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SYNTHESIS AND STEREOCHEMISTRY OF SOME SPIRO-1,3-OXATHIANE DERIVATIVES

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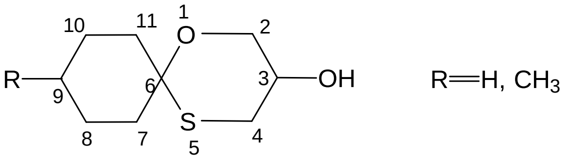
ABSTRACT. The synthesis and the stereochemistry of two new spiro-1,3-oxathianes are discussed. NMR and IR investigations revealed flexible and semi-flexible structures.

INTRODUCTION

In the last years, alkyl 1,3-oxathiane derivatives are strongly used as chiral auxiliaries in asymetric synthesis [1-6].

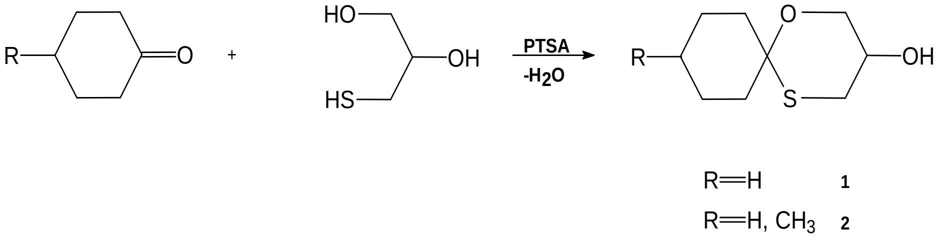
In this context it was considered of interest to develop investigations on the structure and stereochemistry of some new spiro-1,3-oxathianes bearing a hydroxy group in position 3 of the heterocycle (Scheme 1):



Scheme 1

RESULT AND DISCUSSION

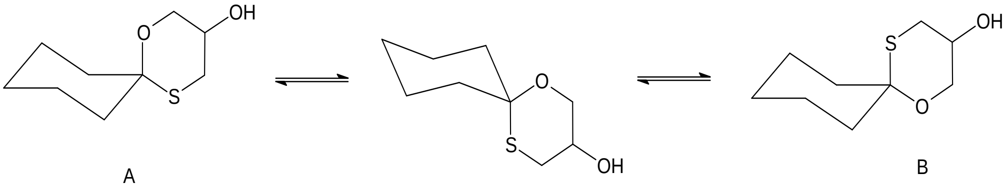
3-Hydroxy-1-oxa-3-thia-spiro[5.5]undecane ***1*** and his 9-methyl derivative ***2*** are obtained by a condensation reaction between the appropiate cyclohexanone and 3-mercapto-1,2-propanediol, in acidic conditions (*para*-toluenesulfonic acid - PTSA) with the azeotropic removal of the resulted water (Scheme 2):



Scheme 2

To avoid the formation of the pentacyclic isomers, the reaction was performed under thermodynamic control (the reaction time was quite long, 48-72 hours, the presence of four compounds (the starting ketome, two pentacyclic isomers and the desired product); at the end of the reaction, there were only two (the starting ketone and the 1,3-oxathiane).

Compounds ***1*** and ***2*** exhibit two diastereisomers: one with the sulfur atom (considered as a substituent of the cyclohexane ring) of the heterocycle in axial position of the ciyclohexane ring (A), the other one with the sulfur equatorial (B). In the case of compound ***1*** because of the small difference between the conformational free enthalpies of a SR group and of an OR [7] group the cyclohexane ring has a flipping structure, which induces a conformational equilibrium between structures A and B (Scheme 3):



Scheme 3

Compound ***1*** is investigated by ^{1}H- and ^{13}C-NMR spectroscopy, IR spectroscopy and mas-spectrometry. These investigations revealed the flexible structure of this compound.

The positions 2 and 4 of the spirane are different. The ^{1}H-NMR spectrum, exhibits for the protons of 2-position, two doublets of doublets (an AB system, with a further splitting of the signals due to the vicinal coupling with the proton of position 3), (Figure 1). For the protons of 4-position a similar group of signals are obtained but with significantly lower difference of chemical shifts. The peaks are overlapped and an assigment was not possible.

