Synthesis and Stereochemistry of Substituted Perhydro-2-thiaindan and 2-Thiadecalin 2,2-Dioxides

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The intramolecular cyclization in basic medium of 2-(α-methylsulphonylphenethyl)cyclohexanone (1) leads to three isomeric 1-benzyl-3a-hydroxyperhydro-2-thiaindan 2,2-dioxides (3), (4), and (5). Under the same conditions three isomeric 4-phenyl-8a-hydroxy-2-thiadecalin 2,2-dioxides (12), (13), and (14), are obtained from 2-α-(methylsulphonylmethyl)benzylcyclohexanone (10). The configurations of the products have been established by spectroscopic and chemical methods.

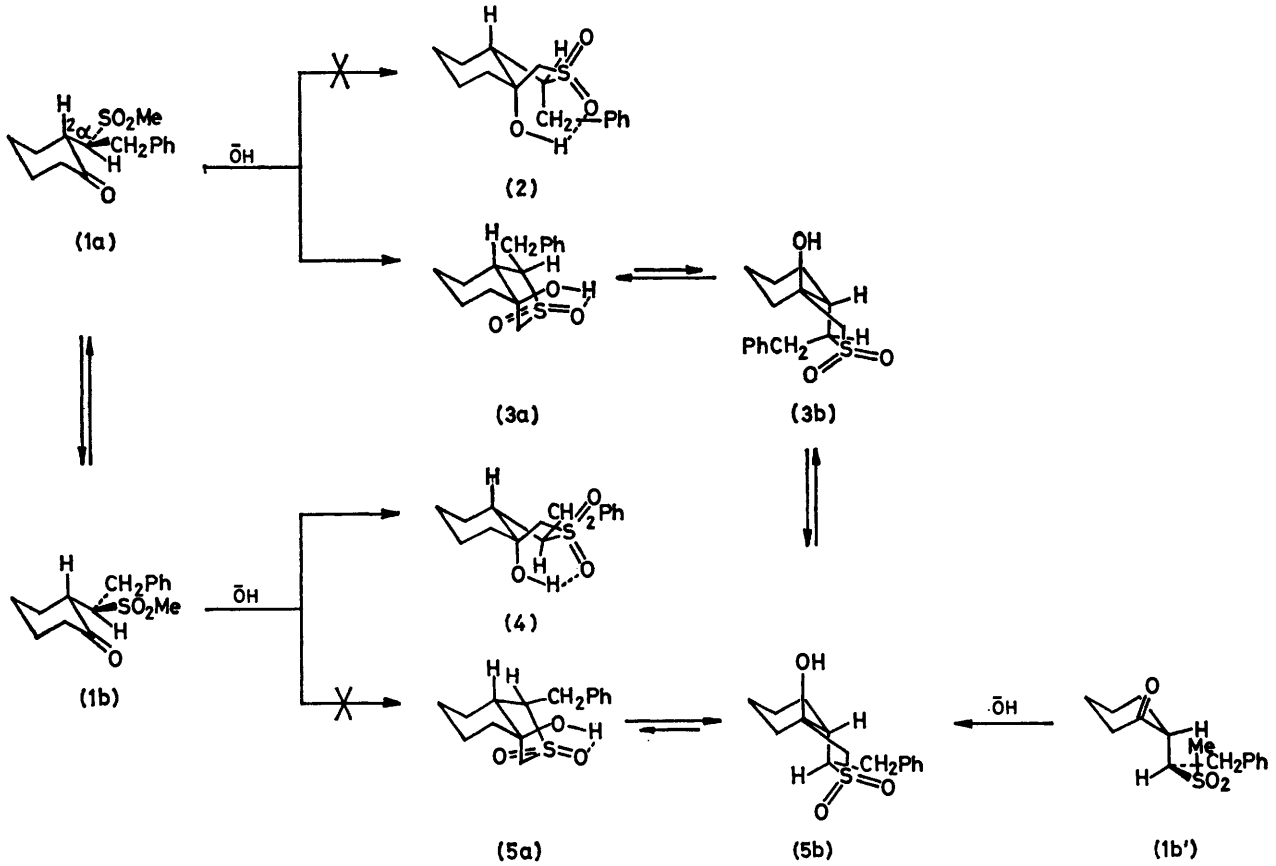
We have previously studied the synthesis, stereochemistry, and reactivity of the hydroxy-sulphones obtained from the cyclization of 2-(2-methylsulphonylethyl)cyclohexanone.[1,2] We have now extended our studies to the cyclization of the methyl sulphonylmethylcyclohexanones (1) and (10) [3] (Schemes 1 and 3), which contain more complex side chains.

