ISOMERISATION OF β-EPOXY SULFONES

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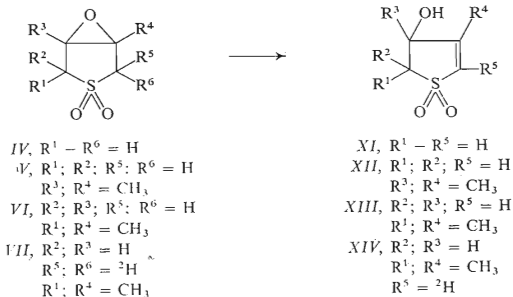
The base-catalyzed isomerisation of β-epoxy sulfones to γ-hydroxy α,β-unsaturated sulfones was shown by kinetic data, isotope effect and stereochemistry to involve an intramolecular synfacial 1--3 hydrogen migration with carbanion-like transition state.

Oxiranes, containing a methylene in the neighbourhood of an alkylsulfonyl group, activated by the oxirane ring, can be isomerised to unsaturated hydroxy sulfones. Thus, 3,4-epoxytetrahydrothiophene 1,1-dioxide has been reported to isomerise to 3-hydroxy-2,3-dihydrothiophene 1,1-dioxide[1], 1-thia-3,4-epoxycyclohexane 1,1-dioxide to 1-thia-4-hydroxy-2-cyclohexene 1,1-dioxide[2], and 3,4-epoxy-3-methyltetrahydrothiophene 1,1-dioxide to a mixture of 4-hydroxy-3-methyl-4,5-dihydrothiophene 1,1-dioxide and 3-hydroxy-3-methyl-2,3-dihydrothiophene 1,1-dioxide[3,4]. This isomerisation is not restricted only to epoxy sulfones but it is a general reaction of oxiranes, containing a hydrogen atom in the α-position to the oxirane ring. It represents also a side reaction in the nucleophilic opening of the ring. Oxiranes, containing no electrophilic functional groups, can be isomerised only by very strong bases, such as lithium diethylamide[5−7], butyllithium[8] or potassium tert-butoxide in dimethyl sulfoxide[9]. This isomerisation was described also for oxiranes with a methylene group, activated with a double[10] or triple[11] bond or a phenyl group[12]. Also in these cases strong bases such as lithium dimethylamide or pulverised potassium hydroxide were used. Epoxy esters were isomerised by the action of sodium methoxide[13]. In the presence of a strongly electrophilic group of the type —SO$_2$R the isomerisation takes place already with very weak bases, e.g. sodium hydrogen carbonate[1], lithium chloride[14], ammonia[1] or amines[15]. The preferred direction of isomerisation was investigated in several papers[5,9,16]. The isomerisation mechanism was studied on cis- and trans-epoxyoctanes, isotopically labelled with ^{2}H in positions 4 and 5; it was suggested[17] that the first reaction step is a base-induced loss of proton from the carbon atom vicinal to the oxirane ring. Stereochemical studies have shown[18,19] that the isomerisation proceeds with cleavage of proton cis to the oxirane ring.

We have now studied the rate and direction of the isomerisation of cyclic epoxy sulfones, containing five- or six-membered ring and determined the isotope effect.

The oxiranes $I-III$ were prepared by oxidation of the double bond with peroxy-benzoic acid, whereas the five-membered ring epoxy sulfones $IV-VII$ were obtained in higher yields by dehydrohalogenation of the corresponding bromohydrins. The isomerisations were catalysed with 0·05M-NaOH in aqueous ethanol or with tri-ethylamine in chloroform. We found that the primary reaction products were only 4-hydroxy-2-unsaturated sulfones whose structure we confirmed by elemental analysis, IR and ^{1}H-NMR spectra. The reaction is several times slower when catalysed with triethylamine in an aprotic medium than when catalysed with hydroxide. The

IV, $R^1-R^6 = H$
V, R^1; R^2; R^5; $R^6 = H$
$\quad R^3$; $R^4 = CH_3$
VI, R^2; R^3; R^5; $R^6 = H$
$\quad R^1$; $R^4 = CH_3$
VII, R^2; $R^3 = H$
$\quad R^5$; $R^6 = {}^2H$
$\quad R^1$; $R^4 = CH_3$

