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# HEXITOL DERIVATIVES CONTAINING A 1,4-OXATHIANE RING—III[1]

## REARRANGEMENT OF A SULFONE ON TREATMENT WITH LAH

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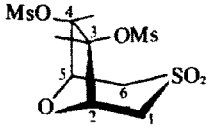
**Abstract**—Treatment of 2,5 - anhydro - 3,4 - di - O - mesyl - 1,6 - thioanhydro - D - glucitol S,S-dioxide (1) with LAH afforded (1*S*,6*R*)-2-thiabicyclo[4.1.0]heptane S,S-dioxide (2) and its (4*R*) - 4 - hydroxy derivative 3 in a ratio of 46:6. Sodium - dihydro - bis(2 - methoxy - ethoxy) - aluminate afforded the same compounds in a ratio of 15:22. The corresponding sulfide 5 underwent no rearrangement under similar conditions. The structure of the products was established by IR, PMR, CMR and MS. A probable reaction mechanism is discussed.

### INTRODUCTION

Reduction of sulfones to the corresponding sulfides with LAH was systematically investigated first by Bordwell and Kellin[2] in 1951. They have shown, that 5-membered cyclic sulfones react easier than 6-membered ones, while open chain aliphatic sulfones are the most resistant towards reduction. Recently diisobutyl aluminium hydride was used for reduction of sulfones,[3] but although a smaller excess of the reagent was required, cyclic sulfones were reduced in a very low yield only.

In our previous work[1,4] we described the synthesis of 1,6 - thioanhydro - hexitol derivatives containing a 1,4 - oxathiane ring in their skeleton. Now we report on the reaction of the corresponding S,S-dioxide 1 with LAH and sodium - dihydro - bis(2 - methoxy - ethoxy) aluminate (NHMA), respectively.

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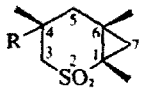
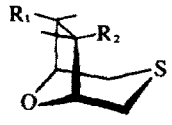
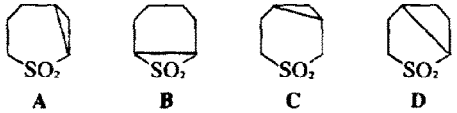



2: R = H
3: R = OH
4: R = AcO

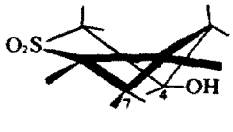



5: $R_1 = R_2 = MsO$
6: $R_1 = OH$; $R_2 = MsO$
7: $R_1 = R_2 = OH$

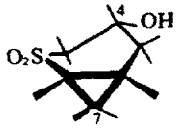



A B C D


E F G




3A (*trans*, 4*S*)




3B (*cis*, 4*R*)

## RESULTS

The reaction of 2,5 - anhydro - 3,4 - di - O - methylsulfonyl - 1,6 - thioanhydro - D - glucitol S,S-dioxide (1) with LAH in THF at room temperature was monitored by TLC. After complete consumption of starting material in 48 h, (1*S*,6*R*) - 2 - thiabicyclo[4.1.0]heptane S,S-dioxide (2) could be isolated as the main product (46%). As byproduct (6%) its (4*R*) - 4 - hydroxy derivative 3 was obtained. Using the less reactive NHMA instead of LAH, compounds 2 and 3 were obtained in a ratio of 15:22. For structure elucidation the hydroxy derivative 3 was converted into its acetate 4 which was investigated together with 2 and 3 by IR, PMR, CMR and MS.

In the mass spectra of compounds 2, 3 and 4 the ions containing the S atom are of very low abundances. This fact and the striking similarity of the fragmentation of 2 to that of pentamethylenesulfone[5-7] indicated the presence of a $SO_2$-function in these compounds.

By analogy with the thoroughly investigated MS behaviour of pentamethylenesulfone[5] structures A or C seemed to be the most probable for compound 2. A fragmentation pattern deduced from structure A is depicted in Scheme 1.