[1] S. Fabrissin, S. Fatutta, and A. Risaliti, *Gazzetta*, 1977, **107**, 15.

[2] S. Fabrissin, S. Fatutta, and A. Risaliti, *J.C.S. Perkin I*, 1977, 1561.

[3] S. Fatutta and A. Risaliti, *J.C.S. Perkin I*, 1974, 2383.

These compounds lead to cyclic hydroxy-sulphones derived from perhydro-2-thiaindan and 2-thiadecalin respectively. Moreover, two *cis*- and two *trans*-isomers are expected from each starting product, because under the reaction conditions (1) and (10) exist as an equilibrium of isomers [(1a), (2*S**,α*S**); (1b), (2*S**,α*R**); (10a), (2*R**,α*R**); (10b), (2*R**,α*S**)] in agreement with the presence of chiral centres at C-2 of the ring and C-α of the side chain.



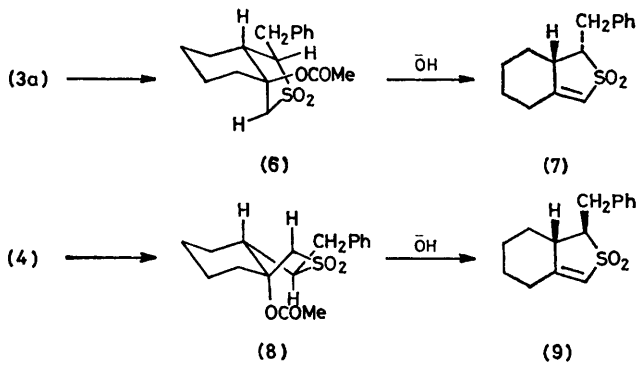
SCHEME 1

Nevertheless, (1) and (10) both furnished only three of the expected isomers in reactions under the same conditions as previously described,[1] *i.e.* in refluxing methanolic KOH.

Compound (1) led to a mixture of three 1-benzyl-3a-hydroxyperhydro-2-thiaindan 2,2-dioxides with m.p.s 179, 185, and 192 °C in a ratio of 20 : 2 : 1 respectively.

Only the isomer with m.p. 192 °C shows an i.r. band (chloroform solutions with increasing dilutions) due to free OH stretching, and consequently this product must have a *cis*-ring junction; it is probably (5b), since the *cis*-ring fused (3) is more stable in the conformation (3a) rather than (3b), in view of the strong steric interaction between the benzyl group and the cyclohexane unit.

The isomer with m.p. 185 °C can be assigned the *cis*-ring fused structure (3a) since it was partially converted into (5b) by alkali-catalysed epimerization at C-1. Acetylation of compound (3) and subsequent elimination of acetic acid in a basic medium afforded the αβ-unsaturated sulphone (7) (Scheme 2). This reaction leaves the stereochemistry at C-1 unchanged, because, at room temperature, αβ-elimination in such acetyl derivatives is very fast (5—10 min) whereas epimerization at C-1, under the same conditions, is very slow (24 h for equilibrium to be reached).