XI, $R^1 - R^5 = H$
XII, R^1; R^2; $R^5 = H$
$\quad R^3$; $R^4 = CH_3$
$XIII$, R^2; R^3; $R^5 = H$
$\quad R^1$; $R^4 = CH_3$
XIV, R^2; $R^3 = H$
$\quad R^1$; $R^4 = CH_3$
$\quad R^5 = {}^2H$

comparative kinetic measurements were performed in aqueous solution with ammonia as catalyst. The reaction order was 1·0 with respect to the oxirane, as determined by half-time measurement; the rate constants were calculated from the integrated equation for a first-order reaction (Table I). As shown by the deuterium effects (Table II) observed for the epoxy sulfones VI anv VII, the proton or deuteron is lost in the rate-determining step; the ratio $k_H/k_{2_H} = 3·5$ (30°C) indicates that in the transition state the C—H bond is only weakened but not broken. The isotope exchange in sulfones is by an order of magnitude slower than isomerisation of the epoxy sulfones. The isomerisation is catalysed even by bases which are unable to form kinetically significant concentrations of carbanion (pH of dimethyl sulfone about 23).
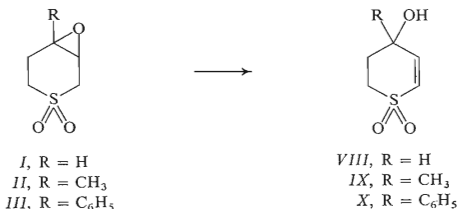

I, R = H
II, R = CH$_3$
III, R = C$_6$H$_5$

$VIII$, R = H
IX, R = CH$_3$
X, R = C$_6$H$_5$

TABLE I
Kinetic Data for Isomerisations of Oxiranes (procedure C)

Oxirane	$k_{21°C}$, min^{-1}	E_a, kJ mol^{-1}	$A \cdot 10^{-10}$, s^{-1}
I	0·17	57 ± 3	18
II	0·21	52	4·6
III	0·19	55	6·6
IV	0·104	59	15
V	0·056	57	5·3
VI	0·087	53	0·72

It follows from the kinetic data (Table I) that the presence of methyl or phenyl in the position 4 relative to the sulfonyl group (sulfones I–III) does not affect significantly the reaction rate, but the lower activation energy and frequency factor A indicate a mutually compensating effect of steric hindrance to solvation of the transition state on the one hand and the electron density at the oxygen on the other. The presence of a methyl group in position 3 (sulfones IV–VI) retards the reaction as the result of a lower frequency factor; this can be due to a steric hindrance to the approach of the base to the hydrogen on $C_{(2)}$. Because of the strong $+I$ effect of methyl on $C_{(5)}$, in sulfones VI and VII the base attacks only the hydrogen (or deuterium) on $C_{(2)}$; this manifests itself by a much lower value of the factor A, i.e. by greater activation entropy. The reaction determining step is the attack of the active hydrogen vicinal to the sulfonyl group by base which results in lengthening of the C—H bond, this bond being not broken in the transition state. The rearrangement involves an intramolecular synfacial 1–3 hydrogen migration; the double bond formation and opening of the oxirane ring (Scheme 1) probably takes place simultaneously.
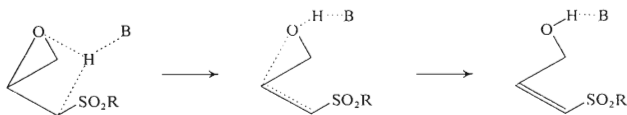
SCHEME 1

EXPERIMENTAL

Melting points were determined on a Boetius (GDR) hot-stage microscope, the analytical samples were dried for 8 h at 66 Pa and temperatures 40°C below their melting points. The IR spectra were measured in tetrachloromethane on a UR-20 spectrophotometer (Zeiss, Jena), the ^{1}H-NMR

spectra on a Varian HA-100 instrument (chemical shifts in ppm, δ scale, internal standard tetramethylsilane). UV spectra were taken on a Unicam SP-700 spectrometer.

