SYNTHESIS AND CONFORMATIONAL ANALYSIS OF GLYOXAL BIS-DITHIOACETALS: 1,4,5,8-TETRATHIADECALIN (HEXAHYDRO-1,4-DITHIINO[2,3-b]-1,4-DITHIIN) AND TRANS-2,3-BIS(METHYLTHIO)-1,4-DITHIANE

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Abstract -The synthesis of the first examples of two new classes of glyoxal bis-dithioacetals: <u>trans</u>-1,4,5,8-tetrathiadecalin and <u>trans</u>-2,3-bis(methylthio)1,4-dithiane, has been performed. The conformation of 2,2'-bis-1,3-dithiolane and <u>trans</u>-2,3-bis(methylthio)-1,4-dithiane in CDCl₃ solution has been studied using ¹H NMR techniques. In the first case an antiperiplanar conformation has essentially been found whereas a 83/17 mixture of diaxial and diequatorial conformers has been observed in the second.

INTRODUCTION.

Stereoelectronic effects (anomeric and exo-anomeric effects) play a fundamental role in determining the preferred conformations and in directing the chemical reactivity in systems of the general type R₂CXY, where X and Y represent electronegative substituents bearing nonbonding electron pairs. Nowadays, there is a generally admitted common electronic interpretation for these effects: systems like those depicted in Figure 1 tend to adopt conformations in which the best donor lone pair is antiperiplanar to the best acceptor bond in order to allow a stabilizing electronic delocalization¹. The delocalization is due to the overlap of a lone pair orbital (n_X or n_Y) with an antibonding σ orbital ($\sigma_C^+_Y$ or $\sigma_C^+_X$) (Figure 1).



Figure 1.

The continuous interest in this area has led in recent years to a considerable amount of experimental and theoretical studies, and the subject has been thoroughly reviewed in some excellent monographs².

Many of the efforts in this field have been devoted to systems containing oxygen and/or halogen atoms, and comparatively less attention has been paid to the study of sulphur compounds. Sulphur displays, however, some differential characteristics relative to oxygen that rendes interesting the study of stereoelectronic effects based on it. From the electronic point of view, the lone pairs of sulphur are higher in energy than those of oxygen and the $\sigma_{C_s}^{\star}$ orbitals are

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lower in energy than the corresponding $\sigma_{\rm C}^{\star}_{-0}$ orbitals³. Sulphur should accordingly be able to behave either as a good donor or as a good acceptor and give rise to important anomeric effects. On the other hand, from a geometrical point of view, sulphur-carbon bonds are considerably longer than oxygen-carbon bonds. This should diminish its effective donating ability, due to a poorer overlap. Moreover, when sulphur is part of an heterocyclic six-membered ring, the steric 1,3-diaxial interactions experienced by any axial substituent on the α -carbon should be smaller than in the corresponding oxygen ring. Conversely, due to the greater steric bulk, an axial sulphur substituent should give rise to stronger 1,3-diaxial interactions than the corresponding oxygen one.

The combined effect of all these factors is such that in most cases the conformational preference of sulphur compounds (the classical thermodynamic manifestation of the anomeric effect) is lower than in the corresponding oxygen compounds^{2,4}. In a given conformation, the variations in bond lengths that can be attributed to the existence of anomeric effects are also smaller in the sulphur than in the oxygen compounds⁵. We would say that, in general, anomeric effects involving the participation of sulphur atoms, though significant, are weaker than in the corresponding oxygen compounds⁶.

The bis-acetals of glyoxal, which include structures like 1,2 and 3, are a class of compounds which has proved to be very fruitful for the study of stereoelectronic effects at oxygen.