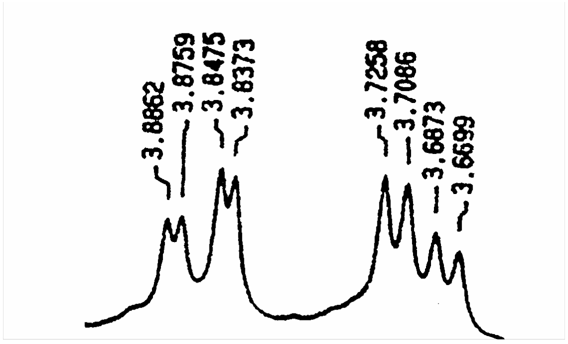


Figure 1

For the anancomeric 1,3-oxathianes, literature date [8-10] indicate a difference between chemical shifts similar to that of 1,3-dioxanes ($\Delta\delta$=0.4-1.0 ppm) for the axial and equatorial protons attached to the carbon atom of the heterocycle placed near the oxygen. A smaller difference ($\Delta\delta$=0.12-0.42 ppm) is predicted for the protons of the axial and equatorial positions of the carbon closer to the sulfur atom.

Despite the fact that for compound ***1***, the geminal protons of positions 2 and 4 exhibit different signals, the small differences between chemical shifts ($\Delta\delta$=0.16 ppm, respectively overlapped peaks) indicate a flexible structure.

IR investigations aprove this conclusion. The IR spectra, recorded at different values of concentration, in benzene, show for the OH group two bands: at 3580 cm^{-1} (hydrogen-bonded OH) and 3667 cm^{-1} (monomeric OH). The increase of the concentrations of the solution led to a higher band for the hydrogen-bonded OH (the other band is almost disappeared) Figure 2).

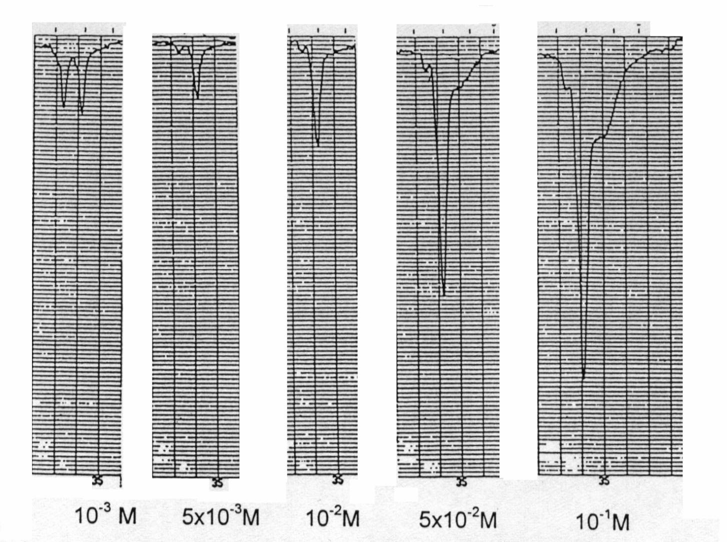


Figure 2

As a consequence, the H-bounds are intermolecular, proving the flipping structure of the compound.

The mass spectra of the compound ***1*** is illustrated in Figure 3; the main fragmentation pattern is shown in Scheme 4:

