SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW SPIRO BENZO-1,3-DIOXANE DERIVATIVES

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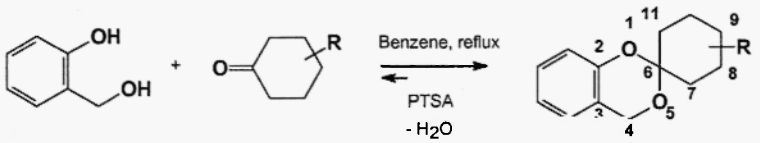
Abstract : The synthesis and the structural analysis of new spiro-benzo-1,3-dioxane derivatives is reported. The stereochemistry of these compounds was studied using ^{1}H-NMR experiments (*rt* and *vt*, respectively) and the single crystal X-ray diffractometry molecular structure determined for one of the derivatives.

Introduction

1,3-Benzodioxanes represent an interesting motif in applied chemistry. Some of these derivatives were reported as agrochemical fungicides (1), biocides (2), pesticides (3, 4), and herbicides (5). Some 1,3-benzodioxanes were found to have anti-inflammatory activity and low toxicity (6), or analgesic, mucolytic, and antipyretic activity (7). Unsaturated spiranes occur in the acidic degradation of steroids (8, 9) or are a part of the skeleton of saponine of *Ruscus aculeatus L.* (10). Despite the large number of papers and reviews (11-15) reporting on the stereochemistry of 1,3-dioxane derivatives, few papers are dealing with the stereochemistry of benzo[4H]-1,3-dioxine derivatives (16). We considered of interest to continue our studies (17-19) on the synthesis and stereochemistry of spirane derivatives and to investigate by NMR spectra and X-ray diffractometry various spiranes exhibiting benzo-1,3-dioxane (benzo[4H]-1,3-dioxine) units.

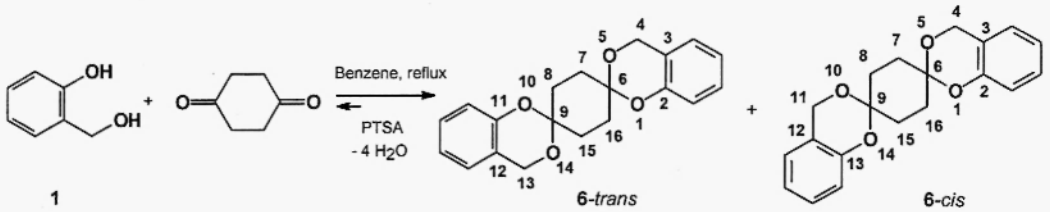
Results and Discussions

Spiro-benzo-1,3-dioxanes **2-7** were obtained in good yields by the ketalization reaction of several cyclohexanones with salicylic alcohol (**1**, Schemes 1 and 2).