The structure of compounds <u>1</u> and <u>2</u>, which are formed in the reaction of <u>trans</u>-2,3-dichloro-1,4-dioxane with ethyleneglycol⁷, was the subject of a long dispute. On the basis of dipole moment measurements, <u>1</u> was initially believed to be <u>trans</u>-1,4,5,8-tetraoxadecalin, whereas the corresponding <u>cis</u> structure was assigned to <u>2</u>⁷. Later on, it was finally shown that <u>1</u> was in fact <u>cis</u>-1,4,5,8-tetraoxadecalin and that <u>2</u> was 2,2'-bis-1,3-dioxolane⁸. Since that moment, many fruitless efforts have been devoted to the synthesis of trans-1⁹.

Much probably, the impossibility of preparing <u>trans-1</u> is due to the unfavourable conformation (lack of stabilization by anomeric effects) of the conceivable transition states leading to it. In favour of this explanation is the fact that the related <u>trans-1,4,5,8-tetraazadecalin</u>, formed through a transition state subject to much weaker anomeric effects, is easily obtained by the reaction of glyoxal with ethylenediamine¹⁰. On the other hand, the synthesis of a great number of dioxane derivatives <u>3</u> has been described from 2,3-dichloro-1,4-dioxane^{9,11}. The <u>cis</u> derivatives have been shown to exist in a degenerate equilibrium between two rapidly interconverting chairs. The <u>trans</u> isomers exist almost exclusively as diaxial conformers except those carrying bulky substituents, where an important population of the diequatorial conformer is found. This is probably due to 1,3-diaxial interactions destabilizing the diaxial-exo-anomeric conformers¹¹.

Among the corresponding sulphur derivatives, glyoxal bis-dithioacetals, only 2,2'-bis-1,3dithiolane <u>5</u> has been reported. It is obtained in the reaction of either glyoxal, glyoxal sulfate or 2,3-dichloro-1,4-dioxane with ethanedithiol^{12,13}, and described as having a gauche conformation in solution on the basis of dipole moment measurements¹³. Neither 1,4,5,8-tetrathiadecalin <u>4</u>, nor 2,3-bis-alkylthio-1,4-dithianes <u>6</u> have been reported so far in the literature.



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In order to test the importance of sulphur based anomeric effects in this class of compounds, we planned to develop syntheses for compounds $\underline{4}$ and $\underline{6}$, to determine their relative stereochemistry and, subsequently, to perform a conformational analysis of the whole series $\underline{4-6}$ by NMR techniques.

RESULTS AND DISCUSSION.

a) SYNTHESIS.

Our primary interest was to develop a synthetic method suitable for the preparation of either $\underline{4}$ or $\underline{6}$. The reported exclusive formation of 2,2'-bis-1,3-dithiolane in the reaction of a series of glyoxal synthons with 1,2-ethanedithiol suggested that this task is not trivial, as also did the fact that as early as in 1969 Fuchs indicated¹⁴ his interest in compound $\underline{4}$ without a further report of results in this field.

In view of this previous experience we decided to start with a preformed 1,4-dithiane system functionalized at positions 2 and 3. Two approaches were possible within this philosophy: the incorporation of an ethylenedithio unit onto a functionalized 1,4-dithiane system (the reverse of path a) and the integration of a CH₂CH₂ unit onto a 2,3-dithio-1,4-dithiane (the reverse of path b)(Figure 2).





In view of the failure of the synthesis according to path a, we centered our attention on the second approach. Although no synthesis of a saturated 2,3-dithio-1,4-dithiane system had been previously reported in the literature, Gais, in 1977, described the preparation of cyclic dithio-hemiacetals from α -chlorothioethers <u>via</u> thiouronium salts¹⁷. This methodology could, in principle, be applied to 2,3-dichloro-1,4-dithiane and it promised to be of great versatility, since the thiolate anions generated by basic treatment of the intermediate thiouronium salt must be able to react with a variety of electrophiles.

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Figure 2.

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When 7 was treated with thiourea in acetone solution a 1:1 <u>cis</u>-trans mixture of bis thiouronium salts 12 was subsequently formed according to NMR spectroscopy (Scheme 2). The salts 12 were treated with aqueous KOH under N $_2$, and a solution of 1,2-dibromoethane in THF was subsequently added, leading to the formation of a complex mixture of products. Along with polymeric materials, the desired 1,4,5,8-tetrathiadecalin 4 and the olefin 13 could be isolated in low yields.