Compound 3 gave a similar pattern, but in addition a relatively abundant peak appeared at $m/e = 44$ (6·2%), which was shifted to $m/e = 86$ (6·5%) in the mass spectrum of the acetylated derivative 4, suggesting the $(CH_2{=}CH{-}OR)^{+\cdot}$ (R=H and $COCH_3$, respectively) structure for this ion.

It must be emphasized, however, that structure G would also be consistent with the MS data obtained, and, because of the unknown effect of a fused cyclobutane ring on the fragmentation[5] of tetramethylenesulfone, neither structures D and F could be ruled out.

In the 60 Hz PMR spectrum of compound 2 only a very crowded, overlapped set of multiplets appeared between 1·0 and 3·0 ppm (Fig 1). In the IR spectrum neither absorption of oxo or hydroxyl groups, nor that of an ether linkage is present, but the intense $\nu_{as}SO_2$ and $\nu_sSO_2$ bands of the sulfone group appear at 1290 and 1310 $cm^{-1}$, respectively.

As indicated by the absence of an $\nu C{=}C$ absorption in the IR spectrum and the PMR signals of the olefinic protons, the sulfone group has to be a member of an overbridged 7-membered ring system. Among the theoretically possible structures (A-F) the symmetrical B and F (C, point group) must be ruled out, as the PMR spectrum can be related to an asymmetric molecule only. The intense $\nu CH$ band at 3020 $cm^{-1}$ in the IR spectrum revealed the presence of a strained fused ring system, too. Structure A could be assigned to 2 based on the following CMR data. On complete decoupling from the protons a spectrum consisting of six lines was obtained (Fig 2). The multiplicity of the signals was established by off-resonance

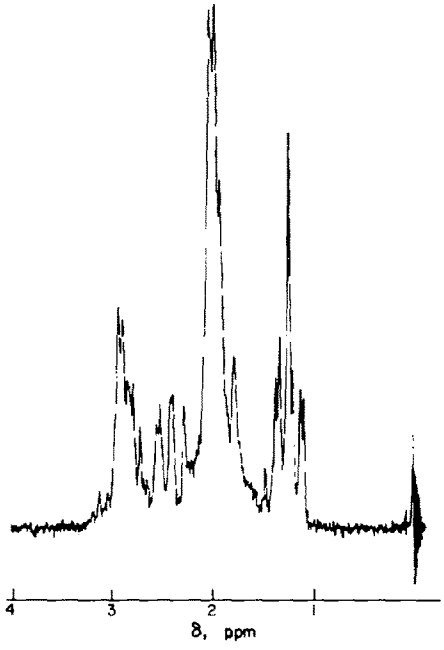
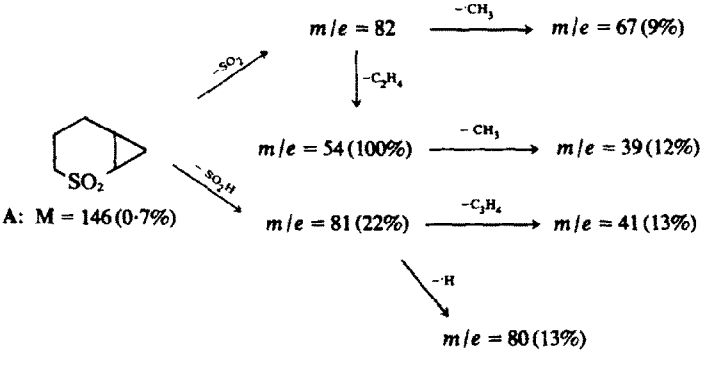



Fig 1.




SCHEME 1.