1-*Thia*-3,4-*epoxycyclohexane* 1,1-*dioxide* (I) was prepared according to ref.[2]; m.p. 126—127°C (ethanol).

1-*Thia*-4-*methyl*-3,4-*epoxycyclohexane* 1,1-*dioxide* (II): 1-Thia-4-methyl-4-cyclohexanol[20] was dehydrated by heating with anhydrous oxalic acid (molar ratio 3 : 1) to 140°C/1333 Pa to give 1-thia-4-methyl-3-cyclohexene (85%). This was oxidized with peroxybenzoic acid (2 equivalents) in chloroform for 2 h at 0°C. The reaction mixture was washed with saturated sodium hydrogen carbonate solution and the chloroform was distilled off. Crystallisation from ethanol afforded 1-thia-4-methyl-3-cyclohexene 1,1-dioxide, m.p. 82—83°C. For $C_6H_{10}O_2S$ (146·2) calculated: 49·29% C, 6·89% H, 21·93% S; found: 48·90% C, 6·99% H, 22·10% S. This sulfone was transformed into the oxirane *II* by treatment with peroxybenzoic acid (2·5 equivalents) in chloroform for 7 days at 15°C. The reaction was followed by thin-layer chromatography on silica gel (detection with alkaline potassium permanganate solution) and the oxirane was isolated by chromatography on a silica gel column; m.p. 147—148°C (ethanol). For $C_6H_{10}O_3S$ (162·2) calculated: 44·43% C, 6·21% H, 19·77% S; found: 44·40% C, 6·31% H, 19·77% S.

1-*Thia*-4-*phenyl*-3,4-*epoxycyclohexane* 1,1-*dioxide* (III) was prepared similarly starting from 1-thia-4-phenyl-3-cyclohexene[21], via 1-thia-4-phenyl-3-cyclohexene 1,1-dioxide, m.p. 128—130°C (ethanol). The oxirane *III* melted at 168—171°C (ethanol). For $C_{11}H_{12}O_3S$ (224·3) calculated: 58·90% C, 5·89% H, 14·30% S; found: 58·71% C, 5·81% H, 14·08% S.

3,4-*Epoxy*-2,3,4,5-*tetrahydrothiophene* 1,1-*dioxide* (IV), m.p. 124—126°C, was prepared according to ref.[13]. The same procedure was used also in the preparation of 3,4-epoxy-3,4-dimethyl-tetrahydrothiophene 1,1-dioxide (V), m.p. 138°C (reported[15] m.p. 138—140°C). For $C_6H_{10}O_3S$ (162·2) calculated: 44·43% C, 6·21% H, 19·77% S; found: 44·62% C, 6·21% H, 19·58% S.

r-2,c-4-*Dimethyl*-t-3,4-*epoxytetrahydrothiophene* 1,1-*dioxide* (VI): 2-Methyl-1,3-pentadiene[22] (50 g), pyrogallol (0·6 g) and sulfur dioxide (50 ml) were kept in an autoclave for 14 days at room temperature to give 2,4-dimethyl-2,5-dihydrothiophene 1,1-dioxide, m.p. 38—39·5°C (ethanol). For $C_6H_{10}O_2S$ (146·2) calculated: 49·29% C, 6·89% H, 21·89% S; found: 49·55% C, 7·01% H, 21·66% S. This sulfone (2 g) was treated with N-bromoacetamide (1·8 g) in water (20 ml), containing 0·1 g of sulfuric acid (stirring and cooling; the temperature must not rise above 50°C); the product was taken up in chloroform and chromatographed on a column of silica gel, yielding r-2,c-4-dimethyl-c-3-bromo-t-4-hydroxy-2,5-dihydrothiophene 1,1-dioxide, m.p. 120—123°C

TABLE II

Ratios of Rate Constants for Isomerisation of the Oxiranes *VI* and *VII*

k_{2_H}, min^{-1}	k_H/k_{2_H}	Temperature, °C
0·020	4·3	21
0·030	3·5	30
0·069	3·04	40