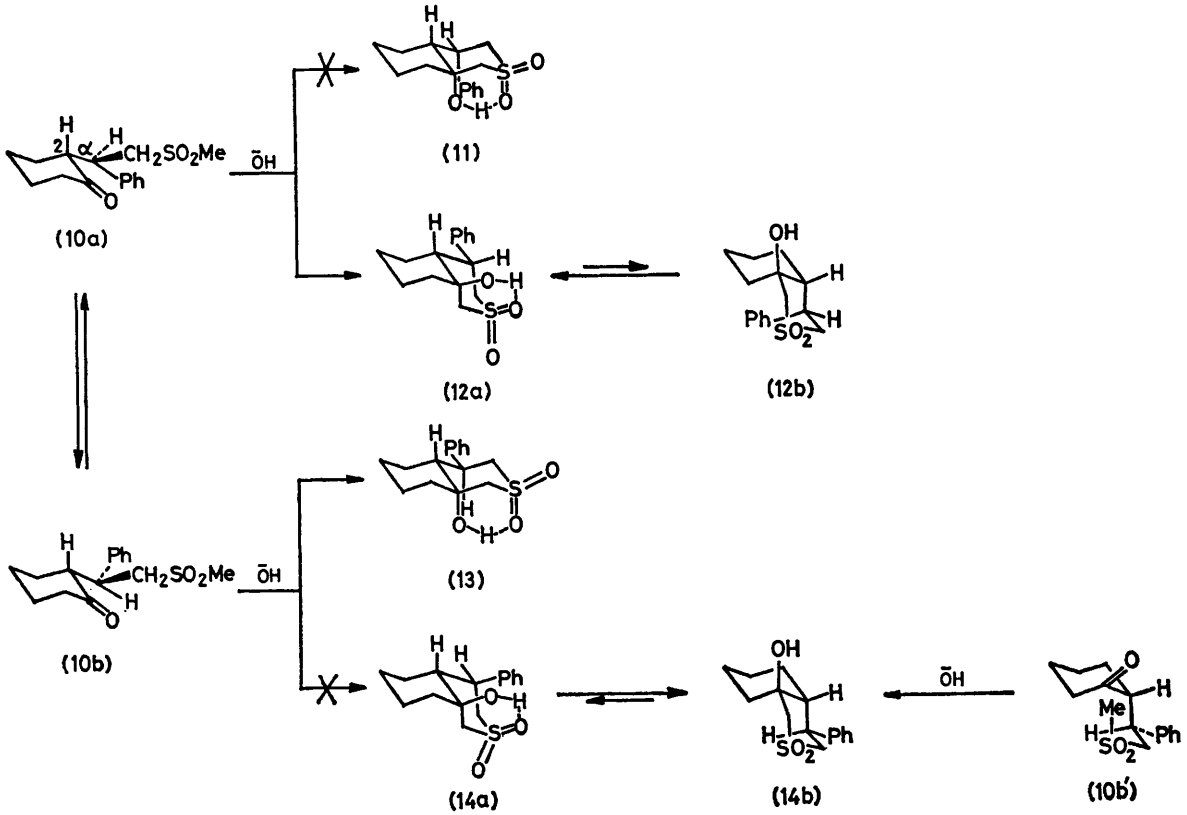
SCHEME 2

Acetylation and αβ-elimination of the third isomer, m.p. 179 °C, furnished an αβ-unsaturated sulphone isomeric with (7). These two olefins can differ only in the configuration at C-1; therefore structure (9) should be assigned to the αβ-unsaturated sulphone obtained

from the product with m.p. 179 °C and consequently the parent hydroxy-sulphone must have structure (4).

Under the usual conditions [1] the sulphonyl-cyclohexanone (10) afforded a mixture of three 4-phenyl-8a-hydroxy-2-thiadecalin 2,2-dioxides with m.p.s 172, 174, and 204 °C, in a ratio of 13 : 4.5 : 1.

undergo αβ-elimination, but afforded the parent hydroxy-sulphone (14b). Pyrolysis of the acetate (15) gave, *via* a *cis*-elimination,[1,4] the αβ-unsaturated sulphone (16), which appeared to be identical to that obtained from the acetate of the product with m.p. 172 °C. This indicates that (14b) and the product with m.p. 172 °C have the



SCHEME 3

In this case also the structure of one isomer was inferred simply from its i.r. spectrum in chloroform solution; only the spectrum of the compound with m.p. 204 °C exhibits a band due to free OH stretching, whilst bands due to the OH group intramolecularly hydrogen-bonded to the SO_2 group are present in the spectra of the isomers with m.p.s 172 and 174 °C (Scheme 3). Therefore structure (14b) with a *cis*-ring junction is attributable to the product with m.p. 204 °C, on the basis of the same arguments as for (5b).