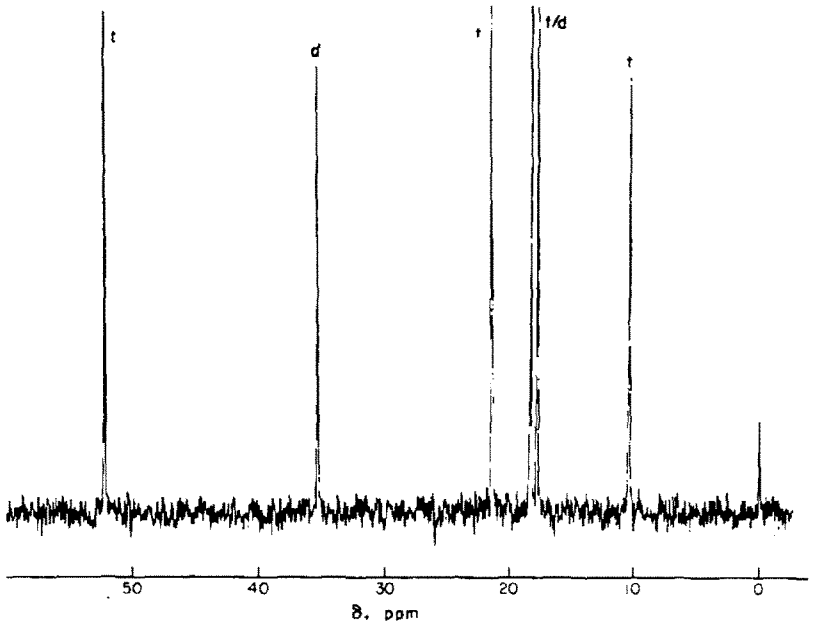



Fig 2.

decoupling technique and the values of the $^{13}C—H$ couplings were determined from the non decoupled multiplet spectrum (Table 1).

The appearance of four triplets and two doublets proves unambigouosly the presence of a bicyclic system in which, according to the triplet at 10·2 ppm, a cyclopropane ring must be incorporated (A or C). The CMR signal of larger rings appears at lower field, e.g. those of cyclobutane at 22·4 ppm[8] and the value of the chemical shift was not found to be less than 15 ppm in its derivatives.[9] The presence of a cyclopropane ring is in accordance with the observed large coupling constants (167·5 Hz), as for cyclopropane derivatives a $^1J_{CH}$ value of 161 Hz, whereas for cyclobutane derivatives one of 134 Hz is characteristic.[10] The magnitude of the coupling constants made the assignment of the signals of all three cyclopropane carbon atoms unambiguous. According to its multiplicity the signal at 10·2 ppm belongs to C-7. The two doublets at 34·9 and 17·5 ppm belong to C-1 and C-6, respectively. The larger paramagnetic shift of the former can be explained by the attached sulfone group. The chemical shift induced by this group proves structure A, as in the other cyclopropyl isomer C two triplets should appear the farthest downfield and the two bridge atoms of the fused ring-system should give signals at higher field with similar chemical shifts. Due to the paramagnetic shift caused by the sulfone group the most downfield signal belongs to C-3. From among the two triplets at 18·1 and 21·2 ppm, respectively, the former belongs to C-5, due to the more pronounced steric compression of this atom compared to C-4.

Table 1. CMR data of compound 2 in $CDCl_3$ solution

| δC(ppm) | Multiplicity | $^1J_{CH}$(Hz) | Assignation |
|---|---|---|---|
| 10·2 | triplet | 167·5 | C-7 |
| 17·5 | dublet | 172 | C-6 |
| 18·1 | triplet | 132 | C-5 |
| 21·2 | triplet | 132 | C-4 |
| 34·9 | dublet | 177·5 | C-1 |
| 51·7 | triplet | 141 | C-3 |

Having established structure 2, the structure of the hydroxy derivative 3 and its acetylated product 4 could be proved. In the IR spectrum of the former the $\nu$OH band appears at 3450 $cm^{-1}$ and in the latter the acetyl-carbonyl at 1735 $cm^{-1}$. The signal of the proton geminal to the OH shows in the 60 MHz PMR spectrum of compound 3 in $CDCl_3$-$(CD_3)_2CO$ solution a symmetrical septet at 4·35 ppm (Fig 3), whereas in DMSO-$d_6$ solution an octet at 4·10 ppm. (The OH signal gives in the former case a broad singulet at 4·0 ppm and in the latter a sharp doublet at 5·3 ppm; due to the CH-OH coupling; $J$ = 4·5 Hz). This pattern can be explained only with the assumption, that the proton geminal to the OH group is flanked by two magnetically equivalent proton pairs, and one of the coupling constants to the vicinal protons is roughly twice as large as the other. This suggests a diaxial and an axial-equatorial coupling, consequently the OH group must be in equatorial position. Furthermore, taking into consideration the somewhat distorted stabile twist conformers (3A and 3B) of the two possible configurations (4*S* and 4*R*) it can be seen, that