1 R = H **2**
R = 9-CH_3 **3**
R = 9-$C(CH_3)_3$ **4**
R = 8(*R*)-CH_3 **5**

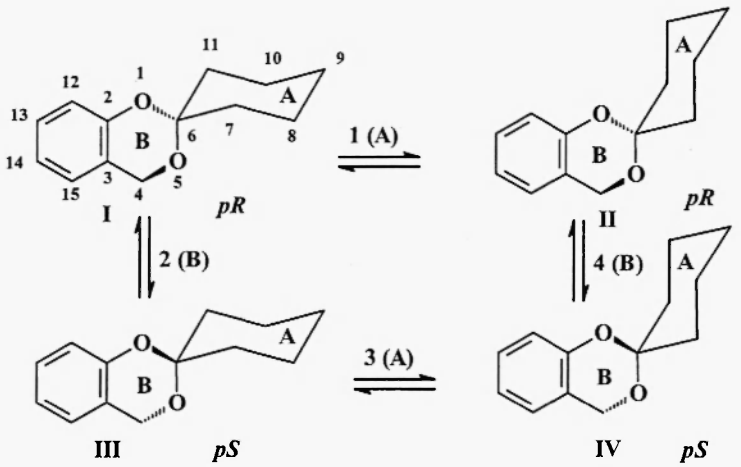
Scheme-1



Scheme-2

Monospirane **2** has flexible structure, both 4[H]-1,3-dioxine (B) and cyclohexane (A) rings are flipping (Scheme 3). 4[H]-1,3-dioxine ring prefers the chiral half-chair conformation (planar chirality) with C^6 and O^5 out of the plain of the aromatic ring. The flipping of the heterocycle determines the enantiomeric inversion [I (*pR*) ⇆ III (*pS*) and II (*pR*) ⇆ IV (*pS*) are enantiomers]. The flipping of the cyclohexane ring represents a diastereomeric equilibrium, structures I and III exhibit the O-C_6H_4- moiety in equatorial orientation while structures II and IV have the O-CH_2-C_6H_4- group in equatorial position (refereed to the cyclohexane ring).

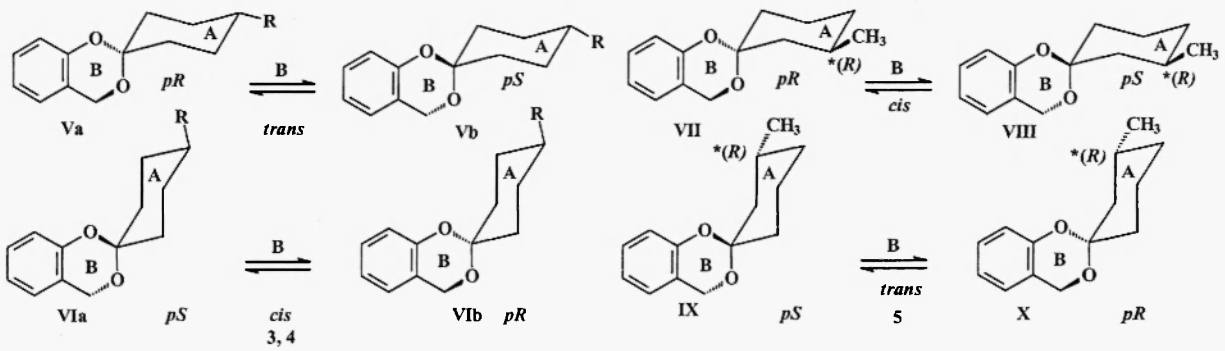
The flexibility of the spirane part of **2** determines the fast equilibrium of all four possible structures and the NMR spectra recorded at *rt* show unique signals at mean values of the chemical shifts (Table 1) for the different diastereoisomers (I, III and II, IV) and for the different orientations of the similar groups



2

Scheme-3

Compounds **3-5** have semiflexible structures, the substituted cyclohexane ring is anancomeric (R is *holding group* and exhibits equatorial orientation) and the 4[H]-1,3-dioxine ring is flipping (Scheme 4). These compounds show *cis* (scheme 4: VIa and VIb; VII and VIII) and *trans* isomers (scheme 4: Va and Vb; IX and X).



Scheme-4

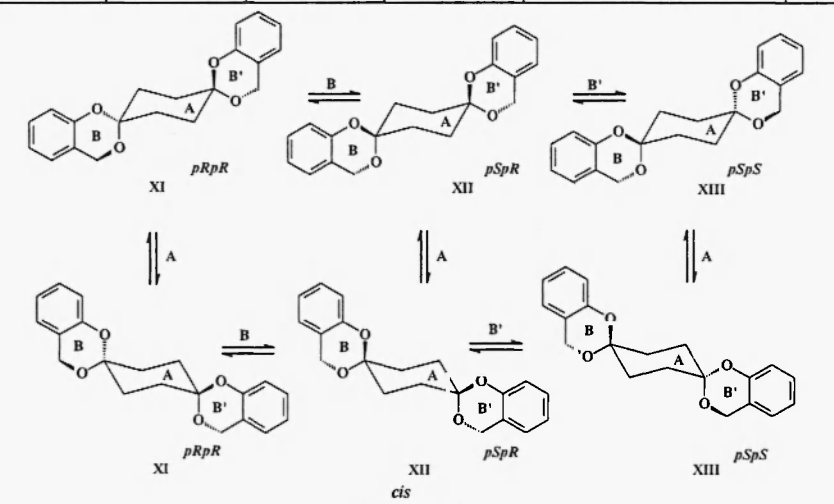
R and O-C_6H_4- are considered as references. At the same time the chirality (planar) of the 4[H]-1,3-dioxine ring determines the chirality of the compounds and the flipping of the heterocycle determines the enantiomeric inversion for **3** and **4** (Va ⇆ Vb; VIa ⇆ VIb) and the diastereomeric equilibrium for **5** (VII ⇆ VIII; IX ⇆ X). The *cis* and *trans* structures could not be isolated as single isomers and the compounds were investigated as mixtures of isomers.