NMR analysis (see below) unambiguously established the trans stereochemistry in 4. The preparation of cis-4 was attempted from the trans isomer by equilibration with butyl lithium in THF. However, hydrolysis after 24 hours at room temperature led only to the unchanged trans-4, along with some decomposition products.

In order to test the validity of this procedure for the preparation of 2,3-bis(alkylthio)-1,4dithianes 6, the solution of bis-thiolate was treated with a solution of methyl iodide in THF (Scheme 3)

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Once again the crude reaction product was a complex mixture containing important amounts of polymeric materials. Column chromatography of this mixture allowed the isolation of trans-2,3bis(methylthio)-1,4-dithiane 6a and of the olefin 14, both in low yields.

The observed parallelism between the alkylations with 1,2-dibromoethane and methyl iodide tends to indicate that the lack of formation of cis derivatives of 1,4-dithiane arises through a common reason. The more plausible explanation for this behaviour is that, under the basic conditions required for the hydrolysis of the diastereomeric mixture of thiouronium salts 12, the cis isomer possessing a thiouronium group and a hydrogen atom in antiperiplanar arrangement eliminates faster than it hydrolises. Most probably, the olefins 13 and 14 arise from the alkylation of the monothiolate 15 formed in the elimination process (Scheme 4)



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b) CONFORMATIONAL ANALYSIS.

The ¹H NMR spectra of <u>trans-4</u>, <u>5</u> and <u>trans-6a</u> were recorded in CDCl₃ solution and the complex signal corresponding to the S-CH₂CH₂-S moiety was analyzed as an AA'BB' system by means of the PANIC program (Figure 3). In every case, the spectrum synthesized from the calculated parameters was superimposable with the experimental one (RMS error less than 0.16 Hz). Moreover, the coupling constants between the homotopic thioacetal protons were measured by means of the ¹³C satellites. All spectroscopic data are summarized in Table 1.

Table 1.- NMR data (in Hz) of glyoxal bis-dithioacetals trans-4, 5, and trans-6a. ¹ From AA'BB' analysis, ² from ¹³C satellite, ³ directly measured, ⁴ a significant broadening of the signals corresponding to protons C,D and E,F is observed. Simulation with PANIC shows that this fact arises from a long range coupling between equatorial protons with J=1-1.5 Hz.



Figure 3.- a) Observed and calculated spectrum of the AA'BB' system in <u>trans</u>-1,4,5,8-tetrathiadecalin <u>4</u>, and b) in 2,2'-bis-1,3-dithiolane <u>5</u>.

The absence of geometrical distortion in the chair conformations of the six membered ring compounds was deduced by calculation of the Ψ dihedral angle of the ring by the Lambert-Buys R-value method ^{18,19} (Table 2).

Table 2.- Coupling constants, R values and ring dihedral angles of glyoxal bis-dithioacetals trans-4, 5 and trans-6a. ¹ $J_{trans}=1/2(J_{AB}+J_{CD})$, ² $J_{cis}=J_{AD}$, ³ According to Lambert, ⁴ According to Buys, since R>3

	Jtrans ¹	Jcis ²	R	Ψ
trans-4	8.05	2.7	2.98	62.3 ³
5	5.05	6.7	0.75	39.2 ³
trans-6a	8.20	2.1	3.90	66.0 ⁴

The R and Ψ values obtained for <u>5</u> are consistent with the 2,2'-bis-1,3-dithiolane structure²⁰. In fact, the 1,3-dithiolane rings of <u>5</u> in the crystal are in a half chair conformation with a puckering of 45°. On the other hand, the calculated Ψ values for <u>4</u> and <u>6a</u> fit well with that reported for 1,4-dithiane (66°), thus proving <u>4</u> and <u>6a</u> to be essentially non distorted 1,4-dithiane systems.