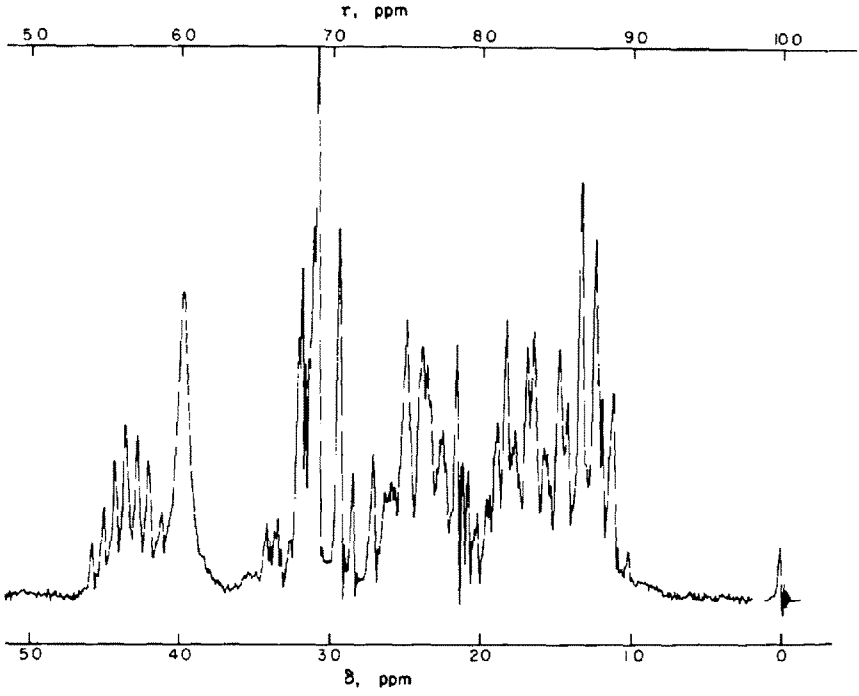



Fig 3.

former is sterically unfavoured because of the steric interaction between H-4 and H-7. Therefore in compound **3** the cyclopropane ring and the hydroxyl are *cis* related (**3B**) corresponding to the 1*S*, 4*R*, 6*R* configuration. Accordingly the observed pattern of the H-4 signal is due to the following relative value of the coupling constants:

$$J_{3a,4a} \approx J_{4a,5a} \approx 2[J_{3e,4a} \approx J_{4a,5e}] \approx 2[J_{4a,4a(OH)}] \approx 9\ \text{Hz}$$

(Fig 4). That means, that in compound **3** the $-\overset{3}{C}H_2-\overset{4}{C}HOH-\overset{5}{C}H_2-$ group represents an $AM_2X_2$ spin-system. This accidental magnetic equivalence of the two pairs of vicinal protons is not valid for the corresponding acetyl derivative **4** in which H-4 shows an unresolved multiplet at 5·32 ppm.