For the hydroxy-sulphones derived from 2-thiadecalin the benzylic C-4 hydrogen atom is not acidic enough to allow epimerization in a basic medium. Consequently the structural relationship between (14b) and the other isomers can be determined only by comparison of the corresponding αβ-unsaturated sulphones (Scheme 4).

For this purpose we prepared the acetates of the isomers with m.p.s 172 and 174 °C. Both underwent αβ-elimination in a basic medium to furnish two different αβ-unsaturated sulphones (16) and (19). Under the same conditions the acetate (15) [from (14b)] did not

[4] C. H. Depuy and R. W. King, *Chem. Rev.*, 1960, **60**, 431.

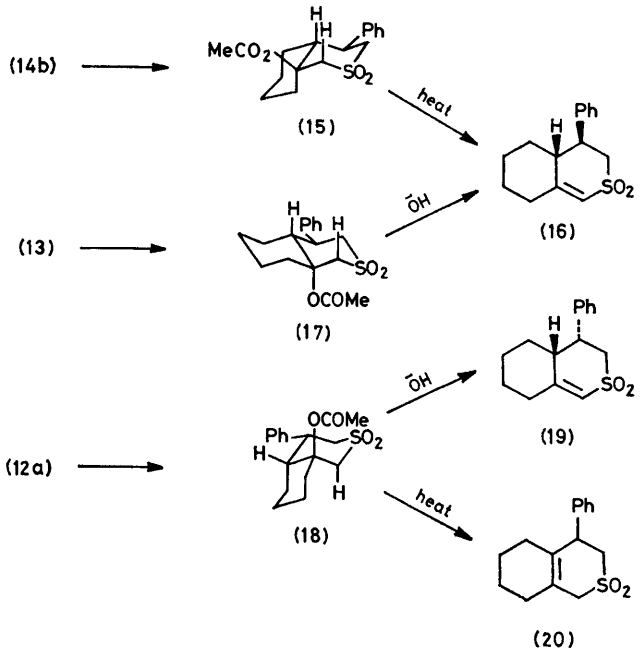
same configuration at C-4 and C-4a; consequently the product with m.p. 172 °C is the isomer (13). Thus, the third isomer must have structure (11) or (12a).

In order to distinguish between these possibilities, we studied the pyrolysis of the acetate obtained from the product with m.p. 174 °C. This reaction gave the olefin (20) as the major product; this result is consistent only with a *cis*-ring junction in the parent acetate [1,4] and so structure (12a) must be assigned to this product.

The failure to form (11) can be attributed to the strong 1,3-diaxial interactions between the phenyl group and the oxygen atoms of both the OH and the SO_2 groups. Since there would be a similar steric hindrance in (14a) also, it is probable that (14b) is not derived from (14a), but more probably from cyclization of (10b') following conformational inversion of (10b).

The 1,3-diaxial interaction between the benzyl group and the hydroxy-group in the perhydrothiaindan (2) is evidently strong enough to prevent the formation of this product. As a consequence of 1,3-diaxial interactions (5b) is probably formed from (1b) through (1b') and not from (5a) (Scheme 1). Nevertheless, in this case, (5b)

and (3a) are in equilibrium under the reaction conditions and therefore (5b) can also be derived from (3a).