The ^{1}H NMR spectra of **3-5** show many signals in the part corresponding to the protons of the cyclohexane ring due to frozen flipping of this ring and to the differentiation of axial and equatorial orientations. The singlet corresponding to the CH_2 protons of the heterocycle is more shielded for the *trans* isomer ($\Delta\delta_{3\text{-}5} = \delta_{cis} - \delta_{trans}$ = 0.05-0.10 ppm).

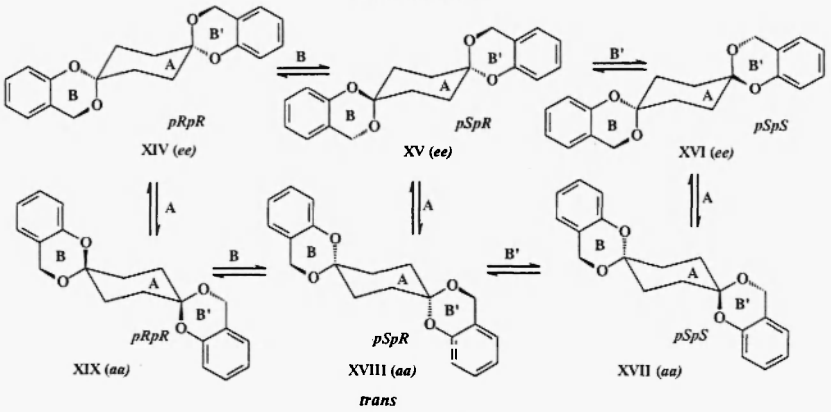
Dibenzo-dispiro derivative **6** exhibits three stereogene elements, two 4[H]-1,3-dioxine rings with planar chirality [20] and the differently substituted cyclohexane ring which determines *cis* and *trans* isomers. *Cis* and *trans* isomers of **6** were separated by flash chromatography and were investigated as single compounds. The chirality of the heterocycles determines *like* (*pRpR*; *pSpS*) and *unlike* (*pRpS* = *pSpR*) structures (Schemes 5 and 6).

Table-1 : ^{1}H NMR chemical shifts (δ, ppm, $CDCl_3$, *rt*) of methylene group of the 4[H]-1,3-dioxine moiety of **2-7**

Compound	**2**	**3**	**4**	**5**	**6-*trans***	**6-*cis***
Protons	4-H				4-H, 13-H	4-H, 11-H
δ_{trans}						
δ_{cis}						



Scheme-5



Scheme-6

Cis isomer (XI-XIII) exhibits the reference groups (–C_6H_4-O-) in axial-equatorial orientations and the flipping of the cyclohexane ring is an homomeric equilibrium, while the flipping of 4[H]-1,3-dioxine rings determines the diastereoisomeric equilibrium (Scheme 5).

Trans isomer (XIV-XIX) exhibits the reference groups either in axial-axial, either in equatorial-equatorial orientations. The flipping of the cyclohexane or of the 4[H]-1,3-dioxine rings represents diastereoisomeric equilibria.

Cis and *trans* isomers are flexible compounds and the flipping of the central cyclohexane ring and of the heterocycles renders in equilibrium all possible isomers (enantiomers and diastereoisomers; *cis*: XI-XII, *trans*: XIV-XIX). The *rt* ^{1}H NMR spectra of *trans* and *cis* exhibit only singlets for the protons of 4[H]-1,3-dioxine rings (**6-*trans***: $\delta_{4,13}$ = 4.85 ppm; **6-*cis***: $\delta_{4,11}$ = 4.86 ppm; Figures 1 and 2). The spectra display a singlet for the protons of the cyclohexane ring of the *trans* isomer and overlapped multiplets for those of *cis* one (**6-*trans***: $\delta_{7,8,15,16}$ = 2.03 ppm; **6-*cis***: $\delta_{7,8,15,16}$ = 1.93-2.09 ppm; Figure 1).The variable temperature ^{1}H NMR experiments (Figure 1) run with 6-*cis* and **6-*trans*** show the freezing of the flipping of the rings at low temperatures (that determines a higher number of signals in the NMR spectra).