The <u>trans</u> nature of the ring junction in <u>4</u> and the <u>trans</u> stereochemistry of the substituents in <u>6a</u> are unambiguously shown either by the high value of J_{EF} or by the whole collection of calculated coupling constants (for instance, by the fact that $J_{AB} \neq J_{CD}$).

<u>trans</u>-1,4,5,8-Tetrathiadecalin $\underline{4}$ has a rigid conformation, which is depicted in figure 4 with the same hydrogen atom designations used in the analysis of the NMR spectrum.



2,2'-bis-1,3-Dithiolane $\underline{5}$ is found in the crystal to exist in an antiperiplanar conformation²¹ and, as indicated above, it was postulated to have a gauche conformation in solution on the basis of dipole moment measurements¹³. However, the value of the coupling constant (J_{EF}) between the dithioacetalic protons, even greater than the corresponding one in <u>4</u> (9.3 Hz <u>vs</u> 8.7 Hz) tends to indicate that the conformational equilibrium depicted in figure 5 is almost completely shifted towards the antiperiplanar conformer <u>5a</u>.



Figure 5.

This behaviour contrasts with that of 2,2'-bis-1,3-dioxolane $\underline{2}$, which exists in the antiperiplanar conformation in the solid state²², but mainly (63%) as a gauche conformer in solution²³.

For compound <u>6a</u>, the conformational equilibrium shown in figure 6 can be postulated. A population analysis of <u>6a</u> can be performed by two independent ways: i) starting from the calculated coupling constants of the AA'BB' system and ii) by using the 13 C satellite directly measured coupling constant between the dithioacetal protons.

In the first case, the observed J_{aa} (J_{AB}) and $J_{ee}(J_{CD})$ values for <u>trans</u>-1,4,5,8-tetrathiadecalin <u>4</u> (J_{aa} =11.8Hz; J_{ee} =4.3 Hz) were taken as standard values in the equations (where x and y are respectively the molar fraction of diaxial an diequatorial conformers):

 $J_{AB}=xJ_{aa} + (1-x)J_{ee}; \quad J_{CD}=yJ_{aa} + (1-y)J_{ee}$



For the second population analysis, the following equation was used (where J_{aa}^{\dagger} and J_{ee}^{\dagger} stand respectively for the diaxial and diequatorial coupling constants between adjacent dithioacetal protons, and x has the same meaning as above)

 J_{EF} in $\underline{4}$ (8.7 Hz) was taken as the standard value for J_{aa}^{*} . Since no experimental value for J_{ee}^{*} is available, J_{CD} in $\underline{4}$ (4.3 Hz) was again taken as standard. This assumption is justified by the fact that in the related field of the 2,3-dialkoxy-1,4-dioxanes, the corresponding coupling constants J_{ee} , measured from deuterated dioxanes, and J_{ee}^{*} , measured from a <u>tert</u>-butyl locked 2,3-dimethoxy-1,4-dioxane, have the same value. Our results, summarized in table 3 indicate a significant predominance of the diaxial conformer.

Table 3.-Diaxial/diequatorial equilibria and free energy differences for <u>trans</u>-2,3-bis(methylthio)-1,4-dithiane.

	from JAB	from J _{CD}	from J _{EF}	Average	
<pre>% diaxial</pre>	84%	80%	86%	83%	
∆G _{ea} (kJ mol ⁻¹)	4.1	3.4	4.5	3.9	

CONCLUSIONS

We have prepared the first examples of two new classes of glyoxal bis-dithioacetals: <u>trans</u>-1,4,5,8-tetrathiodecalin <u>4</u> and <u>trans</u>-2,3-bis(methylthio)-1,4-dithiane <u>6a</u>. We have also performed a conformational analysis of 2,2'-bis-1,3-dithiolane <u>5</u> in CDCl₃ solution, showing that it is essentially found in the antiperiplanar conformation, and of <u>trans</u>-<u>6a</u>, showing the predominance (83/17) of its diaxial conformation.