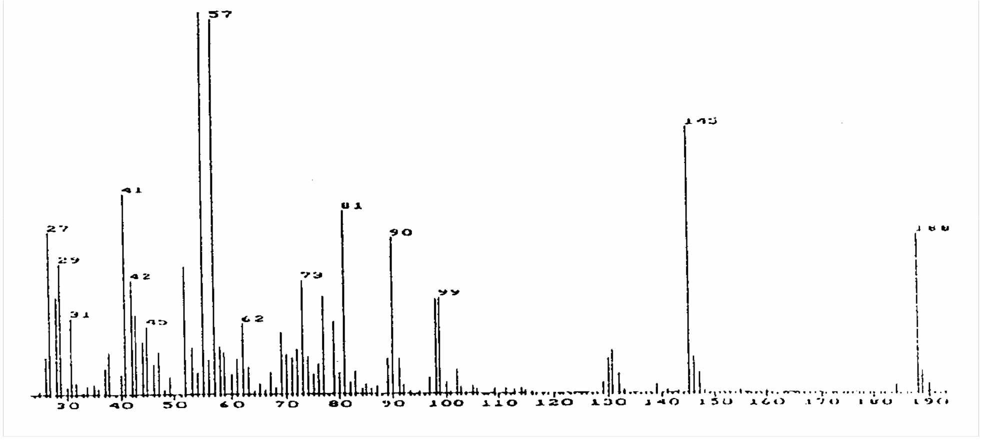
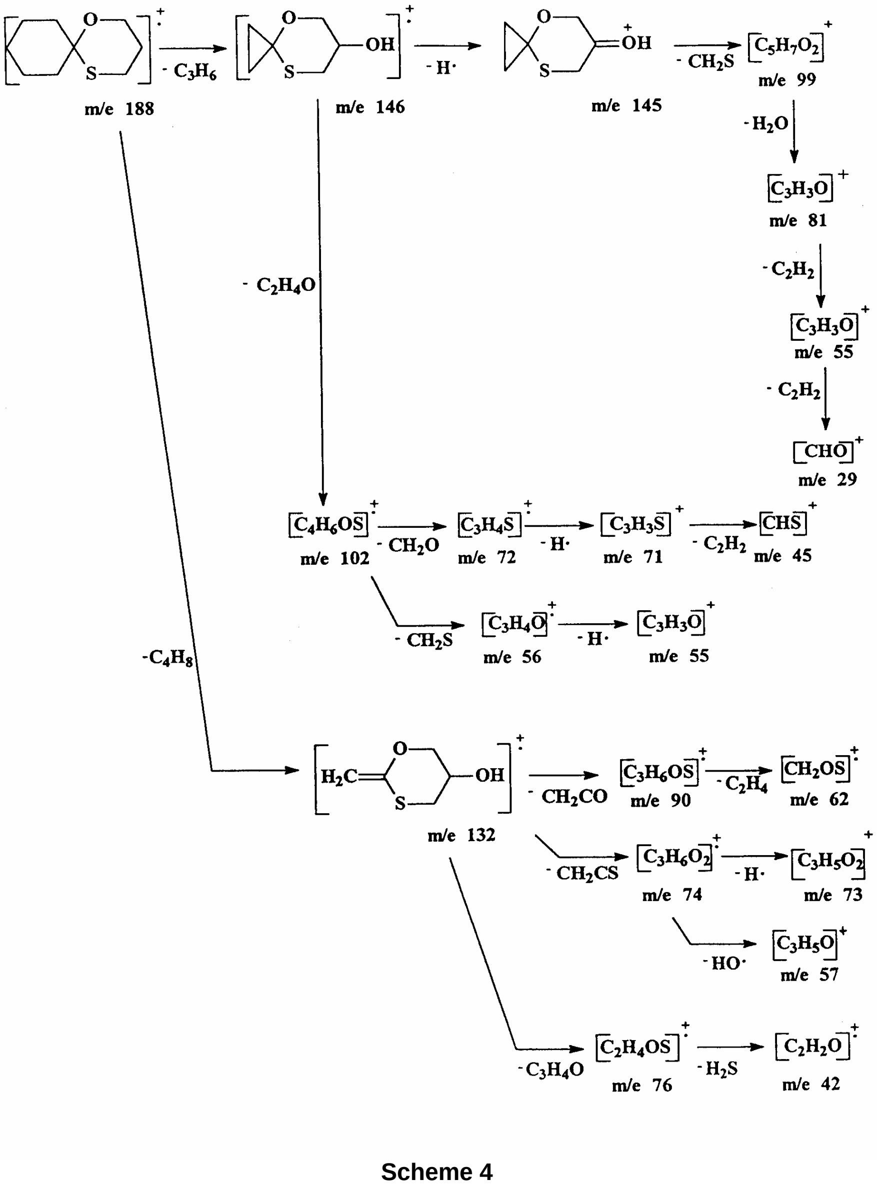


Figure 3



Scheme 4

For compound **2**, with a rigid cyclohexane ring ("holding" methyl group) the changing of one diastereoisomer into the other can occur only by a ring-opening step.

The ^{1}H-NMR spectrum revealed the presence of two diastereoisomers. Two AB systems (doublets of doublets - the further splitting being due to the vicinal coupling with 3-position proton) could be identified (peaks 1,2,3,4,5,6,7,8 and 9,10,11,12,13,14,15,16) (Figure 4):