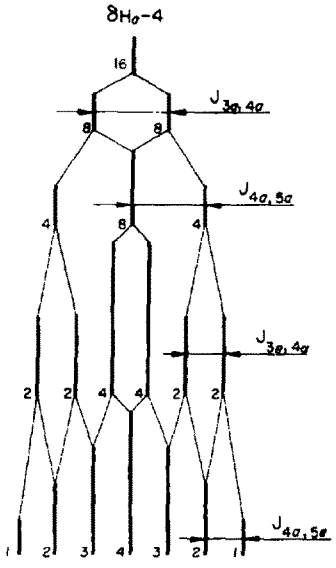
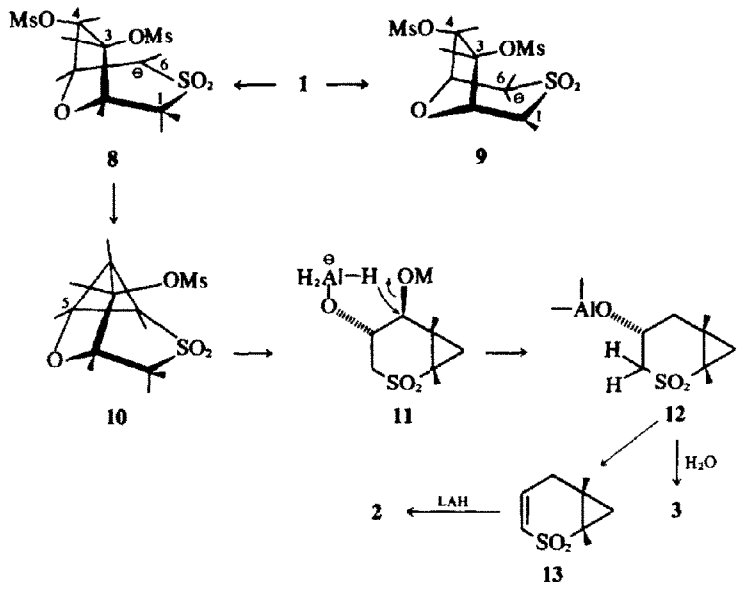



Fig 4.

## DISCUSSION

In order to obtain insight into the mechanism of this rearrangement, the corresponding sulfide **5** was treated with LAH under similar conditions. In this case no rearrangement occurred but the mesyl groups at C-3 and C-4 were split off, yielding besides the 4-hydroxy derivative **6** the corresponding dihydroxy compound **7** in 11% and 29% yield, respectively.

From this fact it became obvious, that the presence of the S,S-dioxide group is essential for a rearrangement of the skeleton. It is well known, that sulfone groups activate the protons of the adjacent methylenes. Accordingly it could be assumed, that the first step of the rearrangement leading to compounds **2** and **3** is a deprotonation of compound **1** at C-6 or C-1 yielding the anions **8** and **9**, respectively (Scheme 2). In the former the carbanion at C-6 can easily attack C-4, which due to



SCHEME 2.

the electron withdrawing effect of the attached mesyloxy group carries a partial positive charge. The exo arrangement of this mesyloxy group to the carbanion favours an intramolecular $S_N2$ reaction with inversion at C-4. The isomeric anion **9** contains the corresponding mesyloxy group at C-3 in *endo* position to the charged C-1 atom, therefore an attack of C-6 at C-3 is sterically unfavoured.

The hypothetical intermediate **10** contains a very strained tetrahydrofuran ring, therefore it can be assumed that the distorted ether bridge will be split selectively at the most strained C-5 atom. The formed derivative **11** contains a *cis* fused [4.1.0] ring-system and *trans* situated vicinal mesyloxy and hydroxy groups—the latter as aluminohydride, which participates in an intramolecular $S_N2$ reaction, removing the mesyloxy group reductively.[11] In the so formed intermediate **12** one of the activated methylene protons, being adjacent to the sulfone group can be split off, thus inducing the formation of **13**. As activated double bonds can be saturated by hydrides, the excess of LAH may reduce the double bond of **13** affording compound **2**. Unchanged **12** should yield on hydrolysis directly the hydroxy derivative **3**.

## EXPERIMENTAL

M.ps are uncorrected. TLC was carried out on Kieselgel G coated microscope slides using 0·1 M $KMnO_4$ and 2 N $H_2SO_4$ (1:1) for detection. Column chromatography was performed on silicic acid. IR spectra were recorded in KBr pellets on a Perkin Elmer 457 spectrometer. PMR spectra were recorded on a Varian-A-60D and Jeol 60-HL spectrometer, respectively, CMR spectra on a Varian XL-100 spectrometer in $CDCl_3$ soln using TMS as internal standard. Mass spectra were recorded on a Varian MAT SM-1 instrument. All evaporations were carried out in a rotary evaporator under diminished pressure, after drying the organic solns over $Na_2SO_4$.