From the point of view of the importance of the anomeric effects based on sulphur, the ready availability of <u>trans</u>-1,4,5,8-tetrathiadecalin tends to indicate, according with very recent <u>ab</u> <u>initio</u> calculations⁶, that these effects are weaker in energetic terms than those based on oxygen. They are, however, strong enough for determining a clear predominance in solution of the diaxial conformer of 6a.

EXPERIMENTAL

NMR spectra were recorded on a VARIAN XL-200 and HITACHI Perkin-Elmer R-24B instruments. $\lambda A'BB'$ systems were calculated using the PANIC simulation program implemented on BRUKER instruments. Mass spectra were taken on a Hewlett-Packard 5930A. Infrared spectra were recorded on a Perkin-Elmer 681 instrument. Melting point of <u>4</u> was determined on a Perkin-Elmer DSC-4; the remaining melting points were determined on a Kofler microscope and are uncorrected. <u>trans</u>-2,3-Dichloro-1,4-dithiane was prepared following the known literature procedure¹⁵.

Reaction between <u>trans-2,3-dichloro-1,4-dithiane and sodium ethanedithiolate.-</u> To a solution of 0.059 mol of sodium ethoxide in 300 ml abs ethanol ethanedithiol (2.3 ml, 0.027 mol) was added. After 1h stirring at room temperature, a solution of <u>trans-2,3-dichloro-1,4-dithiane</u> (2g, 0.018 mol) in 50 ml abs ethanol was added dropwise under N₂. All 2,3-dichloro-1,4-dithiane (2g, 0.018 mol) in 50 ml abs ethanol was added dropwise under N₂. All 2,3-dichloro-1,4-dithiane was consumed after 12h of stirring, as indicated by NMR spectroscopy. When solvent was evaporated under vacuum, the crude experimented an exothermic reaction due to the oxidation of the remaining sodium ethanedithiolate and a white solid appeared. The solid was washed on a filter with water and HCCl₃ and dried. It was characterised by MS, Elemental Analysis and IR as 1,2,5,6,9,10,13,14-octathiacy-clohexadecane <u>11¹⁶</u> (2.3 g, 92% yield). The organic layer of the filtrate was dried and the solvent evaporated. Flash chromatography of the residue on Al₂O₃ (100-125 mesh, Act. 1) eluting with hexane / HCCl₃ mixtures gave 2,3-dihydro-1,4-dithiane <u>10</u> (50 mg, 2% yield), 2,3-dihydro-5,6-dichloro-1,4-dithiin <u>9</u> (210 mg, 6% yield), 1,4-dithiane <u>10</u> (50 mg, 2% yield) and a complex mixture of polymeric products that could not be identified. Minute amounts of 2,2'-bis-dithiolane were also found. 5.- m.p. 135°.¹ NMR (200 Mz) (DCCl₃) δ : 4.7 (s,2H); 3.3-3.1 (m,8H) ppm. IR (KBr) ν : 2960, 2925, 2900, 1410, 1260, 1240, 1190, 1080, 970, 950, 840, 730, 700, 680 cm⁻¹. MS m/e: 212 M⁺+2 (2.2%), 210 M⁺ (12.2%), 105 (100%), 61 (10%), 45 (12.2%).

<u>9</u>.- ¹H NMR (60 MHz)(DCCl₃) δ : 3.4 (s) ppm; IR (KBr) ν : 2960, 2920, 1415, 1290, 1260, 1170, 1130, 920, 865, 760 cm⁻¹. MS m/e : 190 M⁺+4 (8%), 188 M⁺+2 (36%), 186 M⁺ (50%), 160 (69%), 158 (100%), 79 (66%).