SCHEME 4

To the best of our knowledge, there are no literature reports on the stereochemistry of base-promoted αβ-elimination of acetic acid from β-acetoxy-sulphones. In our opinion the formation of (7), (9), (16), and (19) from (6), (8), (17), and (18), respectively, must take place by *anti*-elimination. In fact when the hydrogen atoms α to the SO_2 group are both fixed in a *gauche* conformation with respect to the acetoxy-group, as in the case of the β-acetoxy-sulphones obtained from (5b) and (14b), αβ-elimination in a basic medium does not occur.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R 12B spectrometer (Me_4Si internal standard; solutions in $CDCl_3$) and i.r. spectra (Nujol mulls, unless otherwise noted) with a Perkin-Elmer 257 spectrophotometer. For analytical t.l.c., plates were coated with silica gel G (Merck) and developed with benzene–acetone (90 : 10). For chromatographic columns extra-pure silica (Merck; 70—230 mesh ASTM) was used as the stationary phase and benzene–acetone (90 : 10) as eluant. Gas chromatographic analyses employed a Varian Aerograph (series 1400) chromatograph with a flame-ionization detector.

Cyclization of 2-(α-*Methylsulphonylphenethyl*)*cyclohexanone* (1).—The sulphone (1) [3] (5 g; 17.8 mmol) was heated under reflux for 5 h with potassium hydroxide (10 g; 178 mmol) in methanol (100 ml). The solution was concentrated *in vacuo*, diluted with water, acidified with 10% hydrochloric acid, and extracted with chloroform. The extract was dried and evaporated and the residue (4 g) was chromatographed on silica. The fraction eluted first furnished 1-*benzyl*-1,3,4,5,6,7-*hexahydrobenzo*[c]*thiophen* 2,2-*dioxide* (0.32 g; 8% yield), m.p. 120 °C (from ethanol) (Found: C, 68.4; H, 6.7. $C_{15}H_{18}O_2S$ requires C, 68.7; H, 6.9%); $\nu_{max.}$ 1 308 and 1 127 cm^{-1} (SO_2); δ 6.7 (5 H, m, Ph), 4.3—4.0 (1 H, dd, $HCCH_2Ph$), and 3.6—3.3 (2 H, m, H_2CSO_2). The second fraction provided 1β-*benzyl*-3aα-*hydroxy*-trans-*perhydro*-2-*thiaindan* 2,2-*dioxide* (4) (3.20 g; 80% yield), m.p. 179 °C (from ethanol) (Found: C, 64.6; H, 7.2. $C_{15}H_{20}O_3S$ requires C, 64.3; H, 7.2%); $\nu_{max.}$($CHCl_3$) 3 505 cm^{-1}; $\nu_{max.}$ (Nujol) 3 470 (OH) and 1 310, 1 300 and 1 135 cm^{-1} (SO_2); δ 7.35 (5 H, m, Ph), 4.3—3.9 (1 H, dd, $HCCH_2Ph$), and 3.9 (1 H, s, OH). Further elution afforded the 1α-*benzyl*-3aβ-*hydroxy*-cis-*isomer* (3) (0.32 g; 8% yield), m.p. 185 °C (from ethanol) (Found: C, 64.5; H, 7.2%); $\nu_{max.}$($CHCl_3$) 3 490 cm^{-1}; $\nu_{max.}$ (Nujol) 3 440 (OH) and 1 310, 1 290, and 1 130 cm^{-1} (SO_2); δ 7.35 (5 H, m, Ph), 4.5 (1 H, s, OH), and 4.3—4.0 (1 H, dd, $HCCH_2Ph$). The last fraction furnished the 1β-*benzyl*-3aβ-*hydroxy*-cis-*isomer* (5) (0.16 g; 4% yield), m.p. 192 °C (from ethanol) (Found: C, 64.4; H, 7.1%); $\nu_{max.}$($CHCl_3$) 3 590 and 3 480 cm^{-1}; $\nu_{max.}$ (Nujol) 3 460 (OH), and 1 305 and 1 140 cm^{-1} (SO_2); δ 7.45 (5 H, m, Ph), 4.3—4.0 (1 H, dd, $HCCH_2Ph$), and 2.1 (1 H, s, OH).

