J'=11.7, J''=2.7 Hz, 4-H_{ax}], 3.721[1H, doublet of sextets(overlapped ddt), J=11.7, J'=6.1, J"=2.5 Hz, 2-H_{ax}], 3.757[1H, ddd, J=11.6, J'=5.4, J''=1.6 Hz, 4-H_{eq}], 3.759[1H, ddd, J=11.6, J'=5.4, J''=1.6 Hz, 4-H_{eq}], 3.882[1H, dt(overlapped ddd), J≈J'=11.6, J"=2.6 Hz, 4-H_{ax}] and 3.941[1H, doublet of sextets(overlapped ddq), J=11.7, J'=6.1, J"=2.5 Hz, 2-H_{ax}]. δ_C (C_6D_6) 18.04, 18.11(2-CH_3), 23.22[9-$C(\underline{C}H_3)_3$], 19.13, 19.22(C^3), 23.70, 23.84(C^{10}), 27.75[9-$\underline{C}(CH_3)_3$], 28.96(C^8), 34.88(C^{11}), 34.99(C^7), 43.46, 43.57(C^9), 54.49, 54.79(C^4), 59.70, 59.85(C^2) and 93.47(C^6).

3,8-Dimethyl-1,5-dioxaspiro[5.5]undecane 11. Liquid. bp=80-81°C(1mm col.Hg), 7.75 g (0.041 mol) yield 82 % (Found: C, 71.55; H, 10.88. $C_{11}H_{20}O_2$ requires C, 71.68; H, 10.95), mixture of diastereoisomers (D_1/D_2=51.0/49.0); δ_H (C_6D_6) 0.44, 0.46(3H, d, J=6.8 Hz, 3-CH_3), 0.83, 0.84(3H, d, J=6.4 Hz, 8-CH_3), 0.70-1.90(6H, overlapped peaks, 7-H_{ax}, 8-H_{ax}, 9-H_{eq}, 9-H_{ax}, 10-H_{ax}, 11-H_{ax}), 2.10-2.18(2H, overlapped peaks, 8-H_{eq}, 10-H_{eq}), 2.36-2.46(2H, overlapped peaks, 7-H_{eq}, 11-H_{eq}), 3.17, 3.22[1H, t(overlapped dd), J≈J'=11.3 Hz, 4-H_{ax}], 3.35, 3.39[1H, t(overlapped dd), J≈J'=11.2 Hz, 2-H_{ax}], 3.584, 3.599[1H, ddd, J=11.3, J'=4.7, J"=1.4 Hz, 4-H_{eq}], and 3.630, 3.632[1H, ddd, J=11.2, J'=4.7, J"=1.4 Hz, 2-H_{eq}]. δ_C (C_6D_6) 12.89, 12.96(8-CH_3), 22.12(C^9), 22.19(3-CH_3), 28.56, 28.77(C^{10}), 28.83(C^8), 29.34(C^3), 34.63(C^{11}), 36.01, 37.73(C^7), 65.01, 65.14($C^{2,4}$) and 97.67(C^6).

3,7-Dimethyl-1,5-dioxaspiro[5.5]undecane 12. Liquid. bp=76-77°C(1mm col.Hg), 6.63 g (0.036 mol) yield 72 % (Found: C, 71.77; H, 10.83. $C_{11}H_{20}O_2$ requires C, 71.68; H, 10.95), mixture of diastereoisomers (D_1/D_2= 73.2/26.8); δ_H (C_6D_6) D_1 0.34[3H, d, J=6.7 Hz, 3-CH_3 (eq)], 1.30[3H, d, J=6.7 Hz, 7-CH_3 (eq)], 1.16-1.66(7H, overlapped peaks, 7-H_{ax}, 8-H_{ax}, 8-H_{eq}, 9-H_{ax}, 9-H_{eq}, 10-H_{ax}, 10-H_{eq}), 1.83(1H, m, 11-Hax), 2.25(1H, m, 3-H_{ax}), 2.40(1H, m, 11-H_{eq}), 3.21(1H, t (overlapped dd), J≈J'=11.3 Hz, 4-H_{ax}), 3.38(1H, t (overlapped dd), J≈J'=11.3 Hz, 2-H_{ax}), 3.57(1H, ddd, J=11.3, J'=3.5, J"=1.9 Hz, 4-H_{eq}) and 3.59(1H, ddd, J=11.3, J'=3.5, J"=1.9 Hz, 2-H_{eq}) D_2 0.92[3H, d, J=6.7 Hz, 3-CH_3 (ax)], 1.20[3H, d, J=6.7 Hz, 7-CH_3 (eq)], 1.16-1.66(7H, overlapped peaks, 7-H_{ax}, 8-H_{ax}, 8-H_{eq}, 9-H_{ax}, 9-H_{eq}, 10-H_{ax}, 10-H_{eq}), 1.83(1H, m, 11-H_{ax}), 2.00(1H, m, 3-H_{eq}), 2.40(1H, m, 11-H_{eq}), 3.28(1H, ddd, J=11.3, J'=4.7, J"=1.6 Hz, 4-H_{eq}), 3.32(1H, ddd, J=11.3, J'=4.6, J"=1.6 Hz, 2-H_{eq}), 3.67(1H, dd, J=11.3, J'=3.7 Hz, 4-H_{ax}) and 3.83(1H, dd, J=11.3, J'=3.7 Hz, 2-H_{ax}), δ_C (C_6D_6) D_1: 12.19[3-CH_3(eq)], 13.80[7-CH_3(eq)], 22.69(C^9), 25.18(C^{10}),, 27.02(C^8), 29.34(C^3), 30.95(C^{11}), 40.85(C^7), 65.08(C^4), 65.18(C^2) and 98.67(C^6); D_2: 13.89[7-CH_3(eq)], 14.84[3-CH_3(ax)], 23.61(C^9), 25.01(C^{10}),, 27.53(C^8), 28.96(C^3), 30.95(C^{11}), 40.85(C^7), 63.92(C^4), 64.08(C^2) and 97.98(C^6);

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