Two net coalescence points for **6**-*trans* isomer (T_c = 224 K for the signals belonging to the protons of the cyclohexane ring, T_c' = 220 K for the protons of the heterocycles) and one coalescence point for **6**-*cis* [the signals corresponding to the 4[H]-1,3-dioxine ring (T_c = 217 K)] could be measured.

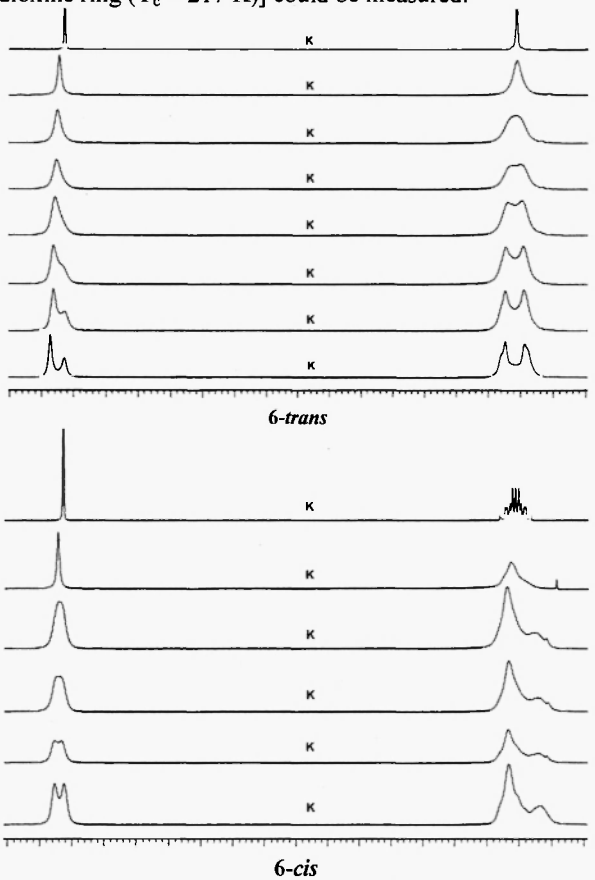


Figure-1 : ^{1}H-NMR spectra (fragments) of **6**-*trans* and **6**-*cis* recorded at different temperatures ($CDCl_3$, 300 MHz)

The solid-state molecular structure was determined for **6**-*trans* (Figure 2) using monocrystal X-ray diffractometry. The ORTEP [22] diagram shows the chair conformation of the cyclohexane ring and the equatorial orientation of the -O-C_6H_4- moieties (-O-CH_2-C_6H_4- fragments are disposed in axial positions). The 1,3-dioxine rings have a half-chair conformation and the two 4[H]-1,3-dioxine ring exhibit different configurations that means the compound crystallized in the centrosymmetric equatorial-equatorial *unlike* isomer (corresponding to the structure XV in scheme 5). The two benzene rings are parallel (dihedral angle 1.4°).

The package of molecules in the monocrystal caused an interesting stacking pattern by the interaction between one benzene ring and one hydrogen atom belonging to the methylene group of the 1,3-dioxine moiety of a neighboring molecule (Figure 3).