Acetyl Derivatives of the Hydroxy-sulphones (3), (4), *and* (5).—The hydroxy-sulphones (3), (4), and (5) were each heated under reflux overnight with acetyl chloride in excess. The unchanged chloride was removed and the solid *acetates* were recrystallised from ethanol. Compound (5) gave 3aβ-*acetoxy*-1β-*benzyl*-cis-*perhydro*-2-*thiaindan* 2,2-*dioxide*, m.p. 218—220 °C (Found: C, 63.4; H, 6.9. $C_{17}H_{22}O_4S$ requires C, 63.3; H, 6.9%); $\nu_{max.}$ 1 720 cm^{-1} (CO), compound (3) gave the 3aβ-*acetoxy*-1α-*benzyl*-cis-*isomer* (6), m.p. 195 °C (Found: C, 63.5; H, 6.9%); $\nu_{max.}$ 1 728 cm^{-1} (CO); and compound (4) gave the 3aα-*acetoxy*-1β-*benzyl*-trans-*isomer* (8), m.p. 176 °C (Found: C, 63.2; H, 7.0%); $\nu_{max.}$ 1 725 cm^{-1} (CO).

Reaction with Ethanolic Potassium Hydroxide of the Acetates (6) *and* (8).—Ethanolic potassium hydroxide (1 g in 30 ml) was added to a solution of (6) or (8) (0.500 g) in absolute ethanol. After 15 min at room temperature, the mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with chloroform. The resulting αβ-unsaturated sulphones were recrystallised from ethanol. Compound (6) gave 1α-*benzyl*-1,4,5,6,7,7a-*hexahydrobenzo*[c]*thiophen* 2,2-*dioxide* (7), m.p. 174 °C (Found: C, 69.0; H, 6.8. $C_{15}H_{18}O_2S$ requires C, 68.7; H, 6.9%); $\nu_{max.}$ 1 625 cm^{-1} (C=C); δ 6.25 (1 H, s, HC=C), and compound (8) gave the 1β-*benzyl*-*stereoisomer* (9), m.p. 155 °C (Found: C, 68.7; H, 6.9%); $\nu_{max.}$ 1 625 cm^{-1} (C=C); δ 6.30 (1 H, s, HC=C). More prolonged reaction time with (6) and (8) gave, because of double bond migration of (7) and (9), 1-benzyl-1,3,4,5,6,7-hexahydrobenzo[*c*]thiophen 2,2-dioxide, m.p. 120 °C, already described. The acetate of the hydroxy-sulphone (5) under the same conditions as described for (6) and (8) gave the parent compound, m.p. 192 °C, in quantitative yield.

Epimerization of the Hydroxy-sulphones (3) *and* (5).—Ethanolic potassium hydroxide (1 g in 30 ml) was added to an ethanolic solution of (3) or (5) (0.500 g in 20 ml). The solution was left at room temperature, and the equilibration was monitored by t.l.c. analysis. After 24 h the relative intensity of the spots corresponding to (3) and (5) showed no further change. The solution was diluted with water, acidified with 10% hydrochloric acid, and extracted with chloroform. The residue, after column chromatography, furnished (3) and (5) in a 2 : 1 ratio in both cases.

Cyclization of 2-α-(*Methylsulphonylmethyl*)*benzylcyclohexanone* (10).—The sulphone (10) [3] (5 g, 17.8 mmol) was