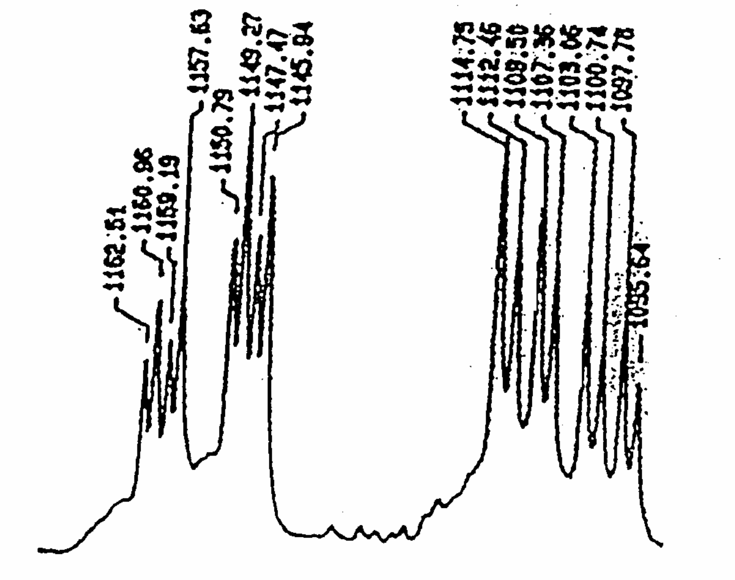


Figure 4

EXPERIMENTAL

General

NMR spectra have been run on a VarianGemini spectrometer, operating at 300 MHz fr protons and 75 MHz for carbon atoms, using $CDCl_3$ as solvent, in 5 mm tubes. The IR spectra were recorded on a SPECORD 75 IR spectrometer. The EI mass spectra have been recorded at 70 eV with a MAT 311 mass spectrometer.

Compounds 1 and 2, general procedure

Stoichiometric amounts of 3-mercapto-1,2-propanediol and carbonyl compound (0.05 mol) with catalytic amounts of ρ-toluenesulfonic acid (0.1 g) were refluxed in 100 ml benzene and the resulted water was removed using a DeanStark trap. After the reaction carried out (48-72 hours, chromatographic control), the catalyst was neutralized after cooling at room temperature (0.1 g KOH, stirring for 0.5 h). The reaction mixture was washed twice with 50 ml water. After drying (Na_2SO_4) the benzene was removed and the spiro-1,3-oxathianes were purified by low pressure distillation.

3-Hydroxy-1-oxa-5-thia-spiro[5.5]undecane ***1***
Yield: 60%; bp: 102-104^{0}C/0.05 mm; $C_9H_{16}O_2S$ (188.13); calc: 57.45 C, 8.98 H, 15.97 S
found: 57.28 C, 8.67 H, 15.77 S

^{1}H-NMR ($CDCl_3$): δ = 4.32 - 4.41 (m, 1H, CH), 3.86, 3.70 (ddd, 2H, AB system, J = 11.6 Hz, J' = 3.1 Hz, J'' = 5.2 Hz), 2.92 - 3.01 (m, 2H, overlapped peaks), 1.27 - 2.10 (m, 11H, overlapped peaks, cyclohexane ring and OH).
^{13}C-NMR ($CDCl_3$): 128.36 (C^6), 81.55 (C^2), 63.70 (C^3), 40.47; 40.11 (C^7, C^{11}), 33.36 (C^4), 25.41: 25.08 (C^8, C^{10}), 24.32 (C^9).

3-Hydroxy-9-methyl-1-oxa-5-thia-spiro[5.5]undecane ***2***
Yield: 58%; bp: 110^0C/ 0.05 mm; $C_{10}H_{18}O_2S$ (202.14); calc: 59.41 C, 8.90 H, 15.86 S
found: 59.21 C, 8.69 H, 15.67 S
^{1}H-NMR ($CDCl_3$, mixture of two diastereoisomers): 4.24 - 4.40 (m, 1H, overlapped peaks, CH), 3.84 - 3.68 (ddd, 2H, AB system, overlapped peaks, J = 11.7 Hz, J' = 3.3 Hz, J'' = 5.1 Hz, J'' = 5.3 Hz), 2.88 - 3.01 (m, 2H, overlapped peaks), 2.35 (s, 1H, OH), 1.00 - 2.20 (m, 8H, overlapped peaks, cyclohexane ring), 0.91 (dd, 3H, overlapped peaks, J - 6.0 Hz, J = 6.4 Hz).
^{13}C-NMR ($CDCl_3$, mixture of two diastereoisomers): 81.76, 81.53 (C^2); 63.70 (C^3); 40.13, 39.82, 39.51, 38.91 (C^7, C^{11}); 34.28, 33.52, 33.26, 32.85, 32.38, 32.07 (C^4, C^8, C^{10}); 31.68, 30.72 (C^9); 21.73, 21.57 (CH_3).

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