1.4.5.8-Tetrathiadecalin <u>4</u>.- To <u>trans</u>-2,3-dichloro-1,4-dithiane (3.2 g,0.018 mol) a solution of thiourea (3 g, 0.039 mol) in 100 ml anh. acetone was added. After 48 h of stirring at room temperature, a white precipitate appeared. Solvent was evaporated under vacuum. The highly hygroscopic mixture of thiouronium salts obtained (NMR (60 Mz) (Acetone-d₆) : 5.6 (s, 2H), 5.52 (s,2H), 3.8-2.9 (m, 8H)), was immediately treated with a solution of 6.04 g (0.107 mol) KOH in 200 ml H₂O purged with N₂, the solution was stirred 30 min. and filtered off under N₂. To this aqueous solution, containing thiolates <u>14</u> and <u>15</u>, was added 1,2-dibromoethane (2.3 ml, 0.027 mol) in 10 ml THF. After 24h of stirring, 200 ml HCCl₃ were added. The organic layer was separated, dried and the solvent evaporated. Flash chromatography of the crude on Al₂O₃ (100-125 mesh, Act. 1) eluting with hexane/HCCl₃ mixtures gave 1,4,5,8-tetrathiadecalin <u>4</u> (180 mg, 5% yield), 2,3-dihydro-5-(2-bromoethylthio)-1,4-dithin <u>13</u> (110 mg, 2% yield) and a complex mixture of products that could not be identified.

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4.- m.p. 134.2° .¹H NMR (200 Mz) (DCCl₃) δ : 4.41 (s,2H), 3.39-2.81 (m, 8H) ppm; ¹³C NMR (DCCl₃) δ : 48.66 (CH₂), 32.69 (CH) ppm. IR (KBr) ν : 2940, 2900, 1405, 1395, 1280, 1255, 1175, 1110, 910, 875, 855, 710, 700, 685 cm⁻¹; MS m/e : 210 M⁺ (2%), 105 (38%), 57 (11%), 45 (100%) Found C, 34.48%; H. 4.71%; S, 60.82%; Calc. for C₆H₁₀S₄ C, 34.25%; H. 4.79%; S, 60.96%; <u>13</u>.- oil.¹H NMR (60 Mz) (CCl₄) δ : 6.6 (s,1H), 3.7-2.9 (m, 8H); IR (film NaCl) ν : 3010, 2940, 2920, 2840, 1520, 1405, 1270, 1185, 910, 840, 825, 785, 675 cm⁻¹. MS m/e : 258 M⁺+2 (26%), 256 M⁺ (23%), 149 (57%), 105 (100%), 46 (63%).

2,3-bis(methylthio)-1,4-dithiane <u>6a</u>.- The same procedure was followed as above but using 3.1 ml (0.049 mol) CH₃I in 10 ml THF. Flash chromatography on neutral $\lambda_{13}O_3$ (100-125 mesh, Act. 1) eluting with hexane/CH₂Cl₂ mixtures gave 2,3-bis(methylthio)-1,4-dithiane <u>6a</u> (170 mg, 5% yield), 2,3-dihydro-5-methylthio-1,4-dithian <u>14</u> (60 mg, 2% yield) and a complex mixture of unidentified products.

<u>6a.</u> - m.p. 72⁰. ¹H NMR (200 Mz) (DCC1₃) δ : 4.02 (s,2H), 3.42-2.63 (m,4H), 2.26 (s,6H) ppm. ¹³C NMR (DCC1₃) δ : 54.03 (CH), 26.19 (CH₂), 15.69 (CH₃) ppm. IR (KBr) 2940, 2900, 1430, 1410, 1390, 1210, 1190, 1150, 960, 940, 900, 860, 790, 745, 685 cm⁻¹. MS m/e: 212 M⁺ (100%), 165 (99%), 105 (53%), 91 (21%). Calc. for C₆H₁₂S₄: C, 33.93%; H, 5.69%; S, 60.38%; Found: C, 34.10%; H, 5.94%; S, 60.44%.

<u>14.</u>- oil. ¹H NMR (200 Mz) (DCC1₃) δ : 6.49 (s,1H), 3.23-3.18 (m,4H), 2.34 (s,3H) ppm. IR (film NaCl) ν : 2900, 1635, 1525, 1410, 1305, 1280, 960, 915, 790 cm⁻¹. MS m/e : 164 M⁺ (13%), 105 (31%), 89 (27%), 61 (100%), 45 (97%).

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