heated under reflux for 3 h with potassium hydroxide (10 g, 178 mmol) in methanol (120 ml). The solution was concentrated *in vacuo*, diluted with water, acidified with 10% hydrochloric acid, and extracted with chloroform. The residue (4 g) was chromatographed on silica. The first fraction furnished 4-*phenyl*-$\Delta^{4a(8a)}$-2-*thiaoctalin* 2,2-*dioxide* (20) (0.30 g, 7.5% yield). (Analytical and spectroscopic data are reported later). The second fraction afforded 8aα-*hydroxy*-4β-*phenyl*-trans-2-*thiadecalin* 2,2-*dioxide* (13) (2.6 g, 65% yield), m.p. 172—173 °C (from ethanol) (Found: C, 64.5; H, 7.3. $C_{15}H_{20}O_3S$ requires C, 64.3; H, 7.2%); $\nu_{max.}$($CHCl_3$) 3 510 cm^{-1}; $\nu_{max.}$ (Nujol) 3 460 (OH), and 1 310, 1 300, and 1 140 cm^{-1} (SO_2); δ 7.25 (5 H, m, Ph) and 4.05 (1 H, s, OH). Compound (13) exists in two crystalline forms as shown by thermal analysis. The stable form was obtained on crystallisation from ethanol and showed an OH band at 3 460 cm^{-1} (Nujol). The metastable form was obtained from apolar solvents (*e.g.* benzene) and exhibited an OH band at 3 510 cm^{-1} (Nujol). The i.r. spectra of both forms, recorded in chloroform, appeared superimposable. The less stable crystals changed into the other form when heated or left at room temperature for a few hours. Further elution afforded 8aβ-*hydroxy*-4α-*phenyl*-cis-2-*thiadecalin* 2,2-*dioxide* (12) (0.90 g, 22.5% yield), m.p. 174—176 °C (from ethanol) (Found: C, 64.2; H, 7.2%); $\nu_{max.}$($CHCl_3$) 3 500 cm^{-1}; $\nu_{max.}$ (Nujol) 3 450 (OH), and 1 310, 1 295, 1 280, and 1 130 cm^{-1} (SO_2); δ 7.25 (5 H, m, Ph) and 4.50 (1 H, s, OH). The last fraction gave the 4β-*phenyl-stereoisomer* (14) (0.20 g, 5% yield), m.p. 204 °C (from ethanol) (Found: C, 64.2; H, 7.1%); $\nu_{max.}$($CHCl_3$) 3 590 and 3 460 cm^{-1}; $\nu_{max.}$ (Nujol) 3 460 (OH), and 1 310 and 1 115 cm^{-1} (SO_2); δ[$(CD_3)_2SO$] 6.85 (5 H, m, Ph) and 3.25 (1 H, s, OH).

Formation of Acetates (15), (17), *and* (18).—The hydroxysulphones (12), (13), and (14) were heated under reflux with excess of acetyl chloride for 1, 3, and 24 h respectively. The unchanged chloride was removed and the solid acetates were recrystallised from benzene–light petroleum. Compound (14) gave 8aβ-*acetoxy*-4β-*phenyl*-cis-2-*thiadecalin* 2,2-*dioxide* (15), m.p. 185—186 °C (Found: C, 63.2; H, 7.0. $C_{17}H_{22}O_4S$ requires C, 63.3; H, 6.9%); $\nu_{max.}$ 1 735 cm^{-1} (CO), compound (13) gave the 8aα-*acetoxy*-4β-*phenyl*-trans-*isomer* (17), m.p. 169—171 °C (Found: C, 63.3; H, 7.0%); $\nu_{max.}$ 1 730 cm^{-1} (CO), and compound (12) gave the 8aβ-*acetoxy*-4α-*phenyl*-cis-*isomer* (18), m.p. 173—174 °C (Found: C, 63.1; H, 7.0%); $\nu_{max.}$ 1 720 cm^{-1} (CO).

Reaction with Ethanolic Potassium Hydroxide of the Acetates (17) *and* (18).—An ethanolic solution of potassium hydroxide (1 g in 30 ml) was added to a solution of (17) or (18) (0.500 g) in dry ethanol. After 5 h at room temperature, the mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with chloroform. The $\alpha\beta$-unsaturated sulphones produced were recrystallised from benzene–light petroleum. Compound (17) gave 4β-*phenyl*-$\Delta^{1(8a)}$-2-*thiaoctalin* 2,2-*dioxide* (16), m.p. 115—116 °C (Found: C, 68.6; H, 6.8. $C_{15}H_{18}O_2S$ requires C, 68.7; H, 6.9%); $\nu_{max.}$ 1 620 cm^{-1} (C=C); δ 6.35 (1 H, s, HC=C), and compound (18) gave the 4α-*phenyl-isomer* (19), m.p. 120—123 °C (Found: C, 68.5; H, 6.9%); $\nu_{max.}$ 1 630 cm^{-1} (C=C); δ 6.35 (1 H, s, HC=C). The acetate (15) under the same conditions furnished, after 10 min, the parent hydroxysulphone (14), m.p. 204 °C, in quantitative yield.