2,5 - *Anhydro* - 3,4 - *di* - *O* - *methylsulfonyl* - 1,6 - *thioanhydro* - D - *glucitol* S,S - *dioxide* (**1**). Compound **5** (3·2 g) was dissolved in a mixture of AcOH (16 ml) and 33% $H_2O_2$ (6 ml) by gentle heating. The soln was kept overnight at room temp and was then evaporated. The residue was twice evaporated with water (20 ml) and was then recrystallized from water (50 ml) giving pure **1** (3·35 g; 95·5%), m.p. 181–183°, $[\alpha]_D^{20} = -28·6°$ (*c* 1, acetone). (Found: C, 27·33; H, 4·20; S, 27·23; O, 40·91. $C_8H_{14}O_9S_3$ requires: C, 27·42; H, 4·03; S, 27·43; O, 41·10%).

*Reduction of sulfone* **1** *with LAH.* A slurry of **1** (7 g) and LAH (4 g) in dry THF (200 ml) was stirred for 48 h at room temp. The excess of LAH was decomposed by addition of a soln of potassium sodium tartrate (4 g) in water (10 ml). The salts were filtered off and washed with hot THF (100 ml). The residue, obtained after evaporation of the filtrate was separated by column chromatography, using EtOAc for elution. The fractions with $R_f$ 0·7 gave on evaporation and recrystallization from $CCl_4$ (10 ml) pure **2** (1·35 g; 46·1%), m.p. 85–87°, $[\alpha]_D^{20} = +5·9°$ (*c* 1, acetone). (Found: C, 49·36; H, 7·13; S, 21·71. $C_6H_{10}O_3S$ requires: C, 49·29; H, 6·90; S, 21·93%).

Evaporation of the fractions with $R_f$ 0·55 gave crude **3** (0·2 g; 6·2%) which on recrystallization from acetone-ether had m.p. 107–108°, $[\alpha]_D^{20} = +9·8°$ (*c* 1, acetone). (Found: C, 44·52; H, 6·41; S, 19·71; $C_6H_{10}O_3S$ requires: C, 44·43; H, 6·22; S, 19·77%).

*Reduction of sulfone* **1** *with NHMA.*[12] A 80% soln of the hydride in benzene (30 ml) was evaporated, deluted with dry THF (100 ml) and reevaporated. The residue was dissolved in THF (100 ml) and **1** was added (3·5 g). The yellow slurry was stirred for 48 h at room temp. The mixture was then worked up as described for the reduction with LAH, to give after column chromatography **2** (0·22 g; 15%) and **3** (0·35 g; 22%), both being identical with those, described above.

*Acetylation of compound* **3**. A soln of **3** (0·32 g) in pyridine (2 ml) and $Ac_2O$ (1 ml) was stored overnight at room temp and was then evaporated. The residue was purified by column chromatography, using $CCl_4$-EtOAc 2:1 for elution. Evaporation of fractions with $R_f$ 0·35 gave after recrystallization from acetone-ether **4** (0·22 g; 55%), m.p. 86–87°, $[\alpha]_D^{20} = +41·5°$ (*c* 1, chloroform), (Found: C, 47·12; H, 6·11; S, 15·62; $C_8H_{12}O_4S$ requires: C, 47·04; H, 5·92; S, 15·70%).

*Reduction of sulfide* **5** *with LAH*. A soln of **5** (3·15 g) in dry THF (100 ml) was treated with LAH (2 g) as described for **1**. The crude syrup, obtained after evaporation of the filtrate afforded on column chromatography two fractions of $R_f$ 0·85 and $R_f$ 0·50 when EtOAc was used for elution. Recrystallization of the residue obtained on evaporation of the first fraction from EtOAc-light petroleum (b.p. 80°) gave **6** (0·26 g; 11%), m.p. 98–100° alone and in admixture with authentic material.[4]

The residue of the evaporated second fraction afforded on recrystallization from acetone the dihydroxy derivative **7** (0·47; 29%), m.p. 113–115° alone and in admixture with authentic material.[1]

*Acknowledgments*—The authors are indebted to Dr. F. W. Wehrli (Varian, Zug, Switzerland) for recording the CMR spectra.

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