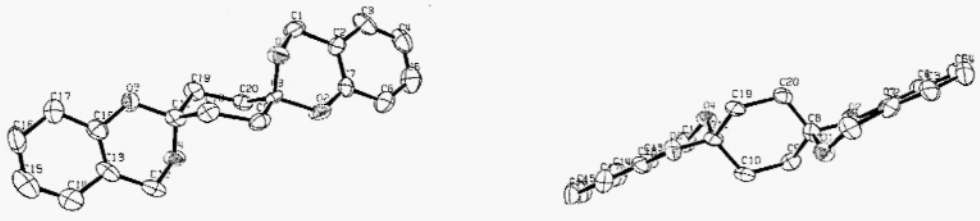


Figure-2 : ORTEP drawings of **6**-*trans* (hydrogen atoms were omitted for clarity)

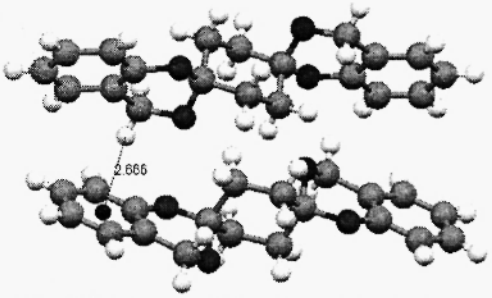


Figure-3 : Mercury drawing [23] of two neighboring molecules in the monocrystal of **6-*trans***

Experimental

^1H and ^{13}C NMR spectra were recorded with Varian Gemini 300 and Bruker ARX 300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent. The assignments of quaternary C (C_{quat}), CH, CH_2 and CH_3 were made on the basis of DEPT or APT spectra. Mass spectra were recorded using a Varian MAT 311 spectrometer. IR measurements were performed with a JASCO FT-IR spectrophotometer in film or in KBr pellets. The solvents were purified according to standard procedures and were distilled prior to use. Column chromatography: silica gel 60 (Merck, Darmstadt), mesh 43-60 nm. Thin layer chromatography (TLC): silica gel layered aluminum foil (60 F_{254} Merck, Darmstadt). Melting points (uncorrected) were taken using a Kleinfeld APOTEK apparatus. Elemental analyses (C, H) were measured at IRCOF, University of Rouen, France, and the results were found to be in good agreement (±0.2%) with the calculated values. The starting materials were purchased from Merck (salicylic alcohol) and Aldrich (cyclohexanones) and were used without further purification..

Compounds **1**, **2** and **4-8** are new, while the synthesis of **3** was already mentioned in the literature.[16]

***Compounds* 1-8 (*General Procedure*)**

A mixture of cyclohexanone (10 mmol), 1.24 g salicylic alcohol (10 mmol) and 5g of Na_2SO_4 in 30 cm^3 of benzene was refluxed for 3 h. The reaction mixture was cooled at *rt* and was added to a mixture of 50 cm^3 of water and 20 cm^3 of methylene chloride. The aqueous layer was separated and extracted two times with 20 cm^3 of methylene chloride. The organic layers were washed with 100 cm^3 of water and 100 cm^3 of brine and then dried on sodium sulfate. The residue was adsorbed on silica gel and was subjected to column chromatography separation (petroleum ether: ethyl acetate = 10:1) to afford the pure products.

1,5-dioxa-benzo[b]spiro[5.5]undecan-2-ene (**2**) colourless resin, η=40%. 'H NMR and IR spectra were found to be identical with the one described in Ref. [20].

8(R)–methyl-1,5-dioxa-benzo[b]spiro[5.5]undecan-2-ene (**3**, $C_{14}H_{18}O_2$) *cis* + *trans* mixture, colourless resin, η=42%. ^1H NMR δ (ppm) 0.93 ppm (3H, d, ^3J=6Hz, 8-CH_3), 1.66-1.74 (7H, m, overlapped peaks, 7-H, 8-H, 9-H, 10-H, 11-H), 2.12 (2H, m, 7-H, 11-H), 4.79, 4.88 (2H, 2s, 4-CH_2), 6.81-6.97 (3H, overlapped peaks, H^{ar}) 7.13-7.16 (1H, m, H^{ar}). EI-MS (M/z): 218 (M^+). Anal. Calcd. for $C_{14}H_{18}O_2$.: C: 77.03, H: 8.31; Found: C: 77.21, H: 8.44.