Isomerization of the Olefins (16) *and* (19).—It is known that $\alpha\beta$- and $\beta\gamma$-unsaturated sulphones are in equilibrium in a basic medium.[1,5-7] On this basis the olefin (20) could be obtained from (16) or (19). The olefin (16) or (19) (0.100 g) was dissolved in dry ethanol; after addition of ethanolic potassium hydroxide (0.200 g in 10 ml) the solution was left at room temperature, the isomerization being monitored by t.l.c. After 96 h the spot corresponding to the starting olefin had disappeared. The solution was diluted with water, acidified, and extracted with chloroform. 4-*Phenyl*-$\Delta^{4a(8a)}$-2-*thiaoctalin* 2,2-*dioxide* (20) was obtained, m.p. 179—180 °C (from ethanol) (Found: C, 68.6; H, 7.0. $C_{15}H_{18}O_2S$ requires C, 68.7; H, 6.9%); $\nu_{max.}$ 1 300, 1 280, and 1 130 cm^{-1} (SO_2); δ 7.1 (5 H, m, Ph), 4.1—2.8 (5 H, complex), and 2.2—1.0 (8 H, complex). The benzylic proton of (20) that would confirm the $\Delta^{4a(8a)}$ position of the double bond cannot be distinguished in the n.m.r. spectrum because of overlap with other signals. Structure (20) was proved by epoxidation and subsequent basic rearrangement[1,8] into 4a-*hydroxy*-4-*phenyl*-$\Delta^{1(8a)}$-2-*thiaoctalin* 2,2-*dioxide*, m.p. 166 °C (from ethanol), which shows a benzylic proton n.m.r. signal (Found: C, 64.9; H, 6.3. $C_{15}H_{18}O_3S$ requires C, 64.7; H, 6.5%); $\nu_{max.}$ 3 408 (OH) and 1 610 cm^{-1} (C=C); δ 7.25 (5 H, m, Ph), 6.1 (1 H, s, HC=C), 4.1—3.3 (2 H, m, H_2CSO_2), 3.2—2.8 (1 H, dd, *HC*Ph), and 2.25 (1 H, s, OH).

Pyrolysis of the Acetates (15) *and* (18).—The pyrolyses were carried out in the injection port of a gas chromatograph; this method, as described previously,[1] proved to be the most convenient for our products. When the injection temperature was high enough, thermal decomposition was immediate and complete and the olefinic derivatives were readily detected in the chromatograms. The acetates were injected as solutions in chloroform under the following conditions.

Acetate (15). The injection port was maintained at 385 °C and the column (SE 30 on Chromosorb W 60—80 mesh 5 : 95; 2 m length) at 210 °C. The olefins (20), (16), and (19) were found to have retention times of 6.0, 7.0, and 9.0 min, respectively, on this column with a nitrogen flow-rate of 30 ml min^{-1}. The chromatogram of the pyrolysed acetate (15) showed only peaks due to (20) and (16) in a 1 : 1 ratio and a trace of an unidentified product, with a retention time of 5.5 min, that was probably the isomeric $\Delta^{8(8a)}$-olefin.

Acetate (18). The injection port was maintained at 325 °C and the column (OV 101 on Chromosorb W 80—100 mesh 10 : 90; 2 m length) at 280 °C. The olefins (20) and (19) were found to have retention times of 13 and 15 min, respectively, on this column with a nitrogen flow-rate of 30 ml min^{-1}. The chromatogram of the pyrolysed acetate (18) exhibited two peaks (area ratio 8 : 2) corresponding to (20) and (19), respectively. Under these conditions a trace of undecomposed acetate (18) (retn. time 16.5 min) was noted.

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