(ethanol); yield 60% A mixture of this product (1·2 g) and freshly prepared barium carbonate (0·6 g) was heated for 5 h to 80°C with stirring. The mixture was filtered, the filtrate taken down *in vacuo* and the residue extracted with hot chloroform. Chromatography on silica gel afforded the epoxy sulfone *VI*, m.p. 75—77°C (ethanol); yielded 85%. For $C_6H_{10}O_3S$ (162·2) calculated: 44·43% C, 6·21% H, 19·77% S; found: 44·73% C, 6·31% H, 19·71% S. ^{1}H-NMR spectrum: 1·45 d, 3 H_a, J_{ad} = 7·5; 1·58 s, 3 H_b; 3·26 d 1 H; 3·40 d, 1 H_c, J_{cc} = 14; 3·32 q, 1 H_d, J_{ad} = 7·5 J_{dc} = 0; 3·33 s, 1 H_e.

2,4-*Dimethyl*-2,5-[5,5-^{2}H]*dihydrothiophene* 1,1-*dioxide*: A mixture of 2,4-dimethyl-2,5-dihydrothiophene 1,1-dioxide (2 g), dioxane (30 ml), deuterium oxide (300 ml) and potassium carbonate (2 g) was stirred at 20°C for 48 h, the solvents were distilled off under diminished pressure, and the procedure was repeated three times. The product was extracted with chloroform and crystallized from ethanol; m.p. 38—39·5°C. The mean degree of deuteration was 0·98, according to mass spectrometry.

r-2,c-4-*Dimethyl*-t-3,4-*epoxy*-[5,5-^{2}H]*tetrahydrothiophene* 1,1-*dioxide* (VII) was prepared by procedure analogous to that for the preparation of the non-deuterated oxirane *VI*; m.p. 75—77°C. ^{1}H-NMR spectrum: 1·41 d, 3 H; 1·55 s, 3 H; 3·32 q, 1 H; 3·36 s, 1 H.

Isomerisation of the Oxiranes

A) 0·1M-NaOH (10 ml) was added to a stirred solution of the oxirane *I*— *VI* (0·5 g) in 50% ethanol (10 ml) and the reaction (at 20°C) was followed by thin-layer chromatography on silica gel. After the end of isomerisation the mixture was neutralized with 0·1M-HCl, the solvents were distilled off, the residue extracted with hot chloroform and the product distilled or crystallized. Physical properties of the unsaturated hydroxy sulfones are given in Table III.

TABLE III
Physical Constants of Unsaturated Hydroxy Sulfones

Compound	M.p., °C	B.p., °C/Pa	Note
VIII	—	152—154/13·3	ref.[2]
IX[a]	66—67	—	—
XI	—	155—157/40	ref.[1] 157/40
XII	91—93	—	ref.[3] 89—90
X[b]	152—153	—	—
XIII[c]	—	160/13·3	bath temperature

[a] ^{1}H-NMR spectrum: 1·45 s, 3 H; 3·15 s, 1 H; 2·40 center of m, 2 H; 3·47 center of m, 2 H; 6·28 m, 2 H; [b] ^{1}H-NMR spectrum: 2·38—3·67 m, 4 H; 2·77 s, 1 H; 6·31—6·55 q, 2 H; 7·38—7·46 m, 5 H; [c] ^{1}H-NMR spectrum: 1·485 d, 3 H; 2·035 d, 3 H; 2·99 s, 1 H; 3·22 m, 1 H; 4·34 d, 1 H; 6·34 s, 1 H.

B) Triethylamine (1 equivalent) in chloroform (10 ml) was added to the oxirane (0·1 g) at 20°C. The further work-up procedure was the same as described under *A*).

C) The kinetic measurements were carried out in 2 mm cells by UV-spectral determination of the concentration increase of the unsaturated hydroxy sulfones. An 0·87M ammonia solution (10 µl) was injected (Hamilton syringe) to a 10^{-3}M aqueous solution (0·5 ml) of oxirane. For each oxirane five measurements at various concentrations and at three temperatures were carried out.

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