9-methyl-1,5-dioxa-benzo[b]spiro[5.5]undecan-2-ene (**4**, $C_{14}H_{18}O_2$) colourless resin, η=40%. ^1H NMR δ (ppm) 0.95 (3H, d, ^3J=6Hz, 9-CH_3), 1.23-1.66 (7H, overlapped, 7-H, 8-H, 9-H, 10-H, 11-H), 2.08 (2H, m), 4.79, 4.87 (2H, 2s, 4-CH_2), 6.85-6.95 (3H, overlapped peaks, H^{ar}) 7.13-7.16 (1H, m, H^{ar}). IR ν (cm^{-1}) 3045.05, 2949.59, 2857.02, 1613.16, 1588.09, 1490.70, 1458.89, 1272.79, 1095.37, 1040.41, 904.45, 752.10. EI-MS (M/z): 218 (M^+). Anal. Calcd. for $C_{14}H_{18}O_2$.: C: 77.03, H: 8.31; Found: C: 77.18, H: 8.20.

9-tert-buthyl-1,5-dioxa-benzo[b]spiro[5.5]undecan-2-ene (**5**, $C_{17}H_{24}O_2$) colourless resin, η=40%. ^1H NMR δ (ppm) 0.89 (9H, d, ^3J=6Hz, 4'-C(CH_3)), 1.02-1.78 (7H, m), 2.15 (2H, m), 4.80, 4.88 (2H, 2s, 4-CH_2), 6.81-6.97 (3H, overlapped peaks, H^{ar}) 7.13-7.17 (1H, m, H^{ar}). IR ν (cm^{-1}) 2952.48, 2924.52, 2854.13, 1614.13, 1589.06, 1459.85, 1376.93, 1273.75, 1238.08, 1088.62, 751.14. EI-MS (M/z): 218 (M^+). Anal. Calcd. for $C_{17}H_{24}O_2$.: C: 78.42, H: 9.29; Found: C: 78.60, H: 9.48.

1,5,10,14-tetraoxa-benzo[b]-benzo[k]dispiro[5.2.5.2]tetradecan-2,11-diene (**6**-*trans*, $C_{20}H_{20}O_4$) white powder, m.p.= 148-9°C. η=27%. ^{1}H NMR δ (ppm) 2.03 (8H, s, 7-H, 8-H, 15-H, 16-H), 4.85 (4H, s, 4-H, 13-H), 6.84-6.97 (6H, overlapped peaks, H^{ar}), 7.14-7.19 (2H, overlapped peaks, H^{ar}). ^{13}C-NMR δ (ppm) 29.17 (CH_2), 60.36 (CH_2), 98.70 (C_{quat}), 116.90 (CH), 119.54 (C_{quat}), 120.37 (CH), 124.46 (CH), 127.92 (CH), 150.66 (C_{quat}). EI-MS (M/z): 324 (M^+). Anal. Calcd. for $C_{20}H_{20}O_4$.: C: 74.06, H: 6.21; Found: C: 74.21, H: 6.09.

1,5,10,14-tetraoxa-benzo[b]-benzo[l]dispiro[5.2.5.2]tetradecan-2,12-diene (**6**-*cis*, $C_{20}H_{20}O_4$) white powder, m.p.= 164-5°C. η=25%. ^{1}H NMR δ (ppm) 1.93-2.09 (8H, m, overlapped peaks, H), 4.86 (s, 4H, 4-H, 11-H), 6.85-6.97 (6H, overlapped peaks, H^{ar}), 7.13-7.19 (2H, overlapped peaks, H^{ar}). ^{13}C-NMR δ (ppm) 29.17 (CH_2), 60.35 (CH_2), 98.71 (C_{quat}), 116.92 (CH), 119.49 (C_{quat}), 120.34 (CH), 124.44 (CH), 127.92 (CH), 150.66 (C_{quat}). EI-MS (M/z): 324 (M^+). Anal. Calcd. for $C_{20}H_{20}O_4$.: C: 74.06, H: 6.21; Found: C: 74.15, H: 6.33.

Conclusions

The structural analysis of new spiro and dispiro-4[H]-1,3-dioxine derivatives carried out using NMR spectra and X-ray diffractometry revealed flexible and semiflexible structures and the *cis*, *trans* (compounds **3-5**) and the *like*, *unlike* (compound **6**) isomerism of these derivatives. The cyclohexane ring prefers the chair conformation, while the 4[H]-1,3-dioxine rings have chiral half-chair conformations. The investigation of the lattice of **6**-*trans* showed important stacking interactions.

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